Natural and Synthetic Cannabinoids for Agitation and Aggression in Alzheimer's Disease: A Meta-Analysis

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ABSTRACT

Objective: This meta-analysis investigated the efficacy of cannabinoids on agitation and aggression in patients with Alzheimer's disease (AD).

Data Sources: Electronic records up to August 2018 were searched from MEDLINE, EMBASE, and PsycINFO. Search terms included *Alzheimer's disease*, *agitation*, *aggression*, and *cannabinoids*.

Study Selection: Double-blind, placebo-controlled studies investigating the effect of cannabinoids on agitation in patients with AD were included. Of the 1,336 records returned, 123 were reviewed and 6 (N = 251 participants) were included.

Data Extraction: Data on demographics, study setting, trial length, intervention, outcomes, and dropouts were extracted.

Results: There was no effect of cannabinoids as a group on agitation (standard mean difference: −0.69, $P = .10$), though there was significant heterogeneity ($\chi^2_6 = 43.53$, $P < .00001$, $I^2 = 86\%$). There was a trend for greater difference in agitation with synthetic cannabinoids over tetrahydrocannabinol ($\chi^2_1 = 3.05$, $P = .08$). Cannabinoids had a larger effect on agitation with greater cognitive impairment ($B = 0.27$, $t_6 = 2.93$, $P = .03$). Cannabinoids did not change overall neuropsychiatric symptoms or body mass index (BMI). However, there was a significant difference in patients with a lower BMI compared to patients with a higher BMI ($\chi^2_1 = 4.63$, $P = .03$). Sedation was significantly greater with cannabinoids compared to placebo (risk ratio = 1.73, $P = .04$), but there were no differences in the occurrence of adverse events or dropouts due to an adverse event between treatment groups.

Conclusions: The efficacy of cannabinoids on agitation and aggression in patients with AD remains inconclusive, though there may be a signal for a potential benefit of synthetic cannabinoids. Safety should be closely monitored as cannabinoid treatment was associated with increased sedation.

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Along with the cognitive deficits that are characteristic of Alzheimer's disease (AD), neuropsychiatric symptoms commonly occur, and they typically increase in prevalence and severity with AD progression.[1] An estimated 60%–90% of AD patients will experience at least one neuropsychiatric symptom during the course of their illness.[2] Agitation is one of the most common and challenging neuropsychiatric symptoms to treat, occurring in 20%–50% of patients with moderate to severe AD.[2–4] In addition to being associated with increased caregiver burden, agitation is also associated with more rapid AD progression, increased risk of falls, weight loss, and mortality.[5–7] Therefore, this neuropsychiatric symptom is important to treat.

Current pharmacologic treatments of agitation in AD have been associated with limited to modest efficacy and questionable safety profiles. For example, despite the modest efficacy of atypical antipsychotics, their associated side effects, such as increased risk of mortality, parkinsonism, and cerebrovascular events, warrants caution when prescribing them to those with AD.[8] Other psychotropic medications that have been investigated for the treatment of agitation in AD include typical antipsychotics, antidepressants, cholinesterase inhibitors, memantine, and benzodiazepines. However, studies have reported contradictory findings regarding their safety and efficacy for the treatment of agitation.[9,10] As such, there is a clinical need to identify a treatment for agitation in AD that is both safe and effective.

The endocannabinoid system has been implicated in modulating AD pathology and symptomatology, positioning itself as a novel pharmacologic target for the treatment of agitation in AD.[11–13] The endocannabinoid system pathway begins with the synthesis of endogenous cannabinoids, which are retrograde messengers that regulate neurotransmission.[14,15] Following postsynaptic release, endogenous cannabinoids bind to G protein–coupled cannabinoid receptors 1 and 2 (CB_1 and CB_2).[16] CB_1 receptors are highly abundant in the central nervous system, particularly in the cerebral cortex and hippocampus, 2 brain structures that are essential in learning and memory function and that are also affected by AD pathology.[17–21] CB_2 receptors, which are more abundant in the cells and tissues of the immune system, have been associated with decreases in the production of proinflammatory molecules in vitro and with the removal of amyloid-β plaques in the brain.[22–24] Animal model studies have demonstrated that deletion of the CB_1 gene is associated with cognitive impairment.[25,26] However, a number of clinical studies have demonstrated that acute and chronic

Clinical Points

- Medications used to treat agitation in patients with Alzheimer's disease (AD) have limited to modest efficacy and are associated with harmful side effects.
- Cannabinoids may offer benefits for agitation in AD due to their unique pharmacologic mechanism.
- Evidence for cannabinoid treatment of agitation in AD remains inconclusive, though there may be a signal for a potential benefit of synthetic cannabinoids.

cannabinoid use are associated with impaired cognitive function[27] in healthy individuals and patient populations such as those with multiple sclerosis[28] and schizophrenia.[29] Cannabinoids such as tetrahydrocannabinol (THC) have psychotropic benefits that may benefit agitation in AD.[30] More specifically, the full and partial CB_1 agonist THC has been reported to have antianxiety, antidepressant, analgesic, and sedative effects in a variety of clinical populations. With the development of oral THC and synthetic cannabinoids, such as nabilone and dronabinol, the therapeutic potential of cannabinoids is now being evaluated.

METHODS

Search Strategy

A literature search was conducted using the methodology recommended by the PRISMA guidelines.[31] MEDLINE, EMBASE, PsycINFO, and Cochrane databases were searched for articles investigating THC or cannabinoids for AD up to August 2018. A sample search strategy (EMBASE) is presented in Supplementary Table 1.

Selection Criteria

Studies were included in the quantitative analysis if they enrolled patients who met diagnostic criteria for possible or probable AD, if agitation and aggression were assessed using a standardized neuropsychological tool before and after drug treatment, and if the study was a placebo-controlled trial. Two independent reviewers examined each article for eligibility, and disagreements regarding inclusion were settled through consensus.

Data Extraction

Two independent reviewers examined each retrieved article for eligibility and extracted data using a data extraction form. We obtained missing data from the study authors when possible. One author of this report entered data into Review Manager (RevMan; Copenhagen, Denmark; The Nordic Cochrane Center, The Cochrane Collaboration; 2015), and the coauthors checked for accuracy. Discrepancies were resolved by consensus.

Evaluation of Quality Reporting

The quality of evidence was evaluated by 2 independent raters using the Newcastle Ottawa Scale and the Cochrane Collaboration's risk of bias tool for assessing quality and risk of bias.[32] Items were modified to better reflect the study population covered in this review. If the majority of reporting and control quality items were satisfied (>50%), the study was rated as having high quality of evidence.

Statistical Analysis

Data from measures of agitation (Cohen Mansfield Agitation Inventory and Neuropsychiatric Inventory [NPI] agitation subscale), overall neuropsychiatric symptoms (NPI total) and cognition (Mini-Mental Status Examination [MMSE]) were extracted from the included studies. Data on changes in weight, body mass index (BMI), occurrence of sedation and somnolence, and adverse events were also extracted.

For continuous data, standardized mean differences (SMDs) or mean differences and 95% confidence intervals (CIs) were calculated using a random-effects model. Random-effects models were used for all analyses, as this method accounted for variable underlying effects in estimates of uncertainty, including differences within and between studies. Additionally, this method is preferable when significant heterogeneity is expected across studies.

Heterogeneity among results was evaluated in a χ^2 analysis. The impact of heterogeneity was quantified using an I^2 index as a measure of inconsistency.[33] When substantial heterogeneity ($I^2 > 40\%$) was encountered, subgroup analyses were completed to examine the effects of study design, cannabinoid type, or patient characteristics. When subgroup analyses did not reveal sources of potential heterogeneity, meta-regression analyses were completed to assess the association between treatment outcomes and demographic characteristics such as baseline MMSE scores, age, and sex. As there were fewer than 10 studies that met inclusion criteria for this meta-analysis, publication bias was not assessed. Imprecision of results was evaluated through an assessment of 95% CIs. When the 95% CIs were wide and associated with a null result, the finding was associated with imprecision.

Effect sizes and heterogeneity were calculated using RevMan (2015). Meta-regressions were calculated using Stata (Release 10.1, StataCorp, College Station, Texas).

RESULTS

Literature Search Results

An initial database search identified 123 primary publications from a total of 1,336 records returned. Of these, 7 articles and 1 abstract investigated synthetic cannabinoids or THC for the treatment of agitation and/or aggression in patients with AD. Two articles[34,35] did not report on placebo-controlled trials and were excluded from review. Of the 6 studies included (see Table 1), 2 investigated THC, 3 investigated dronabinol, and 1 investigated nabilone. Missing data were requested from the author(s) of the original studies when needed.[36–38] There were no clinical trials reporting on the efficacy of cannabidiol for agitation in patients with AD (Supplementary Figure 1).

Table 1. Summary of Study Characteristics

Study	Study Design	Study Duration	Drug Dose	n	Sex (% Male)	Age, Mean (SD), y	Baseline MMSE Score, Mean (SD)	Baseline Agitation Score, Mean (SD)	Baseline NPI Score, Mean (SD)
van den Elsen et al[36]	Parallel, double-blind RCT	3 wk	THC 1.5 mg 3 times daily	THC: 24 Placebo: 26	All: 50% THC: 45.8% Placebo: 53.8%	All: 78.4 (7.4) THC: 79.0 (8.0) Placebo: 78.0 (7.0)	All: 14.8 (6.7) THC: 15.9 (6.7) Placebo: 14 (6.8)	NPI agitation: THC: 5.7 (3.8) Placebo: 6.2 (4.3) CMAI: THC: 58.8 (18.5) Placebo: 61.6 (16.4)	THC: 37.4 (13.7) Placebo: 35.6 (13)
van den Elsen et al[37]	Crossover, double-blind RCT	12 wk (two 6-wk periods)	Period A: THC 0.75 mg twice daily Period B: THC 1.5 mg twice daily	22	68%	76.4 (5.3)	16.9 (7.8)	NPI agitation: 4.1 (2.4) CMAI: 58.3 (17.4)	35 (16.5)
Volicer et al[41]	Crossover, double-blind RCT	12 wk (two 6-wk periods)	Dronabinol 2.5 mg twice daily	15	91.7%	72.7 (4.9)	4 (7.4)	CMAI: Dronabinol first: 95 Placebo first: 76	NA
Walther et al[38]	Crossover, double-blind RCT	5 wk	Dronabinol 2.5 mg once daily	2	100%	Patient A: 75 Patient B: 81	Patient A: 22 Patient B: 17	NPI agitation: Patient A: 0 Patient B: 2	Patient A: 18 Patient B: 44
Walther et al[40] Mahlberg and Walther[39]	Open-label pilot study (Walther et al[40]) with placebo data (Mahlberg and Walther[39])	2 wk	Dronabinol 2.5 mg once daily	6 10	33.3% 40%	81.5 (6.1) 78.2 (10.3)	10.33 (6.28) n/a	NPI agitation: 8.29 (4.39) 12 (0–12)[a]	55.00 (23.78) 54.5 (24–76)[a]
Lanctôt et al[42]	Crossover, double-blind RCT	14 wk (6 wk nabilone, 6 wk placebo; 1-wk washout prior to each treatment phase)	Nabilone (target 1–2 mg)	38	76.3%	87.3 (10.2)	6.5 (6.8)	NPI-NH agitation: 7.1 (3.3) CMAI: 67.9 (17.6)	34.3 (15.8)

[a]Scores are median (range).
Abbreviations: CMAI = Cohen-Mansfield Agitation Inventory, MMSE = Mini-Mental State Examination, NA = not applicable, NPI = Neuropsychiatric Inventory, RCT = randomized controlled trial, THC = tetrahydrocannabinol.

Assessment of Risk of Bias and Quality of Evidence

Risk of bias from the Newcastle Ottawa Scale and the Cochrane Collaboration's risk of bias tool are shown in Supplementary Table 2. Five of 7 studies satisfied the majority of quality reporting items. All patients in the included studies met diagnostic criteria for AD. All studies but 1[39] reported on demographic characteristics in patients treated with drug and placebo. All neuropsychological and cognitive tests were administered by a trained study staff member, and outcomes were assessed objectively. Five studies reported double-blinding of personnel, while 1 study[39,40] compared data from an open-label trial with dronabinol against placebo.

Patient and Study Characteristics

The patient and study characteristics of included studies are summarized in Table 1. A total of 143 AD participants from 6 studies were included. As data from 3 of the 4 crossover trials[37,38,41,42] did not include crossover or treatment-order effects, data from both phases of each participant were included. Additionally, 1 study[36] contributed to 2 effect sizes, resulting in an overall sample size of 251 participants. The participants were elderly and predominantly male and had moderate to severe cognitive impairment (Table 1).

The mean study duration was 4.7 weeks (range, 2–6 weeks). The mean dose for trials with THC was 1.75 mg daily (range, 1.5–4.5 mg, daily), the dose used by all trials with dronabinol was 2.5 mg daily, and the mean therapeutic dose in the nabilone trial was 1.6 mg daily.

Four of the 6 studies were crossover randomized controlled trials (RCTs).[37,38,41,42] As Volicer et al[41] reported significant crossover effects, data from the first phase of the study, and not the second phase, were extracted for analysis. Van den Elsen et al[37] contributed to 2 effect sizes as patients were randomized to 0.75 mg THC (or placebo) twice daily, followed by a 4-day washout period, and then randomized to 1.5 mg of THC (or placebo) twice daily; no significant crossover effects were reported. Lanctôt et al[42] reported no crossover or treatment-order effects in their trial with nabilone.[42] Walther et al[38] did not investigate crossover or treatment-order effects in their crossover trial of 2 patients.

Mahlberg and Walther[39] conducted a pooled-analysis of 2 studies[40,43] to compare the efficacy of dronabinol or melatonin versus placebo for agitation in patients with AD. For the purposes of this meta-analysis, dronabinol data from this trial were extracted from Walther et al[40] and placebo data were extracted from Mahlberg and Walther.[39]

Effect of Drug on Agitation

Six studies were included in this analysis, with 1 study[37] providing 2 effect sizes. There was no significant difference between cannabinoids and placebo (SMD = −0.69; 95% CI, −1.50 to 0.13; $P = .10$). However, as significant heterogeneity was present ($\chi^2_6 = 43.53$, $P < .00001$, $I^2 = 86\%$), we completed subgroup analyses with drug type, trial duration, inclusion of an RCT design, and AD severity.

THC versus synthetic cannabinoids. Two studies,[36,37] 1 of which[37] contributed to 2 effect sizes, investigated the efficacy of THC for agitation, whereas 4 studies[38,40–42] investigated the efficacy of synthetic cannabinoids for agitation. There was no significant benefit of drug over placebo within each subgroup, but there was a signal for an improvement in agitation in those randomized to synthetic cannabinoid compared to placebo (SMD: −1.67; 95% CI, −3.65 to 0.30; $P = .10$). In addition, there was a trending difference between subgroups that favored trials with synthetic cannabinoids over those with THC ($\chi^2_1 = 3.05$, $P = .08$) (Figure 1). However, the synthetic cannabinoids subgroup had significant heterogeneity ($\chi^2_3 = 29.16$, $P < .00001$, $I^2 = 90\%$) and imprecision due to a wide 95% CI.

Trial duration. Three studies[36,38,40] had a trial duration of less than 6 weeks, whereas 3 studies, [37,41,42] 1 of which[37] contributed to 2 effect sizes, had a trial duration of 6 weeks. There was a signal for a potential benefit on agitation only in studies that had a trial duration of 6 weeks (SMD = −1.10; 95% CI, −2.35 to 0.16; 181 patients, $P = .09$). However, this finding was associated with significant heterogeneity ($\chi^2_3 = 40.58$, $P < .00001$, $I^2 = 93\%$) and imprecision due to a wide 95% CI. Furthermore, there were no significant differences between subgroups.

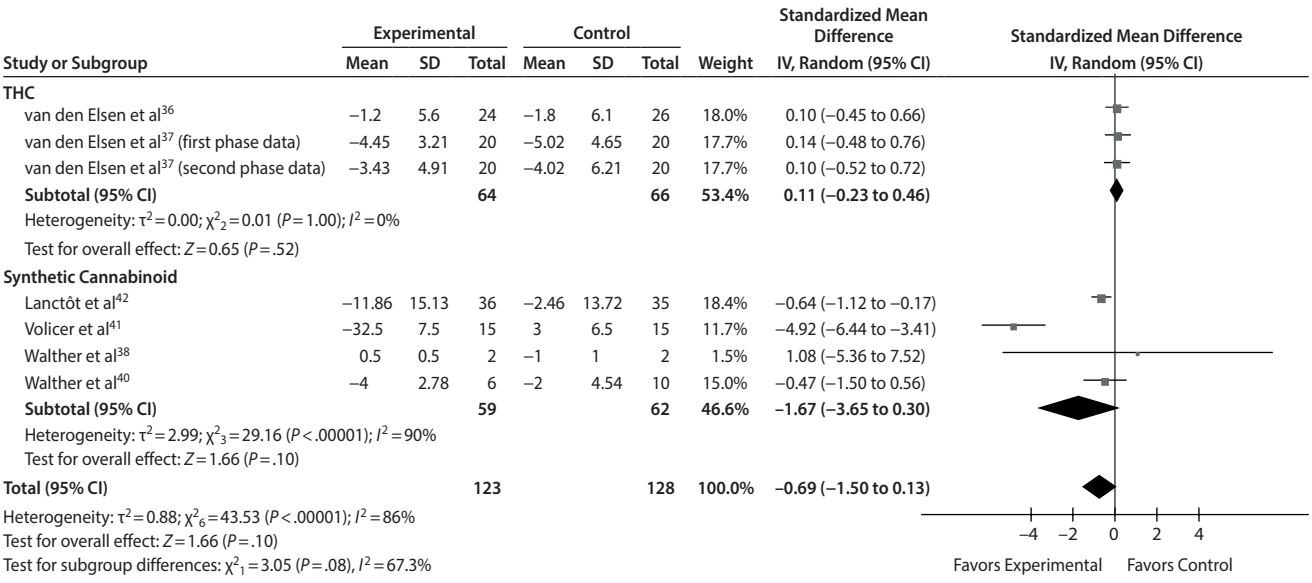
Randomized versus nonrandomized controlled trials. Four studies[36,37,41,42] had an RCT trial design, 1 of which[37] contributed to 2 effect sizes, and 2 studies did not have an RCT design.[38,40] There was no significant effect of drug on agitation in either subgroup, and there were no significant differences between subgroups. Within the RCT subgroup, there was significant heterogeneity ($\chi^2_4 = 43.25$, $P < .00001$, $I^2 = 91\%$).

AD severity. Four studies[36–38,40] included patients with moderate AD (mean ± SD baseline MMSE score = 11.5 ± 6.3), 1 of which[37] contributed to 2 effect sizes. Two studies[41,42] included patients in the more severe stages of AD (mean ± SD baseline MMSE score = 5.9 ± 6.9). Within the moderate (SMD: 0.06; 95% CI, −0.27 to 0.38; $P = .73$; $I^2 = 0\%$) and severe AD (SMD = −0.69; 95% CI, −1.50 to 0.13; $P = .20$; $I^2 = 96\%$) subgroups, there were no significant differences in change in agitation between treatment groups. Due to the lack of additional studies within this subgroup, a meta-regression was completed with mean baseline MMSE scores. This analysis indicated that lower mean MMSE score at baseline was significantly associated with greater improvement in agitation and aggression in drug compared to placebo (B = 0.27, $t_6 = 2.93$, $P = .03$). A meta-regression with mean age (B = 0.15, $t_6 = 0.83$, $P = .44$) at baseline and proportion of males (B = 1.43, $t_6 = 0.31$, $P = .77$) identified no significant associations.

Effect of Drug on Overall Neuropsychiatric Symptoms

Five studies[36–38,40,42] were included in this analysis, 1 of which[37] contributed to 2 effect sizes. There were no significant differences in change in neuropsychiatric symptoms between treatment groups (mean difference = 0.67; 95% CI, −2.82 to

Figure 1. Effects of Cannabinoids on Agitation and Aggression Over the Trial Duration, With Subgroup Differences Between Cannabinoid Type[a]



[a]Effect sizes were calculated using standardized mean differences in a random-effects model.
Abbreviation: IV = inverse variation.

4.16; 229 patients; $P = .71$; $I^2 = 0\%$). Although there were no concerns with heterogeneity, due to a wide 95% CI there were concerns with imprecision of results.

Effect of Drug on BMI

For change in BMI over trial duration, 1 study[41] reported data and 2 other studies[36,42] provided data on request. There were no significant differences in the change in BMI between treatment groups (mean difference = 0.05; 95% CI, −0.15 to 0.25; n = 144 patients; $P = .64$). Due to heterogeneity ($\chi^2_2 = 5.23$, $P = .07$, $I^2 = 62\%$), a subgroup analysis with baseline BMI (high versus low) was completed. Although patients with a higher BMI[36,42] did not report differences in change in BMI between treatment groups, in patients with a lower BMI,[41] there was a significant increase in BMI in those who were randomized to drug, compared to placebo (mean difference = 2.00; 95% CI, 0.21 to 3.79; n = 30 patients; $P = .03$). There were also significant subgroup differences, ($\chi^2_1 = 4.63$, $P = .03$, $I^2 = 78\%$).

Effect of Drug on Occurrence of Sedation/Somnolence

Four studies,[36,37,41,42] 1 of which[37] contributed to 2 effect sizes, reported on the number of patients who experienced sedation or somnolence during study participation. There were significant differences in the number of patients who experienced somnolence and/or sedation, favoring placebo (risk ratio [RR] = 1.73; 95% CI, 1.02 to 2.93;, n = 244 patients; $P = .04$). Although there were no serious concerns with heterogeneity, there were concerns with the imprecision due to a wide 95% CI.

Effect of Drug on Occurrence of Adverse Events and Dropouts Due to Adverse Events

Five studies,[36–38,40] 1 of which[37] contributed to 2 effect sizes, reported on the number of patients who experienced 1 or more adverse events during study participation. However, as both studies by Walther et al[38,40] reported no adverse events in either treatment group, they did not contribute to an effect size in this analysis. There were no significant differences in the number of patients who experienced an adverse event between treatment groups (RR = 1.26; 95% CI, 0.93 to 1.71; 210 patients, $P = .68$).

There were also no significant differences in the number of patients who discontinued the study early due to an adverse event between treatment groups (RR = 1.31; 95% CI, 0.34 to 5.13; 152 patients; $P = .70$). In both analyses, there were no serious concerns with heterogeneity or imprecision of results.

DISCUSSION

This meta-analysis quantitatively investigated the efficacy and safety of cannabinoids for the treatment of agitation in patients with AD. Mechanistically, the endocannabinoid system has been implicated as a novel therapeutic target that may have benefits for agitation and aggression. CB_1 receptors, located in brain areas associated with the limbic system such as the hypothalamus, have been linked to mood-related disorders and AD-related neuropsychiatric symptoms such as aggression.[44] CB_1 hyperactivity and the hypothalamus have also been linked to monoamine neurotransmitter systems such as the serotonergic and

dopaminergic systems, both of which have also been linked to aggression and have been targeted for pharmacologic intervention with antidepressants and antipsychotics.[45–47] Despite mechanistic support for an association between the endocannabinoid system and agitation, we did not identify a significant benefit of cannabinoids over placebo for the treatment of agitation.

Post hoc analyses suggested several potential reasons for this finding. In a comparison of THC to synthetic cannabinoids, the efficacy of THC on agitation has been consistently negative, whereas there was a signal for a potential benefit of synthetic cannabinoids on agitation. Pharmacologic differences between THC and synthetic cannabinoids may contribute to the differences observed between the 2 groups. Specifically, compared to synthetic cannabinoids, the oral THC used by van den Elsen et al[36,37] has a shorter half-life and a shorter time to peak effect.[48] Although these pharmacologic properties may be preferred for the acute symptomatic management of agitation, synthetic cannabinoids may be beneficial for persistent and recurrent agitation that is clinically significant. It is also difficult to compare doses used, as there are no THC equivalents. However, THC may have been relatively underdosed. Compared to the synthetic cannabinoids, THC has a shorter time to maximum concentration, a faster absorption period, and a 2–5 times smaller maximal concentration.[49] Therefore, a higher dose may be required to observe a clinically significant improvement on agitation. The dronabinol trials included in this meta-analysis may have also been underdosed. However, as the retrospective chart review by Passmore[35] noticed a benefit on agitation with a mean dose of 7.03 mg/d, future studies should consider dosing higher than 2.5 mg daily.

Post hoc analyses also suggested that patients with greater AD severity demonstrated greater improvements in agitation when treated with cannabinoids. Consistent with the finding that agitation increases in frequency and severity with AD progression,[50] postmortem studies have reported that anandamide, an endogenous cannabinoid that acts on CB_1 and CB_2, is reduced in the midfrontal and temporal cortices of patients with AD compared to healthy individuals and is correlated with increased amyloid-β pathophysiology and cognitive decline.[51] In addition, fatty acid amide hydrolase, an endocannabinoid metabolizing enzyme, has been shown to be up-regulated in neuritic plaque-associated glia[52] and in peripheral blood mononuclear cells[53] of AD patients, further contributing to the decline in circulating endogenous cannabinoids. As such, exogenously activating the endocannabinoid system through pharmacologic agents may offer greater benefits to patients with greater AD severity. Conversely, postmortem studies have demonstrated that CB_1 density decreases with Braak staging in patients with AD.[54] Although this finding may suggest that patients in the more severe stages of AD may not be able to benefit as well from treatment with an exogenous ligand, the studies included in this meta-analysis collected antemortem data, and subjects were not followed up postmortem. As such, we are unable to comment on whether CB_1 density was associated with our findings. Previous trials with psychotropics have had similar findings with regard to efficacy for agitation and AD severity. For example, a meta-analysis investigating the efficacy of atypical antipsychotics for agitation in patients with AD[8] reported greater improvements in agitation in patients with severe AD compared to those with mild-to-moderate AD. The lack of efficacy in mild-to-moderate AD was very likely due to a floor effect introduced by an overall lower severity of agitation. Additional studies with larger sample sizes are required to provide confirmatory evidence regarding the relationship between efficacy of cannabinoids and severity of AD.

In this meta-analysis, cannabinoid treatment did not demonstrate a significant effect on total neuropsychiatric symptoms compared to placebo. The study by Volicer et al[41] was the only one not included in this analysis as they did not report on change in neuropsychiatric symptoms over treatment duration. However, as patients included in the study by Volicer et al[41] had the lowest mean MMSE scores at baseline, those patients may have also had more frequent and severe neuropsychiatric symptoms as AD severity has been positively correlated with the severity of neuropsychiatric symptoms.[1,55] Therefore, it is possible that cannabinoids may improve neuropsychiatric symptoms in patients with severe AD with more severe neuropsychiatric symptoms. Furthermore, as the endocannabinoid system has been implicated in the regulation of neuropsychiatric symptoms in patients with schizophrenia, depression, bipolar disorder, and posttraumatic stress disorder, additional studies in patients with AD and agitation and aggression are warranted.[56]

We found no significant effect of cannabinoids on BMI in 3[36,41,42] of the 6 studies that reported on the change in BMI over treatment duration. However, Volicer et al[41] reported that dronabinol significantly increased BMI over 6 weeks compared to placebo, a finding associated with a large effect size (2.00). Of relevance, the mean ± SD BMI of patients included in the study by Volicer et al[41] (22.6 ± 2.5) was much lower compared to that of patients included in the studies by van den Elsen et al[36] (25.0 ± 3.5) and Lanctôt et al[42] (24.5 ± 3.9), suggesting that cannabinoids may offer benefits for weight gain in patients who have a low BMI. CB_1 agonism has been associated with increased feeding behavior, food craving, enjoyment during feeding, and energy deposition of fat into adipose tissues.[57] Therefore, endocannabinoid system modulation may offer benefits to patients with AD, since weight loss and anorexia commonly occur in the elderly and have been associated with mortality, increased neuropsychiatric symptoms, and reduced quality of life.[58]

With regard to side effects, the quantitative findings of our meta-analysis suggest cannabinoids are associated with a greater risk of sedation and somnolence compared to placebo and thus should be carefully monitored in future trials. Given the advanced age of this patient population and high risk of sedation associated with cannabinoid use,[59] future trials should consider flexible dosing based on tolerability. The study by Lanctôt et al[42] was the only one included in this meta-analysis that employed a flexible dosing regimen.

Although mild sedation may be a therapeutic benefit in the treatment of a patient with severe agitation or aggression, persistent and excessive sedation is a major concern in patients with advanced AD, as it has been associated with cognitive worsening, impaired gait and balance, increased risk of falls, and reduced food intake.[60]

Two additional reports[34,35] investigated the efficacy of synthetic cannabinoids for agitation or aggression in patients with AD. However, since 1 report was a retrospective chart review[34] and 1 was a single case study,[35] neither was included in the quantitative analysis of our meta-analysis. Woodward et al[34] reported that dronabinol (mean dose = 7.03 mg daily) significantly reduced agitated and aggressive behaviors in patients with AD. They also reported an overall increase in meal completion with dronabinol, though there was no significant increase in weight. The investigators attributed this finding to a short observation period (mean = 16.88 days; range, 4–50 days), and missing data. In a single case study with nabilone (dose = 0.5 mg twice daily), Passmore[35] reported improved agitation and aggression over the 6 weeks of treatment, which persisted for over 3 months. There are currently 3 ongoing placebo-controlled RCTs investigating the use of nabilone (NCT02351882), dronabinol (NCT0272257), and Avidekel oil (20:1 cannabidiol:THC) (NCT03328676) for the treatment of agitation/aggression. Cannabidiol may also have psychotropic benefits for AD patients with agitation, as it has demonstrated anxiolytic benefits in patients with schizophrenia and social anxiety disorder.[61] However, to date cannabidiol has not been investigated in patients with AD. The results of those studies will provide efficacy and safety data on the use of cannabinoids for agitation/aggression and will also provide feasibility data for future trials investigating the therapeutic use of cannabinoids in this patient population.

LIMITATIONS

This meta-analysis quantified the existing evidence on the efficacy and safety of cannabinoid use for agitation and aggression in patients with AD. The limitations in the context of this review should be considered when interpreting the evidence. One major limitation is the small number of studies included in this meta-analysis. However, the results of this meta-analysis add to previous reports based on limited evidence[30] and are timely, as the use of cannabinoids for the treatment of agitation in AD has been gaining interest over the past decade due to the lack of efficacy associated with current pharmacotherapies for agitation and recent changes in the legislation of THC in North America. Furthermore, as cannabinoids are available in capsule form, their therapeutic potential can be studied in a controlled manner.

This meta-analysis included only 251 participants, and the small number of studies contributed to limitations in our subgroup analyses. For example, in the subgroup analysis evaluating efficacy of cannabinoids for agitation in patients with moderate AD and severe AD, only 2 studies[41,42] recruited patients with severe AD. The included studies were also limited by the relatively small sample sizes with large variability, which likely resulted in wide 95% CIs. Additional studies with larger sample sizes that include patients with severe AD are needed to confirm the findings of this meta-analysis.

The short trial duration of the included studies may also be considered a limitation of this meta-analysis. Only 3 studies[37,41,42] had a study duration of 6 weeks, whereas the remaining studies had durations of 2,[40] 3,[36] and 5[38] weeks. As such, the studies included in this meta-analysis may have not had a sufficient trial duration to notice an observable benefit on agitation or aggression, neuropsychiatric symptoms, and weight.

One of the studies included in this meta-analysis was a pooled-analysis of an open-label trial with dronabinol[40] and a trial with a placebo control.[39] As a result, the quality of these data were lowered since the dronabinol trial was not randomized and was not necessarily placebo-controlled. However, as this meta-analysis was limited by the number of studies included, we thought the strengths associated with including this study outweighed its associated limitations.

Three of the studies[37,41,42] included in this meta-analysis were crossover RCTs. An RCT with a crossover design offers advantages in a study population that is difficult to recruit, as each patient acts as his or her own control, meaning required sample size can be halved. However, since Volicer et al[41] reported significant crossover effects, data from the first, and not second, phase of that study were included in our quantitative analysis. Carryover effects from Volicer et al[41] were most likely due to the lack of a washout period between treatment phases. Because cannabinoids are lipophilic compounds, a sufficient washout period is required to reduce carryover effects in a crossover RCT.

None of the included studies investigated or reported on pain. Pain occurs in approximately 50% of patients with AD[62] and in 60%–80% of institutionalized patients.[63] In addition, the majority of these patients experience chronic pain for a minimum of 3–6 months.[64] Since untreated pain is associated with a reduced quality of life, functional status, sleep, and appetite disturbances and increased severity of neuropsychiatric symptoms, the treatment of pain in patients with AD is an important clinical need.[63,65,66] Preclinical studies and clinical studies in non-AD patient populations have also implicated the endocannabinoid system in having benefits for pain, a symptom that is difficult to both treat and identify in patients with AD. THC, a cannabinoid that is a partial and full agonist at CB_1 on glutamatergic and γ-aminobutyric neurons, respectively, and a partial agonist at CB_2, has demonstrated anti-inflammatory properties that may have analgesic effects.[67,68] Furthermore, THC has been shown to have an impact on opioid, serotonergic, and glutamatergic receptors, all of which have been shown to have a role in the development and maintenance of neuropathic pain.[67] As current therapeutic recommendations for pain management in AD have modest efficacy and are associated with side effects, and as pain has been linked to the exacerbation of agitation, future trials investigating

cannabinoids in AD should consider including pain as an outcome measure.[69]

There have been no studies that have investigated the efficacy of cannabinoids on cognitive function as a primary outcome measure in those with AD. Since cannabinoids have been associated with cognitive worsening in other patient populations,[27] future trials should also assess cognition over time as a measurement of safety. Findings from those studies would also inform clinicians and researchers on whether patients who have mild, moderate, or severe AD with agitation should be targeted for treatment with a cannabinoid.

CONCLUSION

The results of this meta-analysis provide little evidence of efficacy for the effect of cannabinoids on agitation in AD. While our findings suggest that THC for the treatment of agitation has been consistently negative, results with synthetic cannabinoids are inconclusive due to substantial heterogeneity. In spite of potential mechanistic linkages between the endocannabinoid system and agitation, other neuropsychiatric symptoms, weight, and pain, there are to date only a small number of studies with small numbers of patients and weak methodologies. Whether this small number is a result of a negative bias toward cannabinoids in mainstream medicine or a healthy skepticism to a class of compounds that might have important adverse effects in frail elderly patients with neurodegenerative disorders is unclear. What is clear, however, is that treatment of agitation and aggression in AD is still an important public health priority, and this potentially useful class of compounds urgently deserves more attention with rigorous studies.

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Supplementary Material

Article Title: Natural and Synthetic Cannabinoids for Agitation and Aggression in Alzheimer's Disease: A Meta-Analysis

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List of Supplementary Material for the article

1. Table 1 EMBASE search strategy
2. Figure 1 PRISMA flow diagram
3. Table 2 Study quality indicators and risk of bias items

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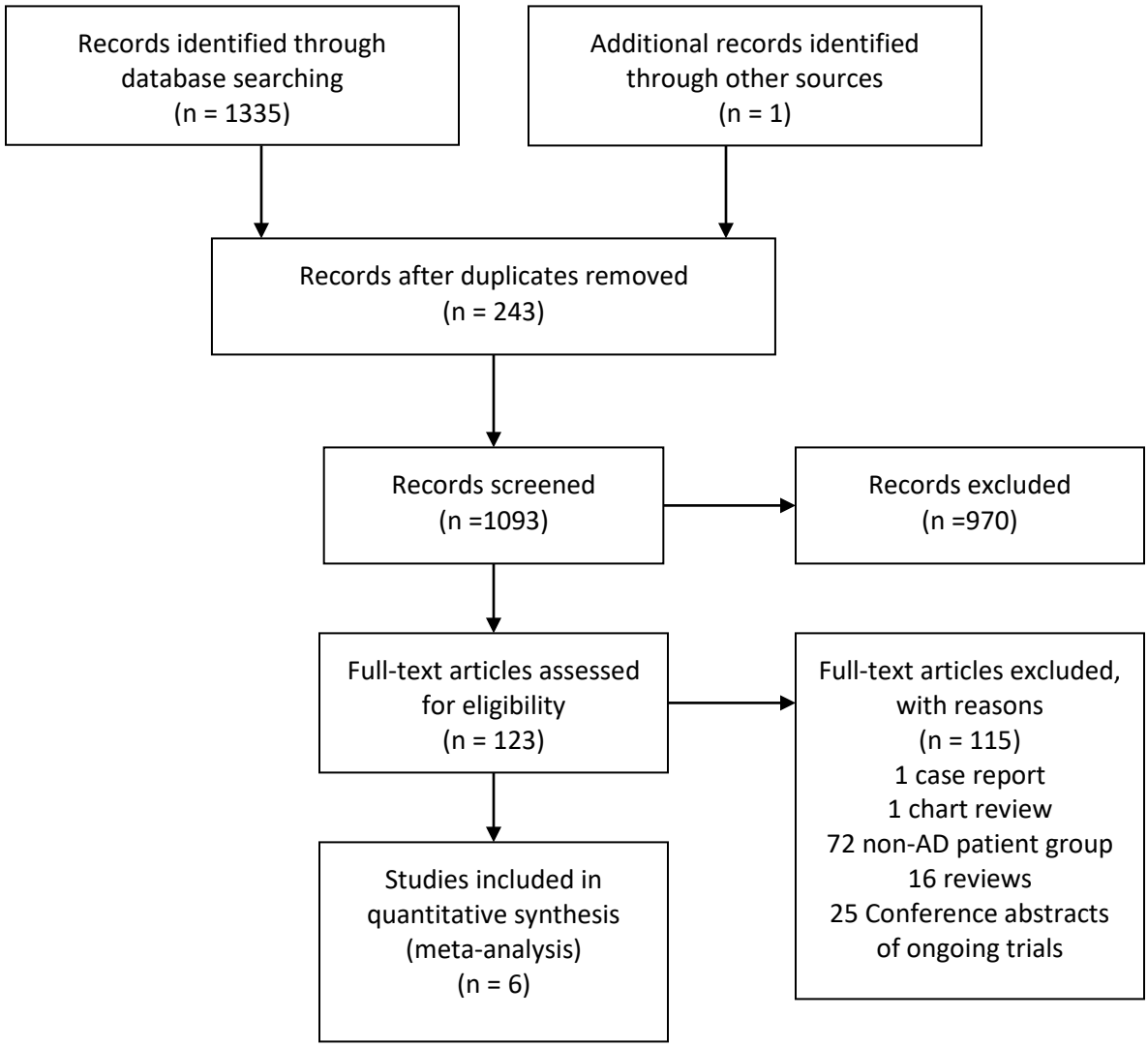
Supplementary Table 1: EMBASE search strategy.

Database: Ovid EMBASE(R) <up to August Week 4 2018> Search	
Strategy:	

1	exp Alzheimer's disease / (150175)
2	exp dementia/ (181070)
3	exp agitation/ (37007)
4	exp aggression/ (64194)
5	exp neuropsychiatric symptoms (5385)
6	exp behavior (1401653)
7	exp cannabinoid (27418)
8	exp THC (9973)
9	exp nabilone (1267)
10	exp dronabinol (7163)
11	exp cannabidiol (3937)
12	1 or 2 (281346)
13	3 or 4 or 5 or 6 (1460962)
14	7 or 8 or 9 or 10 (37354)
15	12 and 13 and 14 (123)



Supplementary Figure 1: PRISMA flow diagram.

Supplementary Table 2: Study quality indicators and risk of bias items

	All patients meet AD criteria	Random sequence generation	Unbiased participant selection	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessments	Similarly aged groups	Similar gender proportions	Similar in other characteristics	Demographics reported	Concomitant medications reported	Medical co-morbidities reported	Tapering/discontinuation protocol reported	**Likelihood of high overall quality**
	General risk of bias items									Reporting quality				
Van den Elsen et al[37]	+	+	?	+	+	+	+	+	+	+	+	+	?	**+**
Van den Elsen et al[36]	+	+	+	+	+	+	+	+	+	+	+	+	?	**+**
Volicer et al[41]	+	?	+	+	+	+	+	+	+	+	+	-	-	**+**
Walther et al[40]	+	?	?	+	+	+	+	+	+	+	+	+	-	**+**
Walther et al[38]	+	-	+	-	-	-	/	/	/	+	+	-	-	**-**
Mahlberg and Walther[39]	+	?	?	?	?	?	?	?	?	?	-	-	?	**?**
Lanctot et al[42]	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+, yes; -, no; ?, unclear