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LEADING ARTICLE

Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is frequently associated with neuropsychiatric symptoms (NPS) such as agitation and aggression, especially in the moderate to severe stages of the illness. The limited efficacy and high-risk profiles of current pharmacotherapies for the management of agitation and aggression in AD have driven the search for safer pharmacological alternatives. Over the past few years, there has been a growing interest in the therapeutic potential of medications that target the endocannabinoid system (ECS). The behavioural effects of ECS medications, as well as their ability to modulate neuroinflammation and oxidative stress, make targeting this system potentially relevant in AD. This article summarizes the literature to date supporting this rationale and evaluates clinical studies investigating cannabinoids for agitation and aggression in AD. Letters, case studies, and controlled trials from four electronic databases were included. While findings from six studies showed significant benefits from synthetic cannabinoids—dronabinol or nabilone—on agitation and aggression, definitive conclusions were limited by small sample sizes, short trial duration, and lack of placebo control in some of these studies. Given the relevance and findings to date, methodologically rigorous prospective clinical trials are recommended to determine the safety and efficacy of cannabinoids for the treatment of agitation and aggression in dementia and AD.

Key Points

Agitation and aggression are commonly present symptoms in Alzheimer's disease (AD).

Six trials have administered synthetic cannabinoids for the treatment of agitation and/or aggression in patients diagnosed with dementia or AD.

Cannabinoids may offer a therapeutically relevant and efficacious treatment option for the management of agitation and aggression in AD.

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder defined by a decline in cognitive and functional abilities. Currently, AD is estimated to affect 35 million people worldwide, and that number is expected to triple by 2050 [1]. AD is also characterized by the frequent occurrence of neuropsychiatric symptoms (NPS), including depression, irritability, aggression, and agitation. These symptoms have been reported to occur in 98 % of patients, with agitation presenting in 55 % of this population at some point in the illness [2]. The most distinguishing features of agitation include excessive fidgeting, restlessness, pacing, shouting, screaming, and motor activities associated with

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anxiety, such as hand wringing. Common symptoms of aggression include shouting as well as verbal insults, hitting, biting others, and throwing objects. Almost all caregivers of patients with agitation and aggression report that these symptoms significantly affect daily functioning and quality of life [3, 4]. The first line of treatment involves non-pharmacological interventions such as person-centered care, structured social interaction, and music therapy [5, 6], with clinical practice guidelines endorsing the judicious use of atypical antipsychotics for dangerous agitation and aggression in spite of potentially serious adverse events, including stroke and mortality [7–9]. However, some researchers have suggested that these adverse effects offset the potential advantages, as efficacy has proven to be limited [10, 11]. Thus, there is a need for alternative treatments that reduce the risk of adverse effects and provide a greater benefit for this population.

Over the past few years, the endocannabinoid system (ECS) has emerged as a potential therapeutic target to treat AD pathology and symptomology. Literature has shown that endocannabinoids may have a beneficial impact on neurodegenerative [12] and neuroinflammatory diseases [13], in addition to playing a neuroprotective role through the activation of the G-protein coupled receptors, cannabinoid 1 (CB1) receptor and cannabinoid 2 (CB2) receptor [14, 15]. Though CB1 receptors are widely distributed in the nervous system and peripheral organs, density is greater in the central nervous system, specifically in the cerebral cortex and hippocampus [16–19]. These two structures are key components of learning and memory function, and are affected in AD progression [20, 21]. CB1 receptors are also more classically associated with anxiety-like and aggressive behaviour in animals [22, 23]. Furthermore, CB2 receptor activation has been shown to reduce the in vitro production of pro-inflammatory molecules [24, 25] and induce the removal of amyloid-beta (Aβ) plaques from human AD tissues [26]. In addition, there is well-documented pre-clinical evidence to suggest that cannabinoid receptor agonists, such as WIN55,212-2 and arachidonyl-2-chloroethylamide, can reduce aggressive behaviours [27, 28]. Herein, we evaluate the clinical evidence examining cannabinoids for the treatment of agitation and aggression in dementia and/or AD. We also review putative mechanisms for cannabinoid benefits in AD, including aberrant neurotransmitter signalling [29–32], reduced inflammation-related Aβ accumulation [26, 33], and tau hyper-phosphorylation [34, 35]. Cannabinoids may provide a novel transmitter-targeted treatment for agitation and aggression and may offer a potentially disease-modifying therapy for AD.

We conducted a systematic search up to January 2015 and included the following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online; National Library of Medicine, Bethesda, MD, USA), Embase (Excerpta Medica Database; Elsevier, Amsterdam, the Netherlands), PsycINFO (American Psychological Association, Washington, DC), and the Cochrane Central Library (the Cochrane Collaboration, Oxford, Oxfordshire, UK). Figure 1 demonstrates the study selection process for this review. Keywords such as 'cannabinoid,' 'cannabidiol,' 'cannabis,' 'tetrahydrocannabinol,' 'aggression,' and 'agitation' were cross-referenced with 'Alzheimer's disease' and 'dementia'. Initial searching yielded 28 journal articles. The search criteria included randomized controlled trials, observational studies, and case studies. Duplicates were excluded, and 15 records were screened. Conference abstracts, posters, and opinion pieces were also eliminated. Review papers and articles that did not evaluate cannabinoids for the treatment of agitation and/or aggression in dementia or AD were also excluded from this section of the review. Inclusion criteria included English publications in which cannabinoids were used for the treatment of agitation and/or aggression in individuals diagnosed with dementia and/or AD. The overall methodology and results of each selected article were examined for final inclusion by three screeners (CL, MR, and SC).

2 Cannabinoid Treatment for Agitation and Aggression in Dementia and Alzheimer's Disease (AD)

To date, six clinical studies have reported the impact of cannabinoid use on agitation and/or aggression with a collective 67 completed participants (see Table 1). All trials included synthetic analogs of delta-9-tetrahydrocannabinol (THC), either administering dronabinol [36–40] or nabilone [41]. A significant portion of all participants had used or were using psychoactive medication to manage their symptoms. The earliest documented placebo-controlled crossover study in which a synthetic cannabinoid was administered in an Alzheimer's patient population was conducted by Volicer et al. [36]. Although the primary outcome of the study concerned food intake with dronabinol use, the authors also explored the effects of dronabinol for the treatment of disturbed behaviour, as measured by the Cohen-Mansfield Agitation Inventory (CMAI) [36]. Over the course of six weeks, CMAI scores significantly decreased in both groups compared with baseline. However, the authors reported a time-by-treatment order effect for CMAI percent change from baseline, and the design of this experiment did not include a washout period. Thus, improvements during the placebo phase may have occurred due to a carry-over effect from active treatment. Adverse events were reported to occur more frequently during the dronabinol phase compared than

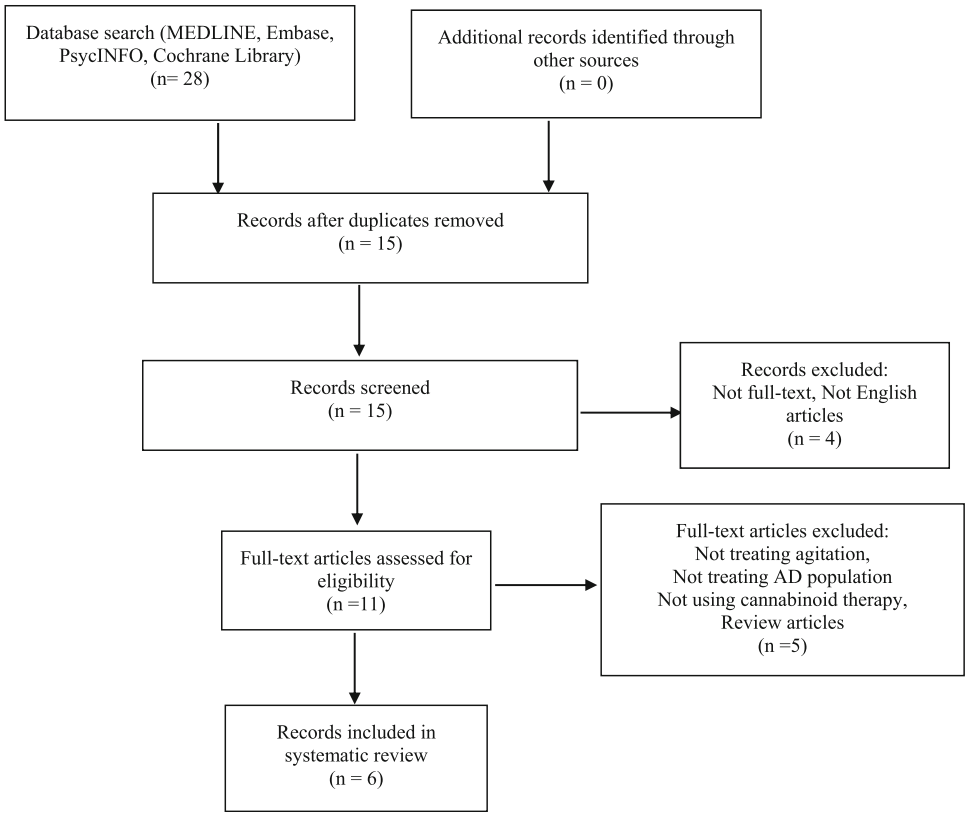

Fig. 1 Study selection process for cannabinoid treatment for agitation and aggression in dementia and Alzheimer's disease (AD)

during the placebo phase and included euphoria, somnolence, and tiredness, but did not result in medication discontinuation.

Walther et al. [37] also conducted a randomized, placebo-controlled, double-blind, crossover study in two patients, and reported a reduction in nocturnal motor activity for both participants with dronabinol treatment. Patient A, who received the active treatment first, showed a persistent reduction in night-time agitation until the third week of the trial (67 % reduction vs. baseline), with nocturnal activity levels returning to baseline values during the second week of placebo administration (week four of the trial) [37]. Night-time agitation was also reduced in patient B, who received the placebo treatment first [37]. However, nocturnal activity increased during the second week of active treatment. No adverse events were reported for either of the two patients.

Similarly, Mahlberg and Walther [38] investigated the effects of dronabinol for the treatment of night-time agitation in seven patients diagnosed with probable dementia of the AD type. Agitation and circadian disturbances were assessed using continuous wrist actigraphy, which calculated the nocturnal motor activity overnight. This placebo-controlled study resulted in a significant reduction in nocturnal motor activity (16 % reduction vs. baseline) in the active treatment group. No adverse events were reported in patients who received dronabinol treatment. Additionally, an open-label pilot study including six patients diagnosed with late-stage dementia and experiencing behavioural disturbances including night-time agitation reported an average relative reduction in nocturnal motor activity of 59 % from baseline (ranging from 13 to 85 % from baseline) during the first two days of dronabinol treatment [39]. No adverse events were reported throughout the trial in patients who received dronabinol treatment.

Evidence from one case report showed a reduction in the severity of overall agitation with nabilone treatment in one patient diagnosed with dementia of the AD type [41]. No adverse events were reported with nabilone treatment, and the patient's NPS remained stabilized three months post-trial. Furthermore, Woodward et al. [40] conducted a retrospective study and found that augmentation with dronabinol significantly reduced aberrant vocalization, motor agitation, aggressiveness, and resistance to care. The addition of the agonist to patients' treatment regimens was shown to correlate with significant decreases in all domains of the Pittsburgh Agitation Scale (PAS) in acutely hospitalized severely demented patients [40]. A total of 26 adverse events were reported during the trial period, and included sedation, delirium, urinary tract infection, and confusion, although none led to medication discontinuation.

Table 1 Description of included clinical trials and case reports evaluating cannabinoids for the treatment of agitation or aggression in dementia and Alzheimer's disease

Study	Design	Participants	Measure(s)	Intervention	Mean dose and duration	Effect on agitation or aggression
Woodward et al. [40]	Retrospective study	40 inpts diagnosed with dementia with behavioral disturbances	PAS	DRO	7.03 mg daily for 16 days	Motor agitation ($z = -4.4423$, $p < 0.0001$) and aggressiveness ($z = -3.9102$, $p < 0.0001$) decreased significantly during tx. 26 AEs were recorded during DRO tx, none of which led to medication discontinuation
Walther et al. [37]	Randomized, PL-controlled, double-blinded crossover trial	Two pts diagnosed with Alzheimer dementia with nighttime agitation	NPI, Actiwatch	DRO	2.5 mg daily at 7 pm for 2 weeks	Pt A: Decreased nocturnal motor activity until the 3rd week of the trial (67 % of BL). During the 2nd week of PL administration (week 4 of the trial), nocturnal activity levels returned to BL values Pt B: Nocturnal motor activity was reduced during the 1st week of tx. In the 2nd week of active tx, nocturnal activity increased again No reported AEs in either of the two pts
Passmore [41]	Case report	One pt diagnosed with dementia of the Alzheimer's type with behavioral disturbances	NR	NAB	0.5 mg daily increased to 0.5 mg bid for 6 weeks	Reduced severity of agitation. No reported AEs
Mahlberg and Walther [38]	PL-controlled study	24 pts diagnosed with probable dementia of the Alzheimer type with agitated behavior. 7 received DRO, 7 received melatonin, 7 received PL	NPI, Actiwatch	DRO	2.5 mg daily for 2 weeks	Reduced nocturnal motor activity vs. BL (16 % of BL). No reported AEs
Walther et al. [39]	Open-label pilot study	6 pts diagnosed with late-stage dementia (5 with AD, 1 with vascular dementia) with behavioral disturbances	NPI, Actiwatch	DRO	2.5 mg daily for 2 weeks	Decreased nocturnal motor activity ($p = 0.028$). Average relative reduction in nocturnal motor activity was 59 % of BL (range 13–85 %) during the first 2 days of tx. No reported AEs
Volicer et al. [36]	PL-controlled, crossover study	11 anorexic pts diagnosed with probable AD who were refusing food and experienced disturbed behavior	CMAI	DRO	2.5 mg daily for 6 weeks	Decreased severity of disturbed behavior as measured by the CMAI. AEs observed more commonly during DRO tx than during PL periods and included euphoria, somnolence, and tiredness, but did not result in medication discontinuation

AD Alzheimer's disease, *AE* adverse event, *BL* baseline, *bid* twice daily, *CMAI* Cohen-Mansfield Agitation Inventory, *DRO* dronabinol, *NAB* nabilone, *NPI* Neuropsychiatric Inventory, *NR* not reported, *PAS* Pittsburgh Agitation Scale, *PL* placebo, *pt(s)* patient(s), *tx* treatment

3 Putative Mechanisms Supporting Cannabinoid Management of Agitation and Aggression in AD

3.1 Neurotransmitter Systems

Aberrant neurotransmission in systems such as serotonin (5-HT) [29], norepinephrine (NE) [29], dopamine (DA) [31], γ-aminobutyric acid (GABA) [30], and acetylcholine (ACh) [32] have all been implicated in the manifestation of NPS, including agitation, aggression, depression, psychosis, and apathy. Endocannabinoid dysfunction may contribute to neuronal damage and neurotransmitter system dysfunction, giving rise to the cognitive deterioration characteristic of AD as well as a wide range of NPS. Evidence supporting the interactions between the ECS and neurotransmitter systems including DA [42, 43], NE [44], 5-HT [45, 46], GABA [47], and ACh [48] have also been well-established in animal models of psychiatric disorders. In studies with CB1 receptor knockout (KO) mice, increases were observed in anxiety, depression, and aggression [49–51]. Uriguen et al. [49] suggested that disrupting the neurotransmission signal, by inhibiting CB1 receptor expression, disrupts the regulation of emotional responses by increasing hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis and increasing corticosterone levels in these KO mice [49]. While endocrine activity has been consistently linked with the development of depressive symptoms [48, 52], its role in anxiety and aggressive behaviours has been disputed [53, 54]. Although the data are limited, the aforementioned evidence in animal model studies supports the role of the ECS in modulating NPS through neurotransmission.

Some clinical and post-mortem studies have also reported associations between these neurotransmitter systems and agitation/aggression in AD. In a recent study of post-mortem brains of AD patients, DA turnover in the cerebellum positively correlated with agitation levels [55]. On the other hand, studies have found that cannabinoids improve DA neurotransmission and tau and amyloid pathology, and have also reported reduced aggression and stereotypy in these treated animals [56]. Similarly, CB1 receptors can inhibit or stimulate the release of NE, a derivative of DA via hydroxylation, depending on receptor localization [44]. Serotoninergic activity has also been linked with aggressive and agitated behaviours in AD. Specifically, post-mortem studies have found both reduced 5-HT levels [55, 57] and reduced 5-HT receptor densities [58, 59] in AD patients with agitation and aggression. Furthermore, Lanctôt et al. [60] and Mintzer et al. [61] found positive associations between agitated and aggressive behaviors and 5-HT dysfunction in AD patients [60, 61]. Additionally, results from anatomical studies have shown that the dorsal raphe, a brain region saturated with 5-HT neurons, also expressed CB1 receptors [62] and the enzymes responsible for the synthesis and metabolism of endocannabinoids [63], suggesting that the ECS may play an important role in the regulation of the 5-HT system. As a result, cannabinoids may be a potential target for modulating neurotransmitter activity involved in the expression of behavioural disturbances prevalent in AD, including agitation and aggression.

3.2 Aβ Plaque Accumulation and Tau Phosphorylation

Evidence has suggested that increased Aβ plaque accumulation and tau hyper-phosphorylation may contribute to NPS such as agitation and aggression [64, 65]. In a mouse model of AD, male rodents with Aβ pathology demonstrated significantly higher levels of aggression towards intruder males during three consecutive encounters than did their non-transgenic counterparts [64]. Other studies with similar models of AD have also reported enhanced aggression in transgenic male mice compared with wild-type controls [65]. In patients with mild cognitive impairment, the presence of agitation and irritability was also associated with abnormal concentrations of Aβ [66]. Taken together, those findings support the association between markers of AD pathology and NPS.

Some studies have also investigated the association between the ECS and Aβ accumulation [26, 67]. Stimulation of the CB2 receptor increased Aβ removal and clearance via enhanced macrophage activity [26] as well as by restoring microglial phagocytic function [67]. Using a mouse model of AD, Martin-Moreno et al. [68] showed that two pharmacologically different cannabinoids, WIN55,212-2 and JWH-133, were also able to increase Aβ transport across choroid plexus cells in vitro [68]. Furthermore, cannabidiol (CBD), arachidonyl-2-chloroethylamide (synthetic CB1 receptor agonist), and WIN55,212-2 treatments have resulted in a reduction in tau phosphorylation [34, 35] via a variety of mediating pathways. One study reported a reduction of the phosphorylated active form of glycogen synthase kinase-3 beta (GSK-3B), a known tau kinase, thereby resulting in Wnt/B—catenin pathway rescue and decreasing neuronal apoptosis [35]. Another study showed that CBD increased the expression of inactive GSK-3B, which in turn resulted in lowered tau hyper-phosphorylation [34]. Adding to this finding, researchers from a clinical trial reported that the phosphorylated tau/total tau ratios were elevated in the frontal cortex of those patients with agitation/aggression and dementia, suggesting that reducing tau phosphorylation may provide symptomatic relief [69].

3.3 Anti-Inflammatory Effects

Researchers have found that infection in peripheral organs, such as pneumonia or urinary tract infection, is often associated with the manifestation of NPS in AD patients [70], suggesting that inflammation may play a role in dementia-associated behavioural disturbances. In support of this, Aβ has been implicated in potentiating a pro-inflammatory effect by increasing its own production through the expression of β-secretase as well as through the activation of microglia and the recruitment of astrocytes [33]. In response, pro-inflammatory cytokines and nitric oxide, a marker for oxidative stress, are released, causing neuronal and synaptic damage [71]. However, the expression of pro-inflammatory cytokines, including, but not limited to interleukins (ILs) such as IL-1β and IL-6, tumor necrosis factor alpha, and interferon gamma, have been shown to decrease after cannabinoid treatment in mice [34]. Furthermore, CB2 receptor activation has been shown to decrease the production of inflammatory molecules in a number of in vitro cell types, including rodent [72, 73] and human microglial cells [24]. Tolon et al. [26] have also demonstrated that the activation of CB2 receptors can induce the removal of native Aβ from frozen human tissues sections by a human macrophage cell line (THP-1). Intraperitoneal administration of the membrane endocannabinoid transport inhibitor, VDM-11, alleviated memory impairments and attenuated resultant neurotoxicity in Aβ-induced rodents [74] and post mortem evidence has suggested that the production of endocannabinoids and subsequent CB receptor activation may be an attempt by the central nervous system to protect itself against AD-induced damage [75].

4 Implications for Neuropsychiatric Symptoms (NPS) and Pain

The effect of cannabinoid compounds on CB1 and CB2 receptors in the brain can create varying pharmacologic responses. Cannabis and some cannabinoids have effective anti-emetic, analgesic, and anxiolytic properties [76]. Moreover, endocannabinoids modulate neuronal, glial, and endothelial cell function, and can exert neuromodulatory, anti-excitotoxic, anti-inflammatory, and vasodilatory effects within the central and peripheral nervous systems [77]. Studies have looked at the role of endocannabinoids in stimulating appetite [78], modulating bone metabolism [79], and relieving pain [80]. As pain is a common underlying cause of NPS, particularly agitation and aggression [81], its treatment may also aid in the treatment of these co-morbid symptoms in AD. For example, a recent study comparing stepped analgesia with usual care in AD patients reported an improvement in agitation that significantly correlated with an improvement in pain [82]. Furthermore, nabilone in particular has been found to reduce pain related to neuropathy [83], fibromyalgia [84], and spasticity [85] and may also be able to help those who are unresponsive to typical pharmacological treatments. Nabilone is also an approved anti-emetic for the treatment of chemotherapy-induced nausea in some countries. Taken together, synthetic cannabinoids such as nabilone may also be able to modulate agitation and aggression by treating pain in AD patients.

5 Conclusion

Synthetic cannabinoid treatment may offer a more advantageous alternative with lower risk profiles than treatment with antipsychotic medications and natural cannabis. Synthetic cannabinoids, such as dronabinol and nabilone, produce effects similar to natural cannabis in humans, but are structurally dissimilar from THC, the psychoactive component found in the cannabis plant [86–88]. Nabilone mimics THC but is a more potent analog, acting on CB1 and CB2 receptors, which are involved in the regulation of many shared features of AD in the frail and elderly, such as pain [89–91]. Although our findings demonstrated that patients responded well to cannabinoid treatment in these clinical studies, methodological weaknesses such as short duration, small sample size, and no placebo control in some trials pose significant limitations. Moreover, most participants had used or were currently taking psychoactive medication concomitantly with cannabinoid treatment.

In addition, the adverse effects of cannabinoid treatments for AD in humans has not been well characterized. Whiting et al. [92] recently conducted a systematic review of the safety and efficacy of synthetic and natural cannabinoids in several indications, including nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis (MS) or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, and Tourette syndrome [92]. The results of that review, which included 79 randomized controlled trials that compared cannabinoids with usual care, placebo, or no treatment, found that cannabinoids were associated with an increased risk of any adverse event, serious adverse event, and withdrawals due to an adverse event. Dizziness, dry mouth, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination were commonly reported adverse events. Other adverse events included nausea, depression, diarrhea, asthenia, anxiety, dyspnea, paranoia, psychosis, and seizures. These side effects were not found in the AD studies, likely because the AD studies evaluated much lower

dosages of nabilone and dronabinol and had smaller sample sizes. While there is some evidence that aggression is a symptom of marijuana withdrawal and abstinence [93, 94], aggression has not been observed as a side effect associated with the medical use of cannabinoids in several disorders including AD, as well as MS, chronic pain, and depression [92].

The small number of studies included in this review highlights the need for further randomized controlled trials to evaluate the safety and efficacy, including the habituation and potential for abuse, of cannabinoids for the treatment of agitation and aggression in severe dementia and AD. There is also a need to better understand the roles of CB1 and CB2 receptors within the context of AD. Although most of the spotlight on cannabinoids has highlighted the psychotropic effects that are primarily mediated by THC acting on CB1 receptors in the brain, CB2 receptor stimulation has shown promising effects in the modulation of inflammation [24] as well as in the treatment of pain [95] and other disease states [96]. Possible future directions include exploring the use of CB2 receptor agonists for the treatment of agitation and aggression, as well as pain, in the AD population. There is also evidence to suggest that CB1 receptor levels remain unchanged and intact in the AD cortex of humans [97]. As a result, future studies should investigate whether CB1 receptor levels may be altered by age or pathology severity as well as how these affected cortical structures contribute to AD symptomology. Lastly, future studies should investigate the effects of cannabinoids on agitation versus aggression, as only one clinical study [40] has reported on the effects of dronabinol augmentation on both motor agitation and aggressiveness. Given the high prevalence of agitation and aggression in patients with moderate to severe AD and the adverse effects associated with antipsychotic treatments, alternative pharmacological options for managing NPS such as synthetic and currently available cannabinoid agonists—such as dronabinol or nabilone—should also be investigated. We suggest conducting randomized controlled clinical trials to evaluate the safety and efficacy of these medications for the management of agitation and aggression in AD.

Compliance with Ethical Standards

Conflict of interest Krista L. Lanctôt has received research grants from the Alzheimer Drug Discovery Fund, the Alzheimer Society of Canada, the National Institute of Health, AbbVie, Lundbeck, Pfizer, Sanofi-Aventis, Janssen-Ortho Inc., and Roche and Wyeth, and honoraria from AbbVie, Pfizer, Janssen-Ortho Inc., and MedImmune. Nathan Herrmann has received research grants from the Alzheimer Drug Discovery Fund, the Alzheimer Society of Canada, the National Institute of Health, Canadian Institute of Health Research, Lundbeck, and Roche, and consultant fees from Lundbeck, AbbVie, and Eli Lilly. Celina S. Liu, Sarah A. Chau, and Myuri Ruthirakuhan report no conflicts of interest.

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