Cannabinoids in Late-Onset Alzheimer’s Disease

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Given the lack of effective treatments for late-onset Alzheimer’s disease (LOAD) and the substantial burden on patients, families, health care systems, and economies, finding an effective therapy is one of the highest medical priorities. The past few years have seen a growing interest in the medicinal uses of cannabinoids, the bioactive components of the cannabis plant, including the treatment of LOAD and other physical conditions that are common in older people. Several in vitro and in vivo studies have demonstrated that cannabinoids can reduce oxidative stress, neuroinflammation, and the formation of amyloid plaques and neurofibrillary tangles, the key hallmarks of LOAD. In addition, in population-based studies, cannabinoids reduced dementia-related symptoms (e.g., behavioral disturbances). The current article provides an overview of the potential of cannabinoids in the treatment of LOAD and related neuropsychiatric symptoms in older people. We also discuss the efficacy, safety, and pharmacokinetics of cannabinoid-based drugs in older people with dementia.

INTRODUCTION
Demographic changes and the rapid aging of the population worldwide will lead to an increase in the prevalence of older people with late-onset Alzheimer’s disease (LOAD), many of whom suffer from multimorbidity.1,2 The term “LOAD” refers to Alzheimer’s disease diagnosed at or after 60 years of age.1 Given the substantial burden of LOAD on patients, their caregivers, and the economy, finding an effective therapy is one of the highest medical priorities of scientists, clinicians, and governments. The past few years have seen a growing interest in the medicinal uses of cannabinoids, the bioactive components of the cannabis plant (Cannabis sativa L.), including the treatment of LOAD and other physical conditions that are common in older people.3–5 The current review provides an overview of the potential of cannabinoids as treatment for LOAD and its related symptoms, focusing on older individuals (≥65 years). The focus on older individuals was done for a number of reasons. (1) The prevalence of dementia caused by LOAD is high in older age groups (about 95% of all cases), whereas early onset Alzheimer’s disease with an onset between 30 and 64 years is rare (<5%) and often linked to familial Alzheimer’s disease, which is associated with a different pathophysiological mechanism and is caused by gene mutations on chromosomes 21, 14, and 1. (2) Older individuals, and especially those with cognitive impairment, have often been excluded or underrepresented in clinical trials,3,5 and it is not possible to directly extrapolate safety and efficacy data for cannabinoid-based drugs obtained in studies involving young adults to older people. (3) Older people with LOAD are more vulnerable to adverse drug reactions, and especially to drugs that act on the central nervous system, such as cannabinoids, than healthy older or younger people.6 This is because of age-related physiological changes (e.g., decrease in liver enzyme activity, lean body mass, renal clearance, and brain volume/receptors) that often alter the pharmacokinetics and pharmacodynamics of drugs.6 (4) Comorbidity is also more common in older people with dementia than in their nondemented counterparts,6 leading to the use of multiple medications and to an increased risk of drug-drug and drug-disease interactions. As it is possible that older people with Alzheimer’s disease and multiple comorbidities might benefit from the use of cannabinoids as a multitarget drug candidate (one drug for several conditions), we reviewed the literature on the potential of cannabinoids in the treatment of dementia and dementia-related symptoms in older people.

LATE-ONSET ALZHEIMER’S DISEASE
Prevalence and pathophysiology
It is estimated that 36 million people suffer from dementia worldwide. This number is expected to reach 115 million people...

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STATE OF THE ART
by 2050, causing a major public health problem with an immense impact on individual patients, their families, health care systems, and economies.1

Alzheimer’s disease is the most common type of dementia, accounting for 60–80% of cases, followed by vascular dementia (10–15%).7 In the United States alone, the prevalence of LOAD has been estimated at 5 million individuals aged 65 years and older, with at least 200,000 (4%) individuals younger than 65 years being affected by young-onset Alzheimer’s disease.7 Alzheimer’s disease, in general, is a progressive, neurodegenerative disease that is characterized by a decline in cognitive and intellectual functions (e.g., memory, executive function, language, and perceptual-motor skills) that significantly interferes with activities of daily living.5 The clinical picture is, however, more complex and frequently involves behavioral and psychological changes. Although its incidence and prevalence increase with advancing age, LOAD is not a normal part of aging.7 LOAD is probably a complex, multicausal syndrome in which component causes, such as genetic, epigenetic, and late-onset environmental factors, increase the likelihood of an individual developing LOAD.8

In general, the brains of patients with Alzheimer’s disease are characterized by the accumulation of amyloid-β protein (Aβ; mainly Aβ1–42 and Aβ1–40) in extracellular senile plaques in various brain regions, but especially in the hippocampus, cerebral prefrontal cortex, and amygdala.9 Aβ protein is generated by the aberrant processing of amyloid precursor protein, a single-pass transmembrane glycoprotein. The second pathological hallmark of Alzheimer’s disease is the presence of intracellular neurofibrillary tangles, formed by hyperphosphorylated tau.9

It has been suggested that neuroinflammation and oxidative stress play an important role in the pathogenesis of LOAD,10 although there are still important missing links in our understanding of Alzheimer’s disease, especially LOAD. The accumulation and aggregation of senile plaques into toxic oligomers in the brain leads to the chronic activation of microglial cells and astrocytes, which surround the plaques, thereby initiating a proinflammatory cascade and oxidative stress that result in the release of potentially neurotoxic substances, such as cytokines, chemokines, reactive oxygen/nitrogen species, complement proteins, and various proteolytic enzymes. This process leads to local inflammation and neuronal death, which subsequently leads to cognitive decline and behavioral changes.10 In addition, mitochondrial dysfunction has been shown to play a key role in LOAD.11 Aβ accumulation inhibits integrated mitochondrial respiration and the activity of key enzymes.11 This may result in increased oxidative stress, the production of reactive oxygen species, and damage to different molecules, including nucleic acids, proteins, and lipids, and endoplasmic reticulum-related protein unfolding.11 Moreover, intracellular Aβ accumulation contributes to the dysregulation of intracellular calcium homeostasis and excessive activation of the N-methyl-D-aspartate subtype of glutamate receptor, inducing excitotoxicity and neuronal death.12

**Treatment of late-onset Alzheimer’s disease**

In general, the progression and treatment of LOAD do not differ from young-onset Alzheimer’s disease. The progression of Alzheimer’s disease from early stages of the disease (asymptomatic or minimally symptomatic) to dementia stages (symptomatic) may take decades. Therefore, successfully targeting the neuropathology of Alzheimer’s disease in an early stage would help diminish the burden of dementia and its associated neuropsychiatric symptoms. However, currently approved pharmacological treatments for Alzheimer’s disease, which include cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-methyl-D-aspartate receptor antagonist memantine, act on symptoms and do not have profound disease-modifying effects. A Cochrane meta-analysis of 13 randomized, double-blind, placebo-controlled trials with donepezil, rivastigmine, and galantamine demonstrated that the three cholinesterase inhibitors are efficacious for mild-to-moderate Alzheimer’s disease, but it is not possible to identify patients who will respond to treatment in advance.13 Although the three cholinesterase inhibitors seem to be equally effective, donepezil seems to give rise to fewer side effects than rivastigmine.13 However, the tolerability of galantamine and rivastigmine (oral form) can be improved to match that of donepezil if the drugs are administered according to a gradual titration routine over more than three months. Donepezil dose titration is more straightforward and lower doses may be effective.13 Rivastigmine is currently also available as a transdermal patch (Exelon patch, Rivastach patch, Prometax patch), which is associated with better patient satisfaction, tolerability, and compliance compared to the oral formulation.14

In the past decades, several attempts have been made to develop disease-modifying drugs for Alzheimer’s disease. One of the most innovative is the development of immunotherapy, based on the stimulation of amyloid plaque clearance from Alzheimer brains via the administration of Aβ antigens (active vaccination) or anti-Aβ antibodies (passive vaccination). The first in vivo immunization study was reported in 1999 by Schenk et al.15 They demonstrated that immunization of transgenic mice with Aβ1–42 prevented the development of beta-amyloid-plaque formation, neuritic dystrophy, and astrogliosis in young mice (with young-onset Alzheimer’s disease) and significantly reduced the extent and progression of Alzheimer’s disease-like pathology in older mice (with LOAD).15 On the basis of these results and those of a phase 1 safety study, a follow-up multicenter, randomized, placebo-controlled, phase 2 double-blind clinical trial was carried out involving patients with mild-to-moderate Alzheimer’s disease.16,17 Patients were randomly assigned to receive intramuscular injections of AN1792 (aggregated Aβ1–42 and an immune adjuvant, QS-21) or placebo. Unfortunately, the trial had to be abandoned as 18 of the 298 included patients (6%) developed meningoencephalitis.16,17 Sixteen of the 18 had received two doses, one had received one dose, and one had received three doses of the study drug before symptoms occurred.16 This severe side effect was caused by an inflammatory T cell response. Postmortem analysis of the brains of participants with Alzheimer’s disease showed that the AN1792 vaccine had significantly reduced the number of amyloid plaques compared to placebo.18 However, the progression of cognitive decline was unchanged and did not correlate with clearance of amyloid plaques, which suggests that plaque clearance is not enough to counter the
progression of Alzheimer’s disease. Since then, several attempts have been made to develop safe and effective drugs, but none have proven effective in phase 3 clinical trials involving patients with mild-to-moderate disease. Causes and factors associated with this failure include the use of inadequate biological and neuropsychological markers for the diagnosis of LOAD, inability to reach a therapeutic dosage (e.g., because of severe adverse events), short treatment duration, poor penetration to the brain, and advanced disease stage. The data of phase 3 studies suggest that mild-to-moderate Alzheimer’s disease has already progressed too far for treatment to be effective in improving neuronal and synaptic damage.

It is important to note that because the neuropathology of LOAD involves multiple hallmarks, it is reasonable to assume that a strategy focusing on multiple targets may be more beneficial than a strategy focusing on one target only.

**Treatment of neuropsychiatric symptoms of late-onset Alzheimer’s disease**

Almost all patients with LOAD (98%) develop neuropsychiatric symptoms at some point. These symptoms include depression, anxiety, agitation, aggression, wandering, pacing, sleep disorders, psychosis, and appetite/eating disorders, and are often distressing to patients and their caregivers, leading to early nursing home placement. Moreover, they are associated with more rapid dementia progression and higher health care costs. An earlier study showed that approximately 30% of the total annual cost of Alzheimer’s disease treatment is directly attributable to the management of neuropsychiatric symptoms. Therefore, effective treatment of the neuropsychiatric symptoms of LOAD may have the potential to modify the disease course, lower costs, and improve the quality of life of affected individuals and their caregivers. Yet no drugs have been approved by either the US Food and Drug Administration or the European Medicines Agency for the treatment of the neuropsychiatric symptoms of Alzheimer’s disease. Studies of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine reported modest or no improvement in neuropsychiatric symptoms. In addition, the N-methyl-D-aspartate receptor antagonist memantine did not improve agitation compared with placebo in patients with moderate-to-severe Alzheimer’s disease (n = 149). Psychotropic medications, such as antipsychotics, benzodiazepines, antidepressants, and antiepileptic drugs, are also frequently used off-label for the treatment of the neuropsychiatric symptoms of Alzheimer’s disease, but they are ineffective in most cases or only have a short-term effect. Moreover, they are associated with serious adverse events in older individuals, including falls, cardiovascular and cerebrovascular events, and even death.

Taken together, there is an urgent need for new effective and safe pharmacological interventions to retard LOAD progression toward dementia (symptomatic) and diminish the burden of neuropsychiatric symptoms.

**THE ENDOCANNABINOID SYSTEM AS MULTITARGET DRUG CANDIDATE**

In the past decade, the medicinal use of cannabis has moved to the forefront of public and scientific debate, and the past few years have seen a growing interest in its medical applications in older people, including those with Alzheimer’s disease and multiple comorbidities. This is not surprising because the cannabis plant (*Cannabis sativa L.*) has been used for centuries to treat a wide range of conditions that are common in older people (e.g., pain, depression, sleep disturbance, and loss of appetite). These broad therapeutic applications are due to the pharmacological effects of its bioactive components, the “cannabinoids.” Currently, more than 60 different cannabinoids have been identified and isolated from the cannabis plant, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most studied. Although the exact mechanism of action and the physiological effects of cannabinoids are still not fully understood, THC seems to be responsible for most of the physical and psychoactive effects of cannabis. Cannabinoids exert some of their multiple effects through an interaction with the endocannabinoid system. This system consists of cannabinoid receptors, endogenous lipid ligands (endocannabinoids), including N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol, and enzymes (e.g., fatty acid amide hydrolase and monoglyceride lipase) involved in the synthesis and degradation of these endocannabinoids. Cannabinoids bind to the cannabinoid receptors CB1 and CB2, both of which are G-protein-coupled receptors. CB1 receptors are mainly expressed in the nervous system (basal ganglia, cerebellum, hippocampus, hypothalamus, and dorsal horn), whereas CB2 receptors are primarily found in cells and organs of the immune system. However, cannabinoids also exert effects by interacting with other cannabinoid receptors in the brain, such as GPR55 receptors and noncannabinoid receptors, such as peroxisome proliferator-activated receptors alpha and gamma, transient receptor potential vanilloid-1 channels, acetylcholine, dopamine, serotonin, gamma-aminobutyric acid, glutamate, norepinephrine, prostaglandins, and opioid peptides. This broad interaction reflects the potential of cannabinoids and the endocannabinoid system as multitarget drug candidates for LOAD.

**THE ENDOCANNABINOID SYSTEM IN AGING AND ALZHEIMER BRAINS**

The endocannabinoid system has been associated with several pathological conditions and processes in aging, including synaptic plasticity (learning and memory), neuroinflammation and neurodegeneration, behavior and mood disorders, regulation of the wake-sleep cycle, immune function, inflammatory diseases, physiological homeostasis, cardiovascular function, bone development and density, pain, motor alterations, and regulation of food intake and energy balance. In this respect, it is important to distinguish between age-related and LOAD-related changes in the endocannabinoid system before it can be considered as a therapeutic target for LOAD. Unfortunately, there have been only a few studies investigating possible age-related and Alzheimer’s disease-related changes in the endocannabinoid system. One of the few such studies reported a significant decrease in cannabinoid receptor binding in various brain regions (cerebellum, cerebral cortex, limbic and hypothalamic structures, and hippocampus) in aged rats compared with young rats. In
another study, receptor binding was decreased in most regions of the basal ganglia in aged rats, except for the globus pallidus, in which binding levels were similar in both aged and young rats.40 The greatest decrease was found in the entopeduncular nucleus (50%), substantia nigra pars reticulata (45%), and lateral caudate putamen (29%). With aging, brain cannabinoid CB1 receptor density in the hippocampus also decreases (30%).41 Although the endocannabinoid system may be influenced by Alzheimer-type neurodegeneration, it is not clear whether these changes are a cause or a consequence of LOAD, and whether these changes are dependent or independent of normal age-related changes. Postmortem studies of Alzheimer brains have reported contradictory results regarding the expression and density of cannabinoid receptors.42–49 Whereas the majority of studies found no changes in the expression and availability of CB1 receptors in Alzheimer brains compared with control brains,42–45 some studies reported a decreased expression of CB1 receptors in Alzheimer brains, mainly in neurons distant from senile plaques.46,47 One study failed to distinguish between age-related and Alzheimer’s disease-related changes in CB1 receptor expression.48 A decreased level of CB1 receptors in the brain may alter the pharmacodynamic effects of exogenous cannabinoids in people with LOAD because the effects of cannabinoids are mainly mediated by CB1 receptors.

CANNABINOIDS IN LATE-ONSET ALZHEIMER’S DISEASE

In vitro and in vivo studies

Targeting the endocannabinoid system has been proposed as a potential approach to the treatment of Alzheimer’s disease.46,49–51 Numerous in vitro and in vivo studies have demonstrated the protective effects of cannabinoids against Aβ peptide and tau phosphorylation, the neuropathological hallmarks of the disease.46,49–51 The endogenous cannabinoids N-arachidonoylethanolamine and 2-arachidonoylglycerol have been found to cause a concentration-dependent inhibition of Aβ neurotoxicity, through the activation of the CB1 receptor and mitogen-activated protein kinase pathways, that regulate cell function (e.g., cell growth, mitosis, survival, and apoptosis).52 Another study demonstrated that the administration of N-arachidonoyl-(2-methyl-4-hydroxyphenyl) amine, a potent cannabinoid reuptake inhibitor, to rats improved Aβ-induced neuronal damage and memory impairment. These positive effects were dependent on early administration of N-arachidonoyl-(2-methyl-4-hydroxyphenyl) amine, which suggests that early pharmacological enhancement of brain cannabinoid levels may protect against Aβ neurotoxicity.53 Ramirez et al.46 reported that intracerebroventricular administration of the synthetic cannabinoid WIN55,212-2 to rats prevented Aβ-induced microglial activation, cognitive impairment, and loss of neuronal markers. The synthetic cannabinoids HU-210, WIN55,212-2, and JWH-133 may block Aβ-induced activation of cultured microglial cells, as judged by mitochondrial activity, cell morphology, and tumor necrosis factor-α release. These effects seem to be independent of the antioxidant action of cannabinoid compounds and are also exerted by a CB2-selective agonist. Moreover, cannabinoids prevent microglia-mediated neurotoxicity after the addition of Aβ to rat cortical cultures.46 The authors concluded that cannabinoid receptors are important in the pathology of Alzheimer’s disease and that cannabinoids can prevent the neurodegenerative process occurring in the disease.46

Other positive results were obtained with exogenous cannabinoids, such as cannabidiol, a nonpsychoactive cannabinoid. CBD has been proposed as an antioxidant neuroprotective agent in neurodegenerative diseases because it inhibits in vivo Aβ plaque formation and decreases reactive oxygen species production and lipid peroxidation.49 Moreover, CBD has been shown to rescue PC12 cells, a rat pheochromocytoma cell line that is used as a model system for studying neuronal cell death, from the toxicity induced by Aβ peptide.54 It has also been reported that CBD inhibits the hyperphosphorylation of tau protein in Aβ-stimulated PC12 neuronal cells by reducing the phosphorylation of glycogen synthase kinase-3beta, which is responsible for the tau hyperphosphorylation in Alzheimer’s disease.55 In addition, glycogen synthase kinase-3beta can block the production of Aβ peptides by interfering with amyloid precursor protein cleavage at the gamma-secretase step.56 Thus, CBD is an attractive drug candidate for the management of LOAD because it reduces the hallmarks of the disease, namely the formation of both amyloid plaques and neurofibrillary tangles.

In a recent study, Martín-Moreno et al.57 compared the effects of cannabinoids on microglial cell function in vitro and on learning behavior and cytokine expression after the intraventricular administration of Aβ to mice. They reported that two cannabinoids, CBD and WIN55,212-2 (synthetic cannabinoid), were able to modulate microglial cell functions and cytokine expression, improving the learning behavior of mice injected with Aβ.57 In addition, Scuderi et al.58, in their study of whether CBD could modulate amyloid precursor protein processing in transfected human neuroblastoma SHSY5Y(APP+), neurons, found that CBD induced the ubiquitination of amyloid precursor protein, which led to a substantial decrease in levels of the full-length protein in neurons and to a decrease in Aβ production. Moreover, CBD promoted the survival of SHSY5Y(APP+) neurons by reducing the rate of apoptosis. All the effects of CBD were dependent on the selective activation of peroxisome proliferator-activated receptors gamma.58 Eubanks et al.59 also pointed out the potential of another exogenous cannabinoid, THC, as a new drug candidate for the treatment of Alzheimer’s disease. They found THC to competitively inhibit the enzyme acetylcholinesterase and to prevent acetylcholinesterase-induced Aβ aggregation even more effectively than acetylcholinesterase inhibitors, the drugs currently registered for Alzheimer’s disease.

In a more recent study, Aso et al.60 evaluated the therapeutic properties of Sativex (combination of THC/CBD) in an animal model of LOAD (AβPP/PS1 mice). These mice exhibit the most relevant features of LOAD, such as cognitive impairment and several pathological alterations, such as Aβ accumulation, dystrophic neurites, synaptic failure, mitochondrial dysfunction, and oxidative stress damage.60 Intraperitoneal administration of THC/CBD (0.75 mg/kg each for 5 weeks) significantly reduced
cognitive impairment. Moreover, it reduced levels of soluble \(\beta_1\), but not those of \(\beta_4\), thereby changing the composition of amyloid plaques in these mice. This suggests that combination treatment with THC/CBD may be more beneficial than treatment with either agent alone.

**Population-based studies**

Unfortunately, there have been no population-based studies of cannabinoids as a potential cure for LOAD. Comparing the preclinical and clinical data of therapeutic properties of cannabinoids with the evidence supporting more investigated approaches for the treatment of LOAD (e.g., cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist), the majority of the evidence of cannabinoids has been based on cellular and animal models that mimic a variety of Alzheimer’s disease-related changes. Moreover, little is known about the safety of cannabinoids in people with LOAD. Previous epidemiological studies have shown that prolonged exposure to cannabinoids could increase the risk of developing psychiatric disorders (e.g., cognitive abnormalities, psychotic illness, and mood disorders), especially in people who already have a vulnerability to develop a psychiatric syndrome.61

Given the interesting results of cannabinoids reported in *in vitro* and *in vivo* studies, population-based studies are urgently warranted, especially sufficiently powered randomized clinical trials that are designed to differentiate between symptomatic improvement and disease modification.

**TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS**

Our literature search in PubMed (February 2015), using the terms “Alzheimer’s disease,” “dementia,” and “cannabinoids,” identified one systematic review, one case report, and four small clinical studies (out of 160 articles) on the effectiveness and safety of cannabinoids in the treatment of people with dementia.

The systematic review62 included only one double-blind placebo-controlled crossover trial. According to the authors, the trial data were presented in such a way that they could not be used for further analysis and there was insufficient quantitative data to validate the results. Therefore, they concluded that there is no evidence that cannabinoids are effective in the treatment of disturbed behavior or other symptoms of dementia.62

In the case report, the synthetic THC nabilone was used in a 72-year-old man with LOAD who had developed behavioral symptoms, including wandering, pacing, disinhibition, agitation, and aggression.63 The patient had previously been treated with donepezil, memantine, gabapentin, trazodone, quetiapine, olanzapine, lorazepam, and citalopram without significant improvement. Nabilone 0.5 mg/day was started and was later increased to 0.5 mg twice daily, which led to a significant improvement in the patient’s behavioral symptoms without emergent side effects during the three-month follow-up.

The four clinical studies of the effectiveness of cannabinoids in the treatment of dementia symptoms included in total 60 subjects, all of whom were treated with the synthetic THC dronabinol.64–67 Table 1 summarizes these studies. In a double-blind placebo-controlled crossover trial, Volicer et al.64 included 15 institutionalized patients with Alzheimer’s disease who refused food. During the 12-week trial, the patients were randomly assigned to placebo first (6 weeks) or dronabinol (2.5 mg twice daily) first (6 weeks). Twelve patients (mean age 72.7 ± 4.9; 11 men) were included in the final analysis. Trial medication was terminated in three participants because one developed a grand mal seizure after the first dronabinol dose and two developed serious intercurrent infections.64 Patients gained weight and agitation decreased during dronabinol treatment. Compared to placebo, dronabinol was associated with tiredness, somnolence, and euphoria64

In an open-label pilot study, Walther et al.65 evaluated the effect of dronabinol on sleep and behavioral disturbances in six patients (mean age = 81.5 ± 6.1; 4 women) with severe dementia (five with Alzheimer’s disease). Participants received 2.5 mg dronabinol daily for 2 weeks. Actigraphy and the Neuropsychiatric Inventory were used to measure the effect of dronabinol on nocturnal motor activity and behavior, respectively. Compared to baseline, dronabinol significantly improved nocturnal motor activity and behavior. No side effects were observed during the study period.65

Subsequently, Walther et al.66 started a randomized, double-blind, placebo-controlled, crossover trial to further evaluate the effects of dronabinol on behavioral disturbances in Alzheimer’s disease. After the inclusion of two patients, the trial was prematurely discontinued because of recruitment failure. The two included patients were 75 and 81-year-old men with LOAD who had been treated with 2.5 mg dronabinol for four weeks for nighttime agitation. In both cases, the administration of dronabinol reduced nighttime activity and strengthened circadian rhythms without any adverse events.

More recently, in a retrospective systematic chart review, Woodward et al.67 evaluated the data of 40 patients with dementia (13 with Alzheimer’s disease; 28 women) who had been treated with dronabinol for behavioral or appetite disturbances. The medical records of included patients were reviewed by geriatric psychiatrists to rate the patients’ behavior before and after seven days of dronabinol treatment, using the Pittsburgh Agitation Scale, Clinical Global Impression, and Global Assessment of Functioning.67 In addition, data were collected on the percentage of food consumed at each meal, sleep duration, and adverse events. The mean duration of dronabinol treatment was 17 days (range = 4–50 days) and the mean dose was 7 mg/day. Administration of dronabinol significantly improved scores on the Pittsburgh Agitation Scale and the Clinical Global Impression, but not on the Global Assessment of Functioning. There were also significant improvements in sleep duration and percentage of food consumed during active treatment. Twenty-six adverse events were reported during dronabinol treatment, with sedation (n = 9), delirium (n = 4), urinary tract infection (n = 3), and confusion (n = 2) being the most frequently reported. However, while it was not possible to assess whether the reported adverse events were associated with dronabinol, none of the adverse events led to medication discontinuation.67

Although the findings from the above-mentioned clinical studies and case report suggest that THC is effective and safe to use...
Table 1. Studies published on cannabinoid-based drugs in patients suffering from behavioral disturbances in dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects / age</th>
<th>Study design</th>
<th>Studied indication</th>
<th>Drug / Dosage</th>
<th>Treatment duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volicer64 (1997) USA</td>
<td>12 AD (11 men, 1 woman)</td>
<td>RCT</td>
<td>Food refusal and disturbed behavior</td>
<td>Dronabinol (THC) 2.5 mg twice/day</td>
<td>12 wk (6 wk THC and 6 wk placebo)</td>
<td>Weight increased more with THC treatment than with placebo. THC treatment decreased severity of disturbed behavior compared with placebo. One dropout during THC treatment, due to seizure. Adverse events were more common during THC treatment than placebo. The top 5 reported adverse events were anxiety/nervousness, emotional lability, tiredness, somnolence, and euphoria.</td>
</tr>
<tr>
<td>Walther65 (2006) Germany</td>
<td>6 (5 AD and 1 VaD)</td>
<td>Open-label</td>
<td>Nocturnal motor activity</td>
<td>Dronabinol (THC) 2.5 mg/day</td>
<td>2 wk</td>
<td>Compared to baseline, THC significantly reduced nocturnal motor activity and agitation. No adverse events were observed.</td>
</tr>
<tr>
<td>Walther66 (2011) Switzerland</td>
<td>2 LOAD A) 75-year-old man B) 81-year-old man</td>
<td>RCT</td>
<td>Agitation and circadian disturbances</td>
<td>Dronabinol (THC) 2.5 mg/day</td>
<td>4 wk (2 wk THC and 2 wk placebo)</td>
<td>THC reduced nighttime activity and strengthened circadian rhythms. No adverse events were observed.</td>
</tr>
<tr>
<td>Woodward57 (2014) USA</td>
<td>40 (12 men, 28 women)</td>
<td>Retrospective systematic chart review</td>
<td>Behavioral or appetite disturbances</td>
<td>Dronabinol (THC) Mean dose 7.03 mg/day</td>
<td>Mean duration: 16.88 d (range 4–50 d)</td>
<td>THC was associated with significant decreases in all domains of the Pittsburgh Agitation Scale. There were also significant improvements in Clinical Global Impression scores, sleep duration, and percentage of meals consumed during treatment. 26 adverse events were reported during THC treatment. The most common were: sedation (n = 9), delirium (n = 4), urinary tract infection (n = 3), and confusion (n = 2).</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; FTD, frontotemporal dementia; LOAD, late-onset Alzheimer’s disease; RCT, randomized controlled trial; THC, tetrahydrocannabinol; VaD, vascular dementia.
in the treatment of dementia-related symptoms in older people, the studies had several limitations that need to be addressed. For example, the studies were either not randomized or included a very limited number of participants (range = 10–40 participants), so that the studies had insufficient power to draw firm conclusions about the safe and effective use of cannabinoids for older people with dementia. Moreover, the THC treatment period was too short (2–7 weeks). Last, all the studies focused on dementia-related symptoms and did not include the assessment of memory and cognitive function as outcome measures. It is of great importance to establish whether cannabinoids, particularly when used long term, affect memory and cognitive functions in frail older people with LOAD. In previous general population studies, prolonged use of cannabis was associated with memory deficits and cognitive impairments.61

More adequately powered randomized clinical trials are needed to confirm the findings of the above-mentioned studies. Until then, individual evaluation of the risk–benefit ratio is needed before cannabinoid-based drugs can be prescribed to frail older individuals with LOAD.

CANNABINOIDS IN THE TREATMENT OF OTHER CONDITIONS IN OLDER PEOPLE

Current prescriptions

Because of the significant therapeutic potential of cannabis and cannabinoids, people aged 65 years and older probably constitute a growing population of potential users.3 Although there are numerous studies of the medicinal use of cannabis (marijuana, cannabinoids based-drugs, and cannabis extracts) in the general population, little is known about its effect in older people.5

In the United Kingdom, between 1998 and 2002, 947 people reported ever having used cannabis for medicinal purposes68; 14% of these individuals were older than 60 years. Medicinal cannabis is mostly used for multiple sclerosis (12% of participants), neuropathy (11%), chronic pain (11%), depression (8%), and arthritis (7%). In the Netherlands, where herbal cannabis (marijuana) is available at community pharmacies, more than 5,500 patients (57% were women) were prescribed herbal cannabis between 2003 and 2010.69 Of these, 31% were aged between 61 and 80 years and 6% were older than 80 years, with an average duration of use of six months and three months, respectively. Hazeckamp et al.70 recently reported the results of an international survey on the medicinal use of cannabis and cannabinoids in 31 countries (e.g., United States, Germany, Canada, France, the Netherlands, and Spain). Of the 953 users of medicinal cannabis (mean age = 40.7 years; 64% men) who completed the survey, 24% were aged between 51 and 60 years, 6% between 61 and 70 years, and 1% older than 70 years. The five most reported medical conditions for medicinal cannabis use were back pain (11.9%), sleeping disorder (6.9%), depression (6.7%), pain resulting from an injury or accident (6.2%), and multiple sclerosis (4.1%).70

Efficacy and safety of cannabinoid-based drugs

There are currently three cannabinoid-based drugs available for medical use, dronabinol, nabilone, and nabiximols. Dronabinol (Marinol; Solvay Pharmaceuticals, Belgium) and nabilone (Cesamet; Valeant Pharmaceuticals International North America, Canada) are both synthetic THC in capsule form. They have been approved in North America and some European countries for appetite stimulation in AIDS-related anorexia and chemotherapy-induced nausea and vomiting. Nabiximols (Sativex, GW Pharmaceuticals, UK) is an oromucosal mouth spray that contains both THC and CBD (ratio = 1:1). It is used for the symptomatic relief of neuropathic pain and muscle spasticity in patients with multiple sclerosis and is available in 15 countries including the United Kingdom and seven other European countries, New Zealand, and Canada, but not in the United States.

Cannabinoid-based drugs that have not yet gained marketing approval are: (1) Namisol (Echo Pharmaceutical, The Netherlands), a THC-based formulation in tablet form.71 This drug is under investigation for the treatment of pain (multiple sclerosis, chronic pancreatitis) and neuropsychiatric symptoms of Alzheimer’s disease (agitation/aggression); and (2) Epidiolex (GW Pharmaceuticals, UK) which is a CBD-based formulation that has recently been tested in children and young adults with treatment-resistant epilepsy.72

Several studies have demonstrated the efficacy and safety of cannabinoid-based drugs in the treatment of different conditions that are highly prevalent in the older population, such as pain, anorexia, and nausea and vomiting.3,5 Although all these conditions are common in older people, and in those with dementia, few studies reported data on older people separately.3,5 Moreover, most preapproval clinical trials of cannabinoid-based drugs excluded older individuals (≥65 years) from participation or did not include sufficient numbers of older participants to compare them with young participants.3,5

Recently, we performed a systematic literature review to identify studies investigating the efficacy and safety of medical cannabinoids in older subjects.5 We found 105 randomized clinical trials that reported the inclusion of older individuals (≥65 years). Of these, only five trials reported data for older individuals separately. These trials included a total of 267 participants (mean age = 47–78 years). Three trials used oral THC and two trials used an oral combination of THC/CBD. The studies found neither THC nor THC/CBD to be effective against dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting. Two studies showed that THC might be useful for the treatment of anorexia and behavioral symptoms of dementia. Adverse events were more frequently associated with cannabinoid treatment than with the control condition, with sedation/drowsiness being the most reported adverse events. None of the studies reported severe adverse effects related to cannabinoid use. Thus, for the moment, no firm conclusion can be drawn about the safety and efficacy of cannabinoid-based drugs in older people.

In general, older people seem to be more susceptible than younger people to the effects of drugs acting on the central nervous system. This can be explained by four important factors.73 (1) Age-related changes in brain volume and number of neurons, as well as alterations in neurotransmitter sensitivity, may increase the pharmacological effect of a drug. (2) Certain neurotransmitter receptors may be selectively affected by age-related changes at
Presynaptic and postsynaptic levels. (3) Age-related changes in receptors, whether they are located at the actual neurotransmitter binding site or within the second messenger or effector system, may change sensitivity to the available neurotransmitter. Altered binding of the neurotransmitter to its receptor site may affect its sensitivity to be blocked by some drugs that act in the central nervous system. (4) Altered drug disposition in older individuals generally results in a higher concentration of psychotropic drugs at central nervous system receptor sites.73 Moreover, synthetic cannabinoids are lipophilic compounds, and age-related physiological changes, such as an increase in adipose tissue and a decrease in lean body mass and total body water, increase the volume of distribution of lipophilic drugs. In addition, age-related changes in hepatic function (decrease in hepatic blood flow and slow hepatic metabolism) can slow the elimination of lipophilic drugs, which can subsequently lead to side effects.

**PHARMACOKINETICS OF CANNABINOIDS**

Relatively little is known about the pharmacokinetics of cannabis and cannabinoids in older individuals, especially in people with LOAD. None of the preapproval clinical trials of cannabinoid-based drugs currently available for clinical use (Marinol, Cesamet, and Sativex) reported pharmacokinetic data for older individuals or people with dementia. Moreover, the most recent studies of cannabinoid-based drugs that included older participants without dementia did not perform separate pharmacokinetic analyses for the older subgroup.71

Carroll et al.74 were the first to report pharmacokinetic data for cannabinoids in older people without dementia. They included 19 participants (12 men; mean age = 67 years; range = 51–78 years) with Parkinson disease who received Cannador (THC 2.5 mg and CBD 1.25 mg per capsule). In most patients, the maximum concentration \( C_{\text{max}} \) of THC was reached within two hours of drug administration, with levels ranging from 0.25–5.4 ng/mL. There was no clear dose response. The authors did not report pharmacokinetic data for subjects older than 65 years.71

In our recent phase 1 study,71 we evaluated the pharmacokinetics of three oral doses of THC (3 mg, 5 mg, and 6.5 mg) in 12 healthy older subjects (6 men; mean age = 72 ± 5 years; range = 65–80 years). One subject was not medication compliant and so the data for 11 subjects (5 men and 6 women) were analyzed. Blood samples were collected before and at 40, 55, and 120 minutes after dosing. There was a wide interindividual variation in plasma concentrations of THC and its active metabolites, 11-hydroxy-delta 9-THC and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol. In one subject, the THC concentration had not reached a maximum by 120 minutes after dosing with 3 mg THC, and in four and five subjects after dosing with 5 mg and 6.5 mg THC, respectively. For subjects for whom \( C_{\text{max}} \) was reached within 120 minutes, the geometric mean THC \( C_{\text{max}} \) was 1.42 ng/mL (range = 0.53–3.48) for 3 mg \( (n = 10) \), 3.15 ng/mL (range = 1.54–6.95) for 5 mg \( (n = 7) \), and 4.57 ng/mL (range = 2.11–8.65) for 6.5 mg \( (n = 6) \).69 However, as the study was initially designed to assess the safety, not pharmacokinetics, of THC, only four blood samples were collected over 120 minutes, which is insufficient for complete pharmacokinetic analysis.71

In another recent study, a randomized, double-blind, placebo-controlled, crossover trial,75 we evaluated the pharmacokinetics of THC in 10 older subjects with dementia (7 men; mean age = 77.3 ± 5.6 years; 9 with Alzheimer’s disease). Subjects were randomly assigned to receive oral THC or placebo twice daily for three days, separated by a four-day washout period. The total treatment period was 12 weeks. Patients received 0.75 mg THC twice daily in weeks 1–6 and 1.5 mg THC twice daily in weeks 7–12. The data of one participant were excluded because insufficient blood was collected for analysis. The median time to reach \( C_{\text{max}} (T_{\text{max}}) \) was one to two hours. THC pharmacokinetics increased linearly with increasing dose, but with a wide interindividual variation (the coefficient of variation of the geometric mean was as high as 140%). The mean \( C_{\text{max}} \) (ng/mL) after the first dose (0–6 hours) was 0.41 (0.18–0.90) for the 0.75 mg dose and 1.01 (0.53–1.92) for the 1.5 mg dose; after the second dose (6–24 hours), the \( C_{\text{max}} \) was 0.50 (0.27–0.92) and 0.98 (0.46–2.06), respectively. To the best of our knowledge, this was the first and only study to date to investigate the pharmacokinetics of THC in subjects with dementia.75

Understanding the pharmacokinetics and pharmacodynamics of cannabinoid-based drugs will help clinicians to maximize the therapeutic benefits and minimize the toxic effects. Therefore, more studies are warranted in this population, especially comparison studies with younger and older adults.

**CONCLUSION**

**Current use and future prospects**

The great burden of LOAD and the lack of adequate therapy explain the increasing number of studies \((in vitro, in vivo, human)\) in this field of medicine. Given the complex multifactorial pathogenesis of LOAD, the development of a drug targeting a single causal factor will be of limited benefit to most patients. The literature consistently reports that the endocannabinoid system is associated with LOAD, and a number of studies have shown that targeting the endocannabinoid system offers a novel pharmacological approach for the treatment of LOAD that may be more effective than currently available drugs. Cannabinoids can reduce oxidative stress, neuroinflammation, and the formation of amyloid plaques and neurofibrillary tangles, the hallmarks of LOAD. Moreover, the cannabinoid THC seems to increase the availability of acetylcholine and prevent acetylcholinesterase-induced Aβ aggregation. Cannabinoids are interesting drug candidates for the treatment of LOAD in older people for other reasons as well. (1) The interactions between the endocannabinoid system and other receptors and neurotransmitters in the brain make cannabinoids not only a potential drug candidate for LOAD, but also for other physical conditions that are common in older people. (2) The cannabis plant is easy and cheap to cultivate, which makes cannabinoids an attractive drug. (3) Cannabinoid-based drugs (oral and mouth spray) have recently been developed and approved for use in a fixed dose, which makes drug delivery and dose control easier than with the smoking route of drug delivery, especially in individuals with cognitive impairment.
In conclusion, currently available studies, both in vitro and in vivo, provide an interesting basis for the innovative use of cannabinoi
doids as a therapeutic approach to LOAD and other comorbidit
ies in older people. However, the lack of population-based stude
ies justifies further research, and especially adequately pow
ered randomized controlled trials, in order to assess the safety,
efficacy, pharmacokinetics, and pharmacodynamics of cannabinoi
d-based drugs in this frail population.

CONFLICT OF INTEREST

The authors declared no conflict of interest.


