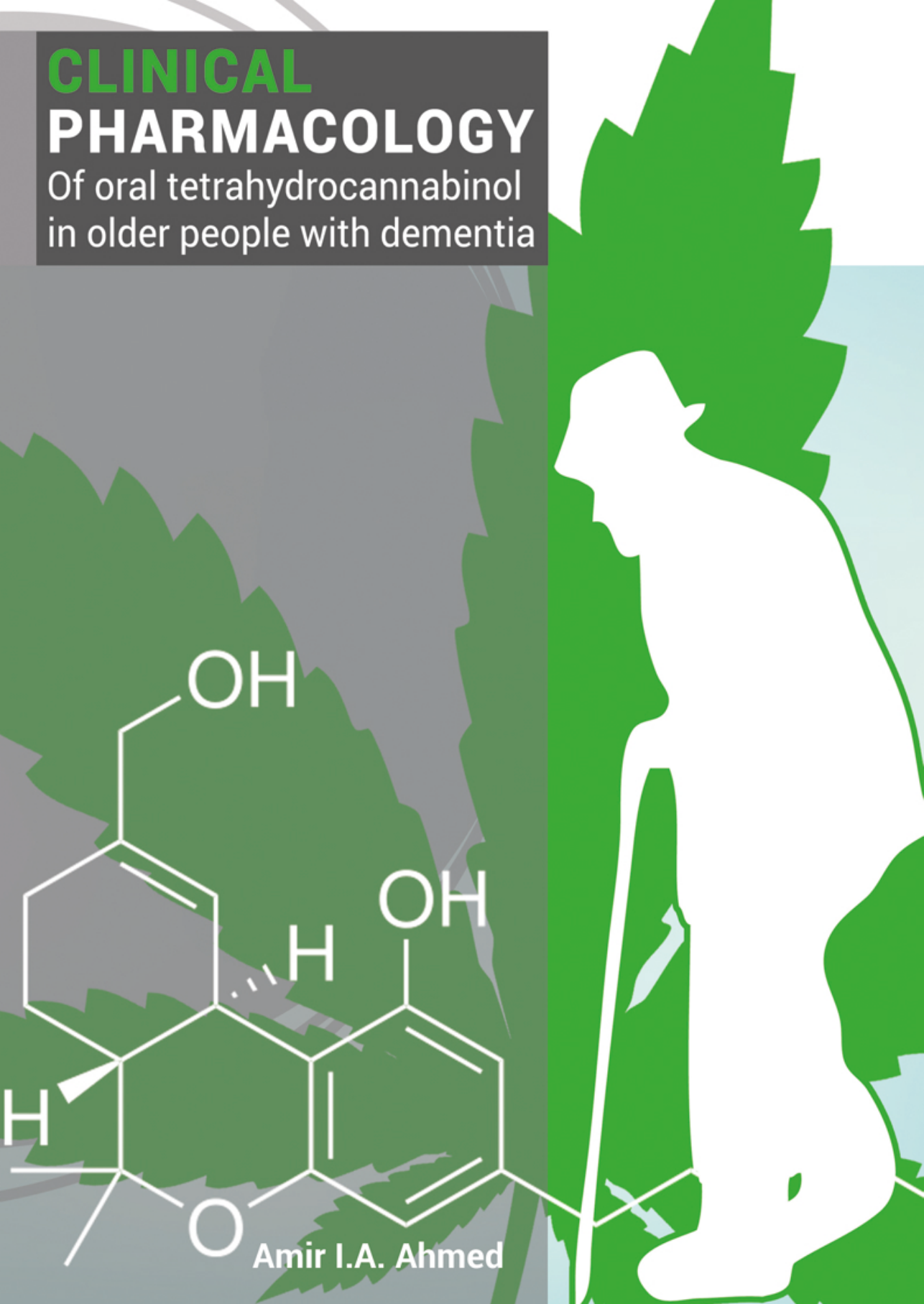
CLINICAL PHARMACOLOGY

Of oral tetrahydrocannabinol in older people with dementia



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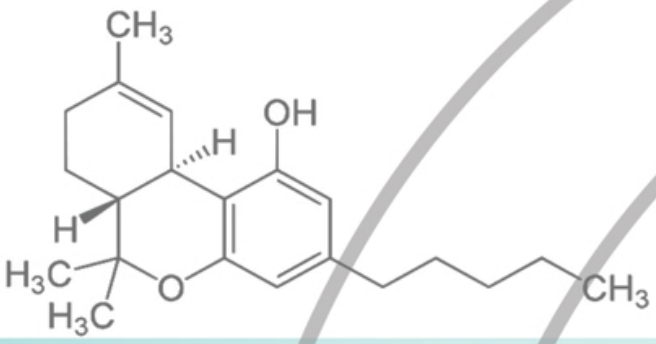
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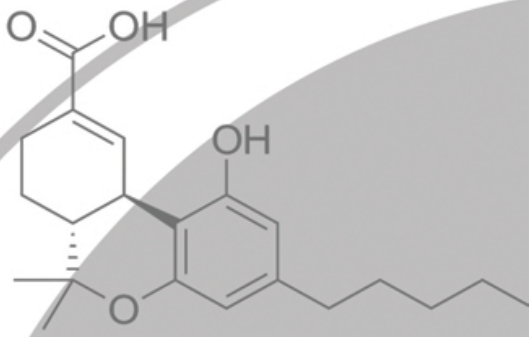
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Clinical pharmacology of oral tetrahydrocannabinol in older people with dementia

Amir Isam Ali Ahmed

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Clinical pharmacology of oral tetrahydrocannabinol in older people with dementia

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Contents

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PART I

General introduction

Partly based on

Cannabinoids in late-onset Alzheimer's disease.
Ahmed AI, van der Marck MA, van den Elsen GA, Olde Rikkert MG.
Clinical Pharmacology & Therapeutics 2015;97(6):597-606.

and

Medicinal use of cannabis and cannabinoids in older adults: where is the evidence?
Ahmed AI, van den Elsen GA, van der Marck MA, Olde Rikkert MG.
Journal of the American Geriatrics Society 2014;62(2):410-411.

Background

Demographic changes and the rapid aging of the population worldwide will lead to an increase in the prevalence of older people with dementia (≥ 65 years), many of whom suffer from multimorbidity.1,2 Given the substantial burden of dementia and its related neuropsychiatric symptoms on patients, their caregivers, and healthcare systems, 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.*), such as in the treatment of dementia, dementia-related neuropsychiatric symptoms, and other physical conditions that are common in older people.[3–5] Tetrahydrocannabinol (also known as delta-9-tetrahydrocannabinol, THC; figure 1) is the main psychoactive cannabinoid and appears to be responsible for most of the physiological effects of the cannabis plant.[6] Therefore, it has been one of the most studied cannabinoids in the past years.[6]

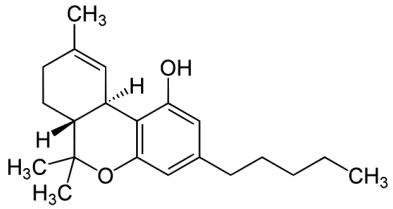

Figure 1 Delta-9-tetrahydrocannabinol (THC)

This thesis focuses on the clinical pharmacology of oral THC in older people with dementia (≥ 65 years), and specifically on its pharmacokinetic and pharmacodynamic effects, including safety and efficacy. The choice to focus on older people with dementia was made for several reasons,[7] as discussed below.

Dementia

Prevalence, pathophysiology, and treatment

Dementia is a syndrome characterized by a progressive, irreversible decline in cognitive functions, such as memory, learning capacity, orientation, executive function, language, and perceptual-motor skills, a decline that interferes with activities of daily living.[1]

The clinical picture is, however, more complex and frequently involves behavioral and psychological changes.

Alzheimer's disease is the most common type of dementia, contributing to 60-80% of all cases, followed by vascular dementia (10–15%), frontotemporal lobe dementia (about 5–10%), and dementia with Lewy bodies (< 5%).[1] However, postmortem studies have shown that many people with dementia have mixed Alzheimer's disease and vascular dementia pathology, which suggests that mixed-type dementia is often underdiagnosed.[8-10] According to the recent report of Alzheimer's Disease International (*World Alzheimer Report 2015*),[1] the number of people suffering from dementia worldwide is estimated at 47 million people.[1] This number is expected to more than triple by 2050, causing a major public health problem with an immense impact on individual patients, their families, healthcare systems, and economies.[1]

In general, clinicians distinguish between late-onset Alzheimer's disease and early-onset Alzheimer's disease. The term "late-onset Alzheimer's disease" refers to Alzheimer's disease diagnosed at or after 60 years of age (about 95% of Alzheimer cases), whereas the term "early-onset Alzheimer's disease" refers to Alzheimer's disease with an onset between 30 and 64 years (about 5% of all Alzheimer cases). Early-onset Alzheimer's disease is often linked to familial Alzheimer's disease, which has a different pathophysiological mechanism from late-onset Alzheimer's disease, involving gene mutations on chromosomes 21, 14, and 1. Although its incidence and prevalence increase with advancing age, late-onset Alzheimer's disease is not a normal part of aging.[11] It is probably a complex, multicausal syndrome in which component causes, such as genetic, epigenetic, and environmental factors, increase the likelihood of an individual developing the disease.[12]

The brains of patients with Alzheimer's disease are characterized by the accumulation of amyloid-β protein (Aβ; mainly $A\beta_{1-42}$ and $A\beta_{1-40}$) in extracellular senile plaques in various brain regions, but especially in the hippocampus, cerebral prefrontal cortex, and amygdala.[13] 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.[13]

It may take decades for Alzheimer's disease to progress from its asymptomatic or minimally symptomatic early stages to its full-blown symptomatic stage with dementia. 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 only on symptoms and do not have profound disease-modifying effects.

Neuropsychiatric symptoms

Almost all patients with dementia, including Alzheimer's disease, develop neuropsychiatric symptoms at some time during the course of the disease.[14] These symptoms, which include depression, anxiety, agitation, aggression, wandering, pacing, sleep disorders, psychosis, and appetite/eating disorders, are often distressing to patients and their caregivers.[14, 15] Furthermore, they are associated with a more rapid progression of dementia, higher healthcare costs, and early nursing home placement.[15-17] An earlier study showed that approximately a third of the total annual cost of Alzheimer's disease treatment is directly attributable to the management of neuropsychiatric symptoms.[17] Therefore, effective treatment of the neuropsychiatric symptoms of dementia may have the potential to modify the disease course, improve the quality of life of affected individuals and their caregivers, and lower healthcare costs.

Yet no drugs have been approved by either the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for the treatment of the neuropsychiatric symptoms of dementia. Studies of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine reported modest or no improvement in neuropsychiatric symptoms.[18] 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).[19] Recently, a phase 2 randomized, double-blind, placebo-controlled trial demonstrated the efficacy of combination therapy with dextromethorphan/quinidine in treating agitation in patients with Alzheimer's disease (n=194).[20] This combination therapy was approved by the FDA and EMA for the treatment of pseudobulbar affect (uncontrollable episodes of crying) in adults with underlying amyotrophic lateral sclerosis or multiple sclerosis. Although the findings of the trial are interesting and seem promising, they have generated considerable discussion, in particular about limitations in the study methodology (last-observation carried forward is not a recommended method for imputing missing data in dementia trials, and bias introduced by the choice of rescue medication, lorazepam) and the funding of the trial by the pharmaceutical industry.[21-23] Moreover, other recently published trials suggest that treatment approaches with already available drugs, such as citalopram, and the management of pain with analgesics may also be effective in reducing agitation in patients with dementia.[24, 25] Currently, psychotropic medications, such as antipsychotics, benzodiazepines, antidepressants, and antiepileptic drugs, are frequently used off-label for the treatment of the neuropsychiatric symptoms of dementia, but they are ineffective in most cases or only have a short-term effect.[26] In addition, they are associated with serious adverse events in older individuals, including falls,[27] cardiovascular and cerebrovascular events,[28] and even death.[29]

Taken together, there is an urgent need for new, effective, and safe pharmacological interventions to diminish the burden of neuropsychiatric symptoms of dementia.

Cannabinoid-based drugs as potential drug candidates for dementia and physical conditions

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).[30] These broad therapeutic applications are due to the pharmacological effects of its bioactive components, the "cannabinoids".[6] Currently, more than 60 different cannabinoids have been identified and isolated from the cannabis plant, with THC and cannabidiol (CBD) being the most studied.[6] 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.[6]

In previous studies, the endocannabinoid system has been proposed as target for the treatment of Alzheimer's disease and dementia-related symptoms.[31-34] 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.[31-34] Moreover, fixed dose, cannabinoid-based drugs have recently become available for medical use. For example, 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.

Although the above-mentioned conditions, such as pain, nausea, and loss of appetite, are very common in older people, preapproval clinical trials of cannabinoid-based drugs excluded old people, especially those with cognitive impairments, from participation or did not include them in sufficient numbers to determine whether they respond differently from younger participants.[35-37] Therefore, it is not possible to directly extrapolate data on the clinical pharmacology of

cannabinoid-based drugs obtained in studies involving young adults to older people.

Why is it important to understand the clinical pharmacology of cannabinoid-based drugs in older people with dementia?

The main goal of clinical pharmacology, as a science, is to understand drug dose-effect relationships in humans. This knowledge is needed to individualize the dose, maximize the therapeutic benefits, and minimize the toxic effects of drugs.[38] However, there is a lack of information in the literature about the clinical pharmacology of cannabinoid-based drugs in older people.

In general, older people with dementia (≥ 65 years) are more vulnerable to adverse drug reactions than healthy older and younger people.[7] This is because they often have multimorbidity[1, 2] and use multiple medications,[1, 2] which increases the risk of drug-drug and drug-disease interactions. Moreover, age-related physiological changes in lean body mass, liver enzyme activities, serum albumin, renal clearance, and dementia-related brain changes (e.g., degeneration of neurons, decreased brain volume and receptors, and dysregulation of neurotransmitters) can lead to altered drug pharmacokinetics and pharmacodynamics. These alterations may increase the sensitivity to the effects of drugs, especially those drugs that act on the central nervous system,[7] such as THC-based drugs. Older people with dementia and multiple comorbidities might benefit greatly from the therapeutic use of THC as a multi-target drug candidate, one drug for several conditions.[3-5] Therefore, there is an urgent need to understand the clinical pharmacology of THC-based drugs in older people before these drugs can be prescribed to frail elderly individuals with dementia and multiple comorbidities.

Main aims of this thesis

The broad mechanisms of action and multiple physiological effects of THC make it a promising drug candidate for older people with dementia and multiple comorbidities. However, the lack of information

in the literature on the pharmacodynamic and pharmacokinetic effects raises questions about the safety and efficacy of oral THC in frail older people with dementia. Therefore, the main aim of the this thesis was to evaluate the pharmacokinetic and pharmacodynamic effects of oral THC in frail older people with dementia.

In the past five years, I worked with Dr. Geke van den Elsen (resident in Geriatric Medicine / researcher) on this project. Dr. van der Elsen mainly focused on the effects of oral THC in the management of dementia-related behavioral disturbances, resulting in her PhD thesis, entitled "Tetrahydrocannabinol in the treatment of neuropsychiatric symptoms in dementia", which she successfully defended in March 2016. As a geriatrician and clinical pharmacologist, I focused mainly on the pharmacokinetic and pharmacodynamic effects of oral THC in frail older people with dementia.

The studies presented in this thesis were performed at the Department of Geriatric Medicine / Alzheimer Center and the Clinical Research Centre Nijmegen of the Radboud University Medical Center, Nijmegen, the Netherlands, and the Department of Psychogeriatric Medicine of the Vincent van Gogh Institute, Venray, the Netherlands. In the clinical trials described in this thesis, Namisol® was used as study medication. Namisol® is a novel THC-based drug formulation (THC ≥ 98%) in tablet form. It was developed using a novel drug delivery technology, Alitra™, to improve the absorption and bioavailability of poorly soluble lipophilic compounds. Both Namisol® and Alitra™ were developed by the Dutch company Echo Pharmaceuticals B.V. (Weesp, the Netherlands). Namisol® has not yet gained marketing approval.

Funding

Our project was supported by a grant from the European Union, the European Fund for Regional Development, and the Dutch province Gelderland (Grant number: 2009-019329), awarded to the consortium of Echo Pharmaceuticals B.V. (Weesp, the Netherlands), the developer of Namisol®, and the Radboud University Medical Center (Nijmegen, the Netherlands). Echo Pharmaceuticals B.V.

had no role in the design of the study, in data collection, analysis, or interpretation, or in the writing of manuscripts and this thesis. None of the research team members or the authors of the articles reported in this thesis have any conflict of interest in relation to the Namisol® project.

Outline of the thesis

PART I General introduction

PART II Cannabinoids in old age and dementia

Little is known about the safety and effectiveness of medicinal cannabis and cannabinoids in older people (≥ 65 years) with dementia. In **Chapter 1**, we summarize and discuss evidence on the effectiveness and safety of medicinal cannabinoids in older people. **Chapter 2** presents an overview of the potential of cannabinoids in the treatment of late-onset Alzheimer's disease and related neuropsychiatric symptoms. We also discuss the efficacy, safety, and pharmacokinetics of cannabinoid-based drugs in older people with dementia.

PART III Efficacy of tetrahydrocannabinol in the treatment of neuro-psychiatric symptoms of dementia

The pharmacological treatment of the neuropsychiatric symptoms of dementia is challenging, because currently available drugs have important drawbacks concerning the benefit-to-risk ratio. In this part of the thesis (**Chapters 3 and 4**), we report the results of two randomized, double-blind, placebo-controlled trials of the effectiveness of oral THC in the treatment of neuropsychiatric symptoms of dementia. We also discuss our findings on the effectiveness of THC for the treatment pain and pain-related behaviors in this frail population.

PART IV Safety, pharmacodynamics, and pharmacokinetics of oral tetrahydrocannabinol

There is a lack of information in the literature on the pharmacodynamic and pharmacokinetic effects of THC-based drugs in older populations. Older people, especially those with cognitive impairment, have often been excluded from or are under-represented in clinical trials. In **Chapters 5 and 6**, we present the results of two clinical studies of the safety, pharmacodynamics, and pharmacokinetics of a novel THC in tablet form, Namisol®. The first study (**Chapter 5**) was a phase 1, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial, in which the safety and pharmacokinetics of three oral doses of THC were evaluated in healthy older people without dementia. In the second study (**Chapter 6**), we evaluated the safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of THC in older people with dementia. We hypothesized that plasma levels of THC would be higher in older people with dementia than in young adults or healthy older individuals without dementia (data from published studies), potentially increasing the pharmacodynamic effects of THC, including its adverse effects.

PART V Pain and pain-related symptoms in dementia

Whereas the majority of patients with dementia still live at home, most studies of pain and pain-related behavioral problems have involved residents of long-term care facilities. Early recognition and adequate treatment of pain in patients with dementia living at home may prevent or reduce pain-related behavioral changes and associated caregiver distress, and subsequently may delay nursing home placement. In this part of the thesis (**Chapters 7 and 8**), we report the prevalence and impact of pain in community-dwelling patients with dementia and the relationship between pain and behavioral and psychological symptoms. We discuss the potential of cannabinoid-based drugs, including THC, as multi-target drug candidates for the treatment of pain and pain-related behavioral and psychological symptoms in patients with dementia.

PART VI Summary

The main findings of the studies are summarized.

PART VII General discussion

Lastly, the main findings are discussed with respect to the literature and recommendations for future research are given.

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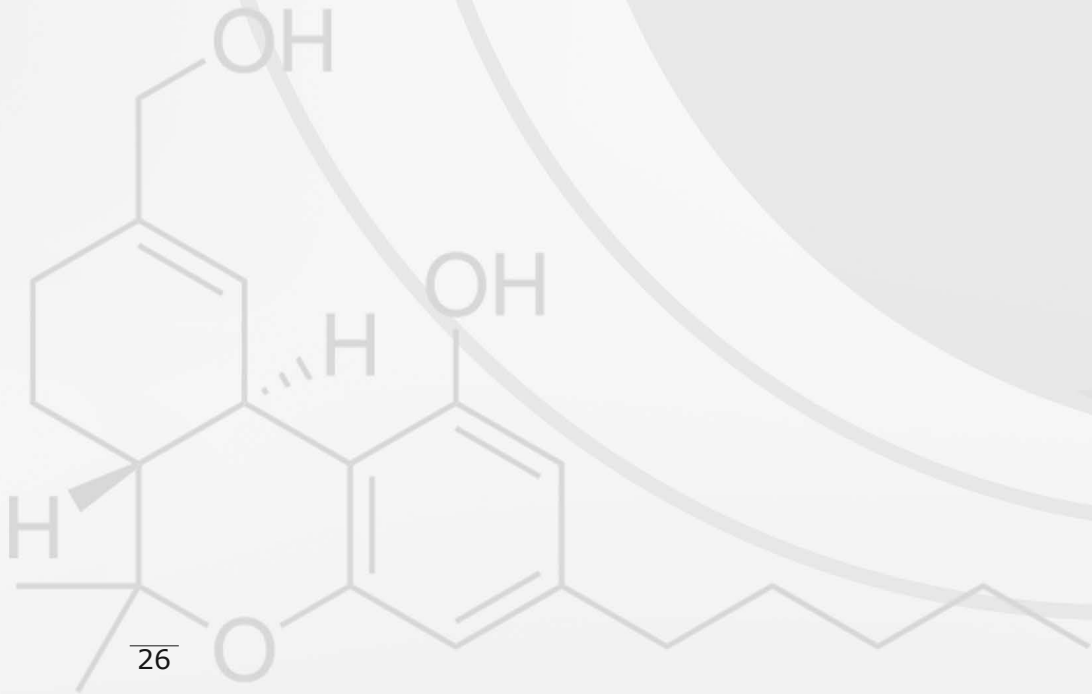
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PART II

Cannabinoids in old age and dementia

Chapter 1

1

Efficacy and safety of medical cannabinoids in older subjects: A systematic review

van den Elsen GA, **Ahmed AI**, Lammers M, Kramers C, Verkes RJ, van der Marck MA, Olde Rikkert MG.

Ageing Research Reviews 2014;14:56-64.

Abstract

This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects.

The literature search was conducted using PubMed, EMBASE, CINAHL and Cochrane Library. We selected controlled trials including solely older subjects (≥65 years) or reporting data on older subgroups. 105 (74%) papers, on controlled intervention trials, reported the inclusion of older subjects. Five studies reported data on older persons separately. These were randomized controlled trials, including in total 267 participants (mean age 47-78 years). Interventions were oral tetrahydro-cannabinol (THC) (n=3) and oral THC combined with cannabidiol (n=2). The studies showed no efficacy on dyskinesia, breathlessness and chemotherapy induced nausea and vomiting. Two studies showed that THC might be useful in treatment of anorexia and behavioral symptoms in dementia. Adverse events were more common during cannabinoid treatment compared to the control treatment, and were most frequently sedation like symptoms.

Although trials studying medical cannabinoids included older subjects, there is a lack of evidence of its use specifically in older patients. Adequately powered trials are needed to assess the efficacy and safety of cannabinoids in older subjects, as the potential symptomatic benefit is especially attractive in this age group.

Introduction

For many centuries the cannabis plant (*Cannabis sativa L.*) has been used worldwide for medical as well as recreational purposes. Possible indications of cannabis, such as cancer pain, cachexia and neuropathic pain, are found in a quickly growing population of older patients. Unfortunately, there are only limited data on the extent of the use of medicinal cannabinoids in older persons. Although international web-based surveys show only a low percentage of older users, in the Dutch setting, more than one third of patients using medicinal cannabis on prescription are over 60 years.[1, 2] On the one hand, this group may highly benefit from medical application of cannabis, because of a greater emphasis on symptomatic and palliative effects of medication, which is directly related to their limited life expectancy. On the other hand, an increased vulnerability of the brain, due to a reduction in cognitive functioning and brain atrophy,[3, 4] and age related changes in pharmacokinetic factors,[5] may result in more severe adverse effects.

Cannabis preparations contain numerous cannabinoids, including delta-9-tetrahydrocannabinol (THC), with psychoactive effects, and cannabidiol (CBD), with neuroprotective, anticonvulsive, antiemetic and anti-inflammatory effects, as the major constituents. These cannabinoids act upon an endogenous cannabinoid system of which two receptors (CB1 and CB2) have been identified.[6, 7] These receptors are mainly located in the central nervous system (CB1 and CB2) and the immune system (CB2).[8, 9]

Several trials studying the efficacy of medical cannabinoids have been conducted, covering a wide range of diseases and conditions, including neuropathic pain, chemotherapy-induced nausea and vomiting and loss of appetite.[10-13] Unfortunately, data on efficacy and safety established in studies with adults cannot simply be extrapolated to the older patient group, due to changes in pharmacokinetic and pharmacodynamic factors associated with increasing age, leading to differences in efficacy and a high risk of developing adverse drug reaction. This can result in drug-related morbidity, hospital admission and mortality.[14, 15] Examples of changes

in pharmacokinetic factors associated with increasing age are a decreased lean body mass, reduction of renal and hepatic clearance and loss of ability to maintain homeostasis.[16, 17] The high prevalence of co-morbidity and related polypharmacy further complicates drug treatment in this population. It is therefore highly relevant to study the effects of medical cannabinoids in older patients separately, before advocating wide spread use.

To date, no review on the efficacy and safety of cannabinoids in older patients has been conducted. Although, the Cochrane Collaboration published a systematic review on cannabinoids in dementia patients,[18] including one small randomized controlled trial (RCT) studying the efficacy of nabilone on anorexia and behavioral disturbances in subjects with severe dementia.[19] In the current systematic review we aimed to provide broader evidence on the safety and efficacy of medical cannabinoids in older subjects, independent of the reasons for prescription or the patients' cognitive status.

Methods

Search strategy

We performed a search of PubMed, EMBASE, CINAHL and Cochrane Library databases up to October 7th 2013 for articles published in English. For PubMed, a comprehensive search was developed, which was adapted to the other databases (see appendices). The search strategy and eligibility criteria were specified in advance and documented in a study protocol. Relevant search term synonyms were determined using Thesaurus and discussion with experts. We used the following terms to determine the subject group: 'aged', 'frail', 'elderly', 'older', 'aging', 'ageing' and 'geriatric'. To determine the intervention we used the terms: 'cannabinoids', 'cannabinoid', 'cannabinol', 'cannabidiol', 'tetrahydrocannabinol', 'marinol', 'cesamet', 'THC', 'CBD', 'sativex', 'nabilone', 'dronabinol', 'delta-9-tetrahydrocannabinol', 'delta-THC', 'cannabis', 'marihuana', 'marijuana' and 'hashish'. The existing clinical query 'Therapy/

Broad' was used in PubMed to select therapeutic studies. Duplicate publications were selected and removed. The final results were ranked alphabetically and received an article specific number.

Eligibility criteria

Two reviewers (GE and ML) conducted the search by independently examining the title and available abstract of each article, in an unblinded manner. Studies were considered for inclusion when they: (1) included exclusively older subjects (defined as ≥ 65 years) or a distinct subgroup of older subjects and provided separate results on this subgroup; (2) studied the efficacy, safety or pharmacokinetics of medical cannabinoids administered by any route, at any dose and for any duration; (3) were prospective, controlled intervention trials and; (4) provided data on efficacy, safety, or pharmacokinetics. Studies were excluded when they (1) included exclusively younger subjects (< 65 years); (2) studied cannabinoids for recreational purposes; (3) studied endocannabinoids or cannabinoid antagonists. Articles that seemed to meet the eligibility criteria based on title or abstract were screened in full text by the same reviewers (GE and ML). In case of disagreement or uncertainty two other researchers (MM and MOR) were consulted to reach consensus. The snowball method was used to manually identify relevant references from the reference lists of included articles.

Data extraction and assessment of methodological quality

A modified Cochrane data extraction sheet was used to extract data from the included articles. Data collection included study design, participant characteristics (including age, gender and number of participants), intervention indication, intervention, outcome measures, results, data on adverse events and pharmacokinetics. The corresponding authors of the included studies were contacted to request details on subject characteristics, study conduct, primary efficacy and safety data, if not sufficiently described in the original articles. When feasible, study analyses were repeated for subjects aged 65 years and older. Additional information was provided by three out of four corresponding authors that were contacted. One

author could not be contacted, as that study was conducted more than 30 years ago.[20] Two corresponding authors provided additional information on study methods, efficacy and safety.[21, 22] One author provided information on study methods, in order to complete the risk of bias table.[19] No primary data from this study could be provided, as these had been discarded years ago.

Quality assessment of all included articles was carried out using a modified Effective Practice and Organization of Care form (EPOC, 2009). This form includes seven criteria for the assessment of risk of bias in individual studies: adequate sequence generation, allocation concealment, introduction of a washout period, incomplete outcome data, blinding, protection against contamination, intention to treat analysis and selective reporting. A consensus-based risk of bias table was constructed.

Data synthesis and analysis

It was not feasible to conduct a meta-analysis, due to the high clinical and methodological diversity. Results of the included studies were therefore analyzed by making qualitative, descriptive summaries.

Results

Selection procedure

The selection procedure is shown in **Figure 1**. The search strategy identified 1676 citations. Adjustment for duplicates left 1296 citations. Of these, 1124 articles were excluded based on screening of title and abstract. 172 full text articles were retrieved and assessed on eligibility. 105 (74%) out of 142 reports of controlled intervention trials studying cannabinoids, included one or more subjects aged ≥ 65 years. Nonetheless, most of these articles did not report data on the older subject group separately. Five studies could be included for analysis as these reported separate data on older subjects.[19-23] The snowball method yielded no further studies.

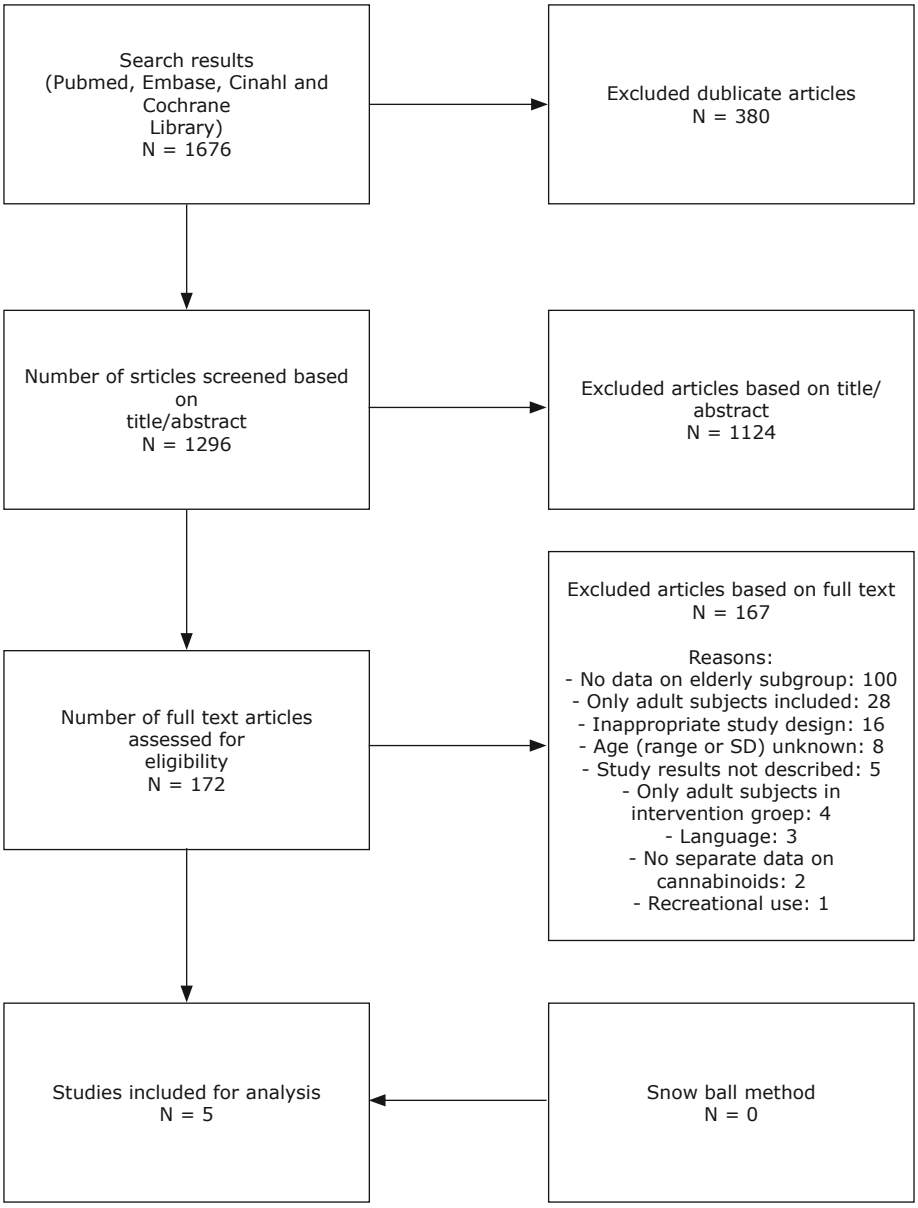

Figure1 Flow diagram of the selection of studies included in this systematic review

Study characteristics

There was a substantial variation in study characteristics among the five included studies, which is outlined in **table 1**. All studies were RCTs with a crossover design, of which one was preceded by an open label dose escalation study.[21] In general, the study sample sizes were small (range 2 to 214 subjects). In total, 267 participants were included of which 262 participants were included in studies' analyses. The mean age of the populations varied from 47 to 78 years. Only two studies assessed the efficacy of medical cannabinoids in an exclusively older (≥ 65 years) population.[19, 22] The three other studies were included in this systematic review as these included older subjects in an open label sub study,[21] reported safety data on an older subgroup,[23] or reported results on efficacy per age group.[20] The interventions existed of THC administered as tablet,[19, 20, 22] and THC in combination with cannabidiol (CBD) administered as tablet,[21] or as sublingual spray.[23] The treatment dosage varied extensively among the included studies, ranging from 2.5 mg,[22] to maximally 62.5 mg of THC daily.[20]

All studies used different outcome measures, linked to the different indications for prescription. Studied indications were anorexia and behavioral disturbances in dementia, dyskinesia in Parkinson's disease, chemotherapy induced nausea and vomiting, and breathlessness in Chronic Obstructive Pulmonary Disease (COPD). The duration of intervention varied from 1 to 42 days per period.

The study from Volicer et al. was the only RCT with more than 10 participants that exclusively included older subjects. Therefore, we report on this study most extensively. This study involved fifteen hospitalized patients with severe Alzheimer's disease, who exhibited food refusal. After baseline measurements, subjects were randomly assigned to dronabinol (THC) 2.5 mg twice daily first or placebo twice daily first. Treatment duration was six weeks, followed directly by the crossover treatment of another six weeks. There was no washout period. Nutritional status was measured by body weight and triceps skin fold thickness (assessed weekly) and plasma albumin and lymphocyte count (assessed at the beginning and end of each

Table 1 Study characteristics of articles reporting on medical application of cannabinoids in older subjects.

Author	Design	Indication	Subjects included (male/ female)	Subjects analyzed (male/ female)	Age in years (range)	Intervention (route)	Dose	Control product (dose)	Duration per cycle (days)	Primary outcomes
Ungerleider et al., 1982	RCT (crossover)	Chemotherapy induced nausea and vomiting in a wide variety of neoplasms	214 (107/107)	214 (107/107)	47 (18-82)	THC (oral/enteral)	7.5 mg to12.5 mg five times daily	Prochlorperazine (10 mg)	≥1	7-point nausea and vomiting score, GIC of appetite and food intake
Volicer et al., 1997	RCT (crossover)	Food refusal and disturbed behavior in Alzheimer's disease	15 (NR/NR)	12 (11/1)	72.7 (65-82)[a]	THC (oral/enteral)	2.5 mg twice daily	Placebo	42	Body weight, skin fold thickness, caloric intake, CMAI, Lawton Observed Affect Scale-Past
Carroll et al., 2004	RCT (crossover) preceded by an open label (OL) study	Levodopa induced dyskinesia in Parkinson's disease	RCT: 19 (12/7) OL: 6 (2/4)	RCT: 17 (10/7)[a] OL: 6 (2/4)	RCT: 67 (51-78) OL: 71 (65-76)	THC:CBD (oral/enteral)	0.034 to 0.25 mg THC/kg daily	Placebo	28	UPDRS Part IV (32-34), UPDRS total score
Pickering et al., 2011	RCT (crossover)	CO_2 induced breathlessness in COPD and healthy subjects	5 patients (NR/NR) 6 healthy controls (NR/NR)	4 patients (2/2) 5 healthy controls (4/1)	Patients: 67 (66-68)[b] Healthy: 58.2 (51-67)[b]	THC:CBD (oral/ sublingual)	2.7:2.5 mg once to four times daily	Placebo	1	Minute ventilation, $PetCO_2$, Visual Analogue Scale
Walther et al., 2011	RCT (crossover)	Agitation in Alzheimer's disease	2 (2/0)	2 (2/0)	78 (75-81)	THC (oral/enteral)	2.5 mg once daily	Placebo	14	NPI, nocturnal motor activity

RCT = randomized controlled trial; OL = open label; GIC = Global Impression of Change; NR = not reported;THC = tetrahydrocannabinol; CBD =cannabidiol; UPDRS IV = Unified Parkinson's Disease Rating Scale, subscale on complications of therapy; COPD = Chronic Obstructive Pulmonary Disease; $PetCO_2$ = end-tidal carbon dioxide pressure; CMAI = Cohen Mansfield Agitation Inventory; NPI = Neuropsychiatric Inventory. [a] Data not reported in study article, but provided by author on request. [b] Data represent the subjects included in the analysis. Baseline age is not reported.

treatment period). Furthermore, behavioral disturbances were measured weekly by Cohen-Mansfield Agitation Inventory (CMAI) and Lawton Observed Affect Scale–Past. In total, eleven subjects completed both treatment periods and were analyzed. One participant died two weeks before completing the study, but was also included in the analysis. The average age was 72.7 years (range 65 to 82 years).

Risk of bias assessment

The risk of bias is reported in **table 2**. This table was finalized after receiving additional information by the corresponding authors.19, 20, 22 Four out of five included studies showed a moderate to high risk of bias in several relevant domains. The study of Volicer et al. was judged to have a high risk of bias. Although the researchers used a random number table for sequence generation, the only person who had access to this table, was also involved in outcome assessment, leading to a bias in allocation concealment and blind assessment of outcomes. Furthermore, no washout period was introduced between the treatment periods, causing a significant risk of carry over effect.

Efficacy

It was not feasible to report summary outcome measures as most studies did not report means and standard deviations per treatment group or study samples were too small to provide a reliable effect size.

THC did not improve chemotherapy related nausea and vomiting,[20] compared to prochlorperazine. In this study, different age groups were compared, but the efficacy on nausea reduction did not differ significantly between groups ($\chi 2 = 2.13$, NS). Furthermore, treatment with THC combined with CBD did not result in a statistical significant improvement of breathlessness in COPD (Pickering et al., 2011) or dyskinesia in Parkinson's disease,[21] compared to placebo. We reanalyzed the primary data on UPDRS total score from *Carroll* et al., including only subjects aged 65 years and older (n=12). This did not result in a significant difference between the treatment arms

Table 2 Risk of bias in the five studies reporting on medical application of cannabinoids in older subjects.

	Adequate sequence generation	Allocation concealment	Washout period introduced	Incomplete outcome data addressed	Blinded outcome assessment	Adequate protection against contamination	Intention to treat analysis	Free of selective reporting
Ungerleider et al., 1982	+	+	+	+	?	-	-	+
Volicer et al., 1997	+*	-*	-	-	-*	-	-	+
Carroll et al., 2004	+	+	+	+	+	+	+	+
Pickering et al., 2011	+	?	+	-	-	-	-	+
Walther et al., 2011	+*	+*	-	+*	+*	-	-	+*

+, yes; -, no; ?, unclear/not reported
* Data not reported in the article, but provided by author on request.

(p=0.27 for total UPDRS before levodopa challenge and p=0.86 for total UPDRS after levodopa challenge).

One study on the efficacy of THC in two patients with Alzheimer's disease showed a decline in nighttime motor activity, measured by wrist actigraphy in one male subject until the third week of treatment.[22] This subject received dronabinol for two weeks, followed by placebo. There was no washout period. Behavioral disturbances declined during the entire 4 week study period, as measured with the Neuropsychiatric Inventory. In the other subject, who received placebo first, nighttime motor activity reduced only during the first week of dronabinol treatment and increased again in the second

week. Behavioral disturbances declined during placebo treatment, but increased again on the first week of dronabinol. The provided primary efficacy data did not allow for statistical analysis, due to the very small sample size.

The publication from *Volicer* and colleagues reported an increase in body weight during the study period of 12 weeks, regardless of the order of treatment. Weight gain was greater for subjects who received dronabinol first. In the first 6-week treatment period subjects receiving dronabinol gained 7.0±1.5 lb compared to 4.6±1.3 lb in subjects receiving placebo. Caloric intake was not changed. Triceps skin fold thickness seemed to increase during the total study period, but was not affected by treatment or order of treatment. Disturbed behavior, as measured with CMAI, decreased during both dronabinol periods and this decrease persisted during the placebo period following dronabinol. Positive affect remained similar during both treatments, while negative affect decreased over the 12 week study period, and more while subjects received dronabinol, compared to placebo. The authors of this study concluded that dronabinol might be useful in the treatment of anorexia and disturbed behavior in patients with dementia. P-values or confidence intervals were not reported, nor were means and standard deviations of the results from secondary outcome measures.

Safety

The results on adverse effects are reported in **table 3**. Two RCTs reported data on adverse events for the total group of participants, including those younger than 65 years. On request, *Carroll* provided safety data per subject in the open label phase, which are added to **table 3**. Overall, adverse events were inconsistently assessed and it was not clear whether these events represent a clinically relevant change. Therefore, we only report the most frequently reported adverse events.

Overall, cannabinoid treatment resulted in more adverse effects than placebo or prochlorperazine (266 vs. 133).19-21, 23 Symptoms of sedation/drowsiness were most frequently reported in the cannabinoid group. One study only assessed the occurrence

of severe adverse events, due to the lack of reliable reporting of adverse events by subjects with severe cognitive disorder.[2]2 In the study with five COPD patients and six healthy controls, two older COPD subjects developed cardiac arrhythmias (Wenckebach block phenomenon and ventricular tachycardia) after receiving 2.7 mg/2.5 mg and 8.1 mg/7.5 mg THC/CBD, respectively.[23] Another older subject with COPD developed symptoms of mild intoxication after 5.4 mg/5 mg THC/CBD, which was not further clarified. This subject was unable to continue the measurements. None of the studies reported cannabinoid related severe adverse effects, although one subject developed a grand mal seizure after first administration of 2.5 mg dronabinol and was withdrawn.[19] The authors stated that it was not clear whether this event was related to dronabinol or progression of Alzheimer's disease. Despite the lack of anticonvulsant treatment, the seizure did not recur. This subject died two months after the event of causes unrelated to study participation.

Pharmacokinetics

One study, with subjects between 51 and 78 years of age receiving oral THC:CBD (0.034–0.25 mg THC/kg), collected blood samples for pharmacokinetic data.[21] The maximum concentration (C_{max}) of THC was reached within 2 h after ingestion of cannabis extract in most patients. C_{max} varied from 0.25 to 5.4 ng/mL THC. There was no clear dose response. In subjects taking the same dose of THC:CBD, a wide variability in blood concentration was seen. No pharmacokinetic data was presented separately for subjects ≥ 65 years.

Discussion

Principal findings and previous literature

This systematic review aimed to evaluate study participation, intervention indications, efficacy and safety of medical cannabinoids in older subjects. The age ranges of subjects described in the papers suggest that elderly are indeed included in research studying medical

Table 3 Results on safety on medical application of cannabinoids in older subjects

Study	N	Intervention	Most frequent reported AEs in number of subjects (cannabinoid vs. control)	**Severe AEs**	**Drop outs (total)**	**Drop outs during cannabinoid treatment**
Ungerleider et al., 1982	214	Oral THC 7.5 mg to12.5 mg five times daily.	Sedation (78 vs. 56, p<0.01)[b] Physiological (62 vs. 24, p<0.01)[c] Psychological (59 vs. 10, p<0.01)[d]	?	75	?[g]
Volicer et al., 1997[a]	12	Oral THC 2.5 mg twice daily.	Anxiety/nervousness (11 vs. 12)[e] Emotional liability (11 vs. 10)[e] Tiredness (9 vs. 5)[e] Somnolence (8 vs. 4)[e] Euphoria (7 vs. 5)[e]	1 grand mal seizure	1	1[h]
Carroll et al. 2004, OL[a]	6	Oral THC:CBD mean achieved daily dose 0.17 mg/kg/day THC. 4/6 subjects did not reach their weight-adjusted target dose THC, due to adverse events, followed by dose adjustment or discontinuation.	Balance disorder (5)[f] Gastro-intestinal disorder (4)[f] Blurred vision (4)[f] Muscle weakness (4)[f]	0	2	2
Carroll et al., 2004, RCT	17	Oral THC:CBD mean dose 0.146 mg/kg daily (0.034 to 0.25). 11/17 subjects did not reach their weight-adjusted target dose THC, due to adverse events, followed by dose adjustment, compared to 9/17 on placebo.	Drowsy/lethargic (9 vs. 6). Detached (4 vs. 0). Dry mouth (4 vs. 1).	0	2	0
Pickering et al., 2011	9	Sublingual THC:CBD 2.7/2.5 mg once to four times daily.	Cardiac arrhythmia (2 vs. 0) Mild intoxication (1 vs. 0) Drowsiness (1 vs. 0)	0	3	3
Walther et al., 2011[a]	2	Oral THC 2.5 mg once daily.	NA	0	0	0

NA = not assessed
[a] results represent an exclusively older subject group.
[b] symptoms grouped as 'sedation' included sleepiness, relaxed, or sluggish.
[c] symptoms grouped as 'physiological' included dizziness, headache, dry mouth, tachycardia, chills or increased pain.
[d] symptoms grouped as 'psychological' included mental clouding, space/time distortion, short-term memory loss or dissociative reaction.
[e] frequency represents the number of reports
[f] data not reported in the article, but provided by the corresponding author on request.
[g] at least two subjects discontinued the study because of dysphoria related to THC. The reasons for overall discontinuation were similar among the two intervention groups
[h] one subject developed a grand mal seizure after first administration of 2.5 mg THC and dropped out.

cannabinoids for several indications. However, separate data on the older subgroup are very rare. The five studies that did report on older subjects showed no efficacy on dyskinesia, breathlessness (versus placebo) and chemotherapy induced nausea and vomiting (versus prochlorperazine). Studies on oral THC in symptomatic treatment of behavioral problems in dementia did not prove efficacy, because of the small sizes and overall low to moderate methodological quality.

Overall, despite the relatively low doses used in the included studies, adverse events were more frequently reported during cannabinoid treatment than during treatment with the control product, especially concerning sedation-like symptoms, as drowsiness, tiredness and somnolence. This is in line with the results of a systematic review on 31 studies on medical cannabinoids in adult subjects, reporting nervous system disorders as the most frequently occurring adverse events (36.7% in RCTs, 39.7% in observational studies), including dizziness, somnolence and sedation.[24] This finding could be of major clinical importance in older patients, as these adverse events may lead to an increased risk of falls, especially when administering higher doses cannabinoids, as THC is known to cause a dose dependent increase in adverse events.[25] In the previous systematic review from Wang et al., the rate of serious adverse events did not differ significantly between cannabinoid group and controls (RR 1.04, 95%CI 0.78–1.39). In our own review, we only found one serious adverse event; the development of a grand mal seizure in an older subject with Alzheimer's disease, directly after receiving 2.5 mg dronabinol.[19]

From previous literature, it is not clear whether cannabinoids induce seizures. Animal studies even suggest that cannabinoid agonists may actually have an anti-epileptic effect,[26-28] while CB1 receptor antagonists lower the seizure threshold.[29] Unfortunately, a possible anti-epileptic effect of cannabinoids could not be demonstrated in human studies.[30] In the light of the current preliminary literature status, caution is needed when prescribing cannabinoids to patients with a history of seizures or to patients with structural brain lesions.

Our search also included one study that reported the occurrence of cardiac arrhythmias in two older subjects with COPD after administration of sublingual THC and CBD combined.[23] Cannabinoids may influence the cardiovascular system, mainly by increasing heart rate.[25, 31, 32] This effect is probably caused by direct CB1 receptor agonism in cardiac tissue, independent of catecholaminergic activity.[33] To our knowledge, no systematically collected data are available on oral cannabinoids and cardiac arrhythmias, except for some case reports describing the occurrence of ventricular fibrillation and paroxysmal atrial fibrillation after smoking marijuana.[34, 35] Taken together, physicians should be reluctant to prescribe medical cannabinoids to (older) patients with a history of severe cardiovascular disease or significant arrhythmia.

Only one study included in our review evaluated the pharmacokinetics of THC in a relatively older subject group.[21] This study showed a high inter-individual variability in various parameters, consistent with data from young adult subjects, which also showed a high variation in t_{max} and C_{max}.[25, 36-38] One must keep in mind that the pharmacokinetic profile of THC is highly dependent on the route of administration. As compared to inhalation, oral and sublingual administration of THC is characterized by a slower absorption, a more extensive first pass effect and a lower rate of drug delivery to the brain, probably resulting in fewer and delayed adverse effects.[31, 37] Remarkably, oral administration results in relatively high plasma concentrations of the metabolite 11-OH-THC, which in turn contributes to psycho-active symptoms.[25] Ageing also affects several relevant pharmacokinetic parameters, such as reduced hepatic clearance, because of an decrease in liver mass and hepatic blood flow,[5] which might increase the bioavailability of THC. On the other hand, ageing might also lead to a higher volume of distribution, a prolongation in half life and lower C_{max}, due to a relative increase in body fat. Exploratory findings from the current systematic review provide too little information to confirm these expected changes in pharmacokinetics of THC in older persons. Direct comparative studies in young versus old subjects are therefore most necessary.

Strengths and weaknesses of the review

This study is the first systematic review on medical cannabinoids in older subjects. It was developed and executed according the Cochrane Collaboration guidelines,[39] using a selection procedure based on strict eligibility criteria and resulting in five controlled clinical trials.

Our search strategy yielded also three open label studies on the efficacy of cannabinoids in older persons.[40-42] All showed positive effects of cannabinoids on behavioral disturbances in dementia, anorexia in long term care residents and psychotic symptoms in Parkinson's disease, respectively. None reported cannabinoid related adverse effects. The absence of a control product and blind assessments, however, might have led to an overestimation of the efficacy of the intervention, which was the main reason not to include these studies in our analysis.

Although only prospective and controlled intervention trials were included for analysis in this review, four out of five included trials still had a moderate to high risk of bias. This raises the question whether these studies are methodologically deficient and could just have been performed better, or whether research on these frail subjects is too difficult and complex in practice to meet the high quality methodological criteria. This is an important and general paradox in the quest for high quality evidence in frail older subjects: the methods needed for high quality evidence are often themselves interventions these subjects can no longer stand or comply to. It is therefore highly relevant to carefully adapt the study methods (including design, inclusion criteria and outcome measures) to the frailty of the target population.

This review addresses the upcoming interest in the use of medical cannabinoids in the older patient. There is a growing number of countries permitting the use of medicinal cannabinoids, including 18 states in the USA.[2, 43] Furthermore, a recent poll among readers from New England Journal of Medicine, showed that a vast majority (76%) of clinicians from a wide variety of countries worldwide would recommend the use of marijuana in a 68-year old woman

with metastatic breast cancer, suffering from pain and nausea. Many responders called for more research on this topic to create a stronger basis of evidence.[44] As such, this review points at an important problem, namely the under-representation of older subjects in clinical studies and study reports on the medical use of cannabinoids. This under-representation of elder participants is however not per se linked to cannabinoids as a treatment intervention, but is also seen in other medical fields, like oncology and cardiovascular medicine.[45, 46] Therefore, it is out most important to include a significant number of older subjects in trials on medical cannabinoids, to be able to draw firmer conclusions to support clinical decisions.

The present study was not without shortcomings. First, we aimed to subtract data on medical cannabinoids exclusively in older subjects. As a consequence, we were not able to answer the question whether there is an effect of age on the efficacy and safety of medical cannabinoids. Hence, this would be an important objective for future research in medical cannabinoids. Second, it was not possible to provide reliable summary measures (e.g. effect sizes) based on the data reported in the original studies. This was caused by three major factors; a high heterogeneity among the included studies, the absence of reported means and standard deviations per treatment group, and the generally very small sample sizes. Therefore, only qualitative and descriptive summaries could be provided.

Conclusions and implications

With the growing number of older patients, there is an urgent need for evidence based therapeutic interventions in this group. Many studies have been conducted on the efficacy and safety of medical cannabinoids in a variety of conditions in adult patients, and in a substantial number of studies, older subjects were included. Nevertheless, our review shows that there is a lack of evidence concerning the use of cannabinoids specifically in older patients, resulting in scarcity of data to guide treatment decisions. Adequately powered trials are needed to assess the efficacy and safety of cannabinoids in older subjects, including a critical evaluation of the

risk-benefit ratio, as the potential symptomatic benefits might be attractive for elderly with specific complaints and limited lifespan expectancy. It is highly worthwhile to conduct well designed studies on the efficacy of cannabinoids in symptom management in dementia, given the initial positive results on weight loss and agitation in this patient population, and the great lack of other effective and safe strategies in this field.

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SUPPLEMENTARY MATERIAL

Appendix 1 – PubMed search strategy

01. Cannabinoids [MeSH Terms]
02. Cannabinoids [tiab]
03. Cannabinoid [tiab]
04. Cannabinol [tiab]
05. Cannabidiol [tiab]
06. Tetrahydrocannabinol [tiab]
07. THC [tiab]
08. CBD [tiab]
09. Marinol [tiab]
10. Cesamet [tiab]
11. Sativex [tiab]
12. Nabilone [tiab]
13. Dronabinol [tiab]
14. Delta-9-tetrahydrocannabinol [tiab]
15. Delta-9-THC [tiab]
16. Cannabis [tiab]
17. Marihuana [tiab]
18. Marijuana [tiab]
19. Hashish [tiab]
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. Aged [MeSH]
22. Frail [tiab]
23. Elderly [tiab]
24. Elder [tiab]
25. Older [tiab]
26. Aging [tiab]
27. Ageing [tiab]
28. Geriatric* [tiab]
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Clinical Query: Therapy/broad = ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial [Publication Type] OR random *[Title/Abstract]

OR random allocation [MeSH Terms] OR therapeutic use [MeSH Subheading])
31. 20 and 29 and 30
32. Limit 31 to English languag

Appendix 2 – EMBASE search strategy

01. (cannabinoids or cannabinoid or cannabinol or cannabidiol or tetrahydrocannabinol or THC or CBD or marinol or cesamet or sativex or nabilone or dronabinol or delta-9 tetrahydrocannabinol or delta-THC or cannabinol or marihuana or marijuana or hashish or cannabis).ti,ab.
02. exp cannabinoid/
03. (frail or elder or older or elderly or aging or geriatric*).ti,ab.
04. aged/
05. 3 or 4
06. 1 or 2
07. 5 and 6
08. exp "clinical trial (topic)"/
09. exp randomization/
10. exp clinical trial/
11. ((clinical and trial) or random*).ti,ab.
12. 8 or 9 or 10 or 11
13. exp drug therapy/
14. 12 or 13
15. 7 and 14
16. limit 15 to English language

Appendix 3 – CINAHL search strategy

01. TI (cannabinoids OR cannabinoid OR cannabinol OR tetrahydrocannabinol OR THC OR CBD OR marinol OR cesamet OR sativex OR nabilone OR dronabinol OR delta-9 tetrahydrocannabinol OR delta-THC OR cannabinol OR cannabidiol OR marihuana OR marijuana OR hashish OR cannabis)
02. AB (cannabinoids OR cannabinoids OR cannabinol OR tetrahydrocannabinol OR THC OR CBD OR marinol OR

cesamet OR sativex OR nabilone OR dronabinol OR delta-9 tetrahydrocannabinol OR delta-THC OR cannabinol OR cannabidiol OR marihuana OR marijuana OR hashish OR cannabis)

03. 01 or 02
04. (MH "Cannabis")
05. 03 or 04
06. TI (frail OR elderly OR elder OR older OR aging OR geriatric*)
07. AB (frail OR elderly OR elder OR older OR aging OR geriatric*)
08. 06 or 07
09. (MH "Aged+")
10. 08 or 09
11. 05 and 10
12. (MH "Drug Therapy+")
13. (MH "Clinical Trials+")
14. TI (clinical and trial)
15. TI (random*)
16. 14 or 15
17. AB (clinical and trial)
18. AB (random*)
19. 17 or 18
20. 16 or 19
21. (MH "Random Assignment")
22. 12 or 13 or 20 or 21
23. 11 and 22

Appendix 4 - Cochrane Library search strategy

01. Cannabis
02. Cannabinoid*
03. 01 or 02
04. Elderly
05. 03 and 04

Chapter 2

Cannabinoids in late-onset Alzheimer's disease

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Clinical Pharmacology & Therapeutics 2015;97(6):597-606.

Abstract

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 non-demented

counterparts,[2] 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 multi-target 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 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.[8] 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, multi-causal 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 $A\beta_{1-42}$ and $A\beta_{1-40}$) 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 neuro-inflammation 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 pro-inflammatory 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 defolding.[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-Daspartate 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 $A\beta_{1-42}$ 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 $A\beta_{1-42}$ 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.[18] 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.[19] 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.[19] 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.[19,20]

It is important to note that because the neuropathology of LOAD involves multiple hallmarks, it is reasonable to assume that a treatment 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.[21] 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.[22] Moreover, they are associated with more rapid dementia progression and higher health care costs.[23,24]

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.[24] 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.[25] 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).[26]

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.[27] Moreover, they are associated with serious adverse events in older individuals, including falls,[28] cardiovascular and cerebrovascular events,[29] and even death.[30]

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.[3–5] 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).[31] These broad therapeutic applications are due to the pharmacological effects of its bioactive components, the "cannabinoids."[32] 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.[32]

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.[32] 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 Narachidonoylethanolamine (anandamide) and 2arachidonoylglycerol, and enzymes (e.g., fatty acid amide hydrolase and monoglyceride lipase) involved in the synthesis and degradation of these endocannabinoids.[33] Cannabinoids bind to the cannabinoid receptors CB1 and CB2, both of which are G protein-coupled receptors.[34–36] 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.[34–36] 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 vannilloid-1 channels, acetylcholine, dopamine, serotonin, gamma-

aminobutyric acid, glutamate, norepinephrine, prostaglandins, and opioid peptides.[37] This broad interaction reflects the potential of cannabinoids and the endocannabinoid system as multitarget drug candidates for LOAD.[4]

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.[38] 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.[39]

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 Narachidonoyl-(2-methyl-4-hydroxyphenyl) amine, which suggests that early pharmacological

enhancement of brain cannabinoid levels may protect against Aβ neurotoxicity.[53]

Ramírez 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 HU210, 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(APP1) 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.[58] Moreover, CBD promoted the survival of SHSY5Y(APP1) 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 $A\beta_{1-42}$, but not those of $A\beta_{1-40}$, 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 review[62] 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 euphoria.[64]

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 discontinuedbecause 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 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

Table 1 Studies published on cannabinoid-based drugs in patients suffering from behavioral disturbances in dementia

Study	Subjects / age	Study design	Studied indication	Drug / Dosage	Treatment duration	Results	
						Efficacy	Safety
Volicer[64] (1997) USA	12 AD (11 men, 1 woman) Mean age 72.7±4.9 (range: 65-82)	RCT	Food refusal and disturbed behavior	Dronabinol (THC) 2.5 mg twice/day	12 wk (6 wk THC and 6 wk placebo)	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.
Walther[65] (2006) Germany	6 (5 AD and 1 VaD*) (2 men, 4 women), Mean age 81.5±6.1	Open-label	Nocturnal motor activity	Dronabinol (THC) 2.5 mg/day	2 wk	Compared to baseline, THC significantly reduced nocturnal motor activity and agitation.	No adverse events were observed.
Walther[66] (2011) Switzerland	2 LOAD A) 75-year-old man B) 81-year-old man	RCT	Agitation and circadian disturbances	Dronabinol (THC) 2.5 mg/day	4 wk (2 wk THC and 2 wk placebo)	THC reduced night time activity and strengthened circadian rhythms.	No adverse events were observed.
Woodward[67] (2014) USA	40 (12 men, 28 women) 13 AD 7 VaD 15 AD/VaD 1 FTD 4 Dementia not otherwise specified Age was not reported	Retrospective systematic chart review	Behavioral or appetite disturbances	Dronabinol (THC) Mean dose 7.03 mg/day	Mean duration: 16.88 d (range 4-50 d)	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).

AD, Alzheimer's disease; FTD, frontotemporal dementia; LOAD, late-onset Alzheimer's disease; RCT, randomized controlled trial; THC, tetrahydrocannabinol; VaD, vascular dementia.

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 purposes[68]; 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.

Hazekamp 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 blockaded 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 cannabinoidbased 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.[5,71] *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_{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.[74]

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_{max} was reached within 120 minutes, the geometric mean THC C_{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).[71] 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,[80] 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_{max} (t_{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_{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_{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 (*vitro*, *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 cannabinoids as a therapeutic approach to LOAD and other comorbidities in older

people. However, the lack of population-based studies justifies further research, and especially adequately powered randomized controlled trials, in order to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of cannabinoid-based drugs in this frail population.

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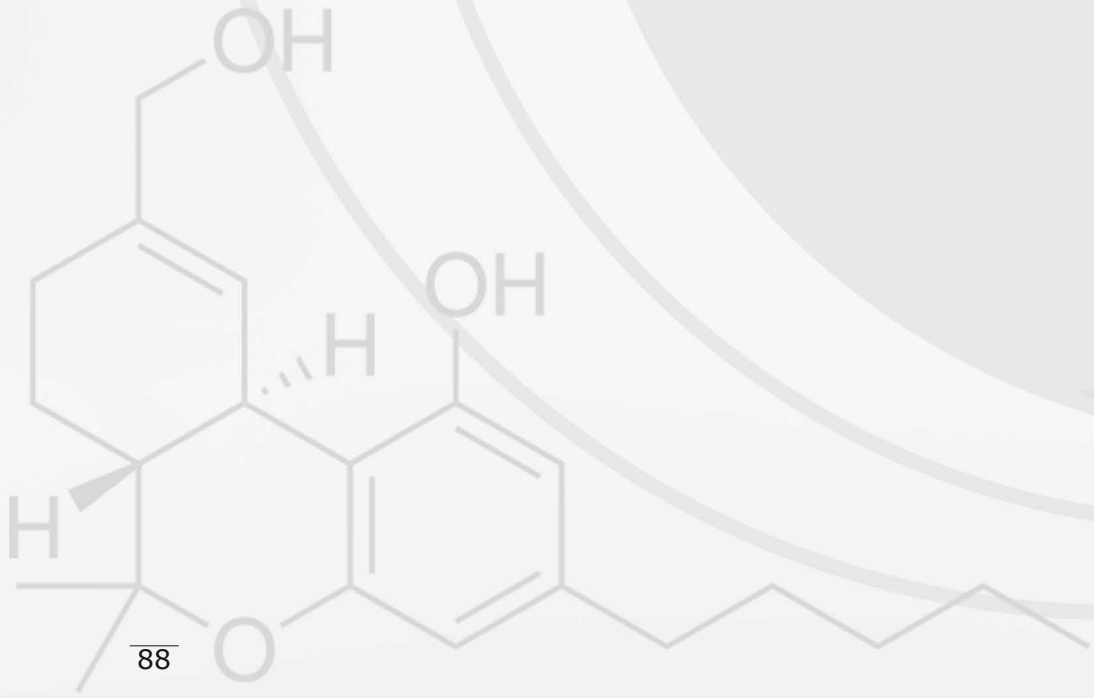
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PART III

Efficacy of tetrahydrocannabinol in the treatment of neuropsychiatric symptoms of dementia

Chapter 3

Tetrahydrocannabinol in behavioral disturbances in dementia: A crossover randomized controlled trial

van den Elsen GA, **Ahmed AI**, Verkes RJ, Feuth T, van der Marck MA, Olde Rikkert MG.

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Abstract

Objectives: Neuropsychiatric symptoms (NPS) are highly prevalent in dementia, while effective pharmacotherapy without important side-effects is lacking. This study aims to assess the efficacy and safety of oral tetrahydrocannabinol (THC) in the treatment of NPS in dementia.

Design: Randomized, double-blind, placebo-controlled, repeated crossover trial, consisting of six treatment blocks of two weeks each.

Setting: Two hospital sites in The Netherlands, September 2011 to December 2013.

Participants: Patients with dementia and clinically relevant NPS.

Intervention: Within each block THC (0.75 mg twice daily in block 1–3 and 1.5 mg twice daily in block 4–6) and placebo were administered in random order for three consecutive days, followed by four-day washout.

Measurements: Primary outcome was change in Neuropsychiatric Inventory score (NPI). Analyses were performed intention-to-treat. Data from all subjects were used without imputation. Sample size required for a power of 80% was 20 patients, because of repeated crossover.

Results: Twenty-two patients [15 men, mean age 76.4 (5.3) years] were included, of whom 20 (91%) completed the trial. THC did not reduce NPI compared to placebo (block 1–3: 1.8, 97.5% CI -2.1 to 5.8; block 4–6: -2.8, 97.5% CI -7.4 to 1.8). THC was well tolerated, as assessed by adverse event monitoring, vital signs and mobility. The incidence of adverse events was similar between treatment groups. Four non-related serious adverse events occurred.

Conclusions: This is the largest randomized controlled trial studying the efficacy of THC for NPS, to date. Oral THC did not reduce NPS in dementia, but was well tolerated by these vulnerable patients, supporting future higher dosing studies.

Introduction

Nearly all patients with dementia experience behavioral and psychological symptoms throughout the course of the disease, including agitation, delusions and aberrant motor behavior.[1] These neuropsychiatric symptoms (NPS) result in a reduction in quality of life and cognitive functioning, are distressing to caregivers and lead to early institutionalization of patients.[2-5] Agitation, on which a recent consensus definition has been developed,[6] is one of the most prevalent dementia-related NPS.[7] Agitated behavior and aggression are commonly treated with antipsychotic agents. In Dutch nursing homes, these are the most frequently prescribed psychotropic drugs in dementia patients.[8] Unfortunately, benefits of their use are mostly limited,[9] while adverse effects are harmful, including stroke and increased mortality risk.[10] Other frequently used psychotropic drugs, such as antidepressants, anti-epileptic drugs and benzodiazepines, also have limited effects and serious side effects in frail dementia patients.[11] Citalopram, for example, is often used in clinical dementia practice to reduce agitation. High doses have indeed been shown effective, yet, the practical application is limited by significant cardiac adverse effects, resulting in a clinically significant prolongation of the QTc interval, compared to placebo [difference QTc adjusted for baseline value: 18.1 ms (6.1 to 30.1), p=0.01].[12] This highlights the need for alternative pharmacological interventions with an improved benefit-to-risk ratio.

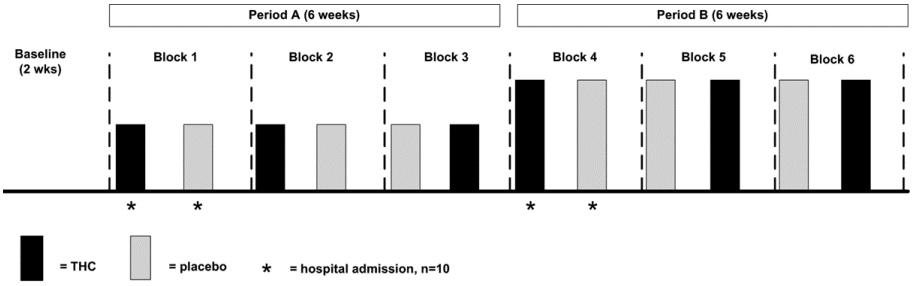
Medical cannabinoids might be such an alternative. Indeed, preliminary studies with oral tetrahydrocannabinol (THC) indicated improvement in agitated behavior and nocturnal motor activity in patients with Alzheimer's disease.[13, 14] Nonetheless, THC may also cause relevant side-effects, such as dizziness and sedation,[15] although data on safety in older patients are lacking.[16] Therefore, in this randomized controlled trial, we aimed to study the efficacy and safety of relatively low doses oral THC on NPS, with a focus on agitation and aggression, in patients with dementia.

Methods

Study design

This was a multicenter, phase II, repeated crossover, randomized, double-blind, placebo-controlled trial, conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and International conference on Harmonisation guidelines and registered at www.clinicaltrials.org (NCT01302340). The study took place at the Alzheimer Centre of the Radboud university medical center (Radboudumc, Nijmegen, The Netherlands) and the Vincent van Gogh Institute (Venray, The Netherlands), between September 2011 and December 2013. It was approved by the certified ethics committee of Radboudumc. Written informed consent was provided before screening by the patient and closest proxy; the first only in case the patient was judged capable to consent. Patients were assessed at baseline, approximately two weeks before start of study medication. Actual study duration was 12 weeks, including two treatment periods of three blocks each (**Figure 1**). In treatment period A (block 1–3), low dose THC treatment of 0.75 mg twice daily was alternated by placebo. The dosage was increased to 1.5 mg THC twice daily in period B (block 4–6). Each block contained two drug periods: THC for three consecutive days, followed by placebo (or vice versa) and separated by a four-day-washout period. As the pharmacodynamic effects of oral THC occurred within 1–2 hours after administration in a previous phase I study,[17] a study period of three days was expected to be sufficient to evaluate the acute effects of THC on behavior. The duration of the washout period of four days was determined based on the terminal half lives of THC (mean 71.9 min) and its active metabolite 11-OH-THC (mean 196 min) after oral administration of 5 mg THC in the same study.[17]

The current crossover study was followed by an optional open label extension phase of six months to assess long-term tolerability and safety, of which the methods and results are reported in the Appendix and **Appendix Table 1**.



Allocation to THC and placebo was randomized per block. Therefore, this schematic overview represents an example of treatment allocations. Period A: 0.75 mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period. Period B: 1.5 mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period

Figure 1 Schematic overview of study design

Changes to study design

Initially, patients were admitted to the hospital during the three intervention days of block 1 and 4, for safety evaluation. The burden of these admissions was however the main reason that patients declined participation. After inclusion of the first 10 patients ('hospital admission group'), the intervention was judged to be safe by the researchers. Therefore, the study protocol was amended, omitting the hospital admissions, which was approved by the ethical committee. In the revised protocol ('ambulatory group'), admissions were replaced by a five-hour day clinic visit (day 1), follow-up phone call (day 2) and home visit (day 3), while safety could still be closely monitored.

Patient eligibility

Patients diagnosed with dementia type Alzheimer, vascular or mixed, according to the NINCDS–ADRA,[18] or NINCDS-AIREN,[19] criteria were eligible for participation if they suffered from clinically relevant neuropsychiatric symptoms [Neuropsychiatric Inventory (NPI) score ≥ 10], with at least agitation or aggression. An informal caregiver had to be available. Initially, patients with mild to moderate

dementia were included [Clinical Dementia Rating Scale (CDR) 0.5–2]. After inclusion of 10 patients, this criterion was broadened to also include patients with severe cognitive disorders (CDR 2–3).
Exclusion criteria were: major psychiatric disorder, severe or instable concomitant illness necessitating treatment changes, frequent falling due to orthostatic hypotension, and a history of alcohol or drug abuse. Patients using tricyclic antidepressants and opioids were excluded. Additionally, as THC is metabolized in the liver through the cytochrome P–450 enzymes (CYP): CYP2C9, CYP2C19 and CYP3A4, patients using drugs from a predesigned list of inhibitors of these enzymes were excluded. Use of concomitant psychotropic medication was allowed.

Intervention and randomization

Active treatment consisted of 0.75 mg and 1.5 mg THC in tablet form (Namisol®, Echo Pharmaceuticals B.V., Weesp, the Netherlands). These dosages were chosen relatively low, based on the positive results of previous preliminary trials using dronabinol,[13,14] in combination with the lack of experience concerning Namisol® in a frail patient group, complying to the generally guiding principle in pharmacological interventions in older patients, namely 'to start low, and go slow'. Placebo tablets were matched to the active treatment for weight, taste, color and size. Patients' caregivers were asked to administer the tablets daily (with the exception of hospital admissions). Study medication was administered at 10 a.m. and 4 p.m., because NPS often occur later on the day, when fatigue and external signals increasingly interfere. The order of administration of THC and placebo was randomized (1:1) per block. Randomization was performed by the Radboudumc pharmacy according to a computer-generated randomization list. The allocation sequence was strictly concealed from participants, caregivers, investigators and all other personnel directly involved in the study. Treatment allocations were not made available until study completion and database lock.

Outcomes

Primary outcome measure

The primary outcome was change in NPS, as measured by NPI.[20] This questionnaire is frequently used to assess neuropsychiatric psychopathology in interventional studies in dementia and sensitive to detect clinical improvement in agitated behavior.[21] It evaluates 12 behavioral domains of which the frequency and severity of NPS are scored by a caregiver. This results in a final score ranging from 0 to 144 (a higher score indicating greater impairment). The 4–point frequency scale was slightly modified to make it suitable for weekly assessment. NPI was assessed at baseline and every third treatment day, resulting in two NPI scores per block.

Secondary outcome measures

Weekly secondary efficacy assessments included Cohen-Mansfield Agitation Inventory (CMAI), a 29-item observation instrument for assessment of agitated behavior[22] and Zarit Burden Interview (ZBI), a 22-item questionnaire to assess caregiver burden.[23]

Safety assessments

Adverse events

Adverse events (AEs) were solicited from patients and their caregivers at all study visits, using open questions and clinical observations. All reports of AEs were recorded, whether or not they were deemed to be related to study treatment. AEs were coded following the classification of Medical Dictionary for Regulatory Activities (MedRA). An AE was defined as serious adverse event (SAE) if it was fatal or life-threatening, required (prolonged) hospitalization, or resulted in persistent or significant disability or incapacity.

Mobility assessments

Influence of study medication on balance and gait was assessed using two functional mobility tests for frail older adults: Tinetti Performance–Oriented Mobility Assessment (Tinetti POMA)[24] and Timed Up and Go (TUG).[25] More extensive quantitative gait and

balance analyses were performed using GAITRite™ and SwayStar™.[26, 27] Only patients who were able to walk ten meters and understood simple instructions were included in these assessments.

Other safety assessments

The occurrence and severity of 'feeling high' and effects on internal and external perception were quantified by using the Bowdle Visual Analogue Scale (VAS) rating of 13 symptom scales[28] during all visits. Other assessments of safety included vital signs, physical examination and weight, laboratory tests, electrocardiography and Delirium Observation Scale.[29] See **Appendix Table 2** for a detailed overview of all assessments.

Monitoring

Source document review and verification was performed on a regular basis by Clinical Research Centre Nijmegen. Monitoring of safety was performed by an independent Data Safety Monitoring Board (DSMB), which met regularly during trial conduction to review unblinded data. The DSMB recommended continuation of the trial without any protocol changes after every review.

Statistical analysis

The study sample size was estimated based on two-sided testing at 0.025 per treatment period, a standard deviation of NPI score of eight points at baseline,[30] a clinically relevant difference of four points[31, 32] and a test-retest correlation of 0.65. Sixteen patients with complete data would be sufficient to provide a power of 80%, due to multiple crossover. As we expected a rather high attrition rate (25%) among the vulnerable patients in this study, we aimed to enroll at least 20 subjects.

Analyses were based on the intention-to-treat principle, which means that data were analyzed according to initial treatment assignment, independent of received treatment, compliance or attrition. Data of all subjects was used in the analysis without imputation. Analyses were performed according to a pre-specified statistical analysis plan, which was finalized before unmasking of treatment assignment. Differences between THC and placebo on

NPI scores were analyzed using Linear Mixed Model with participants as random factor and block (six levels) and treatment (three levels: placebo, 'low dose' THC, 'high dose' THC) as fixed factors. 95% Confidence intervals (CI) were calculated. Analyses were repeated for two dosage regimens versus placebo separately (with 97.5% CI) and for hospital-admission group and ambulatory group separately. Other efficacy outcome measures were analyzed similarly to the primary analysis. Due to a significant effect of type of assessor on CMAI scores (mean difference$_{\text{caregivers vs. research staff}}$ +16.5 points, linear mixed model analysis with random intercept per subject, type 3 test of Fixed Effects, num df=1, den df=302, F=188.47, p<0.0001) analysis of CMAI scores was repeated with additional correction for assessor. The number of AEs was tabulated by system organ class. AEs were assigned to THC or placebo when the event started during treatment or during the subsequent washout period. Differences in AE rates between THC and placebo treatment were compared by non-linear mixed model analysis, assuming Poisson distribution of AEs. Frequency of SAEs was analyzed using descriptive statistics. The correlation between time after THC intake (0–240 min) and vital signs was analyzed in a linear mixed model with 'subject' as random factor and heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) as variables. For body sway during standing tasks, ranges of angular velocities and angles in anteriorposterior direction were calculated. Gait velocity and stride length variability were selected as outcome measures for quantitative gait analysis. Variability was expressed in coefficients of variation (CV) as standard deviation/mean x 100%. Effects of 1.5 mg THC twice daily versus placebo on body sway and gait were analyzed using a dependent t-test or Wilcoxon signed rank test, as appropriate. VAS Bowdle scores could not be obtained from persons with severe cognitive disorders and were therefore only assessed in a part of the study population. Analysis of questionnaires was done as reported elsewhere,[33] using three clusters: 'feeling high', 'internal perception' and 'external perception'. Pharmacokinetic data were also collected during the crossover study; these will be described and published separately.

Results

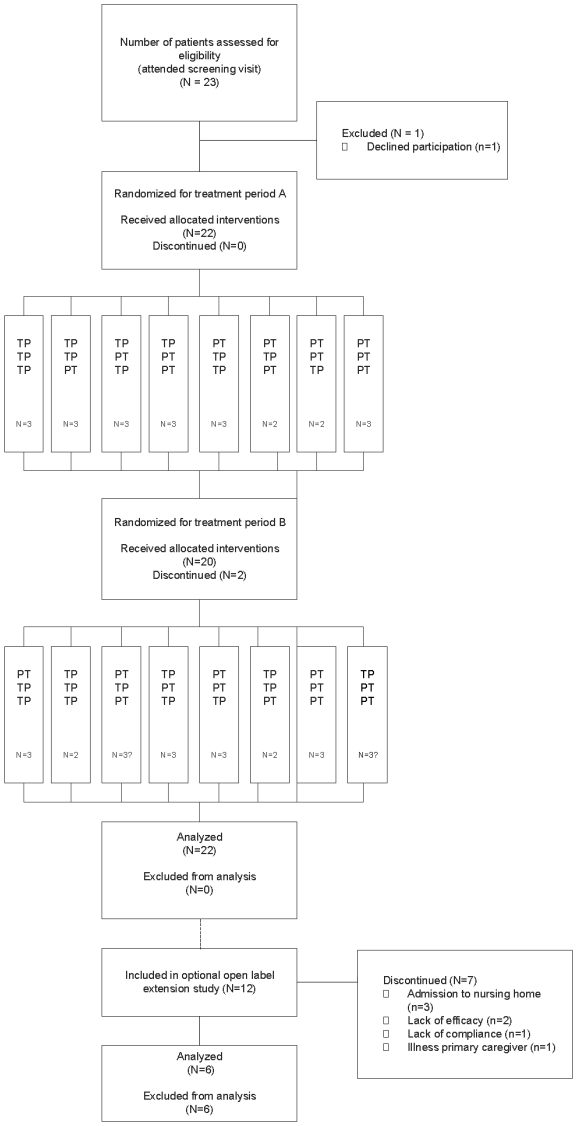
Study participants

In total, 23 patients were assessed for eligibility of whom 22 fulfilled the entry requirements, who were randomized and received study medication (**Figure 2**). Demographic and baseline characteristics are summarized in Table 1 and an overview of co-morbidities is provided in **Appendix Table 3**. Baseline NPI scores were significantly higher in the ambulatory group compared to the hospital admission group (t=-2.56, df=20, p=0.019). Twenty patients (91%) completed the 12-week crossover study and two patients dropped out because of non-related adverse events.

Efficacy

Primary outcome

Study results are presented in **Table 2**. There was no effect of THC treatment compared to placebo on NPI. No differences were found between low dose THC and placebo and between high dose THC and placebo. Analysis per group did also not show significant differences between the interventions. A substantial increase in NPI scores over the 12-week study duration was found (mean increase per week 0.07 points, trend analysis with random intercept per subject, test of Fixed Effects, Num df=1, Den df=234, F=12.92, p=0.0004). This increase was observed in both THC and placebo treatment periods. Furthermore, for the hospital admission group, NPI scores during hospital admissions were significantly lower than scores assessed during home visits. In a post hoc analysis, we explored our data for clinically relevant effects, defined as a reduction of four points or more. Overall, THC versus placebo, induced a clinically relevant decrease in NPI scores in 38.9% of treatment blocks (period A, 33.3%; period B, 44.3%; χ^2=3.19, df=1, p=0.074, $OR_{B\ versus\ A}$ 1.58, 95% CI 0.96 to 2.61). An increase in NPI scores, indicating a clinically relevant worsening of NPS, was found in 31.5% (period A, 36.4%; period B, 26.2%; χ^2=2.88, df=1, p=0.090, $OR_{B\ versus\ A}$ 0.62, 95% CI 0.36 to 1.08).



Abbreviations: T = THC; P = Placebo. Period A: 0.75 mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period. Period B: 1.5 mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period. [a] One patient discontinued in the first block of this period. [b] One patient discontinued in the third block of this period.

Figure 2 CONSORT flow diagram

Table 1 Demographic and baseline characteristics

	All (n=22)	**Hospital admission group** (n=10)	**Ambulatory group** (n=12)
Men, n (%)	15 (68)	7 (70)	8 (67)
Age, mean (SD)	76.4 (5.3)	77.3 (5.6)	75.6 (5.2)
BMI, kg/m^2, mean (SD)	25.7 (3.3)	25.7 (2.7)	25.7 (3.8)
Ethnicity, n (%)			
Caucasian	21 (95.5)	9 (90)	12 (100)
Other	1 (4.5)	1 (10)	0 (0)
Education[a], mean (SD)	4.3 (1.5)	4.0 (1.6)	4.6 (1.3)
Type of dementia, n (%)			
Alzheimer	18 (81.8)	9 (90)	9 (75)
Vascular	1 (4.5)	0 (0)	1 (8.3)
Mixed	3 (13.6)	1 (10)	2 (16.7)
Relevant co-medication, Number of medication (n patients)			
All psychotropic medication	33 (18)	19 (10)	14 (8)
Antipsychotic	2 (2)	1 (1)	1 (1)
Antidepressant	6 (6)	1 (1)	5 (5)
Anxiolytic	7 (5)	0 (0)	7 (5)
Anticonvulsants	1 (1)	1 (1)	0 (0)
Antidementia	17 (11)	16 (10)	1 (1)
MMSE score[b], mean (SD)	16.9 (7.8)	18.5 (6.0)	15.2 (9.2)
NPI score[c], mean (SD)	35.0 (16.5)	26.2 (17.7)	42.3 (11.8)
NPI agitation/aggression score[c], mean (SD)	4.1 (2.4)	3.6 (2.8)	4.6 (2.0)
CMAI score[c], mean (SD)	58.3 (17.4)	54.0 (19.8)	62.0 (15.1)
ZBI score[d], mean (SD)	36.0 (15.1)	34.5 (19.0)	37.3 (11.4)

BMI, Body Mass Index; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; ZBI, Zarit Burden Interview. [a] Education was determined with seven categories where 1 indicates less than six years of primary school and 7 indicates a university degree. [b] Mean MMSE score based on 20 patients (2 missings due to severe cognitive disturbances): 10 patients in hospital admission group and 10 patients in ambulatory group. [c] Mean score of two baseline assessments separated by at least one week. [d] Mean ZBI score based on 21 patients: 10 patients in hospital admission group and 11 patients in ambulatory group.

Secondary outcomes

No significant differences were found between THC and placebo on agitated behavior and caregiver burden, as measured with NPI subscale agitation/aggression, CMAI and ZBI (**Table 2**). Furthermore, no differences were found for low dose THC or high dose THC versus placebo on these variables. Overall, a substantial increase of CMAI and ZBI scores was observed over the 12-week study period.

Safety

Adverse events

In total, 184 AEs of mild to moderate severity occurred during the crossover study period, similarly distributed over the THC (91 AEs) and placebo (93 AEs) conditions (Non Linear Mixed Model Analysis assuming Poisson distribution of AEs, random intercept per subject, t=-0.29, df=21, p=0.77, incidence rate ratio 0.96, 95% CI 0.7 to 1.3) (**Table 3**). There was no increase in occurrence after administration of high dose THC. Four SAEs occurred in three patients, all requiring (prolongation of) hospitalization: a gastroenteritis, increase in dementia-related NPS symptoms, an exacerbation of a previously known vestibular disorder, and symptoms of a malignancy of unknown origin. None of these SAEs were judged to be related to study medication. Two patients dropped out due to the occurrence of symptoms of a malignancy (n=1) and due to extensive use of psychotropic rescue medication (n=1).

Treatment compliance and concurrent medication use

Overall treatment compliance to study medication was high; 98.5% of tablets were administered (THC, 99.5%; placebo, 97.8%). Psychotropic rescue medication (mostly benzodiazepines) was provided similarly over all conditions: in period A eight times (four patients) during THC and 13 times (four patients) during placebo, and in period B ten times (four patients) during THC and seven times (three patients) during placebo.

Table 2 Results on behavior, agitation and caregiver burden

	THC vs. placebo (95%CI)	THC low dose vs. placebo (97.5%CI)	THC high dose vs. placebo (97.5%CI)	THC low dose vs. THC high dose vs. placebo (p-value)	Hospital admission group THC vs. placebo (95%CI)	Ambulatory group THC vs. placebo (95%CI)
Primary outcomes						
NPI total[a]	-0.5 (-3.1 to 2.2)[d]	+1.8 (-2.1 to 5.8)[e]	-2.8 (-7.4 to 1.8)[f]	0.22[d]	-0.1 (-3.1 to 2.8)[g]	-0.8 (-5.0 to 3.4)[h]
NPI agitation/aggression[a]	-0.3 (-0.9 to 0.2)[i]	0.0 (-0.8 to 0.8)[j]	-0.7 (-1.6 to 0.3)[k]	0.29[d]	-0.3 (-1.1 to 0.5)[l]	-0.3 (-1.2 to 0.5)[m]
Secondary outcomes						
CMAI[b]	-1.5 (-4.0 to 1.0)	-1.2 (-5.0 to 2.7)	-1.8 (-5.5 to 1.9)	0.51	-1.3 (-5.5 to 2.9)	-1.6 (-4.6 to 1.4)
ZBI[c]	+0.32 (-0.9 to 1.5)	+1.2 (-0.9 to 3.3)	-0.5 (-2.1 to 1.2)	0.34	+0.5 (-1.5 to 2.5)	+0.3 (-1.1 to 1.7)

Differences between THC and placebo were analyzed using linear mixed model with participants as random factor and block (six levels) and treatment (three levels: placebo, low dose THC, high dose THC) as fixed factors, with 95%CI. Analyses were repeated for two dosage regimens versus placebo (with 97.5% CI) and for hospital-admission group and ambulatory group separately. Differences between placebo, low dose THC and high dose THC were also analyzed using linear mixed model, providing p-values. CMAI scores were analyzed with a correction for type of assessor. THC, Tetrahydrocannabinol; NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; ZBI, Zarit Burden Interview.
[a] 7 missing values (3 on THC, 4 on placebo). [b] 16 missing values (7 on THC, 9 on placebo). [c] 33 missing values (17 on THC, 16 on placebo). [d] t= -0.35, df=228. [e] t=1.05, df=107. [f] t= -1.39, df=100. [g] t= -0.10, df=102. [h] t= -0.37, df=119. [I] t= -1.13, df=228. [j] t=0.0, df=107. [k] t= -1.55, df=100. [l] t= -0.77, df=102. [m] t= -0.82, df=119.

Table 3 Adverse events during crossover study

MedDRA system organ class	THC **Period A** No.	THC **Period B** No.	Placebo **Period A** No.	Placebo **Period B** No.
Severe adverse events (≥grade 3)	0	0	0	0
Mild to moderate adverse events	46	45	48	45
Administration site	3	0	2	2
Blood and lymphatic system disorders	0	0	0	1
Cardiac disorders	1	4	5	1
Ear and labyrinth disorders	3	1	1	3
Gastrointestinal disorder	4	3	4	0
General disorders	6	5	3	6
Injury and procedural complications	3	1	2	2
Investigations	0	0	0	2
Metabolism and nutritional disorders	0	1	2	1
Musculoskeletal disorder	3	3	0	2
Nervous system disorders	9	6	13	6
Psychiatric disorders	9	13	10	15
Renal and urinary tract infections	1	1	1	1
Respiratory disorders	2	6	0	1
Skin and subcutaneous tissue disorders	0	0	2	1
Vascular disorders	2	1	3	1

Numbers are numbers of events. MedDRA, Medical Dictionary for Regulatory Activities; THC, tetrahydrocannabinol. Period A: 0.75mg THC twice daily; period B: 1.5mg THC twice daily.

Other safety outcomes

High dose THC increased SBD by 2.6 mmHg compared to placebo within four hours after first tablet intake, while no effects were found on HR and DBP. Overall, THC did not have an effect on mobility assessed with Tinetti and TUG (**Table 4**). High dose THC did not affect balance when patients were standing on two legs with their eyes open. In the eyes closed condition, body sway increased significantly after administration of THC, compared to placebo (Cohen's d for pitch velocity, 0.59). No effects were found on velocity or stride length variability during walking on preferred speed. Average body weight at the end of the study did not differ from screening (dependent t-test 0.05, 95% CI -1.1 to 1.0). Feeling high was not reported nor observed in any patient. Analyses of questionnaires showed low VAS scores (median for feeling high, 0.30; external perception, 0.30; internal perception 0.24). THC did not have an effect on VAS scores,

with the exclusion of low dose THC on internal perception (mean difference$_{\text{THC vs placebo}}$ 0.025, 95% CI 0.01 to 0.04, Linear Mixed Model Analysis, random intercept per subject, type 3 test of Fixed Effects: Num df=1, Den df=274, F=10.45, p=0.0014), which was judged not to be a clinically relevant increase.

Conclusions

In the present study, we found no benefit of THC treatment (0.75 mg and 1.5 mg twice daily) on NPS in dementia on either of the outcome measures. Although THC failed to improve NPS, intermittent treatment demonstrated safety in older dementia patients. Previous studies all showed positive effects of THC (2.5 to 7.0 mg daily) on behavioral and nighttime disturbances.[13, 14, 34, 35] However, two of these studies were RCTs with a small number of patients (n=2; n=15),[14, 34] one study had a retrospective design[35] and one was an uncontrolled open label study.[13] These factors all introduce bias, possibly leading to an overestimation of the treatment effect.

To date, data on safety of medical cannabinoids in older patients are scarce,[16] while more comprehensive data result from research in younger adult patients.[15] These latter studies report more AEs following THC treatment, compared to placebo (IRR 2.18), especially within the first two treatment weeks (IRR 2.91).[15] Most commonly reported AEs are related to the central nervous system, such as dizziness and somnolence. As the patient characteristics and route of administration in these studies are diverse and the administered dosages significantly higher (5 to 45 mg THC daily), no direct comparison can be made with the results provided in the current study. Concerning dementia patients, previous studies report no adverse events after administration of 2.5 mg THC daily.[13, 34] Nevertheless, administration of higher dosages (5 to 7 mg daily) resulted in the occurrence of AEs, such as sedation, euphoria and delirium.[14, 35]

The current study is the first to assess safety by using reports of adverse events, as well as vital signs and mobility assessments. The lack of relevant side effects suggests that the current dosages are

Table 4 Results of mobility assessments

	THC vs. placebo (95%CI)	**Low dose THC vs. placebo** (97.5%CI)	**High dose THC vs. placebo** (97.5%CI)
TUG[a]	+0.1 (-0.4 to 0.6)[c]	+0.4 (-0.3 to 1.0)[e]	0.05 (-0.6 to 0.7)[g]
Tinetti POMA[b]	-0.1 (-0.4 to 0.3)[d]	+0.1 (-0.4 to 0.5)[f]	-0.2 (-0.6 to 0.2)[h]
	High dose THC Median (range)	**Placebo** Median (range)	**p-value**
SwayStar™ - Standing on two legs eyes open			
Pitch angle (deg)	2.13 (0.90 – 6.05)	2.61 (0.77 – 9.84)	0.41[i]
Pitch velocity (deg/s)	4.91 (1.75 – 15.27)	3.85 (1.43 – 31.45)	0.98*
SwayStar™ - Standing on two legs eyes closed			
Pitch angle (deg)	3.45 (0.82 – 7.84)	2.38 (0.87 – 9.29)	0.01[j]
Pitch velocity (deg/s)	6.70 (1.56 – 35.54)	4.67 (1.82 – 40.99)	0.02[k]
GAITRite™ - Walking on preferred speed			
Velocity (cm/s)	93.10 (58.2 – 132.3)	91.70 (50.2 – 125.1)	0.06*
Stride length variability (%CV)	4.49 (1.70 – 13.54)	4.42 (1.82 – 92.19)	0.41*

TUG and Tinetti POMA scores were assessed weekly and analyzed as a Linear Mixed Model, similarly to the primary efficacy analysis. SwayStar™ and GAITRite™ assessments were performed twice in period B (1.5mg THC and placebo) and were analyzed using a dependent t-test or Wilcoxon signed rank test (the latter indicated by *). TUG, Timed Up and Go; Tinetti POMA, Tinetti Performance-Oriented Mobility Assessment; CV, coefficient of variation. [a] 60 missing values (29 on THC, 31 on placebo). [b] 74 missing values (34 on THC, 40 on placebo). [c] t=0.42, df=162. [d] t= -0.32, df=175. [e] t=1.04, df=75. [f] t=0.41, df=83. [e] t=0.13, df=68. [h] t=0.90, df=72. [i] t=-0.85, df=17. [j] t=2.97, df=17. [k] t=2.50, df=17.

well tolerated when administered for a short duration. This suggests that it might be worthwhile to conduct higher dosing studies, provided that the dose is gradually increased.

To our knowledge, this is one of the largest randomized controlled trial studying the efficacy of THC in dementia patients by using a scientifically sound design. Due to the expected acute psycho-active effects of THC, we chose a repeated measurements design with short intervention periods. This design made it possible to conduct a methodologically valid trial, warranting the need of a relatively small number of subjects, and is therefore suitable for research in frail, dementia patients. The attrition rate in the crossover study was low (9%), and treatment compliance high (98.5%). Most participating caregivers experienced dementia-related NPS as a serious problem, leading to a high internal motivation to complete study participation.

This study also had limitations. Despite the fact that we have included the number of patients needed based on the power analysis prior to study conduction, there are several factors that might have reduced our ability to detect a treatment effect. First, the administered dosages were fixed. We chose our dosages relatively low to minimize safety risks for these frail participants, based on the dosages used in previous studies in dementia patients,[13, 14] and the safety results of the phase I study on healthy young volunteers,[17] expecting dementia patients to be more vulnerable to the psycho-active adverse effects of THC. In retrospect, the dosages administered could have been higher. Second, the intervention period was relatively short, based on the expected acute pharmacodynamic effects of oral THC.[17] The introduction of longer treatment periods might increase the ability to detect an effect, as NPS can vary. Third, the hospital admissions led to significantly lower NPI scores compared to scores assessed during home stays. This may be caused by the daily structure that was offered by the nursing staff and minimal presence of the informal caregiver. Fourth, we found a larger standard deviation in NPI scores than expected, based on previous studies resulting in a lower power.[30] Fifth, although the NPI total score at baseline is comparable to other intervention studies on dementia-related NPS, the severity of agitation is lower, represented by lower baseline NPI

agitation/aggression and CMAI scores.[12, 36] Sixth, we observed an increase in NPI, CMAI and ZBI scores over time. These outcome measures were assessed by an informal caregiver, closely involved in the care for the participant. Therefore, a high burden of study participation or a failure to observe an expected treatment effect, are possible explanations for this increase. Last, we did not include nursing home patients. This was hampered by legislation on drug delivery, despite the fact that these patients probably are the main target group for psychoactive interventions in NPS. This study, however, is an informative step in the development of new drug therapies, specifically targeting this complex patient group.

To conclude, oral THC up to 1.5 mg twice daily did not reduce behavioral disturbances in patients with dementia. Yet, assessments of safety by using reports of adverse events, vital signs and mobility showed that the intervention was well tolerated by this patient group. As we studied a relatively low dose, these results suggest that it might be worthwhile to conduct future higher dose studies in the treatment of dementia-related behavioral disturbances.

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SUPPLEMENTARY MATERIAL

Appendix

Open label extension phase

Methods

At the end of the 12-week study period, patients were asked to participate in an optional, open label extension study when study treatment was well tolerated and intuitively judged to be profitable based on blinded NPI scores. In this extension study, subjects visited the research center at 4 weeks, 3 months and 6 months for assessment of NPI, CMAI, ZBI, mobility, Mini Mental State Examination (MMSE) and safety parameters. All patients who participated in the optional open label extension phase were included in the safety analysis, as assessment of long term tolerability and safety was the primary objective of this study phase. Additionally, patients with three completed NPI scores during this extension phase were included in the analysis of long term efficacy. Mean differences of the three time points were compared using repeated measures ANOVA.

Results

Twelve out of 22 patients (54.5%) entered the open label extension study on the patients' or caregivers' request, of whom five (41.7%) completed this six month treatment period. Reasons for premature discontinuation were: lack of efficacy (n=2), lack of study drug compliance (n=1), illness of the primary caregiver (n=1), and admission to a nursing home (n=3). These latter patients dropped out, as the nursing homes were not in the possession of a permit for handling THC for research purposes, which is mandatory in the Netherlands. Median treatment duration was 140 days (range 15 to 188 days). Two patients received a daily dose THC of 1.5mg, nine patients received 3mg and one patient 4.5 mg THC. In total, 16 adverse events of mild to moderate severity occurred. The most common AEs were 'agitation' (n=2), 'anaemia' (n=2) and 'urinary tract infection' (n=2). One severe adverse event occurred:

a hospitalization in a specialized dementia care unit for further observation of cognition and behavior. Adverse events did not lead to study discontinuation in any of the patients. THC did not affect cognition, mobility or weight. Furthermore, no differences were found on the different time points on NPI, CMAI and ZBI (**Appendix Table 2**).

Conclusion

This preliminary open label study phase showed that long term treatment with low dose THC was well tolerated by patients with dementia and did not affect behavioral disturbances or caregiver burden. These results must be interpreted with caution, as the attrition rate in this phase was high (58.3%).

Appendix Table 1 Results of the open label extension phase

	Week 4 (n=6)	**Week 12** (n=6)	**Week 24** (n=6)	***P*-value**
Safety assessments				
MMSE	18.2 (15.4)[a]	18.6 (3.6)[a]	18.4 (6.8)[a]	0.96
TUG (s)	13.2 (2.7)	15.2 (5.4)[b]	13.6 (4.0)[a]	0.38
Tinetti POMA	25.3 (1.9)	24.4 (4.3)[a]	25.6 (3.2)[a]	0.44
Weight (kg)	79.0 (10.6)	78.2 (10.9)	76.8 (9.4)	0.14
Efficacy assessments				
NPI total	25.3 (11.9)	28.2 (11.1)	23.3 (12.9)	0.70
NPI agitation scale	3.0 (3.3)	3.3 (2.6)	2.2 (3.0)	0.72
CMAI	53.8 (16.1)	53.3 (15.3)	56.6 (22.7)[a]	0.83
ZBI	38.0 (20.5)	42.5 (17.1)	32.4 (15.1)[a]	0.51

Values are means (SD) from all patients with three NPI assessments. Abbreviations: MMSE, Mini Mental State Examination; TUG, Timed Up and Go; Tinetti POMA, Tinetti Performance-Oriented Mobility Assessment; NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; ZBI, Zarit Burden Interview. [a] Results based on five patients. [b] Results based on four patients.

Appendix Table 2 Schedule of assessments per group during trial period.

		Period A										Period B									
		Block 1						Block 2		Block 3		Block 4						Block 5		Block 6	
			W1			W2		W3	W4	W5	W6		W7			W8		W9	W10	W11	W12
		D1	D2	D3	D1	D2	D3	D3	D3	D3	D3	D1	D2	D3	D1	D2	D3	D3	D3	D3	D3
NPI	Hospital			1			1	1	1	1	1			1			1	1	1	1	1
	Ambulatory			1			1	1	1	1	1			1			1	1	1	1	1
CMAI	Hospital	2	2	**2**[a]	2	2	**2**[a]	**1**	**1**	**1**	**1**	2	2	**2**[a]	2	2	**2**[a]	**1**	**1**	**1**	**1**
	Ambulatory	1		1	1		1	1	1	1	1	1		**1**	1		1	1	1	1	1
ZBI	Hospital			1			1	1	1	1	1			1			1	1	1	1	1
	Ambulatory			1			1	1	1		1			1			1	1	1	1	1
										1											
TUG & Tinetti	Hospital	2	2	**2**[b]	2	2	**2**[b]	**1**	**1**	**1**	**1**	2	2	**2**[b]	2	2	**2**[b]	**1**	**1**	**1**	**1**
	Ambulatory	1		1	1		1	1	1	1	1	1		**1**	1		1	1	1	1	1
GR & Sway	Hospital		1			1							1			1					
	Ambulatory	1			1							1			1						
Weight	Hospital	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**1**
	Ambulatory	1		1	1		1	1	1	1	1	1		1	1		1	1	1	1	1
Vital signs	Hospital	**16**[c]	13	13	**16**[c]	13	13	1	1	1	1	**16**[c]	13	13	**16**[c]	13	13	1	1	1	1
	Ambulatory[c]	9[c]		1	**9**[c]		1	1	1	1	1	**9**[c]		1	**9**[c]		1	1	1	1	1
Bowdle	Hospital[d]	4	4	4	4	4	4	1	1	1	1	4	4	4	4	4	4	1	1	1	1
	Ambulatory[e]	2		1	2		1	1	1	1	1	2		1	2		1	1	1	1	1
ECG	Hospital	1			1						1	1			1						1
	Ambulatory	1			1							2			1						1
DOS	Hospital	3	3	3	3	3	3					3	3	3	3	3	3				
	Ambulatory																				
Blood	Hospital																				1
	Ambulatory																				1

NOTE. Bold numbers indicate the assessments which are used in the analyses. Abbreviations: NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; ZBI, Zarit Burden Interview; TUG, Timed Up and Go; GR, GAITRite™; Bowdle, Visual Analogue Scale Bowdle for feeling high; ECG, Electrocardiography.
[a] The first assessment of CMAI was used in the analysis. [b] The first assessments of TUG and Tinetti were used in the analysis. [c] The following vital signs assessments on day 1 of week 1, 2, 7 and 8 were used in the analysis: predose, 15 min, 30 min, 45 min, 1, 2, 3 and 4 hours postdose. During day 3 of week 3 to 6 and 9 to 12, vital signs were assessed irrespective of time to tablet admission. [d] Bowdle VAS on week 1, 2, 7 and 8 (day 1 to 3): 1 and 3 hours postdose. During day 3 of week 3 to 6 and 9 to 12, Bowdle VAS was assessed irrespective of time to tablet admission. [e] Bowdle VAS on week 1, 2, 7 and 8 (day 1): 1 and 3 hours postdose. During day 3 of week 1 to 12, Bowdle VAS was assessed irrespective of time to tablet admission.

Appendix

Table 3 Relevant medical history and co-morbidity

Number of patients (%) with relevant co-morbidity or medical history	All (n=22)	Hospital admission group (n = 10)	Ambulatory group (n=12)
Cardiovascular disorders	17 (77.3)	9 (90.0)	8 (66.7)
Hypertension	8 (36.4)	4 (40.0)	4 (33.3)
Hypercholesterolemia	4 (18.2)	0 (0.0)	4 (33.3)
Rhythm disorder	6 (27.3)	3 (30.0)	3 (25.0)
Vascular disorder	5 (22.7)	2 (20.0)	3 (25.0)
Ventricular hypertrophia	4 (18.2)	3 (30.0)	1 (8.3)
Heart failure	1 (4.5)	0 (0.0)	1 (8.3)
Cardiac ischemia	2 (9.1)	1 (10.0)	1 (8.3)
Vascular disorder	5 (22.7)	2 (20.0)	3 (25.0)
Other	1 (4.5)	3 (30.0)	1 (8.3)
Genito-urinary disorders	14 (63.6)	6 (60.0)	8 (66.7)
Kidney failure	6 (27.3)	3 (30.0)	3 (25.0)
Urinary difficulty	3 (13.6)	1 (10.0)	2 (16.7)
Infection	4 (18.2)	1 (10.0)	3 (25.0)
Surgery	3 (13.6)	1 (10.0)	2 (16.7)
Other	6 (27.3)	3 (30.0)	3 (25.0)
Gastrointestinal disorders	10 (45.5)	3 (30.0)	7 (58.3)
Constipation	2 (9.1)	0 (0.0)	2 (16.7)
Surgery	5 (22.7)	1 (10.0)	4 (33.3)
Infection	3 (13.6)	2 (20.0)	1 (8.3)
Other	3 (13.6)	1 (10.0)	2 (16.7)
Musculoskeletal disorders	8 (36.4)	5 (50.0)	3 (25.0)
Fracture or lesion	6 (27.3)	5 (50.0)	1 (8.3)
Other	4 (18.2)	1 (10.0)	3 (25.0)
Neurological disorders	8 (36.4)	4 (40.0)	4 (33.3)
Cerebrovascular disease	4 (18.2)	1 (10.0)	3 (25.0)
Mobility disorder	2 (9.1)	0 (0.0)	2 (16.7)
Other	4 (18.2)	3 (30.0)	1 (8.3)
Endocrine disorders	7 (31.8)	3 (30.0)	4 (33.3)
Diabetes mellitus	6 (27.3)	2 (20.0)	4 (33.3)
Other	1 (4.5)	1 (10.0)	0 (0.0)
Ear disorders	6 (27.3)	3 (30.0)	3 (25.0)
Loss of hearing	5 (22.7)	2 (20.0)	3 (25.0)
Other	1 (4.5)	1 (10.0)	0 (0.0)
Respiratory disorders	5 (22.7)	2 (20.0)	3 (25.0)
Pneumonia	1 (4.5)	1 (10.0)	0 (0.0)
Chronic obstructive pulmonary disease	1 (4.5)	0 (0.0)	1 (8.3)
Other	3 (13.6)	1 (10.0)	2 (16.7)
Psychiatric disorders	5 (22.7)	3 (30.0)	2 (16.7)
Depression	3 (13.6)	1 (10.0)	2 (16.7)
Delirium	2 (9.1)	1 (10.0)	1 (8.3)
Dermatological disorders	4 (18.2)	1 (10.0)	3 (25.0)
Skin malignancy	4 (18.2)	1 (10.0)	3 (25.0)
Other	2 (9.1)	1 (10.0)	1 (8.3)
Eye disorders	4 (18.2)	1 (10.0)	3 (25.0)
Malignancies	2 (9.1)	0 (0.0)	2 (16.7)

Values are numbers of patients and percentages. The disorders are categorized by Medical Dictionary for Regulatory Activities

Chapter 4

Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial

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Abstract

Objective: To study the efficacy and safety of low-dose oral tetrahydrocannabinol (THC) in the treatment of dementia-related neuropsychiatric symptoms (NPS).

Methods: This is a randomized, double-blind, placebo-controlled study. Patients with dementia and clinically relevant NPS were randomly assigned to receive THC 1.5 mg or matched placebo (1:1) 3 times daily for 3 weeks. Primary outcome was change in Neuropsychiatric Inventory (NPI), assessed at baseline and after 14 and 21 days. Analyses were based on intention-to-treat.

Results: Twenty-four patients received THC and 26 received placebo. NPS were reduced during both treatment conditions. The difference in reduction from baseline between THC and placebo was not significant [mean difference NPI_{total}: 3.2, 95% confidence interval (CI) -3.6 to 10.0], nor were changes in scores for agitation (Cohen-Mansfield Agitation Inventory 4.6, 95% CI -3.0 to 12.2), quality of life (Quality of Life–Alzheimer's Disease -0.5, 95% CI -2.6 to 1.6), or activities of daily living (Barthel Index 0.6, 95% CI -0.8 to 1.9). The number of patients experiencing mild or moderate adverse events was similar (THC, n=16; placebo, n=14, p=0.36). No effects on vital signs, weight, or episodic memory were observed.

Conclusions: Oral THC of 4.5 mg daily showed no benefit in NPS, but was well-tolerated, which adds valuable knowledge to the scarce evidence on THC in dementia. The benign adverse event profile of this dosage allows study of whether higher doses are efficacious and equally well- tolerated.

Introduction

Most patients with dementia will experience neuropsychiatric symptoms (NPS) over the course of their disease.[1] While non-pharmacologic interventions are preferred, data on their efficacy remains limited and the interventions are not easily applicable in clinical practice.[2] Pharmacologic treatment is challenging, as currently available medications have important drawbacks concerning the benefit-to-risk ratio.[3–6] This implicates a serious health care problem, as 62% of community-dwelling patients and up to 80% of nursing home residents have clinically relevant symptoms.[7,8] Structured analgesic treatment has recently been demonstrated to be beneficial for dementia-related NPS and in particular agitation.[9] D-9-Tetrahydrocannabinol (THC), the main constituent of cannabis, has both psychoactive and analgesic properties,[10,11] and might therefore serve as an alternative pharmacologic treatment. Indeed, some preliminary studies suggested improvement in agitation and nocturnal motor activity in patients with Alzheimer disease (AD).[12,13]

The effect of THC on the endocannabinoid system is mediated by 2 cannabinoid receptors: CB_1 receptors are expressed in several brain regions, especially the basal ganglia, cerebellum, hippocampus, amygdala, and hypothalamus; CB_2 receptors are primarily found in cells and organs of the immune system. Therefore, THC probably has a wide range of CB_1-mediated receptor interactions with the endocannabinoid system affecting emotion, cognition, and behavior. Moreover, psychotropic effects are also exerted through interaction with other receptors and neurotransmitters, such as acetylcholine, dopamine, serotonin, g-aminobutyric acid, glutamate, norepinephrine, prostaglandins, and opioid peptides.[14] Interestingly, several animal studies also suggest a neuroprotective effect of cannabinoids in the disease pathology of AD itself, which is primarily based on a reduction in the inflammatory response by microglia cells and the increase of amyloid-b clearance.[15,16] Nonetheless, firm evidence of the efficacy and safety of THC or other cannabinoids in this vulnerable

patient group is lacking and data on older patients in general are scarce.[17]

The current article reports the largest study carried out so far on evaluating the efficacy and safety of oral THC for behavioral disturbances in patients with dementia.

METHODS

Standard protocol approvals, registrations, and patient consents

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice, approved by a certified ethics committee of the Radboud university medical center (Radboudumc) and registered at www.clinicaltrials.org (NCT01608217). Assessments were done by researchers from the Department of Geriatric Medicine of Radboudumc (Nijmegen, the Netherlands) and the Department of Elderly of Vincent van Gogh Institute (psychiatric hospital, Venray, the Netherlands) from November 2012 to June 2014. Participants were recruited from 9 participating institutes throughout the southeast of the Netherlands, including geriatric outpatient clinics (n=2 clinics), psychiatric clinics (n=3), nursing homes (n=3, including in total 6 locations), and a regional network of integrated care for community-dwelling patients with dementia. Written informed consent was provided at screening by the patient and closest involved proxy, the first only in case the patient was judged capable of consent.

Study design

This was a randomized, double-blind, placebo controlled, multicenter, phase II trial. Potential participants were screened for eligibility within 4 weeks prior to start of study medication, by assessment of somatic and cognitive status and severity of behavioral disturbances. Assessments were done at the outpatient clinic, nursing home, or at home, depending on patient preference. Study intervention was initiated after baseline. Efficacy assessments

were scheduled after 14±2 treatment days (phone call) and 21±2 treatment days (visit). For the purpose of safety assessment and compliance, several phone calls were performed by the researchers during the intervention period (days 2, 7, and 14). Follow-up assessments by telephone were performed 2 weeks after study completion.

Participants

Patients diagnosed with AD or vascular or mixed dementia according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[18] or National Institute of Neuro- logical Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences[19] criteria were eligible for participation if they had clinically relevant NPS [minimal Neuropsychiatric Inventory (NPI) score ≥ 10], with symptoms reported on agitation, aggression, or aberrant motor behavior, existing at least 1 month prior to screening. A caregiver had to be available who was in touch with the patient at least twice a week and supervised the patient's care.

Exclusion criteria were current major psychiatric disorders and any severe or instable concomitant illness, in particular seizures, arrhythmias necessitating treatment other than a β-blocker or digoxin, severe heart failure, or any concomitant disease necessitating treatment changes. Other exclusion criteria were frequent falling due to orthostatic hypotension, a history or current alcohol or drug abuse, and use of tricyclic antidepressants, fluoxetine, or carbamazepine. Use of concurrent psychotropic medication was allowed, provided that the dose and frequency were kept stable within 2 weeks before and during trial conduction. Analgesic drugs had to be stopped prior to baseline assessments, although use of analgesic and psychotropic escape medication was allowed.

Changes to study protocol

We initially recruited patients with behavioral disturbances as well as persistent pain complaints to secondarily assess the efficacy of THC on pain in patients with dementia. However, the

number of eligible patients with both symptoms was much lower than predicted from the literature.[20] After inclusion of the first 8 patients, the criterion of pain was omitted. In the amended study, pain assessments were still included, allowing secondary evaluation of the efficacy of THC in reducing pain-related behavior and pain intensity in a subgroup of patients, of which the methods and results are described in **Appendix 1** and **Table 1**.

Intervention and randomization

Active treatment consisted of 1.5 mg THC in tablet form (Namisol®, Echo Pharmaceuticals, Weesp, the Netherlands) 3 times daily for a period of 3 weeks. This daily dose was based on preliminary positive results of previous trials in patients with severe AD.[12,13,21] Control treatment consisted of matched placebo tablets. Additionally, patients received 1,000 mg acetaminophen 3 times daily in case of pain complaints, or of suspected pain in non-communicative patients, based on physical examination at screening and information from the caregiver or physician. Study medication was administered at 9_{AM}, 2_{PM}, and 8_{PM} by the primary caregiver or nursing home staff. Study medication was packed and distributed by the pharmacy of Radboudumc according to Good Manufacturing

Practice. Randomization (allocation ratio 1:1) was performed by an independent statistician using a computer-generated randomization program, of which the algorithm was stratified per center and minimized[22] for NPI score, dementia severity, sex, and current opioid use. Treatment allocation was strictly concealed from participants, caregivers, investigators, and all other personnel directly involved in the study and was not made available until study completion and database lock.

Outcome measures

Primary outcome measure

The primary outcome was change in NPS, measured with NPI.[23] This questionnaire evaluates 12 behavioral domains, including agitation/ aggression and aberrant motor behavior, which were the behavioral domains of interest. The frequency and severity of NPS

were scored per domain by questioning a caregiver, which resulted in a total score ranging from 0 to 144 (a higher score indicating greater impairment). NPI was assessed at baseline, day 14 (by telephone interview), and day 21 by trained researchers.

Secondary efficacy outcome measures

Secondary outcomes included assessment of agitated behavior and aggression [Cohen- Mansfield Agitation Inventory (CMAI)[24]], activities of daily living (Barthel Index[25]), and quality of life [Quality of Life–Alzheimer's Disease Scale (QoL-AD)[26]]. These were all assessed at baseline and day 21. Overall change was assessed by the primary caregiver, using the Caregiver Clinical Global Impression of Change (CCGIC), a 7-point scale ranging from marked improvement to marked worsening from baseline.

Safety assessments

Adverse events

Adverse events (AEs) were solicited from patients and their caregivers at all visits and phone calls up to 2 weeks after study drug discontinuation, using clinical observation, open questions, and a set of questions on possible THC-related adverse symptoms, including the most frequently reported AEs in the phase I study with healthy elderly.[27] AEs were coded following the classification of Medical Dictionary for Regulatory Activities. An AE was defined as serious if it was fatal or life-threatening, required or prolonged hospitalization, or resulted in persistent or significant disability or incapacity.

Other safety assessments

Other safety assessments consisted of evaluation of blood pressure, heart rate, and weight, assessed at screening, baseline, and day 21, and ECG and biochemistry and hematology blood samples, assessed at screening and day 21. The Paired Associate Learning Wechsler Memory Scale–Revised (PAL WMS-R)[28] was used for assessment of possible effects of THC on episodic memory function (baseline and day 21).

Statistical analysis

The study sample size was estimated based on a clinically relevant difference of 4 points on NPI[29,30] a SD of 12 points[31,32] and an estimated correlation with baseline of 0.6 and interclass correlation coefficient of 0.6. Approximately 130 patients were required for a power of 80% (2-sided testing at 0.05). We were not able to enroll this number of subjects within the available time period, due to delay in getting formal approval for THC use at all sites from the Health Care Inspectorate. After trial ending, we performed an analysis to calculate the power to yield a statistically significant difference in favor of THC, in case we would have been able to extend the study to 130 subjects. This analysis is known as the calculation of conditional power. The analysis used 10,000 simulated extensions of the outcome data of the realized sample to the planned sample size, based on the real data that were acquired. Efficacy and safety analyses were based on the intention-to-treat principle and performed in accordance with a prespecified statistical analysis plan, finalized before unmasking of treatment assignment. The primary endpoint, mean difference [including 95% confidence interval (CI)] in NPI total score from baseline to 14 and 21 treatment days, was evaluated in a linear mixed model with participants as random factor and treatment, center, baseline NPI, Clinical Dementia Rating score, sex, current opioid use, and time as fixed factors. All assumptions for regression models were assessed by viewing plots of the residual values to check for linearity and homoscedasticity. Analysis was repeated for all NPI subdomain scores. In a post hoc analysis, we determined the efficacy for 2 subgroups: ambulatory patients and inpatients. Other secondary efficacy outcome measures, weight, and vital signs were assessed similarly to the primary analysis (without data on day 14, as these were not collected). Pearson correlation coefficients were calculated for change from baseline of NPI and CCGIC scores on day 14 and day 21. Due to the limited number of participants included in the PAL WMS-R assessments group, these differences were compared using Mann-Whitney *U* test. For analysis of AEs, the number of patients with at least 1 unique episode was tabulated per treatment group and group difference on incidence (using χ^2) and

severity of AEs (using Mann-Whitney *U*) was analyzed. Statistical analyses were done using SAS version 9.2 and SPSS version 20 for Windows.

Classification of evidence

This interventional study provides Class I evidence that oral THC of 4.5 mg daily is not effective in reducing behavioral disturbances in patients with dementia (ΔNPI_{total}: 3.2, 95% CI 3.6 to 10.0) and is well-tolerated [occurrence of AEs THC vs placebo: 16 (66.7%) vs 14 (523.8%) patients, χ^2, p=0.36].

RESULTS

Study participants

In total, 54 patients were assessed for eligibility, of whom 50 were randomized and received study medication (THC, n=24; Placebo, n=26) (**Figure 1**). Patient characteristics are presented in **Table 1**. Overall, 47 patients (94%) completed the study, while three patients discontinued participation due to the occurrence of AEs (n=2) and withdrawal of informed consent (n=1).

Treatment compliance and concurrent medication use

Median treatment compliance, based on remaining pill count, was 98% (67%–100%) in the THC group and 100% (94%–100%) in the placebo group. Twenty-nine patients received acetaminophen (THC, n=13; placebo, n=16). Four patients (16.7%) in the THC group received escape medication, compared to 2 patients (7.7%, p=0.33) in the placebo group, which consisted of benzodiazepines (oxazepam 5 mg, lorazepam 1 mg) and acetaminophen (500 mg).

Efficacy

Study results are presented in **Table 2**. NPI total score decreased in both treatment conditions after 14 days (THC, p=0.002; placebo, p=0.002) and 21 days (THC, p=0.003; placebo, p=0.001). There was no difference between THC and

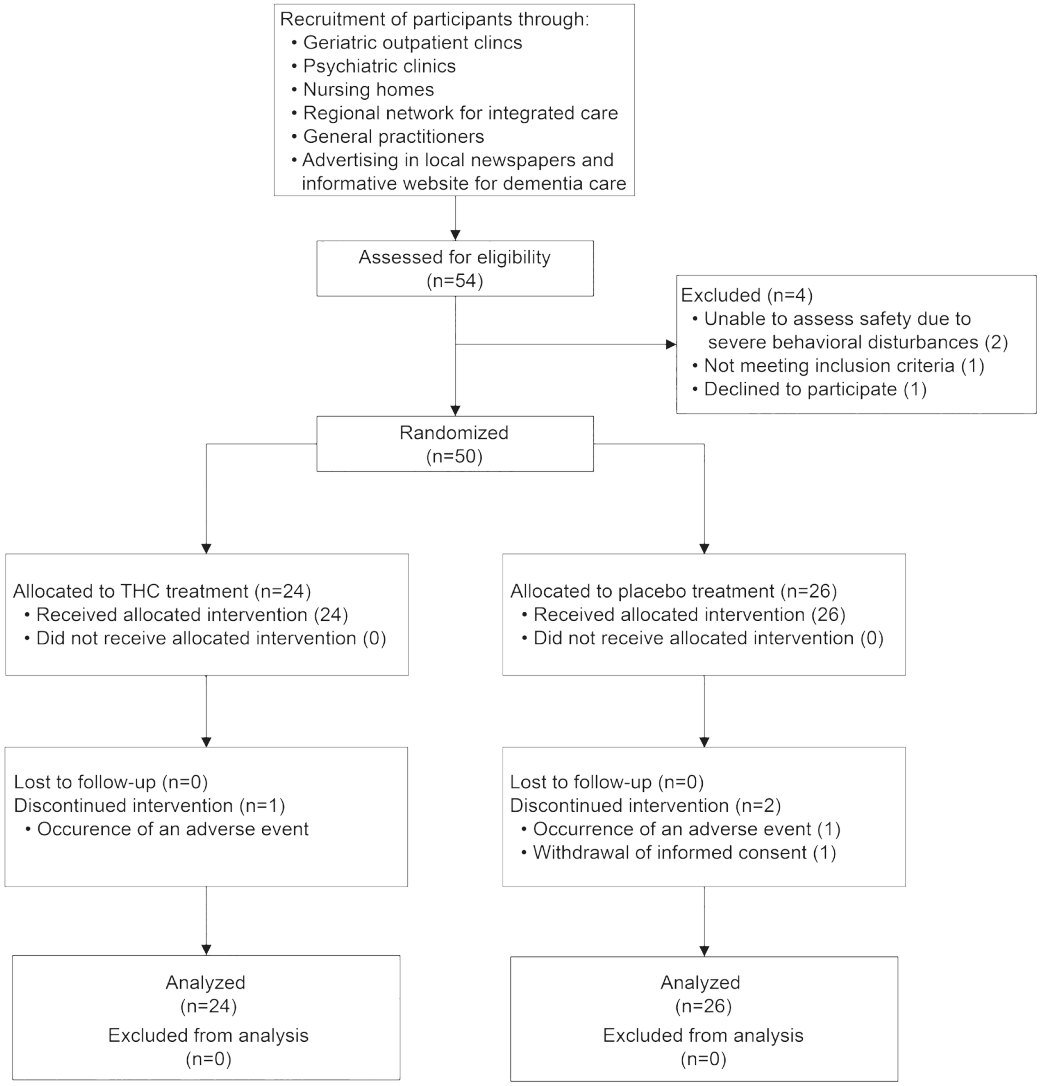

Figure 1 CONSORT flowchart of recruitment and selection

placebo over 21 treatment days (ΔNPI_{total}: 3.2, 95% CI -3.6 to 10.0). Additionally, no differences were observed on agitation ($\Delta NPI_{agitation}$: -0.1, 95% CI -2.0 to 1.9), aberrant motor behavior ($\Delta NPI_{aberrant\ motor\ behavior}$: 0.3, 95% CI -1.0 to 1.7), or other NPI subdomains (see table e-2), except for the domain "eating disorders" in favor of placebo ($\Delta NPI_{eating\ disorders}$: 1.0, 95% CI 0.0–1.92). Analysis per subgroup showed no benefit of THC in community-dwelling patients (ΔNPI_{total}: 5.0, 95% CI -1.8 to 11.7) or in inpatients (ΔNPI_{total}: 1.5, 95% CI -10.0 to 13.1). There were no significant differences between the intervention groups on CMAI, QoL-AD, and Barthel Index. CCGIC scores after 3 weeks showed that 8 (36.4%) patients in the THC group had minimal to marked improvement from baseline, which was not significantly different from 12 patients (50.0%) in the placebo group (χ^2, p=0.35). A strong correlation was observed between NPI and CCGIC scores (day 14: Pearson r=0.65, p<0.001; day 21: Pearson r=0.73, p<0.01). The conditional power to still detect a difference in NPI score of at least 4 points in favor of THC treatment, in case we would have been able to extend the trial from the actual number of subjects (n=47, 23 on THC and 24 on placebo) to the initially planned number of subjects (130, 65 per treatment arm), was 5%.

Safety

Adverse events

The occurrence of AEs was similarly divided along treatment groups (**Table 3**). In the THC group, 16 patients (66.7%) experienced at least 1 AE, compared to 14 (53.8%) in the placebo group (χ^2, p=0.36). Two patients dropped out due to the occurrence of AEs; one patient developed pneumonia within 2 days after initiation of THC treatment, and one patient experienced persistent nausea on placebo. One serious AE occurred during placebo treatment, which was not related to study medication. This patient was admitted to a specialized dementia care unit due to high caregiver burden.

Table 1 Demographics and patient characteristics

	All (n=50)	THC (n=24)	Placebo (n=26)
Men, *n (%)*	25 (50.0)	11 (45.8)	14 (53.8)
Age, yr, *mean (SD*)	78.4 (7.4)	79.0 (8.0)	78.0 (7.0)
Domestic situation, *n (%)*			
Community dwelling	24 (48.0)	13 (54.2)	11 (42.3)
Specialized dementia care unit	13 (26.0)	4 (16.7)	9 (34.6)
Nursing home	13 (26.0)	7 (29.2)	6 (23.1)
BMI, kg/m², *mean (SD)*[a]	25.0 (3.5)	25.0 (3.8)	25.0 (3.4)
Ethnicity, *n (%)*			
Caucasian	50 (100.0)	24 (100.0)	26 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Education, *mean (SD)*[b]	3.8 (1.6)	3.8 (1.6)	3.8 (1.6)
Type of dementia, *n (%)*			
Alzheimer	34 (68.0)	16 (66.7)	18 (69.2)
Vascular	7 (14.0)	3 (12.5)	4 (15.4)
Mixed	9 (18.0)	5 (20.8)	4 (15.4)
CDR ratio, *n (%)*			
1	11 (22.0)	5 (20.8)	6 (23.1)
2	19 (38.0)	9 (37.5)	10 (38.5)
3	20 (40.0)	10 (41.7)	10 (38.5)
MMSE score, *mean (SD)*[c]	14.8 (6.7)	15.9 (6.7)	14.0 (6.8)
Comorbidities, *n (%)*			
Vascular disorders	21 (42.0)	12 (50.0)	9 (34.6)
Nervous system disorders	19 (38.0)	11 (45.8)	8 (30.8)
Gastrointestinal disorders	18 (36.0)	7 (29.2)	11 (42.3)
Musculoskeletal disorders	17 (34.0)	8 (33.3)	9 (34.6)
Renal and urinary disorders	15 (30.0)	7 (29.2)	8 (30.8)
Psychiatric disorders	14 (28.0)	7 (29.2)	7 (26.9)
Other	24 (48.0)	22 (91.7)	20 (76.9)
Concomitant psychotropic medication, *n (%)*[d]			
Antipsychotics	10 (20.0)	7 (29.2)	3 (11.5)
Antidepressants	20 (40.0)	9 (37.5)	11 (42.3)
Benzodiazepines	21 (42.0)	8 (33.3)	13 (50.0)
Anticonvulsants	0 (0.0)	0 (0.0)	1 (3.8)
Cholinesterase inhibitors	8 (16.0)	5 (20.8)	3 (11.5)
Memantine	3 (6.0)	2 (8.3)	1 (3.8)
Melatonin	13 (26.0)	5 (20.8)	8 (30.8)
Concomitant analgesic medication, *n (%)*[d]			
Acetaminophen	15 (30.0)	5 (20.8)	10 (38.5)
NSAIDs	2 (4.0)	1 (4.2)	1 (3.8)
Opioids	2 (4.0)	1 (4.2)	1 (3.8)
Subgroup of patients with pain, *n (%)*[e]	23 (46.0)	8 (33.3)	15 (57.7)

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; VRS, Verbal Rating Scale; PACSLAC-D, Pain Assessment Checklist for Seniors with Limited Ability to Communicate – Dutch version.
[a] 3 missings on THC, 4 missings on placebo.
[b] Education was determined with seven categories where 1 indicates less than six years of primary school and 7 indicates a university degree. 6 missings on THC, 8 missings on placebo.
[c] 11 missings on THC, 10 missings on placebo.
[d] Concomitant medication used at time of screening. All analgesic medication was stopped prior to baseline assessments. When indicated, patients received acetaminophen for the duration of the intervention period.
[e] patients reporting pain, who are able to reliably assess pain intensity using VRS, or patients with a PACSLAC-D score of 4 points or more at baseline.

Other safety outcomes

There were no changes between the groups concerning heart rate, blood pressure, and weight (**Table 2**). Episodic memory scores were available for 18 patients with a mild dementia severity. PAL WMS-R scores decreased by 1.2 points in the THC group and 1.4 points in the placebo group, which was not significantly different (p=1.0).

Table 2 Overview of study results of the application of THC on neuropsychiatric symptoms in dementia

	No	THC	No	Placebo	Mean difference THC vs placebo (95% CI)
Primary outcomes					
NPI total score					
Baseline	24	37.4 (13.7)	26	35.6 (13.0)	
Day 14	19	31.0 (11.3)	23	26.1 (16.9)	
Day 21	23	27.8 (13.1)	24	23.9 (16.8)	+3.2 (-3.6 to 10.0)
NPI agitation/aggression subscale					
Baseline	24	5.7 (3.8)	26	6.2 (4.3)	
Day 14	19	4.1 (4.7)	23	5.0 (3.9)	
Day 21	23	4.5 (4.1)	24	4.4 (4.3)	-0.1 (-2.0 to 1.9)
NPI aberrant motor behavior subscale					
Baseline	24	4.5 (4.6)	26	5.2 (4.1)	
Day 14	19	4.9 (4.0)	23	4.3 (4.2)	
Day 21	23	3.6 (3.9)	24	3.7 (4.3)	+0.3 (-1.0 to 1.7)
Secondary outcomes					
CMAI					
Baseline	24	58.8 (18.5)	26	61.6 (16.4)	
Day 21	23	56.5 (17.5)	24	53.7 (18.3)	+4.6 (-3.0 to 12.2)
Barthel Index					
Baseline	24	13.8 (5.1)	25	13.3 (5.3)	
Day 21	22	13.3 (5.0)	24	12.0 (5.5)	+0.6 (-0.8 to 1.9)
QoL-AD					
Baseline	24	28.3 (4.9)	24	29.6 (5.2)	
Day 21	21	27.5 (4.6)	22	29.1 (5.0)	-0.5 (-2.6 to 1.6)
CCGIC*					
Day 14	20	3.7 (1.0)	25	3.4 (1.2)	
Day 21	22	3.5 (1.3)	24	3.2 (1.4)	+0.2 (-0.5 to 0.9)
Safety assessments					
Heart rate, *bpm*					
Baseline	23	69.8 (11.4)	24	74.5 (12.5)	
Day 21	22	66.3 (8.6)	24	71.6 (8.0)	-3.3 (-7.5 to 0.9)
Systolic Blood Pressure, *mmHg*					
Baseline	23	138.6 (21.2)	24	143.1 (15.9)	
Day 21	22	143.7 (16.8)	24	141.3 (20.9)	+3.4 (-6.5 to 12.2)
Diastolic Blood Pressure, *mmHg*					
Baseline	23	77.5 (8.0)	24	82.0 (10.4)	
Day 21	22	76.9 (7.1)	24	78.2 (9.3)	-1.8 (-6.6 to 3.1)
Weight, *kg*					
Baseline	22	71.0 (14.3)	22	70.9 (13.8)	
Day 21	20	70.4 (13.8)	22	71.1 (12.9)	-0.1 (-0.8 to 0.7)

Abbreviations: NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; QoL-AD, Quality of Life-Alzheimer's Disease Scale; CCGIC, Caregiver's Clinical Global Impression of Change. NOTE. Group numbers are means and standard deviations. Estimates of overall mean differences over day 14 and 21are based on linear mixed model analysis for repeated measures with correction for (subscale) NPI score at baseline, centre, CDR stage, sex, current opioid use, week and using a random intercept. A negative mean difference favors THC for NPI (range 0-144), CMAI (range 29-203) and CCGIC (range 1-7). A positive mean difference favors THC for Barthel Index (range 0-20) and QoL-AD (range 13-52). *7-point scale; 1, marked improvement; 2, moderate improvement; 3, minimal improvement; 4, unchanged; 5, minimal worsening; 6, moderate worsening; 7, marked worsening.

Table 3 Patients experiencing adverse events

MedDRA system organ class and preferred term	THC (n=24)	Placebo (n=26)
One or more adverse event, n (%)	16 (66.7)	14 (53.8)
Severe adverse events, n (%)	0 (0.0)	0 (0.0)
Nervous system disorders	10 (41.7)	13 (50.0)
Dizziness	4 (16.7)	4 (15.4)
Somnolence	2 (8.3)	4 (15.4)
Aphasia	1 (4.2)	1 (3.8)
Bradykinesia	0 (0.0)	1 (3.8)
Miosis	0 (0.0)	1 (3.8)
Muscle spams	0 (0.0)	1 (3.8)
Sensory loss	0 (0.0)	1 (3.8)
Headache	1 (4.2)	0 (0.0)
Muscular weakness	1 (4.2)	0 (0.0)
Balance disorder	1 (4.2)	0 (0.0)
Psychiatric disorders	7 (29.2)	4 (15.4)
Cognitive disorder	3 (12.5)	1 (3.8)
Restlessness	2 (8.3)	1 (3.8)
Agitation	0 (0.0)	1 (3.8)
Euphoric mood	0 (0.0)	1 (3.8)
Apraxia	1 (4.2)	0 (0.0)
Delirium	1 (4.2)	0 (0.0)
Investigations	1 (4.2)	6 (23.1)
Gamma-glutamyltransferase increased	1 (4.2)	2 (7.7)
Aspartate aminotransferase increased	0 (0.0)	2 (7.7)
Blood alkaline phosphatase increased	0 (0.0)	1 (3.8)
Hepatic enzyme increased	0 (0.0)	1 (3.8)
Gastrointestinal disorders	4 (16.7)	2 (7.7)
Nausea	2 (8.3)	1 (3.8)
Diarrhoea	0 (0.0)	1 (3.8)
Abdominal pain, upper	1 (4.2)	0 (0.0)
Gastrooesophageal reflux disease	1 (4.2)	0 (0.0)
General disorders	2 (8.3)	3 (11.5)
Fatigue	2 (8.3)	2 (7.7)
Malaise	0 (0.0)	1 (3.8)
Injury and procedural complications	1 (4.2)	3 (11.5)
Fall	1 (4.2)	3 (11.5)
Respiratory disorders	4 (16.7)	0 (0.0)
Pneumonia	2 (8.3)	0 (0.0)
Chronic obstructive pulmonary disease	1 (4.2)	0 (0.0)
Nasopharyngitis	1 (4.2)	0 (0.0)
Cardiac disorders	1 (4.2)	2 (7.7)

Chest pain	0 (0.0)	1 (3.8)
Syncope	0 (0.0)	1 (3.8)
Presyncope	1 (4.2)	0 (0.0)
Musculoskeletal disorders	3 (12.5)	0 (0.0)
Back pain	1 (4.2)	0 (0.0)
Neck pain	1 (4.2)	0 (0.0)
Pain in extremity	1 (4.2)	0 (0.0)
Eye disorders	0 (0.0)	2 (7.7)
Drye eyes	0 (0.0)	1 (3.8)
Eye heamorrhage	0 (0.0)	1 (3.8)
Renal and urinary disorders	0 (0.0)	2 (7.7)
Renal impairment	0 (0.0)	1 (3.8)
Urge incontinence	0 (0.0)	1 (3.8)
Skin disorders	2 (8.3)	0 (0.0)
Intertrigo	1 (4.2)	0 (0.0)
Skin disorder, NOS	1 (4.2)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (3.8)
Decreased appetite	0 (0.0)	1 (3.8)
Blood and lymphatic system disorders	1 (4.2)	0 (0.0)
Anaemia	1 (4.2)	0 (0.0)
Social circumstances	0 (0.0)	1 (3.8)
Family stress	0 (0.0)	1 (3.8)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; THC = tetrahydrocannabinol. Values are numbers of patients (%)

DISCUSSION

We found no benefit of 4.5 mg oral THC daily on behavioral disturbances in patients with dementia after 3 weeks of treatment. Additionally, there were no benefits for THC on quality of life, activities of daily living, or pain-related behavior and pain intensity (**Appendix**), while THC was safe and well-tolerated. The number of patients experiencing AEs was similar in both groups, while known THC-mediated AEs, such as dizziness, somnolence, and falls, were more frequently reported during placebo treatment. None of the participants reported a feeling "high," nor was behaving "high" observed by caregivers or research staff.

The current trial is the largest randomized controlled trial (RCT) so far studying oral THC in NPS in dementia, with valid

and rigorous trial methods. The study sample was representative for the overall dementia population, in terms of age, dementia severity, and domestic situation. Patients with severe aggressive behavior could not be included, as the study's safety assessments cannot be adequately conducted in this group. Taking into account this limitation associated with this specific patient population, we have included a sample that is representative for the majority of the target population with clinically relevant NPS; the level of behavioral disturbances, assessed by NPI, was moderate and comparable to previous intervention trials.[33–35] We observed an improvement in NPS in both groups over the duration of the study period, which has been reported before.[34,35] The substantial degree of improvement in the placebo group is striking (**Table 2**), and may be due to many factors including attention and support by the study team, expectations of patients and caregivers concerning THC, and training of nursing home personnel (together called the Hawthorne or in- study effect[36]). To correct for this substantial placebo response within individual patients, it might be worthwhile to implement an individually randomized crossover design in future studies. Despite the fact that we studied a vulnerable patient population, the attrition level was low (6%) and adherence high (98%–100%). This suggests a highly motivated group of participants and caregivers, in combination with the occurrence of only mild AEs.

This study has some limitations. Most importantly, we failed to enroll the planned number of patients, despite comprehensive recruitment efforts throughout various health care settings. Rigorous national regulations on medical cannabinoids hindered implementation of the study in the participating clinics. Additionally, fewer than expected patients visiting the clinics had clinically relevant NPS as well as pain. Omitting the latter inclusion criterion significantly stimulated the recruitment. Despite this underenrollment, the conditional power of 5% emphasizes that it was very unlikely that exposure of more participants to the study interventions and assessments would have influenced our conclusion. Contrary to the current RCT,

previous studies all reported positive effects of oral THC (2.5–7 mg daily) in patients with dementia.[12,13,21,37] However, important methodologic factors significantly limit the robustness of these findings: inclusion of small number of patients (n=2 and n=15) and uncontrolled or retrospective study designs. In a previous randomized trial, we studied dosages up to 3 mg THC daily, and did not observe a significant reduction in NPS, nor any relevant AEs or effects on vital functions or mobility (unpublished data, 2014). Therefore, we used a dosage of 4.5 mg THC daily in this study.

Recent developments regarding the extended legalization of marijuana for medical purposes in over 30 US states has stimulated the discussion of the therapeutic potential and safety profile of cannabinoids for various indications.[38,39] Momentarily, effective and safe treatments for NPS in patients with dementia are lacking.[40] Several pharmacotherapeutic options have been explored, such as acetyl- cholinesterase inhibitors and antidepressants,[33,34] but they often have a suboptimal benefit-risk profile. For example, while high-dose citalopram appears to effectively reduce agitation and overall behavioral disturbances, significant cardiac AEs limit its usefulness in this vulnerable population.[34]

Our current trial indicates that 4.5 mg THC daily can be safely administered to patients with dementia. The observation that there was no biological signal of AEs suggests that the dosage was too low, as a psychoactive drug is rarely effective without showing any side effects. Therefore, our results warrant further research using higher dosages of THC in the treatment of dementia-related NPS.

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Appendix

Efficacy of THC in the treatment of pain in dementia patients with neuropsychiatric symptoms

Methods

The efficacy on pain-related behavior and pain intensity was evaluated in a subgroup of patients suffering from NPS as well as pain. This subgroup was defined as follows: 1) patients with persistent pain complaints, who could indicate their own pain intensity reliably, as judged by a research physician, or 2) patients with score of four points or more at baseline on the Pain Assessment Checklist for Seniors with Limited Ability to Communicate, Dutch version (PACSLAC-D). The PACSLAC-D[1] is an observational assessment scale for assessment of pain in non-communicative persons and was used in this study to assess pain-related behaviour at baseline and after 21 days of treatment. Pain intensity was assessed by self-report, using the Verbal Rating Scale (VRS).[2] This is a six-point scale ranging from 'no pain' to 'worst imaginable pain'. VRS assessments were done at every visit by means of an interview with the participant, and on a daily basis using a diary. Efficacy of THC on pain reduction was evaluated in a Linear Mixed Model with participants as random factor and baseline scores as fixed factor. VRS diary scores were not analyzed, as these assessments did not appear to be feasible in this patient group because of their cognitive decline, and resulted in too few available and reliable scores. Pearson correlation coefficients were calculated for change from baseline for PACSLAC-D and VRS interview scores, NPI and PACSLAC-D at day 21, NPI and VRS interview at day 21

Results

In total, 23 patients were included in the subgroup 'pain'. Within this group, more patients received placebo than THC (15 vs. 8 patients).

PACSLAC-D scores were available for 20 patients (THC, n=7; Placebo, n=13), while 13 patients completed the VRS interview assessments (THC, n=4; Placebo, n=9). No treatment differences between THC and placebo were observed on PACSLAC-D (-1.1, 95% CI -6.0 to 3.8) or VRS (-0.03, 95% CI -0.95 to 0.90) (**Appendix Table 2**). Overall, there is an indication that a reduction in PACSLAC-D score is positively correlated with VRS interview score (Pearson's r=0.35, p=0.06). No correlation was found between PACSLAC-D and NPI total score (Pearson's r=0.21, p=0.21) nor between VRS interview and NPI total score (Pearson's r=0.16, p=0.36).

Discussion

Low dose of THC did not result in benefit on pain-related behavior and pain intensity, compared to placebo. Our ability to study the analgesic effects of THC was limited, due to the small number of patients included in the pain assessments, because of lower prevalence of pain related behavioural disturbances than expected and the limitations of pain assessment in this patient group. These results should therefore be interpreted with caution. While self-reporting of pain is often referred to as 'gold-standard',[3] VRS assessments are only suitable for patients with mild dementia severity as it requires the capability of understanding the task and communicating the experienced sensation. Therefore, the PACSLAC-D, an observational assessment scale, is developed for assessment of pain in non-communicative persons.[1] This scale is more appropriate for nursing home patients than for community-dwelling patients, as this first group often express pain and discomfort through changes in behaviour. Future studies on the efficacy of THC as analgesic treatment, which are still warranted, should focus on a more homogeneous patient group, in whom a single pain assessment scale is feasible.

Appendix Table 1 Overview of the results of the application of THC on pain assessments in dementia patients

	n	THC	n	Placebo	Mean difference THC vs placebo (95% CI)
VRS interview					
Baseline	5	2.6 (1.3)	11	3.1 (1.8)	-0.03 (-1.0 to 0.9)
Day 21	4	2.3 (1.0)	9	2.3 (1.0)	
PACSLAC-D					
Baseline	8	8.4 (5.2)	15	7.2 (4.1)	-0.4 (-3.8 to 3.0)
Day 21	7	7.4 (8.0)	13	6.2 (5.5)	

Abbreviations: VRS, Verbal Rating Scale; PACSLAC-D, Pain Assessment Checklist for Seniors with Limited Ability to Communicate-Dutch version.
NOTE. Group numbers are means and standard deviations. Estimates of mean differences are based on linear mixed model analysis for repeated measures with participant as random effects for the subgroup of patients with pain. A negative mean difference favors THC for VRS and PACSLAC-D.

Appendix Table 2 Study results of the application of THC on neuropsychiatric symptoms in dementia for all subdomains of Neuropsychiatric Inventory

	n	THC	n	Placebo	THC vs. placebo (95% CI)
NPI delusions					
Baseline	24	1.8 (3.0)	26	1.8 (3.3)	
Day 14	19	1.9 (3.6)	23	1.3 (2.6)	
Day 21	23	2.0 (3.5)	24	1.5 (2.7)	+0.7 (-0.5 to 1.9)
NPI hallucinations					
Baseline	24	0.8 (2.6)	26	0.3 (1.2)	
Day 14	19	0.3 (1.4)	23	0.3 (1.7)	
Day 21	23	0.0 (0.2)	24	0.3 (1.2)	-0.2 (-0.9 to 0.4)
NPI agitation/ aggression	24	5.7 (3.8)	26	6.2 (4.3)	
Baseline	19	4.1 (4.7)	23	5.0 (3.9)	
Day 14	23	4.5 (4.1)	24	4.4 (4.3)	-0.1 (-2.0 to 1.9)
Day 21					
NPI dysphoria					
Baseline	24	2.9 (4.0)	26	3.4 (3.6)	
Day 14	19	1.6 (2.4)	23	2.1 (2.7)	
Day 21	23	2.3 (2.6)	24	1.8 (2.8)	0.0 (-1.0 to 1.1)
NPI anxiety					
Baseline	24	2.5 (4.0)	26	2.6 (3.7)	
Day 14	19	2.1 (3.5)	23	1.0 (2.6)	
Day 21	23	1.5 (2.8)	24	1.3 (2.3)	+0.5 (-0.7 to 1.8)
NPI euphoria					
Baseline	24	(2.5)	26	0.3 (0.9)	
Day 14	19	0.3 (1.4)	23	0.3 (1.7)	
Day 21	23	0.5 (1.3)	24	0.0 (0.2)	+0.1 (-0.5 to 0.6)
NPI apathy					
Baseline	24	5.0 (3.7)	26	2.5 (3.1)	
Day 14	19	5.1 (3.5)	23	2.4 (3.3)	
Day 21	23	4.1 (3.4)	24	2.3 (3.1)	+0.1 (-1.1 to 1.3)
NPI disinhibition					
Baseline	24	2.5 (3.3)	26	3.1 (3.4)	
Day 14	19	1.5 (2.6)	23	2.1 (3.0)	
Day 21	23	2.1 (3.2)	24	2.4 (3.4)	-0.1 (-1.6 to 1.4)

NPI irritability					
Baseline	24	5.3 (4.3)	26	5.7 (4.8)	
Day 14	19	5.1 (4.0)	23	4.2 (3.8)	
Day 21	23	4.3 (4.1)	24	3.9 (4.1)	+0.7 (-1.1 to 2.4)
NPI aberrant motor behavior	24	4.5 (4.6)	26	5.2 (4.1)	
Baseline	19	4.9 (4.0)	23	4.3 (4.2)	
Day 14	23	3.6 (3.9)	24	3.7 (4.3)	+0.3 (-1.0 to 1.7)
Day 21					
NPI nighttime behavior disturbances	24	2.5 (3.6)	26	2.5 (3.1)	
Baseline	19	1.4 (2.8)	23	2.2 (3.4)	
Day 14	23	0.8 (2.0)	24	1.8 (2.8)	-0.7 (-1.8 to 0.4)
Day 21					
NPI appetite and eating abnormalities	24	3.1 (4.0)	26	2.1 (3.4)	
Baseline	19	2.8 (3.8)	23	0.8 (1.9)	
Day 14	23	2.0 (3.0)	24	0.7 (1.6)	+1.0 (0.0 to 1.9)
Day 21					

Abbreviations: NPI, Neuropsychiatric Inventory
NOTE. Group numbers are means and standard deviations. Estimates of overall mean differences are based on linear mixed model analysis for repeated measures with participant as random effects. A negative mean difference favors THC for NPI subdomains.

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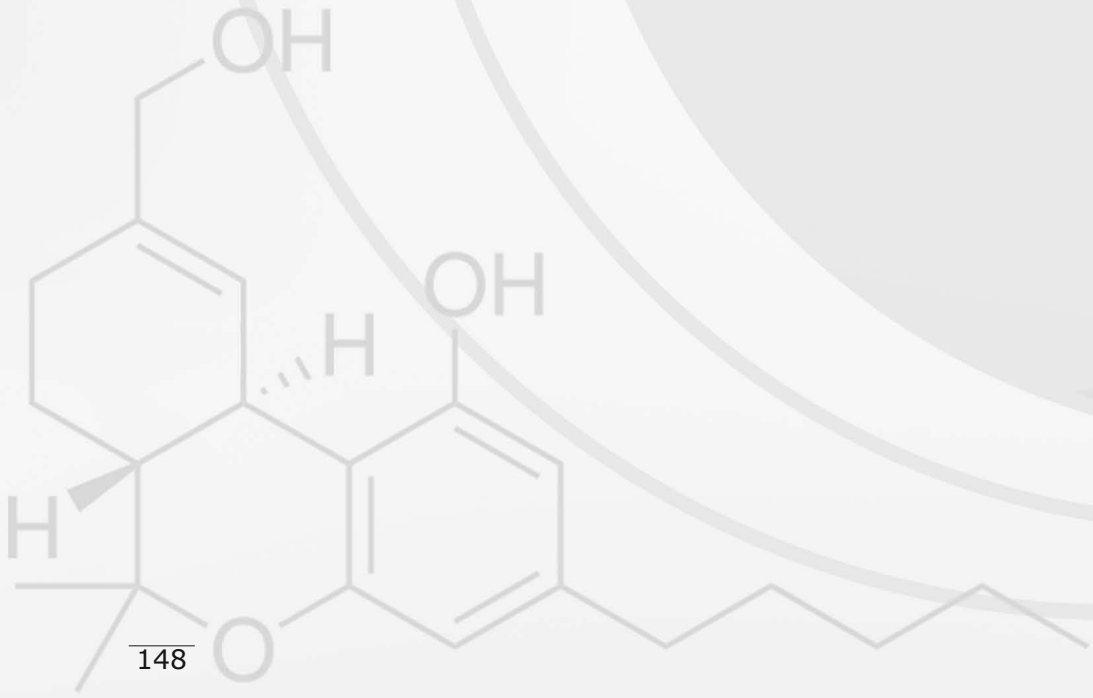
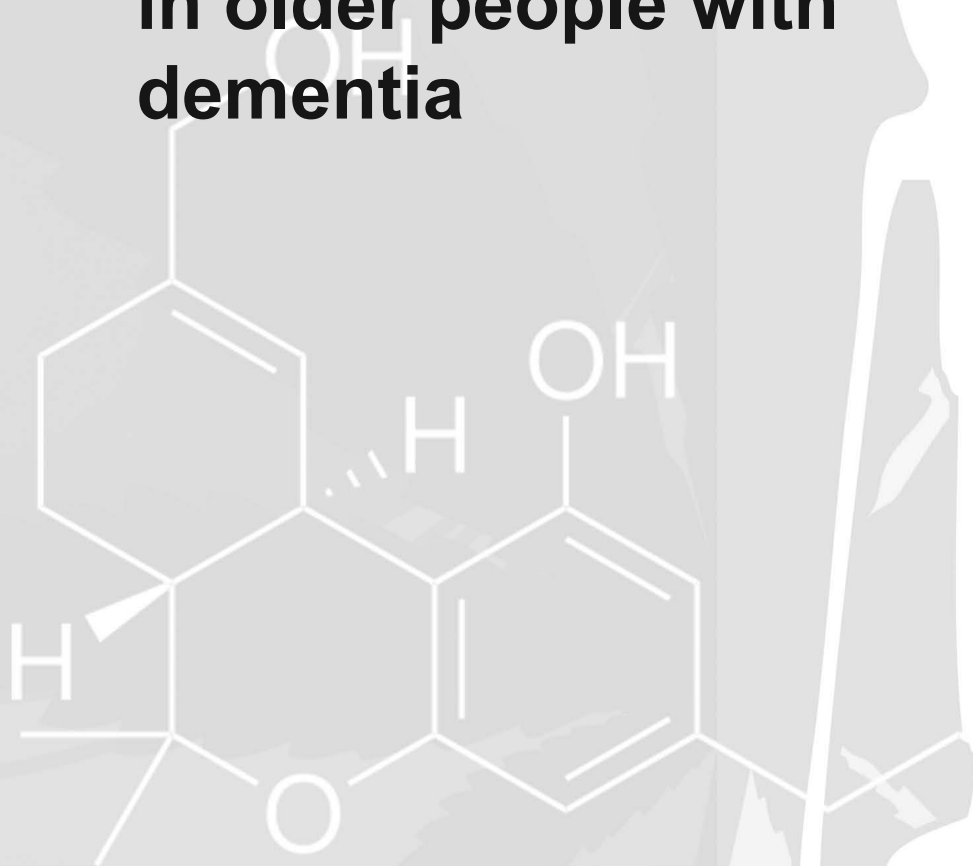


PART IV

Safety, pharmacodynamics, and pharmacokinetics of oral tetrahydrocannabinol in older people with dementia



Chapter 5

Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial

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Abstract

There is a great concern about the safety of THC-based drugs in older people (≥ 65 years), as most of THC-trials did not include such group. In this phase 1, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial, we evaluated the safety and pharmacokinetics of three oral doses of Namisol®, a novel THC in tablet form, in older subjects. Twelve healthy older subjects (6 male; mean age 72±5 years) randomly received a single oral dose of 3 mg, 5 mg, or 6.5 mg of THC or matching placebo, in a crossover manner, on each intervention day. The data for 11 subjects were included in the analysis. The data of 1 subject were excluded due to non-compliance to study medication.

THC was safe and well tolerated. The most frequently reported adverse events (AEs) were drowsiness (27%) and dry mouth (11%). Subjects reported more AEs with THC 6.5 mg than with 3 mg (p=0.048), 5 mg (p=0.034) and placebo (p=0.013). There was a wide interindividual variability in plasma concentrations of THC. Subjects for whom the C_{max} fell within the sampling period (over 2 h), C_{max} was 1.42–4.57 ng/mL and t_{max} was 67–92 min. The AUC_{0-2h} (n=11) was 1.67–3.51 ng/mL. Overall, the pharmacodynamic effects of THC were smaller than effects previously reported in young adults.

In conclusion, THC appeared to be safe and well tolerated by healthy older individuals. Data on safety and effectiveness of THC in frail older persons are urgently required, as this population could benefit from the therapeutic applications of THC.

Introduction

The cannabis plant (*Cannabis sativa L.*) has been used to treat a range of symptoms and diseases for more than 4000 years.[1, 2] Its broad therapeutic applications reflect the various pharmacological and physiological effects of cannabinoids, the bioactive components of the cannabis plant.[3] The plant contains more than 60 cannabinoids, such as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol, and cannabichromene.[3] While the pharmacological effects of most cannabinoids are still not known, THC appears to be responsible for most of the physical and psychoactive effects of cannabis.[3] Cannabinoids exert their effects by binding to two cannabinoid receptors, i.e. CB1, which is expressed primarily in the central nervous system, and CB2, which is found primarily in the immune system and hematopoietic cells.[4-6]

In recent years, cannabinoid-based drugs and non-smoking routes of drug administration have been investigated in clinical trials. To date, there are only two oral cannabis-based medicines (dronabinol and nabilone) available by prescription in some countries, and one available as an oromucosal mouth spray (nabiximols). Dronabinol (synthetic THC) and nabilone (THC analog), are approved by the United States Food and Drug Administration, and in some European countries, for appetite stimulation in AIDS-related anorexia and chemotherapy-induced nausea and vomiting. Nabiximols (Sativexs), which contains both THC and CBD, is approved in the United Kingdom and in some other European countries and Canada, but not in the USA, for the management of pain and spasticity in patients with multiple sclerosis.

Growing interest in the medical use of cannabis has recently led to the development of Namisol®. Namisol® is a novel cannabinoid-based drug formulation that contains THC (≥ 98%) in tablet form. It was developed using a novel drug delivery technology, Alitra™ to improve its absorption and bioavailability.[7] The results of the first trial in humans investigating the optimal route of administration, safety, pharmacokinetics, and pharmacodynamics of the drug showed that Namisol® (5 mg, 6.5 mg, and 8 mg) might have more

favorable pharmacokinetics and pharmacodynamics than currently available cannabinoid-based drugs.[7] This is because Namisol® showed 1) a faster absorption and a shorter time to reach the maximal THC concentrations; 2) a smaller variability in t_{max} (time to maximum plasma concentration) and plasma concentrations; and 3) faster pharmacodynamic effects, which are important for achieving a rapid clinical effect.[7] Klumpers et al.[7] also reported that Namisol® was safe and well tolerated by subjects.[7] However, their study involved only young adults (mean age 21.4 years, range 18–27 years), and so findings cannot directly be extrapolated to older population (65 years and older). Older people are in general more likely to experience adverse drug events, due to a combination of age-related physiological changes (such as a decrease in lean body mass, diminished renal and hepatic clearance) and a high prevalence of comorbidities, which can lead to polypharmacy and drug–drug interactions.[8-10]

The aims of this trial were first, to assess the safety and tolerability of three oral doses of THC (3 mg, 5 mg, and 6.5 mg) in healthy older subjects. Second, to evaluate the pharmacokinetics of THC in older people and to investigate the relationship between the drug0s pharmacodynamic effects and the plasma concentrations of THC and its active metabolites 11-hydroxy-delta-9-THC (11-OH-THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH).

Experimental procedures

Study design and participants

This phase 1, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial (ClinicalTrials.gov ID NCT01740960) was approved by the local ethics committee (Registration number: NL 40591.091.12) and carried out at the Radboud University Medical Center, Nijmegen, The Netherlands. The trial was performed according to the International Conference on Harmonization guideline for good clinical practice, the ethical principles of the Declaration of Helsinki, and the related Dutch laws and regulations. The subjects were healthy elderly volunteers who were recruited between August

and November 2012 through personal contacts and word of mouth. All subjects provided written informed consent before they were screened for eligibility. Inclusion criteria were age 65 years or older; physically healthy, based on a medical history, physical examination, electrocardiography (ECG), results of hematological and biochemical blood tests on screening; and body mass index between 18.0 and 30 kg/m^2. Main exclusion criteria were high falls risk (based on body sway test); regular cannabis use (defined as smoking one or more cannabis cigarettes per week); history of sensitivity/idiosyncrasy to cannabis; history of drug or alcohol abuse; smoking more than ten cigarettes a day; history of severe comorbidities (e.g. COPD GOLD III or IV; heart failure NYHA III or IV) or diabetes mellitus; history of psychiatric or cognitive disorders; consumption of more than six units of (methyl)xanthine products per day (e.g. coffee, tea, cola, chocolate); use of drugs that inhibit CYP2C9, CYP2C19 and CYP3A4, and was not possible to discontinue the use of the drugs during the study period.

Randomization and masking

Subjects were randomly allocated to receive a single dose of 3 mg (two 1.5 mg tablets), 5 mg (one tablet), or 6.5 mg (one 5 mg and one 1.5 mg tablet) of Namisol® or matching placebo in a double-blind, double-dummy manner on each intervention day. Subjects received three tablets per visit, two of 6-millimeter and one of 9-millimeter (Namisol® or matching placebo). This double-dummy technique was used because of difference of the size of Namisol® tablets, 1.5 mg (6 mm) and 5 mg (9 mm). Each subject acted as his/her own control and therefore received all study medications (single dose per visit) in a crossover design on four occasions (visits 1–4). The washout period between the visits was 2 weeks. Namisol® and placebo tablets were identical in appearance. The randomization codes were generated by a computer algorithm for random numbers and could only be accessed by the site pharmacist. Study drugs were labeled with a unique identification number before delivery to the investigators. Sponsor, investigators, site staff, and subjects were masked to assignment.

Interventions

The intervention period (visits 1 to 4) was preceded by a screening visit (visit 0) that occurred maximally 2 weeks before randomization, during which subjects' medical history was taken and they underwent a physical examination, ECG, hematological and bio- chemical blood tests, the Mini Mental State Examination (MMSE), the Geriatric Depression Scale (GDS-30) test, and body sway test, using the SwayStar™. Subjects who fulfilled the eligibility criteria were randomly allocated to receive the trial medications, which were administered orally with 100 mL water.

Subjects were asked to abstain from smoking (12 h) and consuming alcohol (24 h), grapefruit (48 h) or quinine (24 h) and xanthine-containing beverages or foods (12 h) before each intervention. They were asked not to drive a car for 24 h after ingestion of the trial medication or to drink more than 2 glasses of alcohol a day or to smoke more than ten cigarettes per day. All subjects were instructed to contact the investigator if they developed fever (38°C or higher) 3 days before the intervention day and not to start any medication without consulting the investigator. Subjects who used medication that interacts with THC had to discontinue the medication temporarily during the study period (approximately 8 weeks).

Safety assessments

The primary endpoint of the trial was the safety of Namisol®, which was assessed by evaluating the incidence and severity of adverse events using a standardized THC adverse events checklist and spontaneous reporting, vital signs (including systolic and diastolic blood pressure, and heart rate), 12-lead ECG, Visual Analog Scales (VAS-subtest feeling high), and laboratory safety tests (hematology and chemistry). The Test for Attentional Performance (TAP-subtest alertness) and SwayStar™ were used to evaluate the effects of Namisol® on subjects' attention and body sway. On each intervention day, safety was monitored by research staff for 3.5 h after dosing. Moreover, subjects were tele- phoned 24 h after drug (active or placebo) ingestion to determine the occurrence of adverse events after discharge. All adverse events were recorded with regard to

their time of onset, severity, duration, and possible relationship to the study drug. The Medical Dictionary for Regulatory Activities was used for coding adverse events.

VAS-Feeling high: "Feeling high" was assessed with the Bowdle VAS for psychedelic effects.[11] Subjects were asked to score 'feeling high' on a 100-mm horizontal line, with '0' indicating not feeling high and '100' indicating feeling extremely high.

TAP-Alertness: A computerized subtest of the TAP was used to measure alertness (reaction time) under two conditions. First, a simple reaction time to a visual stimulus, a cross "X", appearing on the monitor screen at randomly varying intervals. The subject had to respond as quickly as possible by pressing a key when "X" appeared on the screen. Second, the visual stimulus "X" was preceded by a cue stimulus presented as warning tone. The subject had to respond only when "X" appeared on the screen. TAP scores are given in milliseconds.

Body sway: The SwayStar™ (*http://www.b2i.info/web/index.htm*), a wireless device attached to the trunk (L3–L5), was used to measure body sway over 1 min. The subjects were asked to stand quietly and relaxed with feet slightly apart on a firm surface, first with eyes open for 30 sec and then with eyes closed for 30 sec. The range of pitch velocity scores (anterior–posterior movements) was used for analysis. Scores are given in degrees per second.

Blood sampling and laboratory analysis

Venous blood samples were collected in EDTA-coated tubes (6 mL) before and at 40, 55, and 120 min after dosing, for the measurement of plasma concentrations of THC, 11-OH-THC, and THC-COOH. The tubes were placed on ice and within 60 min were centrifuged for 10 min (2000g, 4 °C). The plasma was pipetted into two 1.5 mL cryotubes, which were stored at -80 °C until analysis. The plasma concentrations were analyzed at the Analytisch Biochemisch Laboratorium b.v. (Assen, The Netherlands), using liquid chromatography/ mass spectrometry/mass spectrometry. The

lower limit of quantification was 0.1 ng/mL for THC and 11-OH-THC, and 0.5 ng/mL for THC-COOH. The analysis was performed using a validated assay according to good laboratory practice standards. The acceptance criteria for an analytical run was based on bioanalytical methods validation for human studies,[12, 13] which included accuracy, precision, selectivity, post-preparative stability, dilution of samples, freeze/thaw stability, refrigerator stability, whole blood stability, and long term stability.

Pharmacodynamic assessments

The VAS-feeling high, TAP-alertness, and body sway were used to evaluate the secondary endpoint of this trial, the relationship between pharmacodynamic effects of Namisol® and the plasma concentrations of THC and its active metabolites. All assessments were carried out directly after blood sampling, pre-dosing and at 40, 55 and 120 min after dosing.

Statistical analysis

Descriptive statistics were used to describe the study population. The continuous data are expressed as means ± standard deviation (±SD), and categorical data are expressed as frequencies. This study is descriptive and explorative. The primary endpoint was the safety of THC, based on incidence and severity of reported adverse events. To explore the association between administered dose of Namisol® (3 mg, 5 mg, and 6.5 mg) and the occurrences of adverse events, Generalized Estimating Equations (GEE) were used to compare the proportion of subjects experiencing one or more adverse events, and random effects analyses with non-linear mixed models (NLMIXED) to compare the number of adverse events per subject per dose, assuming that adverse events had a Poisson distribution. The VAS, TAP, and body sway scores were analyzed in relation to the Namisol® doses, using linear mixed models. The effects of the three Namisol® doses on the plasma concentrations of THC, 11-OH-THC, and THC-COOH, which were measured 40, 55, and 120 minutes after dosing, were analyzed with linear mixed models to take into account the longitudinal character of the data. Pharmacokinetic parameters

including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the curve from t = 0 to 2 h (AUC) were calculated using Phoenix WinNonlin 6.3 (Certara, L.P./Pharsight Ltd). For secondary endpoint of the study, the TAP and body sway scores were analyzed in relation to THC, 11-OH-THC, and THC-COOH plasma concentrations, using linear mixed models. In all linear mixed models we used "volunteer" as a random effect. P values < 0.05 were considered to indicate significance. No correction was made for multiple testing because of the explorative character of study. All statistical analyses were performed using SASMT software (version 9.2).

Results

Baseline characteristics

Twelve healthy elderly subjects (6 male; mean age 72±5 years, range 65–80 years) were randomized. Their demographic characteristics are summarized in **Table 1**. None of the subjects had ever used cannabis and all were in good physical and mental health. Only one subject was a cigarette smoker (average 5 cigarettes/day); 11 subjects used moderate amounts of alcohol. Four subjects had no relevant medical history and did not use medications. The most common health problems were hypertension (n=3) and hypercholesterolemia (n=3). The subjects used an average of 2±2.1 medications, with cardiovascular drugs such as lipid-lowering drugs, aspirin, and beta-blockers being the most commonly used medications.

Safety and tolerability

The data for 11 subjects (5 men and 6 women) were included in the analysis. The data of 1 subject were excluded due to non-compliance to study medication. **Table 2** lists all reported adverse events by dose (40 in total). The first adverse events were observed 20 min after dosing. All adverse events were mild and most occurred between 55 and 120 min after dosing and resolved spontaneously before the end of the intervention day (within 3.5 h after dosing).

Table 1 Demographics and baseline characteristics of subjects randomized in the trial.

Characteristics	n = 12
Male, n (%) Female, n (%)	6 (50) 6 (50)
Age, mean (SD); [range] years	72.1 (5); [65 - 80]
Caucasian race, n (%)	12 (100)
Smokers, n (%)	1 (8)
Cannabis users, n (%)	0 (0)
Alcohol users, n (%) ≤ 2 alcoholic beverage/day, n 3 - 4 alcoholic beverage/day, n	11 (91.7) 8 3
[a]BMI, mean (SD); kg/m^{-2}	26.4 (1.5)
Weight, mean (SD); kg	77.3 (9.8)
Height, mean (SD); meter	170.9 (9.2)
[a]SBP, mean (SD); mmHg	134.3 (10.6)
[a]DBP, mean (SD); mmHg	76.7 (6.9)
[a]HR, mean (SD); beats/minutes	61.3 (10.4)
[a]MMSE-30, mean (SD)	29.8 (0.6)
[a]GDS-30, mean (SD)	0,17 (0.4)
Number of medications used by subject, mean (SD)	2 (2.1)
[b]Concomitant medications, n (%)	
Lipid lowering	7 (58.3)
Aspirin	4 (33.3)
Beta-blockers	3 (25)
Angiotensin-converting-enzyme inhibitors	2 (16.7)
Calcium channel blockers	2 (16.7)
Thiazide diuretics	2 (16.7)
Proton pump inhibitors	1 (8.3)
Laxatives	1 (8.3)
Eye drops	1 (8.3)
Comorbidities, n (%)	
Hypertension	3 (25)
Hypercholesterolemia	3 (25)
Cholecystectomy (past)	2 (16.7)
Valve disease	1 (8.3)
Stable angina	1 (8.3)
Myocardial infarction (past)	1 (8.3)
Colon cancer (past)	1 (8.3)
Glaucoma	1 (8.3)

[a]BMI: body mass index; SPB: systolic blood pressure, DBP: diastolic blood pressure; HR: heart rate; MMSE: mini mental state examination; GDS: geriatric depression scale.
[b]Number of subjects who used one or more medications

There were no serious adverse events during the trial. More subjects reported one or more adverse events with Namisol® 3 mg (5 subjects, p=0.036), 5 mg (5 subjects, p=0.036) and 6.5 mg (7 subjects, p=0.008) than with placebo (1 subject) and overall the subjects reported fewer adverse events with placebo (total 1 event, p=0.013), Namisol® 3 mg (9 adverse events, p=0.048) and 5 mg (8 adverse events, p=0.034) than with Namisol® 6.5 mg (22 adverse events). Overall, the most frequently reported adverse events were drowsiness (27%; including one on placebo), dry mouth (11%), coordination disturbance (9%), and headache (9%). There were no clinically relevant changes in systolic or diastolic blood pressure (difference of 20 mmHg and 15 mmHg at rest, respectively) and heart rate (difference of 20 beats/minute) after the administration of trial medication. The ECG parameters (e.g. QT and RR intervals) were unchanged from screening to the end of trial, and all laboratory test results were within the normal range.

VAS-Feeling high scores indicated that four subjects (three females and one male) "felt high" after THC. Subject A, a 71-year-old woman (BMI 28.1 kg/m^2) had a VAS score of 8 mm 120 min after 3 mg Namisol®, and 13 and 16 mm 55 and 120 min after 5 mg Namisol®, respectively. Subject B, a 68-year-old man (BMI 26.1 kg/m^2), had VAS scores of 9 and 7 mm 55 and 120 min after 5 mg Namisol®, respectively. Subject C, a 71-year-old woman (BMI 26.5 kg/m^2), had a VAS score of 25 mm 120 min after 6.5 mg Namisol®, and subject D, a 73-year-old women (BMI 23.5 kg/m^2), had a VAS score of 6 mm 120 min after 6.5 mg Namisol®. No significant changes were found in subjects' attentional performance (TAP-scores p=0.18) or body sway (eyes open p=0.18; eyes closed p=0.16) after the administration of trial medication.

Table 2 Overview of all 40 drug-related adverse events reported by subjects or observed by investigator during the trail

Type of adverse events n (%)		**Placebo** n=11	Namisol			[a]**Total**
			3 mg n=11	**5 mg** n=11	**6.5 mg** n=11	
1	Drowsiness[b]	1 (9)	5 (45)	2 (18)	4 (36)	12 (27)
2	Dry mouth	0 (0)	0 (0)	2 (18)	3 (27)	5 (11)
3	Coordination disturbance	0 (0)	1 (9)	1 (9)	2 (18)	4 (9)
4	Headache	0 (0)	1 (9)	1 (9)	2 (18)	4 (9)
5	Concentration problem	0 (0)	0 (0)	1 (9)	2 (18)	3 (7)
6	Blurred vision	0 (0)	0 (0)	0 (0)	2 (18)	2 (5)
7	Relaxation	0 (0)	1 (9)	0 (0)	1 (9)	2 (5)
8	Euphoria	0 (0)	1 (9)	0 (0)	1 (9)	2 (5)
9	Dizziness	0 (0)	0 (0)	1 (9)	1 (9)	2 (5)
10	Nausea	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
11	Dry eyes	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
12	Malaise	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
13	Visual hallucinations	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
[c]Total number of adverse events / dose		1, *p=0.013*	9, *p=0.048*	8, *p=0.034*	22, *p=1*	40
[d]Number of subjects (out of 11) with one or more adverse events, n (%)		1 (9), *p=1*	5 (45), *p=0.036*	5 (45), *p =0.036*	7 (64), *p=0.008*	18 (41)

[a]Total number of reports per adverse event
[b]Number (n) and percentages (%) of subjects reported an adverse event
[c]*P*-values based on pairwise comparisons of Namisol® 6.5 mg (reference) with placebo, and with the doses of 3 mg and 5 mg, using NLMIXED analyses.
[d]*P*-values based on pairwise comparisons of each of Namisol® doses with placebo (reference), using Generalized Estimating Equations analyses.

Pharmacokinetic parameters

The mean THC, 11-OH-THC, and THC-COOH concentration–time curves are shown in **Figure 1**. Plasma concentrations of THC, 11-OH-THC, and THC-COOH were dose-dependent and significantly increased with increasing the dose of Namisol ($p < 0.0001$). **Table 3** lists the mean pharmacokinetic parameters of THC. There was a wide inter-individual variability in plasma concentrations of THC, 11-OH-THC and THC-COOH. In one subject the THC concentration had not reached a maximum by 120 min after 3 mg Namisol®, and in four and five subjects after 5 mg and 6.5 mg Namisol®, respectively. For subjects for whom C_{max} fell within the sampling interval (120 min), the geometric mean THC C_{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).

Table 3 The mean pharmacokinetic parameters of THC after administration of single dose Namisol®

Parameters (mean and range)	3 mg (n=11)	5 mg (n=11)	6.5 mg (n=11)
THC[a]	1.2 (0.13-3.48)	1.9 (0.26-6.95)	2.61 (0.23-8.65)
11-OH-THC[a]	1.69 (0.47-4.34)	2.34 (0.37-8.37)	3.12 (0.37-8.61)
THC-COOH[a]	13.9 (1.27-27)	19.3 (2.23-48.8)	26.6 (3.51-56.8)
AUC_{0-2h} (h ng/mL)	1.67 (0.80-4.14)	2.61 (0.97-7.55)	3.51 (1.26-11.45)
	3 mg (n=10)	**5 mg (n=6)**	**6.5 mg (n=5)**
[b]C_{max} (ng/mL)	1.42 (0.53-3.48)	3.15 (1.54-6.95)	4.57 (2.11-8.65)
[b]T_{max} (h)	0.92 (0.67-0.92)	0.92 (0.67-0.92)	0.67 (0.67-0.92)

[a]Plasma concentrations
[b]Reported for subjects who reached the C_{max} within 2 hour

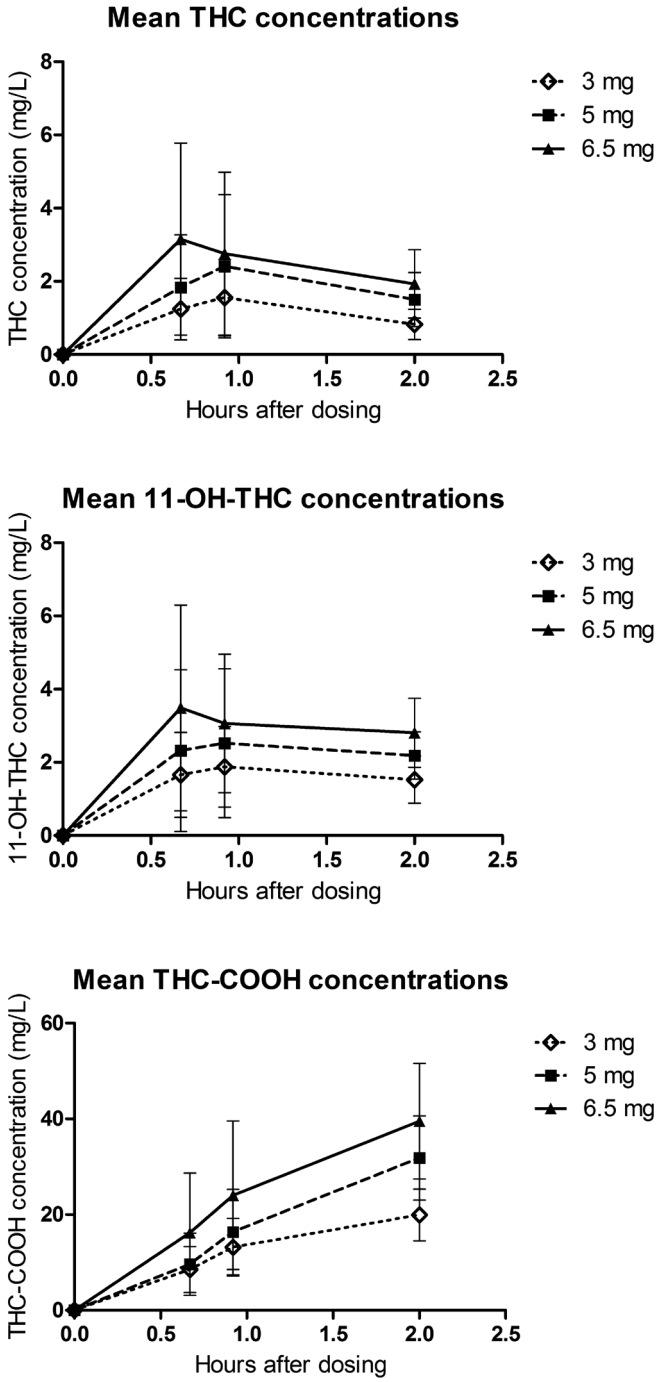

Figure 1 Mean THC, 11-OH-THC and THC-COOH concewntration-time curve

Pharmacokinetic/pharmacodynamic effects

Since only 7 of 174 (4%) "feeling high" measurements had scores higher than "0", it was not possible to calculate the association between the VAS-feeling high and the plasma concentrations of THC, 11-OH-THC, and THC-COOH. Body sway-eyes open scores were not associated with the plasma concentrations of THC (p=0.14), but with the concentrations of its metabolites. An increase of 1 ng/mL in 11-OH-THC and THC-COOH plasma concentrations was accompanied by a mean increase in body sway with eyes open of 0.08 degrees/second (p=0.006; 95% CI: 0.02–0.14) and 0.008°/s (p=0.024; 95% CI: 0.001–0.014), respectively. Furthermore, increases in plasma concentrations were associated with increase in body sway with eyes closed. An increase of 1 ng/mL in THC, 11-OH-THC, THC-COOH plasma concentrations was accompanied by a mean increase in body sway with eyes closed of 0.09 degrees/second (p=0.0002; 95% CI: 0.04–0.13), 0.12°/s (p<0.0001; 95% CI: 0.08–0.16), and 0.007°/s (p=0.0087; 95% CI: 0.002–0.012), respectively. However, there were no significant differences in the body sway scores between Namisol® and placebo and therefore, observed changes in body sway scores associated with the plasma concentrations are clinically not relevant. TAP- alertness scores were not associated with the plasma concentrations of THC (p=0.52), 11-OH-THC (p=0.65), or THC-COOH (p=0.84).

Discussion

Safety and tolerability

Owing to the broad therapeutic applications of cannabinoids, older individuals are probably the fastest growing population of users, with an estimated prevalence between 6.5% and 37% of medicinal cannabis users aged between 60 and 93 years.[14-17] However, the growing interest in the medical applications of cannabinoids should be accompanied by discussion of their safety and efficacy in older patients.[17] Several randomized clinical trials have demonstrated the safety and efficacy of cannabinoid-based medicines in the treatment of conditions that are common in older individuals.[18-21] However,

most of these trials either did not include older subjects or, if they were included, did not analyze data by age group, which makes it difficult to draw firm conclusions about the safety and efficacy of cannabinoids in older patients.[17]

To our knowledge, this is the first phase 1 trial of the safety and pharmacokinetics of a cannabis-based medicine that included solely older individuals. Single oral doses of Namisol® of 3 mg, 5 mg, and 6.5 mg were generally safe and well tolerated by the healthy older individuals. The 6.5 mg dose was associated with more adverse events than the lower doses, but there was no significant difference in the incidence of adverse events between the 3 mg and 5 mg doses. The most frequently reported adverse events were drowsiness (27%) and dry mouth (11%). All adverse events were mild and resolved spontaneously within 3.5 h. There were no moderate or serious adverse events. Four of the eleven subjects reported "feeling high" after the administration of Namisol®, but only 4% of VAS scores were higher than "0". The sensation was mild in intensity (VAS scores ranging between 6 mm and 25 mm, out of 100 mm) and of short duration. In the previous study of Namisol® in young adults (mean age 21 years), 85% and 100% of subjects had at least one adverse event after 5 mg and 6.5 mg, respectively, and one subject dropped out because of drug- related syncope with the 5 mg dose; all adverse events were mild to moderate in severity.[7] Our findings, with zero drop-outs and 45% and 64% of subjects reporting only mild adverse events with the 5 mg and 6.5 mg doses, respectively, suggest that THC is tolerated better by older individuals (mean age 72 years) than by younger individuals, a finding which we had not anticipated. However, the low rate of unwanted (side) effects in older individuals may be correlated with a lower rate of wanted (therapeutic) effects. Further studies are required to assess the effectiveness of the three doses Namisol® in the treatment of conditions in older individuals.

Pharmacokinetic and pharmacodynamic effects

Our findings showed substantial inter-individual variation in plasma concentrations of THC, 11-OH-THC, and THC-COOH, which

is in line with previous studies that included individuals of different ages, but did not report data for older patients separately.[7, 22, 23] In some subjects, THC concentrations did not reach a maximum within the sampling period of 120 min after dosing. This is in contrast with previously published data for young adults, where maximal concentrations of THC were reached between 39 and 56 min after oral Namisol®.[7] For subjects for whom C_{max} fell within the sampling period, the mean C_{max} (3.15 ng/mL with the 5 mg dose and 4.57 ng/mL with the 6.5 mg dose) was similar to that reported for young adults (2.92 ng/mL with 5 mg and 4.43 ng/mL with 6.5 mg).[7] In this study, the sample schedule was based on previously published data for young adults,[7] but did not cover a full pharmacokinetic curve in older subjects. Therefore, and because of the limited number of samples collected, the pharmacokinetic data should be handled with caution when extrapolating to other studies. Unfortunately, it was not possible to compare our data with those of other pharmacokinetic studies involving older subjects, because we did not find any pharmacokinetic studies of THC that reported data separately for older individuals.

In our trial, the first pharmacodynamic effects of THC occurred 20 min after dosing and the maximal effects were reported between 55 and 120 min. These results are quite promising for achieving a rapid clinical effect when compared with the action of dronabinol, which has an onset of action between 30 min and 1 h, and maximal effects between 2 and 4 h.[24] We found no significant differences in body sway scores (eyes open and closed) after the administration of THC. Body sway-eyes open scores were associated with plasma concentrations of 11-OH-THC, and THC-COOH, but not THC. This is in line with previous studies that showed a larger effect after 11-OH-THC administration than after THC administration.[25-27] Comparison of the effects of THC and placebo showed that although higher plasma concentrations of THC and its metabolites were associated with higher body sway-eyes closed scores in our older subjects, this effect was not clinically relevant and would not increase the risk of falls.

Interestingly, the pharmacodynamic effects of THC were smaller than we had expected for older people, based on the effects seen in young adults.[7] A possible explanation for this could be the age-related physiological changes such as delayed gastric emptying time, decreased gastrointestinal motility and absorption surface which could affect the absorption and bioavailability of THC. Furthermore, cannabinoid receptors (CB1 and CB2) are G protein-coupled receptors.[28] Impairments in intracellular function and levels of G-proteins have been observed with aging,[29] which may alter the pharmacodynamics in older adults. Further comparison studies are required to compare the pharmacokinetic and pharmacodynamic effects of THC in younger and older adults.

Strengths and limitations of the study

The primary strengths of our study were, first, its design, a randomized, double-blind, placebo-controlled trial. Second, it is the first randomized, controlled trial of the safety and pharmacokinetics of cannabis-based medicine that exclusively included older subjects, so that our findings add to the sparse literature on the safety and pharmacokinetics of THC in older people. A potential limitation of our study is that we could not perform a complete pharmacokinetic analysis of THC in older individuals because the study was primarily designed to assess the safety and tolerability of THC and therefore, only four blood samples were collected (over 120 min). We are currently investigating the efficacy of THC in the treatment of pain and behavioral disturbances in patients with dementia. In one of these studies, we will be collecting a sufficient number of blood samples to allow a complete pharmacokinetic analysis of THC and its metabolites in older subjects. In conclusion, Namisol®, a novel THC in tablet form, appeared to be safe and well tolerated by healthy older individuals. Data on safety and effectiveness of cannabinoid-based medicines in frail older persons with multiple comorbidities are urgently required, as this population could benefit from the therapeutic applications of cannabinoids.

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Chapter 6

Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia

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Abstract

RATIONALE

Data on safety, pharmacodynamics, and pharmacokinetics of tetrahydrocannabinol (THC) are lacking in dementia patients.

METHODS

In this randomized, double-blind, placebo-controlled, crossover trial, we evaluated the safety, pharmacodynamics, and pharmacokinetics of THC in ten patients with dementia (mean age 77.3±5.6). For 12 weeks, participants randomly received oral THC (weeks 1–6, 0.75 mg; weeks 7–12, 1.5 mg) or placebo twice daily for 3 days, separated by a 4-day washout period.

RESULTS

Only 6 of the 98 reported adverse events were related to THC. Visual analog scale (VAS) feeling high, VAS external perception, body sway-eyes-open, and diastolic blood pressure were not significantly different with THC. After the 0.75 mg dose, VAS internal perception (0.025 units; 95% CI 0.010–0.040) and heart rate (2 beats/min; 95% CI 0.4–3.8) increased significantly. Body sway-eyes-closed increased only after 1.5 mg (0.59°/s; 95% CI 0.13–1.06). Systolic blood pressure changed significantly after both doses of THC (0.75 mg, -7 mmHg, 95% CI -11.4, -3.0; 1.5 mg, 5 mmHg, 95% CI 1.0–9.2). The median t_{max} was 1–2 h, with THC pharmacokinetics increasing linearly with increasing dose, with wide interindividual variability (CV% up to 140%). The mean C_{max} (ng/mL) after the first dose (0–6 h) 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 h), the C_{max} was 0.50 (0.27–0.92) and 0.98 (0.46–2.06), respectively.

CONCLUSIONS

THC was rapidly absorbed and had dose-linear pharmacokinetics with considerable interindividual variation. Pharmacodynamic effects, including adverse events, were minor. Further studies are warranted to evaluate the pharmacodynamics and efficacy of higher THC doses in older persons with dementia.

Introduction

In recent years, there has been increased interest in the medical applications of delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid of the cannabis plant (*Cannabis sativa L.*). A number of studies have demonstrated its effectiveness in the management of clinical conditions that are very common in older people, such as neuropsychiatric symptoms (e.g., agitation and aggression) in dementia, pain (e.g., neuropathic and spasticity in multiple sclerosis), and anorexia.[1-4]

These therapeutic effects of THC are mediated primarily by two cannabinoid receptors: CB1 and CB2.[5-7] CB1 receptors are mainly expressed in the basal ganglia, cerebellum, hippocampus, hypothalamus, and dorsal horn,[8] and CB2 receptors are primarily found on immune cells and tumor cells.[9] THC also interacts with other receptors and neurotransmitters in the brain, such as acetylcholine, dopamine, serotonin, gamma-aminobutyric acid, glutamate, norepinephrine, prostaglandins, and opioid peptides.[10] These broad and complex interactions underlie the potential pharmacological effects of THC as multitarget drug candidate for the management of behavior, mood, pain, and anorexia in patients with dementia. Oral, fixed-dose THC-based drugs have recently been developed. For example, dronabinol (Marinol®) and nabilone (Cesamet®) have been approved in North America and some European countries for appetite stimulation in AIDS-related anorexia, chemotherapy-induced nausea/vomiting, and pain. Namisol® is the most recently developed THC-based formulation in tablet form but has not yet gained marketing approval.[11]

Unfortunately, preapproval clinical trials of oral THC excluded old persons from participation or did not include sufficient numbers, and most recent studies that included older participants did not perform separate analyses for the older subgroup.[12-14] Studies of the potential effectiveness of THC in older individuals should include assessment of its safety, and especially in individuals with dementia, many of whom are frail and vulnerable.[12] To date, only four small studies have investigated the safety and efficacy of THC as treatment for

the neuropsychiatric symptoms of dementia.[15-18] All studies found THC to be effective and safe in older people with dementia, but as the studies were either not randomized or included a limited number of patients, it is not possible to draw firm conclusions about the safe and effective use of THC in these individuals. Furthermore, none of the studies investigated the pharmacokinetics of THC in this population. We found only one study in the literature that evaluated plasma THC concentrations (peak levels only) in older individuals (age 51–78 years), but these individuals were not demented.[19] Drug pharmacokinetics and pharmacodynamics in older people may be altered by age-related physiological changes, multiple comorbidities, or use of other medications. Aging is accompanied by an increase in adipose tissue, a decrease in lean body mass, and a decrease in total body water,[20] changes which increase the volume of distribution of lipophilic drugs such as THC. Moreover, a decrease in hepatic blood flow and the slower metabolism of older individuals can slow the elimination of lipophilic drugs, thereby potentially increasing exposure and side effects.[21] In addition, dementia-related changes in brain volume, number of neurons, and alteration in neurotransmitter sensitivity make older patients with dementia more sensitive to drugs that act on the central nervous system.[20] Taken together, we hypothesize that the administration of THC to older people with dementia may lead to a higher THC concentrations, which subsequently lead to an increase in pharmacodynamic effects, including adverse effects, compared with previously published data for young adults[11] or healthy older individuals without dementia.[22] Understanding the pharmacodynamics and pharmacokinetics of THC in older, frail, dementia patients will help clinicians to minimize side effects and maximize benefit. Therefore, the aim of the present study was to evaluate the safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of THC in older persons with dementia.

Methods

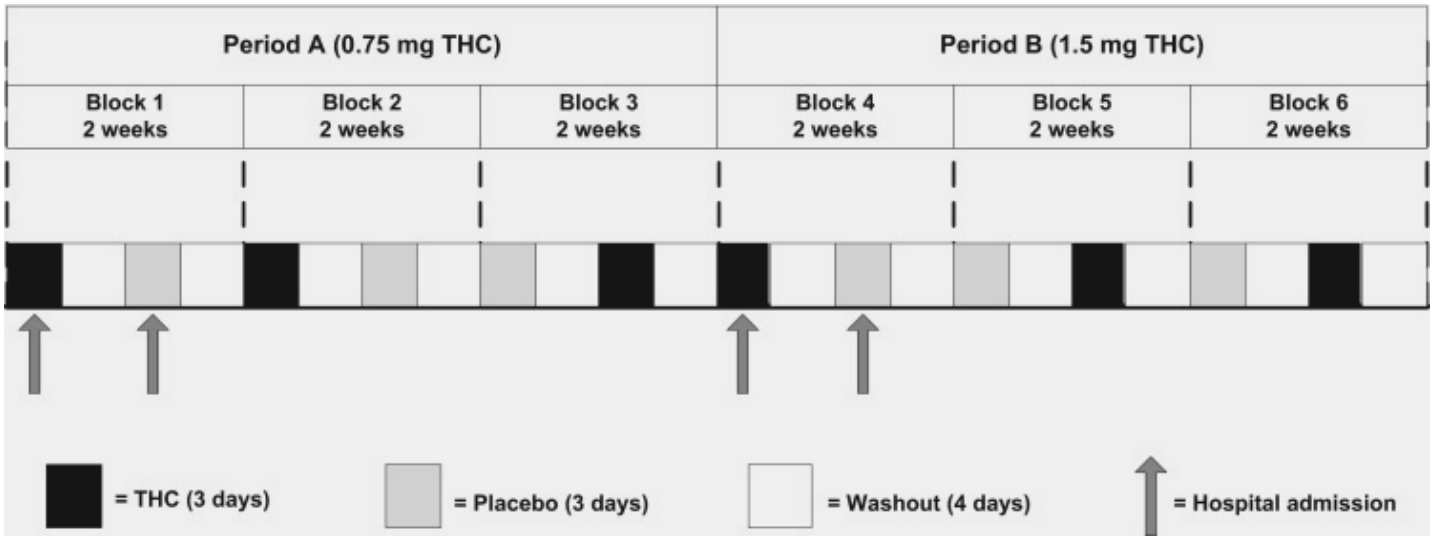
Study design and participants

This study was part of a multicenter, phase II, repeated crossover, randomized, double-blind, placebo-controlled, multiple-dose escalation trial of the effectiveness of THC in the treatment of the neuropsychiatric symptoms of dementia [http:// www.clinicaltrials.gov, clinical trial identifier number NCT01302340]. The study was carried out at the Radboud University Medical Center, the Netherlands. Results concerning the effectiveness of THC in the management of the neuropsychiatric symptoms of dementia will be reported separately.

Figure 1 provides an overview of the study design. The study consisted of two treatment periods, A and B. Each period consisted of three treatment blocks, resulting in a total of six blocks (period A, blocks 1 to 3; period B, blocks 4 to 6). Each block lasted 2 weeks, giving a total study duration of 12 weeks. In each block, participants received oral Namisol®, a novel THC in tablet form,[11] and matching placebo (ratio 1:1) in a double-blind crossover manner for 3 days, separated by a 4-day washout period. In period A, patients received 0.75 mg THC twice daily, and in period B, the dose was increased to 1.5 mg twice daily. Namisol® and placebo were identical in appearance and taste, and both were taken under nonfasting conditions with water at 10 a.m. and 4 p.m. Study participants stayed overnight at the study site on the three intervention days (THC and placebo) of blocks 1 and 4 for safety reasons and to facilitate blood sampling, resulting in a total of four 3-day admissions. The randomization codes were generated by an independent pharmacist, using a computer algorithm for random numbers. Sponsor, investigators, study staff, and participants were masked to assignment.

Participants had been diagnosed with dementia type Alzheimer, vascular dementia, or mixed Alzheimer/vascular dementia, according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA)[23] or Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINCDS-AIREN)[24]

Figure 1 Overview of the treatment period (THC and placebo were administered at random) (this is an example of random allocation of treatment)



criteria. All patients had had clinically relevant neuropsychiatric symptoms, including at least agitation and/or aggression, in the past 30 days (Neuropsychiatric Inventory score ≥ 10),[25] and had an informal caregiver who looked after the participant at least once a week. Main exclusion criteria were major psychiatric disorders (e.g., major depression or suicidal ideation, psychosis, mania, or current delirium), current history of severe comorbidities, frequent falling due to orthostatic hypotension, history of current alcohol or drug abuse, and use of tricyclic antidepressants, opioids, or drugs from a predesigned list of cytochrome (CYP)2C9, CYP2C19, and CYP3A4 inhibitors. Written informed consent was obtained from participants (if they were able to consent and to sign) and their legal representatives. The study was approved by the local ethics committee and was performed according to the International Conference on Harmonization guideline for good clinical practice, the ethical principles of the Declaration of Helsinki, and relevant Dutch laws and regulations.

Safety and tolerability assessments

The safety and tolerability of THC were assessed subjectively and objectively, by evaluating the incidence and severity of adverse events, carrying out physical examinations, laboratory tests (hematology and clinical chemistry), and a 12-lead electrocardiogram, and assessing vital signs. The psychedelic effects were assessed with visual analogue scales (VAS), and body sway (postural stability) was measured using the SwayStar™ (see details below). During the study period, adverse events reported by patients and caregivers or observed clinically were recorded with regard to their time of onset, severity, duration, and causal relationship to study drugs. The causality was assessed by a research physician, blinded to treatment allocation, using a five-point scale: (1) unrelated, adverse event was clearly not related to the intervention; (2) unlikely, adverse event was doubtfully related to the intervention; (3) possible, adverse event may be related to the intervention; (4) probable, adverse event was likely related to the intervention; and (5) definite, adverse event was clearly related to the intervention. A serious adverse event

was defined as any event that was fatal or life-threatening, that required (prolonged) hospitalization, or that resulted in persistent or significant disability or incapacity. All adverse events were coded using the Medical Dictionary for Regulatory Activities.

Pharmacodynamic effects

The scores for psychedelic effects, body sway, and vital signs were used to evaluate the pharmacodynamic effects of THC.

1. Psychedelic effects: The Bowdle VAS for psychedelic effects was used to evaluate feeling high, internal perception (inner feelings that do not correspond with reality, including mistrustful feelings), and external perception (misperception of an external stimulus or change in awareness of surroundings).[26, 27] Subjects were asked to score their perceptions on a 100-mm horizontal line, with "0" indicating no effect and "100" indicating extreme effect. The VAS was assessed 1 and 3 h after dosing on day 1 of weeks 1, 2, 7, and 8, in patients who were able to understand the instructions and perform the task. A recent study showed that individuals with dementia can use the VAS in a similar way to those without dementia.[28]
2. Body sway: Body sway was assessed within 2 h of dosing on the second day of admission of weeks 1, 2, 7, and 8. Body sway was measured (30 s eyes open and 30 s eyes closed) with the SwayStar™, a wireless device attached to the trunk (*http://www.b2i.info/web/index.htm*).
3. Vital signs: Systolic and diastolic blood pressure and heart rate were measured on day 1 of weeks 1, 2, 7, and 8, before and at 15, 30, 45 min, and 1, 2, 3, and 4 h after the first dose.

Blood sampling and laboratory analysis

Venous blood samples were collected during hospital admission before and at 11, 30, 45 min, and 1, 1.5, 2, 3, 4, and 6 h after the first dose, and before and at 11, 30, 45 min, and 1, 1.5, 2, 3, 4, 6, and 18 h after the second dose (in total covering a 24-h period). Plasma was separated by centrifugation (2000 × g, 4 °C, 10 min) and stored at −80 °C until analysis. After unblinding, blood samples

collected in the THC treatment period were analyzed at the Analytisch Biochemisch Laboratorium b.v. (Assen, the Netherlands), using liquid chromatography with tandem-mass spectrometer detection. The lower limit of quantification was 0.1 ng/mL for THC and its active metabolite 11-OH-THC. The analysis was performed using a validated assay according to good laboratory practice standards.[29]

Pharmacokinetic analysis

Noncompartmental analysis was performed using Phoenix WinNonlin software version 6.3 (Certara, L.P./Pharsight Ltd) to determine the pharmacokinetics of THC and 11-OH-THC. The following pharmacokinetic parameters were calculated for the 24-h period: terminal half-life ($t_{1/2}$), area under the curve (AUC) from 0 to 24 h (AUC_{0-24h}), and apparent clearance (CL/F, being the dose/AUC_{0-24h}). The following parameters were calculated for the two curves (curve 1, 0–6 h after the first THC dose; curve 2, 6–24 h after the second dose) separately: the maximum plasma concentration (C_{max}), the time to reach C_{max} (t_{max}), AUC from 0 to 6 h (AUC_{0-6h}), and AUC from 6 to 24 h (AUC_{6-24h}), using the linear-up log-down trapezoidal rule. Concentration-time graphs were plotted for the two doses. Geometric means plus 95 % confidence intervals were calculated for each pharmacokinetic parameter for each dose. The coefficients of variation (CV%) of the geometric means were calculated to describe the interindividual variability in pharmacokinetic parameters. The geometric mean ratio (GMR) plus 90% confidence intervals of AUC_{0-24h}, CL/F, and $t_{1/2}$ of the 1.5 mg dose versus the 0.75 mg dose were also calculated.

Statistical analysis

This study is descriptive and explorative, and therefore, no sample size calculation was performed. Descriptive statistics were used to describe the study population. Continuous data are expressed as means ± standard deviation (±SD), and categorical data are expressed as frequencies and percentages. The compliance to study medication was calculated for the whole study sample. Differences in adverse event rates between THC and placebo were compared by

Wilcoxon signed ranks test. The VAS scores were clustered and log-transformed, and the scores are expressed as units, as described previously.[11, 27] The 90% range of pitch velocity (anterior–posterior movements) scores of the SwayStar™ was used to analyze body sway. Scores are given in degrees per second. The VAS, body sway, and vital signs scores were analyzed in relation to the THC dose, using linear mixed models with participants as a random effect. Statistical analyses were performed using SAS™ software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Participants

The data of ten patients with dementia were analyzed. Their demographic characteristics are summarized in **Table 1**. The mean age of participants was 77.3±5.6 years; their mean body mass index was 25.7±2.7 kg/m^2; seven participants were men; and nine participants had Alzheimer's disease. Overall, treatment compliance to study medication was high, and almost 98% (THC 99%; placebo 97.5%) of the trial drugs were taken.

Safety and tolerability assessments

All participants completed the study as scheduled. In general, THC was safe and well tolerated by these older individuals with dementia. In total, 98 adverse events were reported during the study period. More adverse events were reported with placebo (55 adverse events) than with THC (43 adverse events) (period A, 0.75 mg THC 21 adverse events and placebo 30 adverse events, p=0.290; period B, 1.5 mg THC 22 adverse events and placebo 25 adverse events, p=0.435).

Thirteen (13 %) of the reported adverse events were considered to be possibly (n=12) or probably (n=1) related to study drugs (THC and placebo). Of these, only six adverse events (6% of total adverse events) were considered to be (possibly) related to THC, two with 0.75 mg (dizziness and fatigue in one patient each), and four with

1.5 mg (agitation in three patients and fatigue in one patient). All were mild and transitory in nature. There were no THC-related serious adverse events. THC treatment was not associated with changes in the patients' physical state, laboratory test results (hematology and clinical chemistry), or ECG parameters (e.g., QT and RR intervals).

Pharmacodynamic results

THC did not cause significant changes in scores for VAS feeling high, VAS external perception, body sway with eyes open, and diastolic blood pressure (**Table 2**). The 0.75-mg dose, but not the 1.5 mg dose, was associated with a statistically significant increase in VAS internal The 1.5 mg dose, but not the 0.75-mg dose, significantly increased body sway with eyes closed (0.59°/s, 95% CI 0.13, 1.06). The 0.75 mg dose significantly decreased systolic blood pressure (−7.2 mmHg, 95% CI −11.4, −3.0), whereas the 1.5 mg dose significantly increased systolic blood pressure (5.1 mmHg, 95% CI 1.0, 9.2). Heart rate increased significantly after the administration of the 0.75 mg dose only (2 beats/min, 95% CI 0.4, 3.8). None of the changes in the pharmacodynamic parameters was associated with an adverse event. perception scores (0.025 units, 95% CI 0.010, 0.040).

Pharmacokinetic results

Pharmacokinetic parameters are summarized in **Tables 3** and **4**. The data of one person were excluded because no blood samples were taken after the first THC dose of 0.75 mg, and only a limited amount of blood was taken after the second dose. Although one subject was non-Caucasian, his pharmacokinetic data were within the range of the others. The median t_{max} was between 1 and 2 h and was not dose dependent. For the 0.75-mg dose, the median t_{max} was reached 1.5 h (range 0.75 – 3.08) after the first dose and 2 h (range 0.5 – 2.07) after the second dose; for the 1.5-mg dose, the median t_{max} was reached 1h (range 0.5 – 2.2) after the first dose and 2 h (range 0.5 – 3.02) after the second dose (**Table 3**). Plasma concentrations of THC and 11-OH-THC increased linearly with increasing dose, but there was considerable interindividual

Table 1 Baseline demographic characteristics

Characteristics	n = 10
Male, n (%)	7 (70)
Age, mean (SD) years	77.3 (5.6)
BMI, mean (SD); kg/m^{-2}	25.7 (2.7)
Ethnicity, *n*	
Caucasian	9
Other	1
Type of dementia, n	
Alzheimer	9
Vascular	0
Mixed	1
MMSE score, *mean (SD)*	18.5 (6.0)
Smokers, n	0
Comorbidities, n	
Cardiac rhythm disorder	5
Hypertension	5
Ventricular hypertrophy	3
Diabetes	2
Electrolyte disturbances	2
Kidney function disorder	2
Vitamins deficiency	2
Hypercholesterolemia	1
Liver function disorder	1
Orthostatic hypotension	1
Medications, n	
Anti-dementia drugs[a]	16
Memantine	9
Rivastigmine	5
Galantamine	2
Antihypertensives[a]	11
Anticoagulants	4
Blood glucose lowering drugs	3
Antidepressants	1
Antiepileptics	1
Antipsychotics	1
Proton pump inhibitor	1
Other	12

[a] Some participants used a combination of drugs within the same medication group

Table 2 Pharmacodynamic effects of THC doses

Parameters[a]	THC 0.75 mg versus placebo (n=10)	THC 1.5 mg versus placebo (n=10)
VAS Feeling high (U)[b]	-0.010, [95%CI: -0.037; 0.017]; p=0.47	0.002, [95%CI: -0.024; 0.028]; p=0.90
VAS External perception (U)[b]	0.012, [95%CI: -0.005; 0.029]; p=0.16	-0.014, [95%CI: -0.031; 0.003]; p=0.11
VAS Internal perception (U)[b]	0.025, [95%CI: 0.010; 0.040]; p=0.001[c]	-0.002, [95%CI: -0.014; 0.010]; p=0.75
Body sway, eyes open (degree/second)	0.37, [95%CI: -1.31; +2.10]; p=0.63	0.26, [95%CI: -0.91; 1.44]; p=0.67
Body sway, eyes closed (degree/second)	0.61, [95%CI: -0.63; +1.85]; p=0.30	0.59, [95%CI: +0.13; +1.06]; p<0.05[c]
Systolic blood pressure (mmHg)	-7.2, [95%CI: -11.4; -3.0]; p<0.001[c]	5.1, [95%CI; 1.0; 9.2]; p< 0.05[c]
Diastolic blood pressure (mmHg)	0.2, [95%CI: -2.0; 2.3]; p=0.86	-0.1, [95%CI: -2.2; 2.0]; p=0.92
Heart rate (beats/min)	2.1, [95%CI: 0.4; 3.8]; p<0.05[c]	-0.4, [95%CI: -2.0; 1.3]; p=0.66

[a] All parameters are presented as: Mean, [95% confidence intervals (CI)]; P-values. [b] Log transformed Visual Analog Scale (VAS) [scores in mm + 2]. Scores are given in units (U). [c] Statistically significant P-values (α = 0.05).

variation in plasma concentrations and hence in pharmacokinetic parameters (**Figure 2**). For THC, C_{max} and AUC CV% ranged from 90 to 140%, and for 11-OH-THC from 38% to 62%. The elimination phase of THC was faster than that of 11-OH-THC. The geometric mean ratio of the THC AUC_{0-24h} versus the 11-OH-THC AUC_{0-24h} was 1.7 (95% CI 1.1, 2.9) and 1.9 (95% CI 1.0, 3.6) for the 0.75- and 1.5-mg doses, respectively. Individual THC and 11-OH-THC AUCs are presented in **Figure 3**. Two participants had a high THC exposure after the 0.75-mg dose. Their AUC_{0-24h} was 8.0 and 8.4 ng h/mL compared with a value ranging between 0.9 and 2.7 ng h/mL in the other participants. Three participants had a high exposure after the 1.5-mg dose. Their AUC_{0-24h} was 13, 19, and 20 ng h/mL compared with a value ranging between 1.2 and 4.1 ng h/mL in the other participants. One participant had a greater increase in THC AUC after the 1.5-mg dose than the other participants; the AUC GMR for this subject was 7 compared with 1.7–2.5 (range) for the other participants. The same was seen for 11-OH-THC, but less pronounced (**Figure 3**).

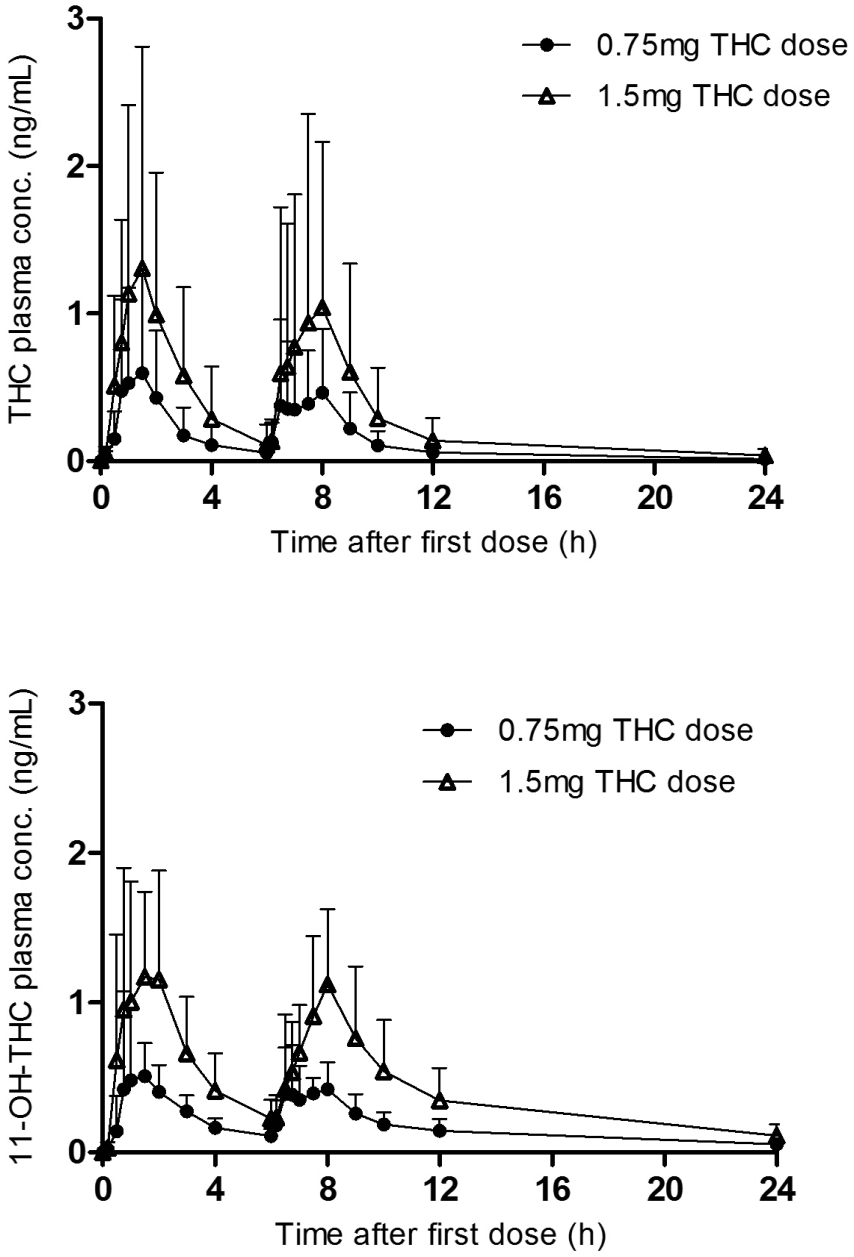


Figure 2 The mean concentration time profiles of THC and 11-OH-THC for both the 0.75- and 1.5-mg doses over 24 h

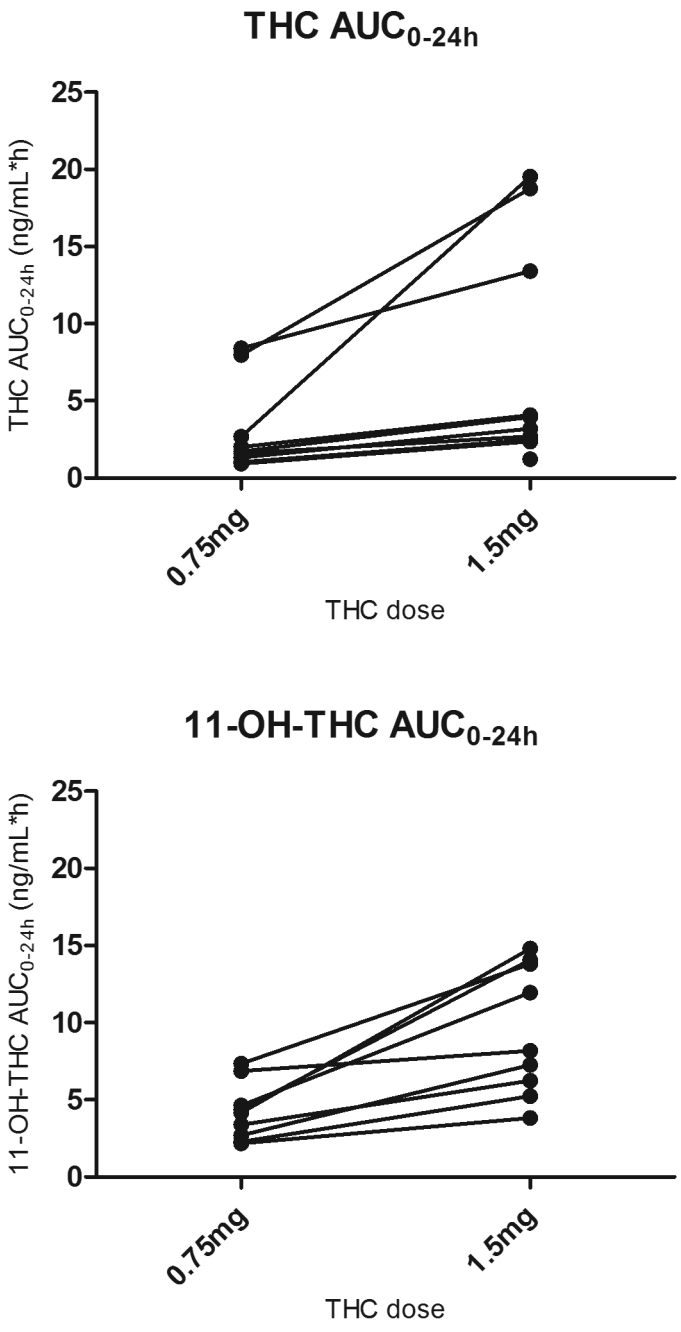


Figure 3 Individual pharmacokinetic parameter graphs

Table 3 Pharmacokinetic parameters of THC and 11-OH-THC

Parameters[a]	THC		11-OH-THC	
	0.75 mg (n=9)	**1.5 mg (n=10)**	**0.75 mg (n=9)**	**1.5 mg (n=10)**
$AUC_{0\text{-}24}$ (ng/mL^{-1}h)	2.21 [96] (1.19-4.12)	4.66 [122] (2.35-9.25)	3.86 [46] (2.76-5.42)	8.92 [50] (6.35-12.54)
CL/F (L/h)	0.68 [96] (0.36-1.26)	0.64 [122] (0.32-1.28)	0.39 [46] (0.28-0.54)	0.34 [50] (0.24-0.47)
$t_{1/2}$ (h)	5.08 [39] (3.81-6.77)	5.06 [37] (3.92-6.54)	7.80 [31] (6.19-9.82)	6.77 [61] (4.54-10.10)
C_{max} curve 1 (ng/mL^{-1})	0.41 [138] (0.18-0.90)	1.01 [112] (0.53-1.92)	0.56 [62] (0.36-0.87)	1.21 [61] (0.90-1.64)
t_{max} curve 1 (h)	1.5 (0.75-3.08)	1.01 (0.5-2.2)	1.5 (0.75-3.08)	1.76 (0.75-3.02)
C_{max} curve 2 (ng/mL^{-1})	0.50 [94] (0.27-0.92)	0.98 [140] (0.46-2.06)	0.55 [54] (0.37-0.82)	1.21 [44] (0.90-1.64)
t_{max} curve 2 (h)	2 (0.5-2.07)	2 (0.5-3.02)	1.00 (0.5-2.07)	1.76 (0.75-3.02)
$AUC_{0\text{-}6h}$ curve 1 (ng/mL^{-1}h)	0.88 [124] (0.42-1.85)	2.01 [136] (0.97-4.17)	1.37 [45] (0.99-1.90)	3.35 [55] (2.31-4.84)
$AUC_{6\text{-}24h}$ curve 2 (ng/mL^{-1}h)	0.98 [90] (0.54-1.77)	2.04 [115] (1.06-3.94)	1.47 [38] (1.11-1.95)	3.46 [47] (2.51-4.78)

[a]All parameters are presented as: geometric mean [coefficients of variation %] (95% confidence intervals)
AUC: area under the curve; CL/F: oral clearance; $t_{1/2}$: half-life; C_{max}: peak plasma concentration, t_{max}, time to reach C_{max}.

Table 4 Geometric mean ratios of THC and 11-OH-THC

.

Parameters	THC	11-OH-THC
AUC_{0-24} (ng/mL^{-1}h)	2.40 (1.83-3.16)	2.25 (1.82-2.77)
CL/F (L/h)	0.83 (0.63-1.10)	0.89 (0.72-1.10)
$t_{1/2}$ (h)	1.00 (0.72-1.39)	0.88 (0.58-1.34)

Geometric mean ratio 1.5 mg versus 0.75 mg over one dosing interval (90% CI)

Discussion

Safety and tolerability

Older people with dementia and physical comorbidity could greatly benefit from the therapeutic application of cannabinoids. Recent studies have demonstrated that low doses of THC are effective in protecting the brain from neuro-inflammation-induced cognitive damage.[30-32] Although THC-based drugs have recently been approved for clinical use, there are only few data on their safety in older individuals with dementia. Our data demonstrate that THC doses of 0.75 and 1.5 mg twice daily are safe and well tolerated by older individuals with dementia. Only 6 of the 98 reported adverse events were related to THC treatment. All adverse events were mild and resolved spontaneously without any intervention. Our findings are in line with previously published studies showing that THC doses up to 5 mg/day are safe to use in older individuals with dementia.[15-17] It is important to note that the safety data presented in this study are based upon short-term use of THC in older subject with dementia. Further studies are warranted to evaluate the long-term use of THC in this population.

Pharmacodynamics

Overall, THC had fewer pharmacodynamic effects, including adverse events, than we had expected for frail older individuals with dementia, based on the effects reported by Klumpers et al.[11] in young adults (mean age 21 years). We found no statistically significant

changes in participants' feeling high, external perception, body sway with the eyes open, and diastolic blood pressure after THC. The changes in internal perception, body sway with eyes closed, systolic blood pressure, and heart rate after THC were not considered clinically relevant, as they were small and were not associated with adverse events. The current findings are consistent with our previous findings from a phase 1 study of Namisol® in healthy older individuals without dementia (n=11, mean age 72 years).[22]

Pharmacokinetics

On the basis of the AUC and C_{max} values, THC has linear pharmacokinetics in elderly individuals with dementia, showing a doubling of the AUC and C_{max} with doubling dose from 0.75 to 1.50 mg. However, there was considerable interindividual variation in plasma concentrations of THC and 11-OH-THC, which is in line with our data from a phase 1 study involving healthy older individuals,[22] and with the results of studies involving individuals of different ages.[11, 19, 33] The median t_{max} was reached 1–2 h after THC dosing, as has been previously reported for healthy older individuals without dementia.[22] In contrast, Klumpers et al.[11] reported a shorter t_{max} between 39 and 56 min in young adults after Namisol® administration. The AUC_{0-6h} for older persons with dementia was two times higher than would be expected on the basis of data for young adults administered Namisol® (individual concentrations were retrieved and AUC_{0-6h} was calculated).[11] A possible explanation for the discrepancies in t_{max} and AUC_{0-6h} is that, in the current study, THC was taken in non-fasting state, whereas Klumpers et al.[11] administered THC to fasting young adults. Stott et al.[34] in their investigation of the effect of food on the absorption and bioavailability of cannabinoids, found that the t_{max} for THC was reached about 2–2.5 h later in the fed state than in the fasting state: the mean AUC and C_{max} for THC and 11-OH-THC were one fold and threefold higher, respectively, in the fed state than in the fasting state. Age-related factors, such as delayed gastric emptying time, decreased splanchnic blood flow, decreased gastrointestinal motility, and decreased absorption surface, could also affect the absorption and bioavailability of THC in older individuals. It was not

possible to compare our data with data from other pharmacokinetic studies involving older individuals with dementia because we did not find any relevant studies that reported data separately for this group.

The relatively high THC exposure in two participants seems to have been due to a diminished metabolism of THC to 11-OH-THC, as in both participants the 11-OH-THC/THC ratio of the AUC_{0-24h} was less than 1 for both doses, whereas it was almost 2 in the other participants. However, the sum of 11-OH-THC plus THC AUC_{0-24h} was higher in these two participants than in the other participants, but this higher THC exposure was not associated with adverse events.

Strengths and limitations

The main strengths of the current study were, first, its design. In this randomized, double-blind, placebo-controlled, repeated crossover study, study staff and participants were masked to assignment and participants served as their own control. This design strengthened the validity of the safety and pharmacodynamic data. Second, our study is the first to evaluate the pharmacokinetics and pharmacodynamics of THC in older individuals with dementia, a frail subgroup of older persons. Therefore, this study can be added to the limited literature available on this subject.

The most notable limitation is that we probably used a very low THC dose-escalation regimen, 0.75 to 1.5 mg, as only 6 of the 98 reported adverse events were related to THC treatment and the pharmacodynamic effects were in general smaller than we had expected for this subgroup of older persons. A future dose-escalation study is required to determine the maximum tolerable dosage. This will help to maximize effectiveness while keeping side effects acceptable.

Conclusion

Our findings suggest that low THC doses are safe and well tolerated by frail older persons with dementia. Oral THC was rapidly absorbed, showing dose-linear pharmacokinetics with maximum plasma concentrations being reached between 1 and 2 h after

dosing, although there was considerable interindividual variability. Overall, THC showed smaller pharmacodynamic effects in frail older individuals than expected on the basis of data for young healthy adults. These reassuring data warrant further pharmacodynamic and efficacy studies with higher THC doses in older patients with dementia.

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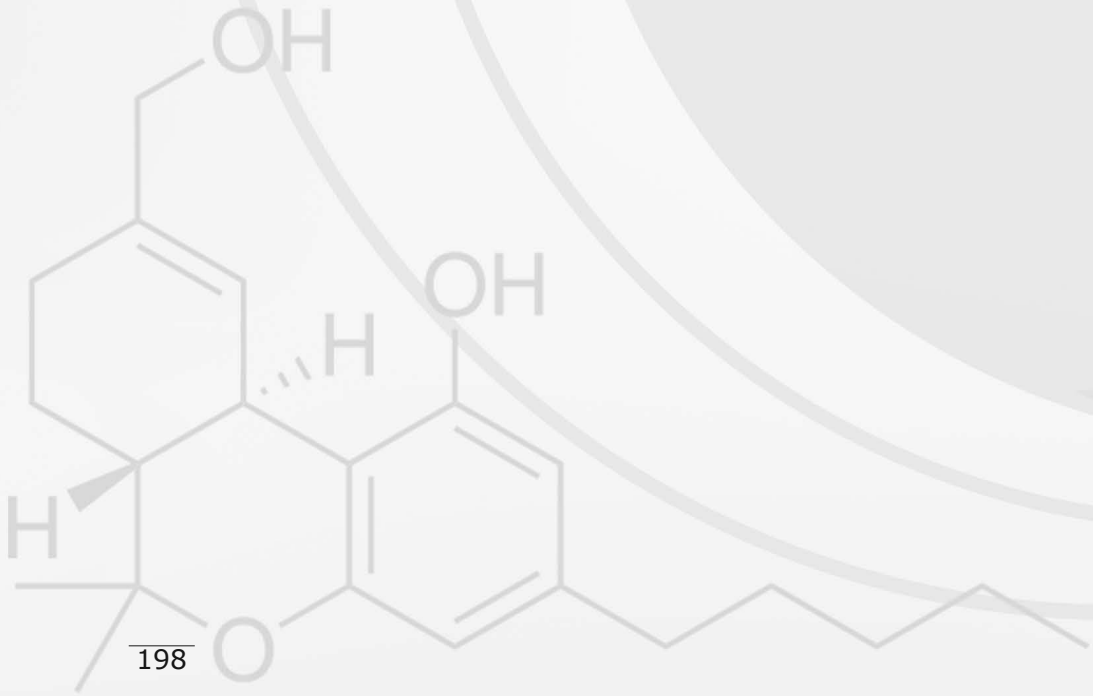

PART V

Pain and pain-related symptoms in dementia

Chapter 7

Prevalence and impact of pain and pain-related behavioral problems in community-dwelling dementia patients

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Submitted

ABSTRACT

OBJECTIVES: To determine the prevalence and impact of pain in dementia patients and the relationship between pain and behavioral and psychological symptoms.

DESIGN: Cross-sectional.

SETTING: Community-based.

PARTICIPANTS: Dementia patients and caregivers.

MEASUREMENTS: Pain and its impact on activities of daily living (ADL) and sleep at night was assessed by means of questionnaires completed by dementia patients and their caregivers. Behavioral and psychological symptoms were assessed using the Neuropsychiatric Inventory-Questionnaire (NPI-Q), Cohen-Mansfield Agitation Inventory (CMAI), and the Cornell Scale for Depression in Dementia (CSDD).

RESULTS: Of the questionnaires sent out to 701 patient-caregiver dyads, 390 (56%) were returned. The questionnaires of 386 patient-caregiver dyads were sufficiently complete and included in the analysis. Mean patient age was 81.3±7.2 years. The prevalence of pain reported by patients and caregivers was 61%. Of those with pain, 72% experienced chronic pain, 50% reported pain in multiple locations, 29% did not use any pain medications and, 56% and 27% reported that pain negatively influenced their ADL and sleep at night, respectively. The mean total NPI-Q, CMAI, and CSDD scores were significantly higher in patients with pain than in patients without pain: 8.2 vs 5.6 ($p<0.001$), 42.3 vs 38.6 ($p=0.012$), and 7.1 vs 4.4 ($p<0.001$), respectively. Also, the mean total NPI-Q caregiver-distress score was significantly higher among caregivers of patients with pain than among those of patients without pain (10.3 vs 6.7, $p<0.001$).

CONCLUSION: Pain is common and often undertreated among community-dwelling dementia patients. It is associated with decreased ADL, sleep disturbances, behavioral and psychological symptoms, and caregiver distress. Our findings underline the importance of routinely assessing and treating pain as part of the overall management of behavioral problems in dementia patients.

Introduction

Pain is a significant and growing healthcare problem among older people with dementia, because aging is accompanied by an increased risk of chronic painful disorders including degenerative disease of discs and joints, osteoporotic fractures, fall-related injuries, diabetic neuropathy, cardiac pain, and cancer.[1, 2] The reported prevalence of pain among dementia patients varies from 28% to 90%,[3-6] with the wide range reflecting methodological differences between studies (e.g., setting, pain definition, assessment instrument/scale, pain location, and sample size).

The past decade has shown a growing interest in pain and pain-related behavioral changes among older patients with dementia. Several studies have shown that pain management is suboptimal in these frail individuals because of their cognitive impairment and diminished communication skills, with the result that pain is often underreported, unrecognized, and consequently undertreated.[7, 8] Although self-report is generally considered the "gold standard" in the assessment of pain,[9] patients with dementia, especially individuals with moderate and severe dementia, are often less able to express their pain and discomfort verbally. Instead, they may express their pain via facial expressions, body movements, and behavioral disturbances, such as agitation, aggression, aberrant motor disturbance, depression, and sleep problems.[3] The latter symptoms are often not recognized as manifestations of pain, but are instead labeled as behavioral and psychological symptoms of dementia (BPSD).[10, 11] This means that patients with dementia who experience pain are more likely to receive psychotropic medications than adequate pain treatment.[12-14] This again may lead to functional decline, falls, reduced quality of life, and increased healthcare costs.[15-17] In line with these findings, a recent study showed that effective treatment of pain with analgesics in patients with dementia (n=175) significantly improved agitation and reduced unnecessary prescriptions for psychotropic drugs.[18] These results emphasize the importance of recognizing, assessing, and treating pain effectively as

part of the overall treatment and prevention of behavioral problems in dementia patients.[18]

While the majority of patients with dementia still live at home, most studies of pain and pain-related behavioral problems have involved residents of long-term care facilities (e.g. residential and nursing homes).[19] Early recognition and adequate treatment of pain in dementia patients living at home may prevent or reduce pain-related behavioral changes and associated caregiver distress, and subsequently may delay nursing home placement.

As there is little known about pain and pain-related behavioral problems in patients with dementia living in the community, we aimed: first, to determine the prevalence of pain in this population, using information provided by both patients and their caregivers; second, to evaluate the impact of pain on activities of daily living (ADL) and sleep; third, to investigate the relationship between pain and behavioral and psychological symptoms in individuals with dementia; and finally, we discuss the potential of oral tetrahydrocannabinol, a cannabinoid of the cannabis plant (*Cannabis sativa L.*), as multi-target drug candidate for the management of pain and pain-related behavioral and psychological symptoms in patients with dementia.

Methods

The current cross-sectional, community-based, prevalence survey was part of the recruitment procedure of a multi-center, phase II, randomized, placebo-controlled, double-blind trial of the effectiveness and safety of tetrahydrocannabinol (THC) in the treatment of behavioral disturbances and pain in patients with dementia (ClinicalTrials.gov Identifier: NCT01608217).[20] The main trial was approved by a certified ethics committee of the Radboud university medical center. According to the Dutch law on medical research, the current survey did not require additional approval. Patients and caregivers were informed about the nature and purpose of the survey through their case managers of the dementia-support organization.

Participants and procedure

Self-administered postal questionnaires were sent to all patients with dementia and their informal caregivers (701 patient-caregiver dyads), who received support from the local dementia-support organization [Help with Dementia; www.hulpbijdementie.nl] in North Limburg, a province in the Southeast of the Netherlands. To maximize the response rate, all patients and caregivers had the opportunity to ask their case managers for assistance with completing the questionnaires.

Pain questionnaire

The questionnaire was developed by the research team, with input from the case managers of the dementia-support organization and patients' relatives (n=4). The questions were specifically designed to be short, understandable, easy to answer, and only related to current symptoms without memory dependent reporting of past symptoms. We used the questionnaire to collect information on demographics, type of dementia, severity of dementia based on the Clinical Dementia Rating Scale (if known),[21] pain, pain-related behavioral and psychological symptoms, and the impact of pain on patients and caregivers. The questionnaire was divided into two parts. Part one was designed to collect information from the patients. The assessment of pain in this part was based on patients' self-report using a single question "Do you have pain right now? Yes, No". Participants who reported pain were asked to provide more detailed information on their pain including location(s), duration, cause of pain, and use of pain medications. Pain was defined as chronic if it lasted for more than three months. The effect of pain on patients' ADL and sleep at night was assessed, based on single questions, "Does pain keep you from doing daily activities (e.g., housework, bathing, dressing, social activities)? Yes, No"; and "Does pain keep you from sleeping at night? Yes, No", respectively.

Part two of the questionnaire was designed to collect information from informal caregivers. In this part, the caregivers rated patients' pain. The caregivers were asked single questions, which could be answered with "Yes" or "No": 1) Do you think that the patient is

in pain?; 2) Do you think that the patients' behavior has changed (since the diagnosis of dementia)?; and 3) Do you think that the change in patients' behavior is related to the pain?. Caregivers were also asked to complete the following validated clinical instruments: the Neuropsychiatric Inventory-Questionnaire (NPI-Q),[22] the Cohen-Mansfield Agitation Inventory (CMAI),[23] and the Cornell Scale for Depression in Dementia (CSDD)[24], to assess changes in patient behavior and symptoms of depression. The impact of pain-related behavioral changes on caregivers was evaluated by using the scores of the NPI-Q, sub-question "caregiver distress".

Statistical analysis

Analyses were performed using SPSS, version 20. Descriptive statistics were used to present the demographic characteristics. The continuous data are expressed as means ± standard deviation (±SD), and categorical data are expressed as frequencies and percentages. Questionnaires were included in the analysis if both patients and caregivers responded. Individuals with dementia were categorized as "Patients with pain", when they or their caregivers said that they experienced pain. The variables NPI-Q total score, NPI-Q caregiver distress, CMAI and CSDD, violated the assumption of a normal distribution and therefore, a non-parametric test (Mann-Whitney U) was used to compare patients with and without pain. In addition, a multiple regression analysis was used to determine the influence of presence of pain, age, gender, type of dementia, and severity of dementia on the total NPI-Q score. Univariate and multivariate analyses were performed to assess the significance of all variables.

Results

Patient characteristics

Of the questionnaires sent out to 701 patient-caregiver dyads, 390 (56%) were returned to the research office. Of these, 386 questionnaires (patient-caregiver dyads) were sufficiently complete

and included in the analysis. **Table 1** provides patients' characteristics. The mean age of the included patients was 81.3±7.2 years, 61.4% (n=235) were women and 41% (n=159) were diagnosed with Alzheimer's disease. The prevalence of pain was 60.9% (n=235) based on patient self-report and 61.9% (n=239) based on caregiver report, as in four questionnaires patients reported no pain whereas the caregivers did. Fifty-one percent (n=122) of the patients reported pain in one location and 48.9% (n=117) reported pain in two or more locations. Most patients (71.5%, n=171) experienced chronic pain, with musculoskeletal pain (muscles, neck, shoulders, back, and extremities) being the most frequently reported type of pain (77.3%, n=180). In total, 28.5% (n=68) of patients who reported pain did not use any pain medications. Overall, acetaminophen was the most commonly used pain medication (53.6% of the patients with pain), followed by non-steroidal anti-inflammatory drugs (5% of the patients with pain). Interestingly, 12 patients reported using pain medication even though they did not report pain (**Table 1**).

Impact of pain on ADL and sleep

More than half of the patients with pain (56%; n=134) reported that pain negatively influenced their ADL and 26.8% (n=64) reported that pain affected their sleeping at night.

Behavioral and psychological symptoms

There were significant differences in behavioral and psychological symptoms between the group of patients with pain and the group of patients without pain (**Table 2**). The mean total NPI-Q, CMAI, and CSDD scores were significantly higher in patients with pain than in patients without pain (8.22 vs 5.57, p<.001), (42.26 vs 38.57, p=.012) and (7.08 vs 4.39, p<.001) respectively. Also, the mean NPI-Q caregiver distress score was significantly higher for the caregivers of patients with pain than for the caregivers of patients without pain (10.32 vs 6.69, p<.001) (Table 2). Patients with pain had significantly higher scores than patients without pain on the following NPI-Q sub-scales: delusions, agitation, depression, anxiety, and appetite disturbances (**Table 2**). Patients who used

Table 1 Demographic and clinical characteristics of participants with dementia

	Total	Patients with pain	Patients without pain
n (%)	386 (100)	239 (61.9)	147 (38.1)
Age, mean (SD) years	81.3 (7.2)	81.6 (7.1)	81 (7.5)
Female, n (%)	235 (60.9)	151 (63.2)	84 (57.1)
Type of dementia, n (%)			
Alzheimer's disease	159 (41.2)	84 (35.1)	75 (51)
Vascular dementia	63 (16.3)	44 (18.4)	19 (12.9)
Mixed dementia*	81 (21)	56 (23.4)	25 (17)
Other	65 (16.8)	39 (16.3)	26 (17.7)
Not reported	18 (4.7)	16 (6.7)	2 (1.4)
CDR ratio, n (%)			
1 (mild)	163 (42.2)	93 (38.9)	70 (47.6)
2 (moderate)	105 (27.2)	65 (27.2)	40 (27.2)
3 (severe)	27 (7.0)	17 (7.1)	10 (6.8)
Not reported	91 (23.6)	64 (26.8)	27 (18.4)
Use of pain medication, n (%)			
No	203 (52.6)	68 (28.5)	135 (91.8)
Yes	183 (47.4)	171 (71.5)	12 (8.2)
Acetaminophen	137 (35.5)	128 (53.6)	9 (6.1)
NSAIDs	13 (3.4)	12 (5)	1 (0.7)
Weak opioids**	8 (2.1)	8 (3.3)	0
Strong opioids**	11 (2.8)	11 (4.6)	0
Anti-psychotics	1 (0.3)	1 (0.4)	0
Anti-depressants	3 (0.8)	2 (0.8)	1 (0.7)
Anti-migraine	1 (0.3)	1 (0.4)	0
Unknown	9 (2.3)	8 (3.4)	1 (0.7)

CDR = Clinical Dementia Rating scale; NSAID = non-steroidal anti-inflammatory drug.
*Mixed dementia: Alzheimer's disease / Vascular dementia
**Weak opioids: Tramadol en codeine. Strong opioids: morphine (patch), oxycodone, fentanyl (patch)
and buprenorphine (patch)

Table 2 Comparison of the NPI-Q, CMAI and CSDD scores between the two groups using Mann–Whitney U test

Parameters	**Patients with pain n=239**	**Patients without pain n=147**	**U**	**Z-score**	***P*-value**
NPI-Q total score	8.22 (7)	5.57 (4)	10084	-4.039	<.001
CMAI	42.26 (38)	38.57 (36)	10961	-2.468	.012
CSDD	7.08 (6)	4.39 (3)	9576	-4.356	<.001
NPI-Q caregiver distress	10.32 (8)	6.69 (4)	10025	-3.682	<.001
NPI-Q sub-scales					
Delusions	0.54 (0)	0.26 (0)	11613.5	-3.032	.003
Agitation	0.78 (0)	0.50 (0)	11571	-2.698	.007
Depression	1.11 (1)	0.59 (0)	9803.5	-4.639	<.001
Anxiety	0.74 (0)	0.36 (0)	11164	-3.386	.001
Appetite disturbances	0.78 (0)	0.50 (0)	11579.5	-2.658	.007

pain medication had significantly higher scores on both the CMAI (p=.021) and CSDD (p=.004) compared to patients who did not use any medication for their pain. In the multivariate model, the presence of pain and the severity of dementia predicted 9.6% of the total NPI-Q score (p<.001), whereas age, gender and type of dementia did not contribute significantly to the prediction of the total NPI-Q score.

Discussion

This study, with a large sample size, confirms the high prevalence and impact of pain in patients with dementia who are still living at home. Our data show that over 60% of patients with dementia living at home experience pain, using both self-report and caregiver-report. Pain affected their ADL, sleeping at night, and it is significantly related to their behavioral disturbances.

To the best of our knowledge, there are only six studies in the literature (PubMed, up to March 01, 2016), that reported the prevalence of pain in community-dwelling dementia patients using both self-report and caregiver-report.[25-30] **Table 3** summarize these studies. Compared to most studies, our study shows a higher pain prevalence, with a higher degree of concordance between patient and caregiver reports of patients' pain (61% and 62%, respectively). However, Hunt et al.[30] recently reported a similar prevalence and concordance rates between patient and caregiver reports (62.7% and 64.4%, respectively) in a large study of 802 patient-caregiver dyads. It is important to mention that our data cannot be directly compared with those of the studies of table 3, due to methodological differences in study design, sample size, pain assessment tools, and measured pain duration. However, all these studies address the high prevalence of pain in dementia patients who are still living at home and the importance of assessing and treating pain in this population, specifically in the presence of physical frailty. The majority of our patients with pain experienced chronic pain (72%), with musculoskeletal pain being the most common type of pain (77%), and women (63%) were more likely to experience pain than were men (37%). These findings are consistent with those of previously published studies.[25-31] Another important finding was the high prevalence (almost one third) of untreated pain among respondents

who experienced pain. Several factors may contribute to this undertreatment. For example, many older adults/caregivers may consider pain to be a natural part of aging and therefore do not seek medical treatment. Also, pain may not be reported by patients or recognized by caregivers/physicians, because of patients' diminished communication skills. Lack of awareness among physicians and other health care providers may also contribute to under-recognition of pain in dementia patients.

Impact of pain on ADL and sleep

Fifty-six percent of our patients with pain reported that pain interfered with ADL and one third reported that pain negatively influenced their sleep at night. The relationship between daytime physical inactivity and pain-related sleep disturbances may be cyclical, since sleep disturbances lead to persistent fatigue and excessive daytime sleepiness, resulting in decreased daytime functioning.[32] Increased physical activity is recognized as an important factor in decreasing behavioral disturbances and improving cognitive function, social interaction, and quality of life in people with dementia.[33, 34] Pain limits physical activities, either because activities exacerbate pain or because individuals fear pain induced by these activities. These two factors, "feeling pain" and "fear of feeling pain", may also reinforce each other, leading to a vicious circle together with impaired functioning and dependence.[35]

Pain and behavioral and psychological symptoms

Currently, most of the available information regarding the association between pain and pain-related behavioral disturbances in dementia has come from studies conducted in nursing home residents,[19] with much less information available from studies conducted in community-dwelling dementia patients.[6, 28, 29] Our data show that pain was significantly associated with behavioral and psychological symptoms in patients with dementia who are still living at home. Previous studies have consistently demonstrated the negative impact of behavioral and psychological changes among dementia patients on caregivers.[6, 15, 36-38] In the literature, depression,

Table 3 Studies reported the prevalence of pain in community-dwelling older patients with dementia using patients' self-report and caregiver report

Study	Design / number of participants	Mean age of participants	Prevalence of pain		Method used to measure pain
			Self-report	Caregivers	
Mäntyselkä et al. [25] 2004 Finland	Cross-sectional population-based survey. 75 dementia patients.	Patients: 83 years (female: 73%).	40% (n=30 out of 75) **Comment**: 64 of dementia patients could answer the questions regarding pain themselves, while the caregiver assessed the perceived pain in 11 cases.	**Comment**: caregivers were not always included. Only if the patient unable to report pain (n=11).	Subjects were asked during an interview about perceived pain during the preceding month. The caregiver was asked about the subject's pain symptoms if necessary, and the interviewer and geriatrician assessed the presence of pain during the interview and medical examination.
Shega et al. [26] 2004 USA	Prospective cohort study. 115 patient-caregiver dyads.	Patients: 84.1±6.7 years (female:76%). Caregivers: 61.1±13.3 years.	32%	52%	Face-to-face interviews using the Verbal Descriptor Scale (variable: pain right now)
Murray et al. [27] 2012 USA	Retrospective cohort study. 150 patient-caregiver dyads.	Patients: 81±7 years (female: 73%). Caregivers: 62±14 years.	42% (n=48 out of 115) **Comment**: 35 dementia patients were unable to respond to questions resulting in 115 for whom interview data were available.	30% (n= 46 out of 150)	Face-to-face interviews using an open ended format questions(variable: pain in the last week)
Jensen-Dahm et al. [28] 2012 Denmark	Data collected from a randomized, controlled trial. 321 patient-caregiver dyads.	Patients: 76.2 ± 7.1 years (female: 55%). Caregivers: 66±12.7 years.	32.9%	52%	Pain was assessed as part of the EuroQol EQ-5D (caregiver- and self-rated), (variable: pain today).
Orgeta et al. [29] 2015 UK	Cross-sectional study. 488 patient-caregiver dyads	Patients: 75.55 (range: 54-95) years (female: 50%). Caregivers: 69.83 (range: 23-91) years.	45%	59%	Pain was assessed as part of the EuroQoL EQ-5D
Hunt et al. [30] 2015 USA	Cross-sectional cohort study. 802 patient-caregiver dyads	Patients: 67.2% were aged 80 and older (female: 65%)	62.7%	64.4%	Pain was measured during an interview using a two-question verbal descriptor scale (VDS), (variable: pain in the last month)

agitation, aggression, psychosis, and sleep disturbances were most commonly cited as symptoms that caregivers found distressful.[39] In fact, all these symptoms were common in our dementia patient with pain.

Interestingly, patients who used pain medication had significantly higher CMAI (agitated behavior) and CSDD (depressive symptoms) scores than patients who did not use any medications for their pain. A possible explanation for this finding is that the patients on analgesic therapy may have experienced more severe pain, which was not well controlled, while the patients without analgesics may have experienced milder pain, which did not necessitate pain medications so far.

Strengths and limitations

Our findings, which are based on a large sample, contribute to the sparse literature on the prevalence and impact of pain and pain-related behavioral symptoms in patients with dementia who are still living at home. However, a number of methodological limitations should be considered when interpreting the results. First, while our questionnaire included validated measurement scales such as NPI-Q, CMAI and CSDD, the questions about pain and their impact were newly developed by the research team, though these questions bear significant resemblance to other validated scales such as the Brief Pain Inventory and the Three-item Scale PEG.[40, 41] Second, the data collection was based on patient and caregiver report, which may have been influenced by the cognitive functions of the individuals with dementia. For example, answers may have been subject to recall bias. Although self-report is considered the gold standard in pain assessment, its validity in people with dementia is questionable because these individuals often have disturbed perception, thought content, expression, and communication skills. Therefore, we strongly recommended that self-report should always be accompanied by caregiver observation. Third, pain at a single time point, namely "right now", was the variable being examined to determine the prevalence of pain, and not pain over a longer period of time (weeks or months). This may have led to underestimation

of the prevalence of pain. Fourth, the severity of pain was not evaluated in our study. Data regarding pain severity may help to improve our understanding of the relationship between pain severity and the occurrence of specific behavioral symptoms in dementia patients.[6] Finally, we did not collect information about whether our patients were helped to complete the questionnaires by the case managers or caregivers, which may have introduced bias that led to a higher degree of concordance between patient and caregiver reports of patients' pain.

Clinical implications and future directions

The management of pain and pain-related behavior disturbances in patients with dementia is a complex issue, with numerous controversies within the current evidence-base. For example, previous studies and clinical guidelines consistently reported the importance of enhancing pain assessment in patients with dementia, especially in those with diminished communication skills.[31, 42-45] However, currently there are no standardized assessment tool for pain in nonverbal older people with dementia, and most available tools have poor reliability, validity and clinical utility.[42-45] In addition, despite the fact that enhancing pain assessment may improve pain management, information regarding pharmacological interventions for pain in dementia patients is lacking in the literature.[43, 44] Furthermore, currently available analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs, opioids, antidepressants, anticonvulsants, neuroleptics, and corticosteroids, are often ineffective, contraindicated, or cause severe adverse events in older people with dementia,[11, 43] which contribute to undertreatment of pain in this population. There are still significant gaps in the evidence-base that limit the accurate assessment and the effective management of pain in people with dementia. Further research is urgently warranted to develop reliable and valid observational instrument for assessing pain in clinical and nonclinical settings, and to develop novel therapies for pain in this frail population.

Tetrahydrocannabinol as a multi-target drug candidate for pain and pain-related behavioral and psychological symptoms in dementia

As mentioned in section "METHODS", this study was part of the recruitment procedure of a randomized, placebo-controlled, double-blind trial of the effectiveness tetrahydrocannabinol (THC) in the treatment of behavioral disturbances and pain in patients with dementia.[20] THC is the main psychoactive cannabinoid of the cannabis plant (Cannabis sativa L.), and appeared to be responsible for most of its physical effects.[46] Several randomized controlled trials have demonstrated the potential role of THC in the treatment of pain.[47] THC exerts some of its multiple therapeutic effects through an interaction with the endocannabinoid system. THC acts as a partial agonist of the two cannabinoid receptors, CB1, which mainly located in the central, and peripheral nervous systems, and CB2, which primarily found in cells of the immune system.[48-50] Also, THC exerts effects by interacting with other cannabinoid and non-cannabinoid receptors in the brain, such as acetylcholine, dopamine, serotonin, gamma-aminobutyric acid, glutamate, norepinephrine, prostaglandins, and opioid peptides.[51] This broad and complex interactions reflect the potential of THC as multi-target drug candidate for the treatment of pain and behavioral disturbances in dementia patients. However, the data of our recently published study,[20] showed that THC dose up to 4.5 mg daily did not improve pain intensity (assessed with Verbal Rating Scale),[52] and pain-related behavior [assessed with Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC-D)],[53] in older patients with dementia, compared to placebo. In fact, these results must be understood within the context of several major limitations. First, the small number of participants in the subgroup of pain (total: 23 participants: THC 8 and placebo 15); and second, the diminished communication skills in dementia patients that influence the ability to self-report. In our study, only 13 out of the 23 participants with pain were able to respond to the Verbal Rating Scale (self-reporting). Moreover, although the observational tool PACSLAC-D has strong

psychometric properties and is simple to use,[18] the tool contains observation items that are not specifically for pain, but overlap with those of behavioral and psychological symptoms of dementia. Therefore, it is often difficult to distinguish whether the observed behaviors are pain-related or dementia-related behaviors. Finally, in order to prevent side-effects we probably used too low oral THC doses, as the overall results of the pharmacodynamic parameters of THC such as effectiveness, side effects, systolic and diastolic blood pressure, and heart rate, were small.[20]

Conclusion

Pain was common and often undertreated among community-dwelling dementia patients. It was associated with diminished ADL, sleep disturbances, behavioral and psychological symptoms, and caregiver distress. Overall, our findings support the importance of routinely assessing whether individuals with dementia are in pain, in order to treat pain and to reduce the burden of pain-related behavioral problems in dementia patients and its associated caregiver distress. However, the loss of communication ability in dementia patients limits self-report of pain. Therefore, a standardized, reliable, and valid observational tool is needed for assessing pain in nonverbal patients in clinical and nonclinical settings. Facial expressed emotion recognition software, if also valid in recognizing mood changes in dementia, are an exciting new option for early pain detection. In addition, there is a strong need for novel effective and safe pharmacological interventions for pain and behavioural disturbances in dementia. Although oral THC is a potential multi-target drug candidate, more randomized controlled trials are needed to evaluate its effectiveness and safety in the treatment of pain and pain-related behavioral disturbances in older people with dementia.

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Chapter 8

Cannabinoids for pain in dementia: the good, the bad, and the ugly

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To the Editor: Greater risk of dementia and painful chronic conditions or diseases, such as degenerative disc and joint disease, diabetic neuropathy, and cancer, accompany aging.[1] Thus, many older individuals with dementia may be in pain. The reported prevalence of pain in elderly adults varies from 28% to 88%,[2–4] the wide range probably being due to differences in sample sizes, setting, onset and type of pain, and methods used to measure pain.

WHAT IS THE PROBLEM?

Pain is difficult to assess and treat in individuals with dementia. Although self-report is generally considered the best way to assess pain, this is difficult in individuals with dementia, especially those with moderate to advanced dementia, because they are less able to articulate the pain and discomfort they feel.[5] Instead, they may express their pain and discomfort behaviorally, as agitation, aggression, pacing, wandering, screaming, yelling, and sleep disturbances, although these behaviors are often not recognized as symptoms of pain but instead as behavioral and psychological symptoms of dementia[6] so that individuals with dementia are more likely to receive psychotropic medication, and not pain medication, to treat these manifestations of pain.[7]

Over the past decade, a number of observational pain scales have been developed for use in nonverbal older persons with dementia,[5, 8] but there is no standardized assessment tool. Moreover, most available instruments have poor reliability and validity. A randomized controlled trial reported that the use of a stepwise pain protocol based on the treatment recommendations of the American Geriatrics Society significantly reduced behavioral disturbances and pain in individuals with moderate to severe dementia (n=175),[9] indicating that adequate treatment of pain reduces behavioral disturbances, but currently available drugs for the management of pain, such as acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, antidepressants, and antiepileptic drugs, are often not effective or cause serious adverse reactions in older persons.

CANNABINOIDS AS A MULTITARGET DRUG CANDIDATE

Recent studies have demonstrated the potential of cannabinoids, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), to manage the symptoms of pain and dementia.[10] Two cannabinoid receptors, CB1 and CB2, mediate the psychoactive, behavioral, and analgesic effects of cannabinoids. CB1 receptors are highly expressed in the cortex, basal ganglia, cerebellum, and hippocampus, whereas CB2 receptors are mainly expressed in the immune system.[11] Cannabinoids also interact with other receptors and neurotransmitters in the brain, such as acetylcholine, dopamine, gamma-aminobutyric acid, serotonin, glutamate, norepinephrine, prostaglandins, and opioid peptides.[11] This wide range of interactions reflects the potential pharmacological effects of cannabinoids in the management of behavior, mood and pain.

Cannabinoid-based medicines, such as dronabinol (THC), nabilone (THC) and nabiximols (combination of THC and CBD), have been recently become available in some countries, and a systematic review of randomized trials showed them to be effective in the management of pain, being safe and well tolerated,[10] but none of the 18 trials included in the review recruited participants with dementia or provided separate data for older persons (≥ 65), if these individuals were included in the study.

To the best of the knowledge of the authors, there have been only two randomized clinical trials of the effect of cannabinoids on behavioral disturbances in individuals with dementia. In both trials, participants with Alzheimer's disease were treated using dronabinol. The first trial reported that 2.5 mg of THC twice a day was effective in the treatment of anorexia and behavioral disturbances, and the second reported that 2.5 mg of THC once a day reduced nocturnal motor activity and agitation,[12,13] although both trials were small, involving 12 and two participants, respectively.

WHAT NEEDS TO HAPPEN

Accurate assessment of pain is crucial for adequate pain management. In turn, this requires a reliable and valid observational tool for assessing pain in nonverbal individuals with dementia in clinical and nonclinical settings. Although cannabinoids are a potential multitarget treatment, randomized controlled trials are needed to evaluate their safety and efficacy in the treatment of pain and pain-related behavioral disturbances in older adults with dementia.

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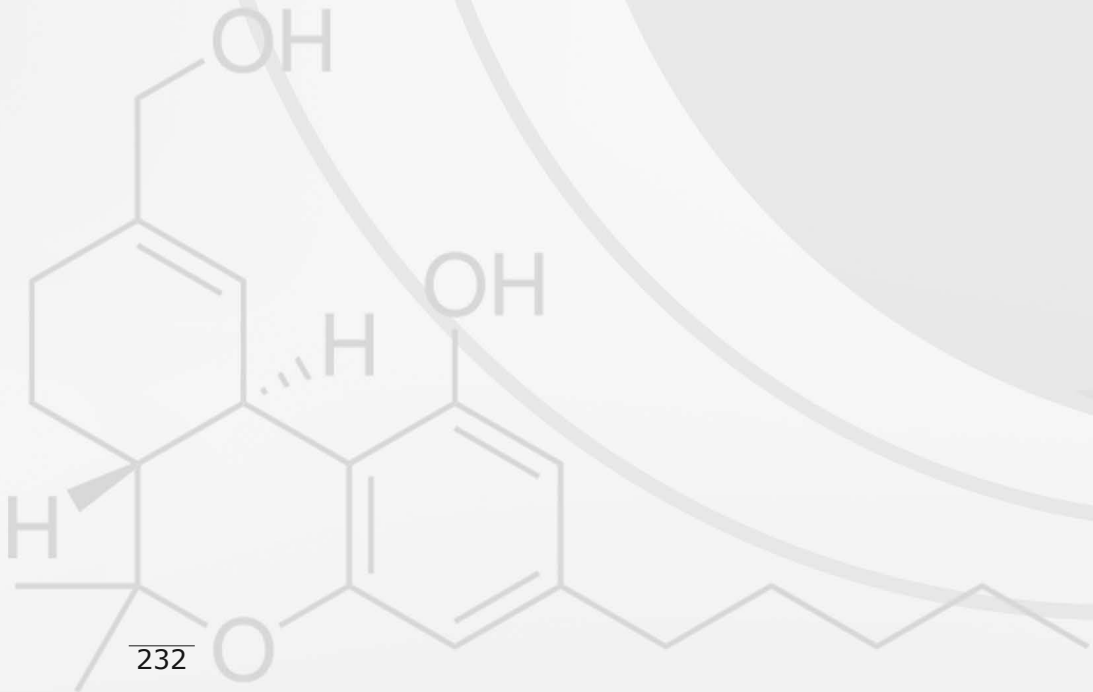


PART VI

Summary

Summary

The main aim of the studies described in this thesis was to evaluate the clinical pharmacology of oral tetrahydrocannabinol (THC) in older people with dementia, specifically:

1. To evaluate current evidence in the literature on the medicinal use of cannabis and cannabinoids in older people (**PART II**);
2. To evaluate current evidence in the literature on the potential of cannabinoids in the treatment of late-onset Alzheimer's disease and related neuropsychiatric symptoms (**PART III**);
3. To evaluate the pharmacodynamic (including side effects) and pharmacokinetic effects of oral THC in older people and individuals with dementia (**PART V**);
4. To evaluate the effectiveness of THC in the treatment of neuropsychiatric symptoms of dementia (**PART IV**);
5. To evaluate the effectiveness of THC in the treatment of pain and pain-related behavioral disturbances in older people with dementia (**Chapter 4** and **PART VI**).

PART II Cannabinoids for older people with dementia

In **Chapter 1**, we performed a systematic review to integrate evidence on the indications, efficacy, and safety of medical cannabinoids in older people. Despite the large number of studies of cannabinoids in the general population (1296 articles), only five randomized clinical trials were identified that reported separate data for older individuals. On the basis of these studies, cannabinoids would appear not to be effective in the treatment of dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting. Two studies with small samples (n=2 and n=15) showed that THC might be useful in the treatment of anorexia and dementia-related behavioral symptoms. The most frequently reported cannabinoid-related adverse events were sedation-like symptoms (e.g., drowsiness, tiredness and somnolence).

In **Chapter 2**, based on evidence in the literature (*in vitro*, *in vivo* and population-based studies), we reviewed the potential of cannabinoids in the treatment of late-onset Alzheimer's disease and related neuropsychiatric symptoms. Several *in vitro* and *in vivo* studies have demonstrated that targeting the endocannabinoid system offers a novel pharmacological approach to the treatment of late-onset Alzheimer's disease that may be more effective than currently available drugs. A number of studies have shown that cannabinoids can reduce oxidative stress, neuroinflammation, and the formation of amyloid plaques and neurofibrillary tangles, the hallmarks of late-onset Alzheimer's disease. Moreover, the cannabinoid THC seems to increase the availability of acetylcholine and prevent acetylcholinesterase-induced Aβ aggregation. Unfortunately, our literature search did not identify any population-based studies of cannabinoids as a potential cure for this type of Alzheimer's disease. We found only four clinical studies of the effectiveness of cannabinoids in the treatment of dementia-related symptoms (in total 60 subjects treated with the synthetic THC dronabinol) and one case report in which the synthetic THC nabilone was used. Although the findings from the above-mentioned clinical studies and case report suggest that THC is effective and safe to use in the treatment of dementia-related symptoms in older people, the studies had several important methodological limitations that made it impossible to draw firm conclusions about the safe and effective use of THC in these patients.

*The findings of **PART II** highlighted three important points: first, the under-representation of older people in clinical trials of cannabinoid-based drugs, resulting in a lack of evidence on their safety and efficacy in this population; second, currently available in vitro and in vivo studies provide an interesting basis for the innovative use of cannabinoids as a therapeutic approach to dementia and dementia-related symptoms; and third, there is an urgent need for adequately powered randomized controlled trials to assess the evidence for, and the risk–benefit ratio of, cannabinoid-based drugs in older people with dementia.*

PART III Efficacy of THC in the treatment of neuropsychiatric symptoms of dementia

The proof of concept research question whether THC can reduce the neuropsychiatric symptoms of dementia is described in **Chapter 3** and **Chapter 4**. The study presented in **Chapter 3** was a multicenter, phase 2, repeated crossover, randomized, double-blind, placebo-controlled trial. For 12 weeks, 22 patients with dementia and clinically relevant neuropsychiatric symptoms [15 men, mean age 76.4±5.3 years] were randomized to receive oral THC (weeks 1–6, 0.75 mg; weeks 7–12, 1.5 mg) or placebo twice daily for 3 days, separated by a 4-day washout period. Although the THC dose up to 3 mg daily was safe and well tolerated by the patients, it was not more effective than placebo in treating neuropsychiatric symptoms. Overall, THC had only minor pharmacodynamic effects, including side effects, based on vital signs (systolic and diastolic blood pressure, and heart rate), mobility and balance scores, body weight, and scores for feeling high, external, and internal perceptions. **Appendix Chapter 3** provides the data of an open-label extension phase 2 study that followed the crossover period. Of the 12 included participants in this phase (55% of total study participants), only 5 (42% of total study participants) completed the 6-month treatment period. The reasons for discontinuation were not related to adverse events. Long-term treatment with low-dose THC had no effect on neuropsychiatric symptoms. Given the small number of participants in the open-label study (n=5), the results should be interpreted with caution.

In **Chapter 4**, we describe a multicenter, phase 2, randomized, double-blind, placebo-controlled trial. Fifty patients with dementia and clinically relevant neuropsychiatric symptoms were randomly assigned (ratio 1:1) to receive THC 1.5 mg (n=24) or matched placebo (n=26), three times daily for 3 weeks. THC doses up to 4.5 mg were safe and well tolerated by the older patients with dementia. Compared to placebo, THC did not significantly improve neuropsychiatric symptoms (Neuropsychiatric Inventory), agitated behavior (Cohen-Mansfield Agitation Inventory), quality of life (Quality of Life–Alzheimer's Disease), or activities of daily living (Barthel

Index). In addition, in a subgroup of patients with persistent pain (n=23) (**Appendix Chapter 4**), THC did not reduce pain intensity (Verbal Rating Scale) or pain-related behavior (Pain Assessment Checklist for Seniors with Limited Ability to Communicate).

In conclusion, THC in doses up to 4.5 mg daily appeared safe and well tolerated by older patients with dementia. However, THC was not effective in the treatment of neuropsychiatric symptoms, pain, and pain-related behavior. The absence of significant pharmacodynamic effects, including side effects, suggests that the administered THC doses were too low.

PART IV Safety, pharmacodynamics, and pharmacokinetics of oral tetrahydrocannabinol in older people with dementia

In **Chapter 5**, we performed a phase 1, randomized, placebo-controlled, crossover trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of a single oral dose of 3 mg, 5 mg, or 6.5 mg THC in 12 healthy older individuals (6 male; mean age 72±5 years). The data for 11 subjects were included in the analysis. THC was safe and well tolerated. The most frequently reported adverse events were drowsiness (27%) and dry mouth (11%). Participants reported more adverse events with THC 6.5 mg than with 3 mg (p=0.048), 5 mg (p=0.034), or placebo (p=0.013). Overall, the pharmacodynamic effects of THC were smaller than the effects previously reported for young adults. Compared to placebo, THC administration was not associated with significant changes in systolic and diastolic blood pressure, heart rate, feeling high scores, body sway, and subjects' attentional performance. Plasma concentrations of THC, its metabolites 11-hydroxy-delta-9-THC (11-OH-THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) increased dose dependently with increasing THC dose ($p < 0.0001$), but there was a wide interindividual variability in plasma concentrations. Unfortunately, we could not perform a complete pharmacokinetic analysis, because we collected only four blood samples (over 120 min) per subject. In contrast to data for young adults, THC concentrations did not reach a maximum in some participants during the 120-min sampling period. In subjects in whom the maximum concentration (C_{max})

was reached within the sampling period, C_{max} was 1.42–4.57 ng/mL and time to reach C_{max} (t_{max}) was 67–92 min. The area under the curve (AUC) from 0 to 2 h (n=11) was 1.67–3.51 ng/mL.

A complete pharmacokinetic analysis was performed in a study involving older individuals with dementia (**Chapter 6**). This pharmacokinetic study was part of the phase 2, randomized, double-blind, placebo-controlled trial described in **Chapter 3**. We evaluated the safety, pharmacodynamics, and pharmacokinetics of THC in ten patients with dementia (mean age 77.3±5.6). Only 6 of the in total 98 adverse events were considered to be (possibly) related to THC. All were mild and transitory in nature. Also, in this study, THC had fewer pharmacodynamic effects in older individuals with dementia than expected based on the effects reported for young adults. We found no statistically or clinically significant changes in participants' feeling high, external perception, body sway with eyes open, and diastolic blood pressure after THC. The statistically significant changes in internal perception, body sway with eyes closed, systolic blood pressure, and heart rate after THC were not considered clinically relevant, as they were small and were not associated with adverse events. After THC administration, the median t_{max} was 1–2 h. THC had dose-linear pharmacokinetics in older individuals with dementia, showing a doubling of the AUC and C_{max} with doubling of the dose from 0.75 to 1.50 mg. However, there was considerable interindividual variation in plasma concentrations of THC (coefficient of variation up to 140%) and 11-OH-THC (coefficient of variation up to 62%), which is in line with our data from a phase 1 study involving healthy older individuals (**Chapter 5**). The mean C_{max} (ng/mL) after the first dose (0–6 h) 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 h), the C_{max} was 0.50 (0.27–0.92) and 0.98 (0.46–2.06), respectively.

*On the basis of our data from **PART V**, THC in doses up to 6.5 mg and 4.5 mg daily were safe and well tolerated by healthy older individuals and older individuals with dementia, respectively. Overall, the pharmacodynamic effects of THC in older adults, including*

those with dementia, were smaller than the effects previously reported in young adults. THC was rapidly absorbed and had dose-linear pharmacokinetics with considerable interindividual variation. Further studies are warranted to evaluate the pharmacodynamics and pharmacokinetics of higher THC doses in older people with dementia.

PART V Pain and pain-related symptoms in dementia

Chapter 7 reports data on the prevalence and impact of pain in patients with dementia and the relationship between pain and behavioral and psychological symptoms. This cross-sectional, community-based, prevalence survey was part of the recruitment procedure of the THC effectiveness trial described in **Chapter 4**. Self-administered postal questionnaires were sent to patients with dementia and their informal caregivers (701 patient–caregiver dyads). Of these, 390 (56%) were returned. The questionnaires of 386 patient–caregiver dyads were sufficiently complete for analysis. Our data showed that pain is common (over 60% of participants) and often undertreated (almost 30%) among community-dwelling patients with dementia. It is associated with diminished activities of daily living, sleep disturbances, behavioral and psychological symptoms, and caregiver distress. Our findings, which are unique for being based on a large sample, contribute to the sparse literature on the prevalence and impact of pain and pain-related behavioral symptoms in patients with dementia who are still living at home.

In the research letter presented in **Chapter 8,** we discuss the challenges in assessing and treating pain in patients with dementia, particularly in those with moderate and severe dementia, who are less able to articulate the pain and discomfort they feel. We concluded that studies, preferably well-designed trials, are needed that specifically focus on the effect of cannabinoids on pain and pain-related behavioral disturbances in patients with dementia. This is warranted, as the study reported in **Chapter 7** showed that pain is common and has negative effects on dementia patients and their caregivers. As mentioned in **Chapter 2**, the broad interactions of cannabinoids with the endocannabinoid system and

different neurotransmitters in the brain underscore the potential of cannabinoids as multi-target drug candidates for the treatment of pain and pain-related behavioral disturbances in older people with dementia. However, accurate assessment of pain is crucial for adequate pain management, but most available assessment tools for nonverbal older individuals with cognitive impairments have a poor reliability, validity, and clinical utility.

*Overall, the findings of **PART VI** support the importance of routinely assessing pain in patients with dementia, in order to treat pain and to reduce the burden of pain-related behavioral problems and the associated caregiver distress. Although cannabinoids are a potential multi-target treatment, randomized controlled trials are needed to evaluate their safety and efficacy in the treatment of pain and pain-related behavioral disturbances in older people with dementia.*

Samenvatting

Summary in Dutch

Samenvatting

Het voornaamste doel van de studies beschreven in dit proefschrift was om de klinische farmacologie van tetrahydrocannabinol (THC) in tabletvorm te evalueren bij ouderen met dementie, in het bijzonder:

1. Evaluatie van het huidig bewijs uit de literatuur over het medicinale gebruik van cannabis en cannabinoïden bij ouderen (**Deel II**);
2. Evaluatie van het huidig bewijs uit de literatuur over de mogelijkheden van cannabinoïden bij de behandeling van laat beginnende Alzheimer en daaraan gerelateerde neuropsychiatrische symptomen (**Deel III**);
3. Evaluatie van de farmacodynamische (inclusief bijeffecten) en farmacokinetische effecten van orale toediening van THC bij ouderen en personen met dementie (**Deel V)**.
4. Evaluatie van de effectiviteit van THC bij de behandeling van neuropsychiatrische symptomen van dementie (**Deel IV**);
5. Evaluatie van de effectiviteit van THC bij de behandeling van pijn en pijn gerelateerde gedragsstoornissen bij ouderen met dementie (**Hoofdstuk 4** en **Deel VI)**

Deel II Cannabinoïden bij ouderen met dementie

In **Hoofdstuk 1** voerden wij een systematische review uit voor het integreren van bewijs van indicaties, werking en veiligheid van medicinale cannabinoïden bij ouderen. Ondanks het grote aantal studies naar cannabinoïden binnen de algemene populatie (1296 artikelen), werden slechts vijf gerandomiseerde klinische trials geïdentificeerd die aparte data rapporteerden voor ouderen. Op basis van deze studies bleken cannabinoïden niet effectief te zijn voor de behandeling van dyskinesie (bewegingsstoornissen), benauwdheid en misselijkheid en braken na chemotherapie. Twee studies met kleine groepen (n=2 en n=15) lieten zien dat THC nuttig kan zijn in de behandeling van verminderde eetlust en gedragsproblemen bij dementie. De meest gerapporteerde bijwerkingen waren sederende effecten (zoals duizeligheid, vermoeidheid en slaperigheid).

In **Hoofdstuk 2** herzagen we de mogelijkheden van cannabinoïden binnen de behandeling van laat beginnende Alzheimer en daaraan gerelateerde neuropsychiatrische symptomen. Verscheidene *in vitro* en *in vivo* studies hebben laten zien dat het richten van het endocannabinoïde systeem een nieuwe farmacologische benadering voor de behandeling van laat beginnende Alzheimer biedt welke effectiever kan zijn dan momenteel beschikbare medicamenten. Een aantal studies hebben laten zien dat cannabinoïden kunnen zorgen voor een verlaging in oxidatieve stress, zenuwontsteking en de vorming van amyloïde plaatjes en neurofibrillaire knopen**,** de kenmerken van laat beginnende Alzheimer. Bovendien blijkt de cannabinoïde THC de beschikbaarheid van acetylcholine te vergroten en acetylcholinesterase-geïnduceerde Aβ aggregatie tegen te gaan. Helaas heeft onze literaire zoektocht geen populatie-gebaseerde studies van cannabinoïden als mogelijke behandeling voor de ziekte van Alzheimer aangetroffen. Wij vonden slechts vier klinische studies naar de effectiviteit van cannabinoïden bij de behandeling van dementie-gerelateerde symptomen (in totaal 60 proefpersonen die zijn behandeld met de synthetische THC dronabinol) en één case report waarin de synthetische THC nabilone werd gebruikt. Hoewel de bevindingen van de bovengenoemde klinische studies en het case report suggereren dat THC effectief is en veilig kan worden gebruikt bij de behandeling van dementie-gerelateerde symptomen bij ouderen, hadden de studies verscheidene belangrijke methodologische beperkingen die het onmogelijk maakten om eenduidige conclusies te trekken over het veilig en effectief gebruik van THC bij deze patiënten.

*De bevindingen van **Deel II** wierpen licht op drie belangrijke punten: ten eerste de ondervertegenwoordiging van ouderen in klinische trials met cannabinoïde-gebaseerde medicamenten, resulterend in een gebrek aan bewijs over hun veiligheid en werkzaamheid binnen deze populatie; ten tweede bieden momenteel beschikbare in vitro en in vivo studies een interessante basis voor het innovatief gebruik van cannabinoïden als therapeutische benadering voor dementie en dementie-gerelateerde symptomen; en ten derde*

is er dringend behoefte aan gerandomiseerde gecontroleerde studies met voldoende deelnemers voor het vaststellen van bewijs voor, en het risico-voordeel ratio van cannabinoïde-gebaseerde medicamenten bij ouderen met dementie.

Deel III Werkzaamheid van THC bij de behandeling van neuropsychiatrische symptomen van dementie

Het bewijs van de onderzoeksvraag of THC de neuropsychiatrische symptomen van dementie kan verminderen is beschreven in **Hoofdstuk 3** en **Hoofdstuk 4**. De studie gepresenteerd in **Hoofdstuk 3** was een multicenter, fase 2, gerandomiseerde, double-blind, placebo-gecontroleerde trial. Twee en twintig patiënten met dementie en relevante neuropsychiatrische symptomen [15 mannen, gemiddelde leeftijd 76.4±5.3 jaar] krijgen gedurende 12 weken THC in tabletvorm voor drie dagen, afgewisseld met placebotabletten. Na elke behandelperiode (THC of placebo) kregen deelnemers vier dagen geen onderzoeksmedicatie. In de eerste 6 weken kregen deelnemers 0.75 mg THC tweemaal per dag. In de volgende 6 weken werd THC verhoogd naar 1.5 mg tweemaal per dag. Hoewel de THC dosis tot 3 mg per dag veilig was en goed werd getolereerd door de patiënten, was het niet effectiever dan placebo bij de behandeling van neuropsychiatrische symptomen. Over het algemeen had THC slechts weinig farmacodynamische effecten, waaronder bijeffecten, gebaseerd op vitale kenmerken (systolische- en diastolische bloeddruk en hartslag), mobiliteits- en balansscores, lichaamsgewicht, en scores voor 'high' voelen, externe en interne percepties.

Bijlage Hoofdstuk 3 biedt de data van een open-label uittreksel fase 2 studie die de crossover periode volgde. Van de 12 deelnemers die waren betrokken in deze fase (55% van het totaal aantal deelnemers aan de studie), voltooiden slechts 5 (42% van het totaal aantal deelnemers aan de studie) de 6-maanden durende behandelperiode. De redenen om te stoppen waren niet verbonden aan bijeffecten. Langetermijnbehandeling met een lage THC dosis had geen effect op neuropsychiatrische symptomen. Gezien het

kleine aantal deelnemers in de open-label studie (n=5) dienen de resultaten met voorzichtigheid te worden geïnterpreteerd.

In **Hoofdstuk 4** beschrijven wij een multicenter fase 2 gerandomiseerde, double-blind, placebo gecontroleerde trial. Vijftig patiënten met dementie en neuropsychiatrische symptomen werden willekeurig ingedeeld (ratio 1:1) om 1.5 mg THC (n=24) of placebo (n=26), drie maal dagelijks voor 3 weken te gebruiken. THC doseringen tot 4.5 mg waren veilig en werden goed getolereerd door de oudere patiënten met dementie. Vergeleken met placebo was THC niet effectiever in de behandeling van neuropsychiatrische symptomen (middels Neuropsychiatric Inventory), geagiteerd gedrag (middels Cohen-Mansfield Agitation Inventory), kwaliteit van leven (middels Quality of Life–Alzheimer's Disease), of dagelijkse activiteiten (middels Barthel Index). Daarnaast leidde THC niet tot een vermindering van pijn (middels Verbale Schaal) of van pijn gerelateerd gedrag (middels Pain Assessment Checklist for Seniors with Limited Ability to Communicate).

Concluderend bleek THC in doseringen tot 4.5 mg per dag veilig voor en goed getolereerd door oudere patiënten met dementie. THC was echter niet effectief bij de behandeling van neuropsychiatrische symptomen, pijn en aan pijn gerelateerd gedrag. De afwezigheid van significante farmacodynamische effecten, waaronder bijeffecten, veronderstelt dat de gebruikte THC doseringen te laag waren.

DEEL IV Veiligheid, farmacodynamiek, en farmacokinetiek van orale inname tetrahydrocannabinol bij ouderen met dementia

In **Hoofdstuk 5** voerden we een fase 1 gerandomiseerde, placebo, gecontroleerde, crossover trial uit om veiligheid, farmacokinetiek en farmacodynamiek van 3 mg, 5 mg, en 6.5 mg THC in tabletvorm bij 12 gezonde ouderen te testen (6 mannelijk; gemiddelde leeftijd 72±5 jaar). De data van 11 deelnemers werd meegenomen in de analyse. THC was veilig en werd goed getolereerd. De meest gerapporteerde bijwerkingen waren misselijkheid (27%) en droge

mond (11%). Deelnemers rapporteerden meer bijwerkingen bij 6.5 mg THC dan bij 3 mg (p=0.048), 5 mg (p=0.034), of placebo (p=0.013). Over het algemeen waren de farmacodynamische effecten van THC kleiner dan de eerder vermelde effecten bij jongvolwassenen. Vergeleken met placebo werd THC toediening niet in verband gebracht met significante veranderingen in systolische en diastolische bloeddruk, hartslag, scores van 'high' voelen, lichaamszwaai, en het concentratievermogen van de proefpersoon. Plasmaconcentraties van THC, zijn metabolieten 11-hydroxy-delta-9-THC (11-OH-THC) en 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) namen gelijkmatig toe met de THC dosering (p < 0.0001), maar er was een ruime interindividuele variabiliteit in plasmaconcentraties. Helaas konden wij geen complete farmacokinetische analyse uitvoeren, omdat slechts vier bloedsamples (over 120 min) per proefpersoon waren verzameld. In tegenstelling tot de gegevens bij jongvolwassenen, bereikten THC concentraties geen maximum in sommige proefpersonen tijdens de 120 minuten durende bemonsteringsperiode. Bij proefpersonen die de maximale concentratie (C_{max}) binnen de bemonsteringsperiode bereikten, was C_{max} 1.42–4.57 ng/mL en de tijd om C_{max} te bereiken (t_{max}) bedroeg 67–92 min. Het gebied onder de curve (AUC) van 0 tot 2 uur (n=11) was 1.67–3.51 ng/mL.

Een complete farmacokinetische analyse is uitgevoerd in een studie bij ouderen met dementie (**Hoofdstuk 6**). Deze farmacologische studie was deel van de fase 2, gerandomiseerde, double-blind, placebo gecontroleerde trial beschreven in **Hoofdstuk 3**. Wij evalueerden de veiligheid, farmacodynamiek en farmacokinetiek van THC bij tien patiënten met dementie (gemiddelde leeftijd 77.3±5.6). Slechts 6 van de in totaal 98 bijwerkingen werden als (mogelijk) gerelateerd aan THC beschouwd. Alle waren mild van aard en kortstondig van duur. In deze studie had THC ook minder farmacodynamische effecten bij ouderen met dementie dan verwacht gebaseerd op de effecten gerapporteerd bij jongvolwassenen. Wij vonden geen statistisch of klinisch significante veranderingen in het 'high' voelen, de externa perceptie, lichaamszwaai met open ogen, en diastolische bloeddruk van proefpersonen na het gebruik van

THC. De statistisch significante veranderingen in interne perceptie, lichaamszwaai met gesloten ogen, systolische bloeddruk, en hartslag na THC werden niet als klinisch relevant beschouwd, omdat deze klein waren en niet in verband konden worden gebracht met bijwerkingen. Na THC opname was de mediaan t_{max} 1-2 uur. THC had een dosis-lineaire farmacokinetiek bij ouderen met dementie, met een verdubbeling van de AUC en C_{max} bij verdubbeling van de dosis van 0.75 naar 1.50 mg. Er was echter een aanzienlijke interindividuele variatie in plasmaconcentraties van THC (coëfficiënt van variatie tot 140%) en 11-OH-THC (variatiecoëfficiënt tot 62%), hetgeen correspondeert met onze data van een fase 1 studie bij gezonde ouderen (**Hoofdstuk 5**). De gemiddelde C_{max} (ng/mL) na de eerste dosis (0–6 uur) was 0,41 (0.18–0.90) voor de 0.75 mg dosis en 1.01 (0.53–1.92) voor de 1,5 mg dosis. Na de tweede dosis (6–24 uur), was de C_{max} respectievelijk 0.50 (0.27–0.92) en 0.98 (0.46–2.06).

*Op basis van onze data uit **DEEL V**, was THC in dagelijkse doseringen tot 6.5 mg en 4.5 mg veilig en werd het goed getolereerd door respectievelijk gezonde ouderen en ouderen met dementie. Over het algemeen bleken de farmacologische effecten van THC bij ouderen, waaronder ook ouderen met dementie, kleiner dan de eerder gerapporteerde effecten bij jongvolwassenen. THC werd snel geabsorbeerd en had een dosis-lineaire farmacokinetiek met aanzienlijke interindividuele variatie. Verder onderzoek is nodig om de farmacodynamiek en farmacokinetiek van hogere THC doseringen bij ouderen met dementie te bestuderen.*

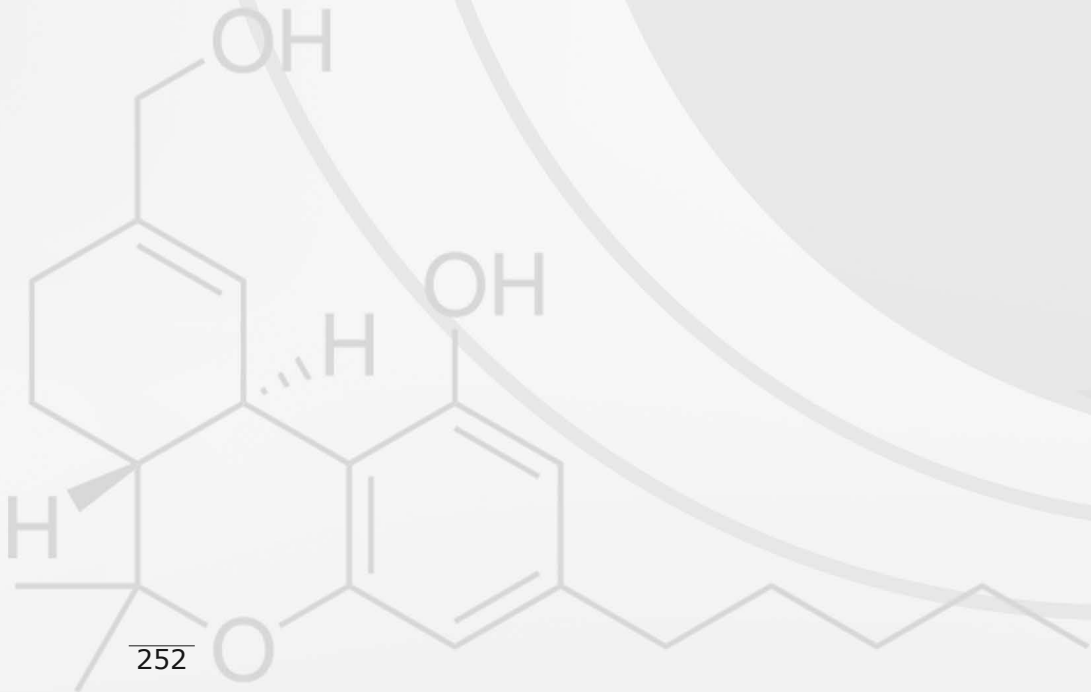
DEEL V Pijn en aan pijn gerelateerde symptomen bij dementie

Hoofdstuk 7 rapporteert data over het voorkomen en de impact van pijn bij patiënten met dementie en het verband tussen pijn en gedrags- en psychologische symptomen. Dit cross-sectioneel, populatie gebaseerd, prevalentie-onderzoek was een deel van de rekruteringsprocedure van de THC effectiviteitstrial zoals beschreven in **Hoofdstuk 4**. Vragenlijsten om zelf in te vullen

werden verstuurd aan patiënten met dementie en hun informele zorgverleners (701 patiënt–mantelzorger koppels). Hiervan werden er 390 (56%) teruggestuurd. De vragenlijsten van 386 patiënt–mantelzorger koppels werden voldoende ingevuld voor analyse. Onze data toonden dat pijn veel voorkomt (meer dan 60% van de deelnemers) en vaak niet voldoende wordt behandeld (bijna 30%) bij thuiswonende patiënten met dementie. Het fenomeen pijn wordt in verband gebracht met verminderde dagelijkse activiteiten, slaapstoornissen, gedrags- en psychologische symptomen, en minder spanning voor zorgverleners. Onze bevindingen, welke uniek zijn wegens hun basering op een groot aantal deelnemers, dragen bij aan de geringe literatuur over het voorkomen en de impact van pijn en pijn gerelateerde gedragssymptomen bij thuiswonende patiënten met dementie.

In de onderzoeksbrief gepresenteerd in **hoofdstuk 8,** bespreken wij de uitdagingen die optreden bij de beoordeling en de behandeling van pijn bij patiënten met dementie, voornamelijk bij patiënten met matige en ernstige dementie, die minder goed in staat zijn om pijn en de ongemakken die ze ervan ervaren te communiceren. Wij concludeerden dat studies, vooral goed ontworpen trials, die zich specifiek richten op de effecten van cannabinoïden bij pijn en pijn gerelateerde gedragsstoornissen nodig zijn bij personen met dementie. Dit is gerechtvaardigd omdat de studie beschreven in **hoofdstuk 7** aantoont dat pijn gemeenschappelijk is en negatieve effecten heeft op personen met dementie en hun verzorgers. Zoals vermeld in **hoofdstuk 2**, duiden de brede interacties tussen cannabinoïden, het endocannabinoïdensysteem en andere neurotransmitters in de hersenen, op het potentieel van cannabinoïden als mogelijke multi-target medicamenten voor de behandeling van pijn en aan pijn gerelateerde gedragsstoornissen bij ouderen met dementie. Nauwkeurige vaststelling van pijn is echter cruciaal voor een adequate omgang met pijn, maar de meeste beschikbare beoordelingsinstrumenten voor non-verbale ouderen met cognitieve beperkingen hebben een lage betrouwbaarheid, validiteit en klinische bruikbaarheid.

*Over het algemeen ondersteunen de bevindingen van **DEEL VI** het belang van zowel het regelmatig vaststellen van pijn bij patiënten met dementie als om pijn te behandelen en de last van aan gedrag gerelateerde problemen te verlagen en zodoende verlichting te bieden aan de verzorgers. Hoewel cannabinoïden een mogelijke multi-target behandeling bieden, zijn gerandomiseerd gecontroleerde trials nodig voor het vaststellen van hun veiligheid en werkzaamheid bij de behandeling van pijn en pijngerelateerde gedragsstoornissen bij ouderen met dementie.*



PART VII

General discussion

1. Introduction

In the past decade, the medicinal use of cannabis and cannabinoids has moved to the forefront of public and scientific debate, and the last few years have seen a growing interest in the medical use of these drugs in older people, for example, in the treatment of dementia, dementia-related neuropsychiatric symptoms, and other physical conditions that are common in old age.[1-5] Tetrahydrocannabinol (THC) appears to be responsible for most of the physical and psychoactive effects of the cannabis plant[6] and has attracted attention as a promising drug candidate with broad therapeutic applications. This growing interest led to the development of two synthetic THC-based drugs in capsule form, namely, dronabinol and nabilone, which are currently approved for medicinal use in several countries. However, to date, there is a great lack of information in the literature on the pharmacodynamics and pharmacokinetics of oral THC in older people with dementia. Older people, especially those with dementia and multiple comorbidities, may benefit greatly from the broad therapeutic applications of THC. This means that there is a need for knowledge of the pharmacodynamics and pharmacokinetics of THC-based drugs in this frail population, in order to maximize therapeutic benefit and to minimize side effects.

The studies described in this thesis focused on the clinical pharmacology of oral THC in older people with dementia, in particular, its pharmacokinetic and pharmacodynamic effects. We used a novel THC-based formulation in tablet form, Namisol® (THC ≥ 98%), which has not yet gained marketing approval, in our studies.

2. Past and current state of knowledge of clinical pharmacology of oral THC in older people with dementia

When preparing for our clinical trials in 2011, we performed a pharmacological-oriented literature search for studies of the oral use of THC in older people with dementia. At that time (2011), we found only two randomized clinical trials[7, 8] and one open-label study[9] of the effectiveness of oral THC (dronabinol) in the treatment of dementia-related symptoms. The three studies, which included only

Table 1 Studies published on THC-based drugs in patients with dementia-related symptoms.

Study	Subjects / age	Study design	Studied indication	Drug / Dosage	Treatment duration	Results	
						Efficacy	Safety
Volicer et al.[7] (1997), USA	12 AD (11 men, 1 woman) Mean age 72.7±4.9 (range 65–82 years)	RCT	Food refusal and disturbed behavior	Dronabinol (THC) 2.5 mg twice/day	12 wk (6 wk THC and 6 wk placebo)	Weight increased more with THC than with placebo. THC decreased severity of disturbed behavior compared with placebo.	One dropout during THC treatment, due to seizure. Adverse events were more common with THC than with placebo. The top 5 reported adverse events were anxiety/ nervousness, emotional lability, tiredness, somnolence, and euphoria.
Walther et al.[8] (2006), Germany	6 (5 AD and 1 VaD) (2 men, 4 women), Mean age 81.5±6.1	Open-label	Nocturnal motor activity	Dronabinol (THC) 2.5 mg/day	2 wk	Compared to baseline, THC significantly reduced nocturnal motor activity and agitation.	No adverse events were observed.
Walther et al.[9] (2011), Switzerland	2 AD A) 75-year-old man B) 81-year-old man	RCT	Agitation and circadian disturbances	Dronabinol (THC) 2.5 mg/day	4 wk (2 wk THC and 2 wk placebo)	THC reduced nighttime activity and strengthened circadian rhythms.	No adverse events were observed.

Woodward et al.[11] (2014), USA	40 (12 men, 28 women) 13 AD 7 VaD 15 AD/VaD 1 FTD 4 Dementia not otherwise specified Age was not reported	Retrospective systematic chart review	Behavioral or appetite disturbances	Dronabinol (THC) Mean dose 7.03 mg/day	Mean duration: 16.88 d (range 4–50 d)	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).
Shelef et al.[12] (2016), Israel	11 AD (6 men, 5 woman) Mean age 73.2±8.59	Open-label	Behavioral and psychological symptoms of dementia	Cannabis oil (2.5 mg THC) n=7 received 2.5 mg twice/day n=3 received 7.5 mg twice/day	4 wk	Compared to baseline, cannabis oil significantly reduced the scores of the Clinical Global Impression scale and the following domains of the Neuropsychiatric Inventory scale: delusions, agitation/ aggression, irritability, apathy, and sleep, and caregiver distress.	3 of 11 patients developed adverse events: 1 patient dropped out because of dysphagia, which was probably not related to THC use; 1 patient with a history of falls developed pelvic fracture after a fall; and 1 patient developed confusion with THC 5 mg bid. The symptoms improved after the THC dose was decreased to 2.5 mg bid.

AD, Alzheimer's disease; FTD, frontotemporal dementia; LOAD, late-onset Alzheimer's disease; RCT, randomized controlled trial; THC, tetrahydrocannabinol; VaD, vascular dementia

patients with dementia aged 65 years and older, showed that THC was effective and safe to use in older patients with dementia.[7-9] There were no studies of the pharmacokinetics of THC in older patients with dementia. Moreover, we found only one study that reported plasma THC plasma concentrations (peak levels only) in subjects aged 51–78 years, but these individuals did not have dementia.[10] Two years later, we performed a broad systematic review of the literature (up to October 7, 2013) on the medicinal use of cannabinoids in older people, including individuals with dementia (**Chapter 1**). This systematic literature search revealed three additional studies that included non-demented subjects from different age groups and performed analyses for the older group separately. These studies showed that cannabinoids were not effective as treatment for dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting. A new literature search in February 2015 (**Chapter 2**) revealed an additional retrospective systematic chart review study.[11] The study evaluated the data of 40 geriatric patients with dementia who had been treated with oral THC (dronabinol) for behavioral or appetite disturbances; however, the age of the patients was not reported. The authors concluded that THC was safe and effective to use in the treatment of dementia-related symptoms.[11]

During the writing of this discussion, I updated the literature search reported in **Chapter 2** to February 4, 2016. I found one new open-label prospective study of the safety and efficacy of cannabis oil (containing 2.5 mg THC) for the treatment of the behavioral and psychological symptoms of dementia [11 patients, mean age 73.2 years].[12] THC doses of 2.5 mg twice/day (n=7) and 7.5 mg twice/day (n=3) appeared to be safe and effective in the treatment of these symptoms. **Table 1** summarizes all studies published to date on THC-based drugs in patients with dementia.

Taking the above into account, there is little information in the literature about the clinical pharmacology of oral THC in older people with dementia. The number of studies available is very limited compared with the huge number of publications on cannabis (PubMed 14,746 papers, February 4, 2016) and cannabinoids (PubMed 13,188 papers, February 4, 2016). This lack of information about THC in

older people, particularly in those with dementia, emphasizes the urgent need for more clinical trials because older people may derive substantial benefit from the therapeutic use oral THC. The studies carried out in this population and presented in this thesis add to the sparse literature on the clinical pharmacology of oral THC in older people with dementia.

3. Clinical pharmacology of oral THC in older people with dementia

3.1. Effectiveness and safety aspects

Although effectiveness and safety are both aspects of the pharmacodynamic effects of oral THC, they are discussed separately to provide a better overview of findings.

3.1.1. Is oral THC effective in the treatment of dementia-related symptoms?

Dr. Geke van den Elsen has recently discussed our findings on the effectiveness of oral THC in dementia patients in her thesis, entitled "*Tetrahydrocannabinol in the treatment of neuropsychiatric symptoms in dementia, 2016*" (ISBN: 978-90-9029499-5). In brief, our data showed that oral THC in doses up to 4.5 mg/day was not of therapeutic benefit in patients with behavioral and psychological symptoms of dementia, compared to placebo (**Chapters 3 and 4**). In contrast, all published studies to date (**table 1**) have shown that THC is effective in the treatment of dementia-related symptoms, such as behavioral disturbances, loss of appetite, and sleep problems. However, the studies were either not randomized controlled trials,[8, 11, 12] or included a very small number of participants.[7, 9] Such methodological factors may introduce bias, leading to overestimation of the therapeutic value of oral THC in older people with dementia. However, there are other explanations for the discrepant results. 1) The short treatment duration with oral THC. In previous studies (table 1), THC treatment lasted between 2 and 6 weeks, whereas in our crossover study described in **Chapter 5** treatment duration was shorter (3 days treatment with oral THC followed by a 4-day

washout period). 2) The THC doses used in our trials were relatively low compared with those used in other studies (**Chapter 3**: up to 3 mg/day and **Chapter 4**: up to 4.5 mg/day). And 3) Age-related and dementia-related physiological factors, which will be discussed below in section 4 "**Pharmacodynamics of oral THC**"

3.1.2. Is oral THC safe to use in older people and dementia patients?

Despite the rapid increase in the prevalence of older people,[13] including those with dementia, and the possible therapeutic benefits of oral THC in the treatment of dementia-related symptoms and other physical comorbidities in these individuals, preapproval clinical trials of oral THC (dronabinol and nabilone) have excluded older individuals, especially those with cognitive impairments, from participation or did not include sufficient numbers of older participants to allow comparison of their data with those of young participants (**Chapters 1 and 2**). Furthermore, the first (phase I) trial involving humans that investigated the optimal route of administration, safety, pharmacokinetics, and pharmacodynamics of Namisol® included only young participants (mean age 21.4 years, range 18–27 years),[14] and therefore findings cannot directly be extrapolated to older people (**Chapters 1 and 2**).

In view of this lack of evidence, we conducted the first (to our knowledge) phase 1 clinical trial of the safety and pharmacokinetics of an oral THC-based medicine in older individuals (**Chapter 5**). We evaluated three oral doses of Namisol® (3, 5, and 6.5 mg) in healthy older individuals aged 65 and older. The selection of THC doses was based on the data of a phase 1 study of the safety of Namisol® (5, 6.5, and 8 mg) in young adults (18–27 years).[14] All 9 participants experienced adverse events with the 8-mg dose, with dizziness being the most frequently reported adverse event. Because of the high prevalence of adverse events in young adults and the high falls risk of older people (because of dizziness), we did not include an 8-mg dose (**Chapter 5**).

We found that a single oral dose of THC up to 6.5 mg/day was safe and well tolerated by healthy older individuals (**Chapter 5**). More subjects reported

one or more adverse events with 6.5 mg (7/11 subjects) than with 3 mg (5/11 subjects), 5 mg (5/11 subjects), or placebo (1/11 subject). The most reported adverse events in older participants were drowsiness (27% of participants) and dry mouth (11% of participants). In contrast, 85% and 100% of young adults had at least one adverse event after 5 mg and 6.5 mg THC, respectively, and one young participant dropped out because of drug-related syncope with the 5-mg dose. The adverse events reported by the young adults were mild to moderate in severity,[14] whereas none of the older subjects dropped out, and 45% and 64% reported only mild adverse events with the 5-mg and 6.5-mg doses, respectively. This suggests that older individuals (mean age 72 years) tolerate THC better than young individuals (mean age 21.4 years). This will be discussed in more detail in section 4 "**Pharmacodynamics of oral THC**".

The data of phase 2 studies (**Chapters 3 and 4**) involving older people with dementia showed that oral THC in doses up to 4.5 mg daily was well tolerated by patients with dementia. There were no serious adverse events related to THC treatment, or THC-related dropouts. These findings are consistent with those of previously published studies that included older individuals with dementia (**Table 1**). However, in three out of the five studies presented in table 1, higher doses of THC were used than in our studies: Volicer et al.[7] used a THC dose of 5 mg/day, Woodward et al.[11] used a mean THC dose of 7.03 mg/day, and Shelef et al.[12] used a THC dose up to 15 mg/day.

It is important to note that the safety data from our studies (**Chapters 3 to 6**) are mainly based on short-term use of oral THC. Previous studies suggested that prolonged use of cannabis is associated with memory deficits and cognitive impairments.[15, 16] None of the previously published studies (**Table 1**), including our studies, included assessment of memory and cognitive functions as outcome measures. Therefore, further studies are warranted to evaluate the safety, also in terms of memory and cognitive functions, of long-term use of THC in older people with dementia.

4. Pharmacokinetics of oral THC

Pharmacokinetics refers to the effect of the body on a drug and describes the absorption, distribution, metabolism, and elimination of a drug. These pharmacokinetic processes can be affected by age-related physiological changes, physical comorbidities (drug–disease

interactions), and polypharmacy (drug–drug interactions). **Table 2** presents the most important pharmacokinetic changes observed with aging.[17-19]

Most of the information available about the pharmacokinetic and pharmacodynamic effects of THC comes from studies involving young recreational cannabis users. There is much less information available from clinical studies of patients using cannabis for medical purposes. In general, the route of THC administration and the THC formulation determine its rate of absorption. Inhalation and intravenous routes of administration provide the most rapid delivery of THC, with peak THC plasma concentrations being reported within minutes (3–10 min),[20, 21] whereas oral administration delays absorption (1–4 h).[22-23]

Table 2 Pharmacokinetic changes observed with aging.[17-19]

Parameters	Altered physiology	Comments
Absorption	↓Gastrointestinal blood flow ↓Gastric acid secretion ↑Gastric pH ↓Gastric emptying time ↓Gastrointestinal motility	May diminish the absorption of several drugs. Time of onset of action may be delayed.
Distribution	↓Total body water ↓Lean body mass ↑Body fat ↓Albumin	Increased volume of distribution of lipid-soluble drugs, resulting in prolonged half-life and duration of action. Increased free fraction of drug.
Metabolism	↓Hepatic blood flow ↓Hepatic mass ↓Enzyme induction ↓Activity in mixed function oxidase system	Reduced hepatic clearance of drugs, leading to toxicity. Increased potential for drug interactions. For elderly patients, dosage should be reduced for hepatically cleared drugs.
Elimination	↓Renal blood flow ↓Number of functioning nephrons ↓Kidney mass / size ↓Glomerular filtration rate	Reduced renal clearance of drugs, leading to accumulation of renally cleared drugs.

In our studies, oral THC (Namisol®) was rapidly absorbed in older individuals, with a median time to reach the maximum concentration (t_{max}) of 1–2 h. The plasma concentrations of oral THC and its metabolites dose dependently increased with increasing THC dose. In both healthy individuals **Chapter 5**) and individuals with dementia (**Chapter 6**), there was substantial interindividual variation in plasma concentrations of THC and its metabolites, which is in line with previously published studies that included individuals of different ages.[14, 25] Older people, especially those with dementia, tend to be more sensitive to drugs that act on the central nervous system, such as THC.[26] For this reason, and because of the wide interindividual variation in plasma THC concentrations, it is important to tailor THC doses, to minimize side effects. This can be achieved by starting at a low dose and gradually increasing the dose until the desired therapeutic effect is obtained.

Although our phase 1 study (**Chapter 5**) was the first randomized, controlled trial of the safety and pharmacokinetics of a THC–based medicine that exclusively included older subjects, we failed to perform a complete pharmacokinetic analysis. This was because the study was primarily designed to assess the safety and tolerability of oral THC, and so only a limited number of blood samples (4 per subject) were collected. In addition, because maximal THC concentrations were reached 39–56 min after Namisol® administration in the phase 1 study involving young adults,[14] we considered that blood sampling over 120 min would be suitable time span for a pharmacokinetic analysis. When the maximum plasma concentration (C_{max}) was reached within 120 min, the mean C_{max} was similar to that reported for young adults given Namisol®.[14] In our older population, oral Namisol® had a C_{max} of 1–2 h, shorter than that reported in studies of individuals of different ages given dronabinol (1–4 h), nabilone (2–4 h), or oral-mucosal THC + cannabidiol (CBD) (Sativex®, 3–4 h).[22-23, 27-29] This difference is probably due to the novel lipophilic compound delivery technology, Alitra™, used to increase the absorption of Namisol®.[14] In contrast, the t_{max} of THC in older adults was longer than the t_{max} reported for young adults (39–56 min), and THC exposure (area under the concentration-time curve 0–6

h, AUC_{0-6h}) was two times higher in older adults than in young adults administered Namisol®. These discrepancies in t_{max} and AUC could be related to a THC–food interaction, which will be discussed below, or due to age-related physiological factors, such as delayed gastric emptying time, decreased splanchnic blood flow, decreased gastrointestinal motility, and decreased absorption surface, all of which could affect the absorption and bioavailability of THC in older adults.

Table 3 summarize the pharmacokinetic parameters of THC and 11-OH-THC after oral administration of Namisol® in young[14] and old adults (**Chapter 5**).

4.1. Effect of food on the pharmacokinetics of THC

Although we did not specifically investigate whether the intake of food can alter the pharmacokinetics of THC in older people, such an interaction is possible. Below, I discuss THC–food interactions and the role of aging, based on information from the literature.

The mechanism underlying drug–food interactions are complex and can be further complicated by age-related physiological changes, drug–drug interactions, and drug–disease interactions. In fact, the pharmacokinetics of lipophilic compounds such as THC can be affected when they are co-administered with food, with both the rate [measured as C_{max} and t_{max} values] and extent [measured as AUC] of drug absorption from the gastrointestinal tract being affected.[30] Drug–food interactions may result in increased, delayed, or decreased systemic drug bioavailability.[30, 31] For example, the intake of a high-fat meal or increased secretion of bile salts following food intake might improve the solubility and rate of dissolution of lipophilic compounds such as THC, thus increasing the rate of absorption.[31] On the other hand, food can delay drug absorption or decrease the rate of absorption as a result of a slow gastric emptying and/or increased gastric pH, leading to a decreased C_{max} and a longer t_{max}.[30] Delayed gastric emptying and an increase in gastric pH may also occur as part of normal aging process (**Table 2**).[26]

Table 3 Pharmacokinetic parameters of THC and its metabolites after oral administration of Namisol® in young and old adults (Phase 1 studies).

Parameters	3 mg	5 mg	6.5 mg	8 mg
		Young adults (mean age 21.4±3.3 years)[a]		
	(n=0)	(n=13)	(n=9)	(n=9)
THC				
C_{max} (ng/mL)		2.92 (51)	4.43 (42)	4.69 (62)
t_{max} (min)		56.0 (73)	39.3 (20)	43.6 (26)
$t_{1/2}$ (min)		71.9 (24)	80.0 (22)	78.8 (21)
11-OH-THC				
C_{max} (ng/mL)		4.68 (42)	5.94 (44)	6.10 (53)
t_{max} (min)		74.1 (68)	46.1 (28)	78.4 (63)
$t_{1/2}$ (min)		196.0 (33)	318.7 (54)	314.1 (58)
		Old adults (mean age 72±5 years)[b]		
	(n=11)	(n=11)	(n=11)	(n=0)
THC[c]	1.2 (0.13–3.48)	1.9 (0.26–6.95)	2.61 (0.23–8.65)	
11-OH-THC[c]	1.69 (0.47–4.34)	2.34 (0.37–8.37)	3.12 (0.37–8.61)	
THC-COOH[c]	13.9 (1.27–27)	19.3 (2.23–48.8)	26.6 (3.51–56.8)	
AUC_{0-2h} (h ng/mL)	1.67 (0.80–4.14)	2.61 (0.97–7.55)	3.51 (1.26–11.45)	
	(n=10)	(n=6)	(n=5)	
C_{max} (ng/mL)[d]	1.42 (0.53–3.48)	3.15 (1.54–6.95)	4.57 (2.11–8.65)	
t_{max} (h)[d]	0.92 (0.67–0.92)	0.92 (0.67–0.92)	0.67 (0.67–0.92)	

[a] Data are presented as means with coefficient of variation (%)
[b] Data are presented as means and ranges
[c] Plasma concentrations
[d] Reported for subjects who reached the C_{max} within 2 hours

In the study reported in **Chapter 6**, Namisol® was administered to older participants in non-fasting state, which probably led to delayed absorption of THC, and prolonged exposure relative to that reported for young adults administered Namisol® in fasted state.[14] In practice, it is difficult to establish whether delayed absorption and increased exposure are caused by the nutritional state of an older individual or by normal aging. We have not found any studies that evaluated the effects of food on the pharmacokinetics of oral THC. Most available studies on oral THC and food focused on the effects of THC on food intake (appetite stimulation). One study assessed the effect of food on the single-dose bioavailability of the oromucosal spray nabiximols (Sativex®) [THC 10.8 mg / CBD 10 mg], using a fed–fasted crossover design (n=12 males, mean age: 28.5 years).[32] The study results showed that food intake can increase the rate (C_{max} and t_{max}) and extent (AUC) of exposure to THC and 11-OH-THC, with the mean AUC and C_{max} being 1–3 times higher when the oromucosal spray was administered under fed conditions.[32] Moreover, the absorption of THC was also delayed, with the t_{max} for THC increasing from mean 1.5 h (range 0.75–2.00 h) in the fasted state to 4 h (range 2.00–4.08 h) in the fed state, giving an absorption delay of 2.5 h. For 11-OH-THC, t_{max} also increased from mean 2.13 h (range 1.00–2.50 h) in the fasted state to 4.03 h (range 2.53–12.00 h) in the fed state, giving an absorption delay of 2 h.[32] It is important to note that the study included only young adults (mean age 28.5 years), and therefore data cannot be directly translated to older adults.

The development of a novel drug formulation, such as THC-based drugs, should include an assessment of the effect of food on the pharmacokinetics of the drug, especially in older people. This knowledge is needed in order to provide patients with specific instructions regarding drug use (e.g., dosage, appropriate administration time). It might also be useful when trying to interpret drug failure or side effects.

5. Pharmacodynamics of oral THC

Pharmacodynamics refers to the physiological effects of drugs on the human body. All drugs have specific mechanisms of action, both for their therapeutic effects and their side effects. The aging process may increase or decrease the sensitivity to particular drugs, especially drugs that affect the central nervous system.[26] This is because advancing age may be accompanied by changes in the affinity of drugs at specific receptor sites or in the number of receptor sites. In practice, sometimes it is difficult to determine whether the differences in the effect or response to a drug in an individual older person are due to pure age-related pharmacodynamic changes (e.g., reduced number of receptors) or age-related pharmacokinetic changes (e.g., concentration of drug that reaches the target). In general, THC can affect most organ systems, as summarized in **Table 4**.[6, 33-35] The intensity, type, and duration of these effects in general depend on the plasma THC concentration.

5.1. THC mechanisms of action

In our clinical trials (**Chapters 3 to 6**), we investigated a wide range of THC pharmacodynamic parameters, including the effect of THC on dementia-related behavioral disturbances, adverse events, systolic and diastolic blood pressure, heart rate, electrocardiographic parameters, clinical chemistry parameters, psychedelic effects (feeling high, internal and external perceptions), attentional performance, and mobility (body sway and gait). The first pharmacodynamic effect (a side effect) of THC occurred 20 min after dosing. This is quite promising for achieving a rapid therapeutic effect, for example, when treating pain. However, overall, oral THC showed smaller pharmacodynamic effects, including side effects, than we had expected for older people with dementia, based on the effects reported in young adults.[14] There are several possible explanations for these discrepancies. First, we used a very low THC dose in our clinical trials; however, we found oral THC not to be

Table 4 Pharmacodynamic effects of tetrahydrocannabinol.[6, 33-35]

Body system	Effects
Central Nervous System	
Psychological	Euphoria "feeling high", dysphoria, anxiety/panic, reduction of anxiety, hallucinations, depersonalization, precipitation or aggravation of psychosis.
Perception	internal perception (inner feelings that do not correspond with reality, including mistrustful feelings), external perception (misperception of an external stimulus or change in awareness of surroundings), hallucinations, distortion of time perception.
Sedative	Sleepiness, somnolence, drowsiness.
Cognitive and psychomotor performance	slowing of reaction time, difficulty in concentration and performance of complex tasks, memory impairment, decreased learning ability, enhanced creativity and skilled activities.
Motor function	Increased or decreased motor activity, ataxia, dysarthria, tremulousness.
Appetite	Increased appetite
Analgesic	pain relief.
Anti-emetic	Anti-emetic effect with acute doses, but tolerance may occur with chronic use . Hyperemesis may occur with high doses or chronic use.
Body temperature	Decrease of body temperature.
Cardiovascular System	
Heart rate/rhythm	Tachycardia with acute dosage due to vagal inhibition by inhibited release of acetylcholine; bradycardia with long-term use due to the development of tolerance. Premature ventricular contractions, atrial fibrillation, ventricular arrhythmia also seen with acute doses.
Peripheral circulation	Vasodilatation, orthostatic hypotension, hypertension (in horizontal position), conjunctival redness.
Cardiac output	Increased cardiac output and myocardial oxygen demand.
Cerebrovascular System	

Cerebral blood flow	Increased with acute dose and decreased with long-term use.

Respiratory System

Bronchi	Bronchodilation.
Pulmonary function (FEV1; FVC)	Improve with acute dose.

Gastrointestinal System

Motility	Reduced gastrointestinal motility and decreased gastric/ colonic emptying.
Liver	Increased risk of hepatic steatosis/fibrosis, especially in patients with Hepatitis C.
Pancreas	High risk of pancreatitis long-term use of high dose.

Musculoskeletal system

Muscles	Increased muscles relaxation and reduced muscles spasticity.
Bon	May negatively impact bone healing.

Immune System

General effect	Immunomodulatory effects with suppressive and/or stimulatory effects; anti-inflammatory and anti-allergic effects.

of therapeutic benefit in the treatment of behavioral disturbances in patients with dementia (**Chapters 3 and 4**). The combination of a low rate of unwanted (side) effects and a low rate of wanted (therapeutic) effects raises the question whether THC doses were high enough for appropriate pharmacodynamic responses. Second, age- and dementia-related changes in the body and brain influence how the body handles a drug, relative to how drugs are handled in young subjects, and these changes may be further complicated by multiple comorbidities and related polypharmacy, which all can lead to drug–drug and drug–disease interactions.[26] For example, age-related physiological changes, such as delayed gastric emptying time, decreased gastrointestinal motility, and absorption surface, could affect the absorption and bioavailability of THC. Furthermore, dementia-related changes in the brain, such as degeneration of neurons, loss of neural circuits, decreased number of receptors and neurotransmitters (e.g., dopamine, and serotonin), may alter the pharmacodynamics of THC. Moreover, cannabinoid receptors (CB1 and CB2) are G protein-coupled receptors,[40] and impairments in the intracellular function and levels of G-proteins have been observed with normal aging,[41] which may also alter the pharmacodynamics of THC in older adults. Third, food may also affect the pharmacokinetics of THC (see above, *Effect of food on the pharmacokinetics of THC*). In our clinical trials, oral THC was administered to older participants in a fed state, which probably delayed absorption and increased THC exposure, relative to absorption and exposure measured in young adults administered THC in a fasted state.

In conclusion, the pharmacodynamic effects of oral THC in older adults, including patients with dementia, were smaller than expected based on its effects previously reported in young adults. The combination of low rate of unwanted (side) effects and low rate of wanted (therapeutic) effects suggests that the THC doses used in our trials were too low. Further efficacy and safety studies are warranted to evaluate the pharmacodynamics and pharmacokinetics of higher THC doses in younger and older adults, including those with dementia.

6. THC for pain in dementia

Pain is a significant and growing healthcare problem among older people with dementia, because aging is accompanied by an increased risk of chronic painful conditions, such as degenerative disease of discs and joints, osteoporotic fractures, fall-related injuries, diabetic neuropathy, angina, and cancer.[42, 43] In the cross-sectional prevalence survey described in **Chapter 7**, we found that pain was highly prevalent among community–dwelling patients with dementia. In over 60% of participants, pain was reported by both patients and caregivers. Moreover, pain was associated with behavioral and psychological symptoms, decreased activities of daily living, sleep disturbances, and caregiver distress. Symptoms such as delusions, agitation, depression, anxiety, and appetite disturbances were significantly more common in patients with pain than those without pain. Our findings underline the importance of routinely assessing and treating pain as part of the overall management of behavioral problems in patients with dementia. Adequate treatment of pain in patients with dementia living at home may prevent or reduce pain-related behavioral changes and associated caregiver distress, and subsequently may delay nursing home placement. However, currently available pain medications, such as acetaminophen, nonsteroidal anti–inflammatory drugs, opioids, antidepressants, and antiepileptic drugs, are often not effective, contraindicated, or cause serious adverse events in older people. Given these limitations of currently available medications, finding an effective and safe therapy for pain in older people should be given priority.

Previous randomized control trials have demonstrated the potential of cannabinoids, including oral THC, in the management of pain,[44] but none of these trials included participants with dementia or provided separate data for older persons (≥ 65), if these individuals were included in the study. In contrast, our data from a phase 2, randomized, double-blind, placebo-controlled trial (**Chapter 4, Appendix**) showed that, compared with placebo, THC in doses up to 4.5 mg daily did not diminish pain intensity (assessed with Verbal Rating Scale) or improve pain-related behavior (assessed with Pain Assessment Checklist for Seniors with

Limited Ability to Communicate) in older patients with dementia. However, these results should be interpreted with caution because of important potential limitations. First, few patients were treated with THC. Of the 23 patients included in the subgroup 'pain', 8 were randomized to receive THC and 15 to receive placebo. Moreover, the study was initially designed to include patients with dementia, behavioral disturbances and persistent pain, to secondarily evaluate the effectiveness of THC in relieving pain. Although pain is common and associated with behavioral disturbances in patients with dementia (**Chapter 7**), it was very difficult to recruit patients with both symptoms. Therefore, after we had succeeded in recruiting 8 patients, we amended the study protocol to omit pain as a strict inclusion criterion. In the amended protocol, pain assessments were still included, to allow secondary evaluation of THC effectiveness in pain. Second, it is a challenge to assess pain in cognitively impaired older people, particularly in those with moderate or severe dementia, because they are less able to articulate the pain and discomfort they feel. This point has been addressed and discussed in **Chapter 8**. A number of observational pain tools have been developed for use in nonverbal older people with cognitive impairments, but as yet there is no standardized assessment tool.[45] Moreover, most available assessment tools have poor reliability, validity, and clinical utility.[45] In our study described in **Chapter 4,** we used two tools to assess pain in our patients: 1) the Pain Assessment Checklist for Seniors with Severe Dementia (PACSLAC–D),[46] an observational checklist; and 2) the Verbal Rating Scale (VRS), a self-report scale.[47] Although PACSLAC–D has strong psychometric properties and is simple to use,[48] the checklist contains observation items that are not specific for pain, but overlap with those for the behavioral and psychological symptoms of dementia. This makes it difficult to determine whether the observed behaviors are related to pain or dementia. In addition, only 13 of the 23 participants with pain were able to understand and to use the VRS (self-reporting). Changes in a patient's ability to articulate pain verbally represent an important challenge in the assessment and treatment of pain, since self-report is considered the gold standard of pain assessment.[49] In our phase 1 trial involving

healthy older people (**Chapter 5)**, the first pharmacodynamic effects of THC (Namisol®) occurred 20 min after dosing and the maximal effects occurred between 55 and 120 min. This suggest that the drug has a rapid pain-relieving effect compared with dronabinol, which has an onset of action between 30 min and 1 h, and a maximal effect between 2 and 4 h.[20]

In summary, the accurate assessment of pain in patients with dementia is crucial for adequate pain management. In turn, this requires a reliable and valid observational tool for assessing pain in nonverbal individuals with dementia in clinical and nonclinical settings. Although oral THC is a potential multi-target drug candidate with a promising pharmacodynamic profile, more randomized controlled trials are needed to evaluate its effectiveness in the treatment of pain and pain-related behavioral disturbances in older people with dementia.

7. Conclusions and recommendations

The main aim of the studies described in this thesis was to evaluate the clinical pharmacology of oral THC in older people with dementia, specifically its pharmacokinetics, pharmacodynamics, safety, and efficacy.

7.1. Conclusions

1. Despite the large number of publications on cannabinoids, including THC, there is still a significant lack of information on its clinical pharmacology in older people with dementia.
2. The results of in vitro and in vivo studies provide an interesting basis for the innovative use of cannabinoids as therapeutic approach to dementia and dementia-related symptoms.
3. THC in doses up to 6.5 mg daily and 4.5 mg daily is safe and well tolerated by healthy older people and by older people with dementia, respectively. THC has a very low rate of adverse effects in both groups.
4. Overall, the pharmacodynamic effects of THC in older people, including those with dementia, are smaller than the

pharmacodynamic effects previously reported in younger people.

5. THC in doses up to 4.5 mg daily is not effective in the treatment of the neuropsychiatric symptoms of dementia, pain, and pain-related behavior.
6. The combination of a low rate of unwanted (adverse) effects and a low rate of wanted (therapeutic) effects suggests that the THC doses used in our trials were too low.
7. THC is rapidly absorbed in older people and has dose-linear pharmacokinetics with considerable interindividual variation.
8. Pain is common among community-dwelling patients with dementia. It is associated with diminished activities of daily living, sleep disturbances, behavioral and psychological symptoms, and caregiver distress. Our findings underline the importance of routinely assessing and treating pain as part of the overall management of behavioral problems in dementia patients.

7.2 Recommendations

Despite the large number of publications on THC-based drugs, many aspects of their clinical pharmacology remain unclear in older people with dementia. Older people with dementia and multiple comorbidities might benefit from the use of THC as a multi-target drug candidate, a drug for several conditions (e.g., behavioral disturbances, pain, and loss of appetite). The work presented in this thesis may fill some of the gaps that exist in our current knowledge of the pharmacodynamics and pharmacokinetics of oral THC in older people with dementia. On the basis of our findings, future studies of the pharmacodynamics and pharmacokinetics of THC that may be relevant to older patients with dementia are suggested below.

7.2.1. Evaluation of higher THC doses

The main challenge for the near future is to find the right THC dose for older people with dementia. The choice of dose to manage behavioral disturbances and pain in patients with dementia should be based on achieving maximum therapeutic benefit with minimum

toxic effects. However, the fear of potential psychoactive adverse effects in patients with dementia often interferes with population-based studies. Our clinical trials data showed that this fear, which is probably unfounded, may lead to under-dosing of THC-based drugs. Future studies of oral THC should evaluate higher THC doses. On the basis of our findings (Chapters 3 to 6) and the findings of others (Table 1), we believe that THC doses up to 5 mg twice daily can be given safely to older patients with dementia, but this should be tested in a randomized, double-blind, placebo-controlled trial with a crossover design. The crossover design is the best way to evaluate brief drug exposures with immediate and transient effects.

7.2.2. Population pharmacokinetic/pharmacodynamic modeling

There is little information in the literature on the pharmacokinetic/pharmacodynamic relationship of oral THC in older people. Given the substantial interindividual variation in the pharmacokinetics and pharmacodynamics of oral THC, and the importance of ensuring adequate dosing in frail older patients with dementia, it would be helpful if there were a population pharmacokinetic/pharmacodynamic model to guide the search for an optimal THC dose. Such a simulation model, which takes into account the variability component, would make it possible to match a particular therapeutic target with a target dose.

7.2.3. Pharmacodynamics and pharmacokinetics evaluation: Older versus younger adults

It is important to determine whether age affects the pharmacodynamics and pharmacokinetics of THC in older adults, and whether this effect is of therapeutic relevance. Although in the studies described in this thesis data for older patients were compared with published data for young adults, there were important differences between studies in terms of given doses, dose schedule, number of blood samples, sampling time, fasting versus fed states, and type of tests used for pharmacodynamic evaluation. It would be better to

directly compare young and old subjects in the same study, in order to allow better evaluation of parameters and to minimize bias.

7.2.4. Evaluation of food intake on THC pharmacokinetics

The development of a novel drug formulation, such as oral THC, should include the assessment of the effects of food on the pharmacokinetics of the drug, especially in older people. The discrepancies between t_{max} and AUC values measured in our older participants (**Chapter 5**) and those reported for young adults could be related to a THC–food interaction or age-related physiological changes. Therefore, it is of great interest to evaluate the effect of food on the pharmacokinetics of oral THC. This would help us to better understand whether the altered pharmacokinetics in young and old individuals are food- or age-related.

7.3. Take-home message

The lack of information about the pharmacokinetic and pharmacodynamic effects of THC in older people with dementia warrants further research. Until then, careful evaluation of the risk–benefit ratio is needed before oral THC can be recommended and prescribed to frail older dementia patients.

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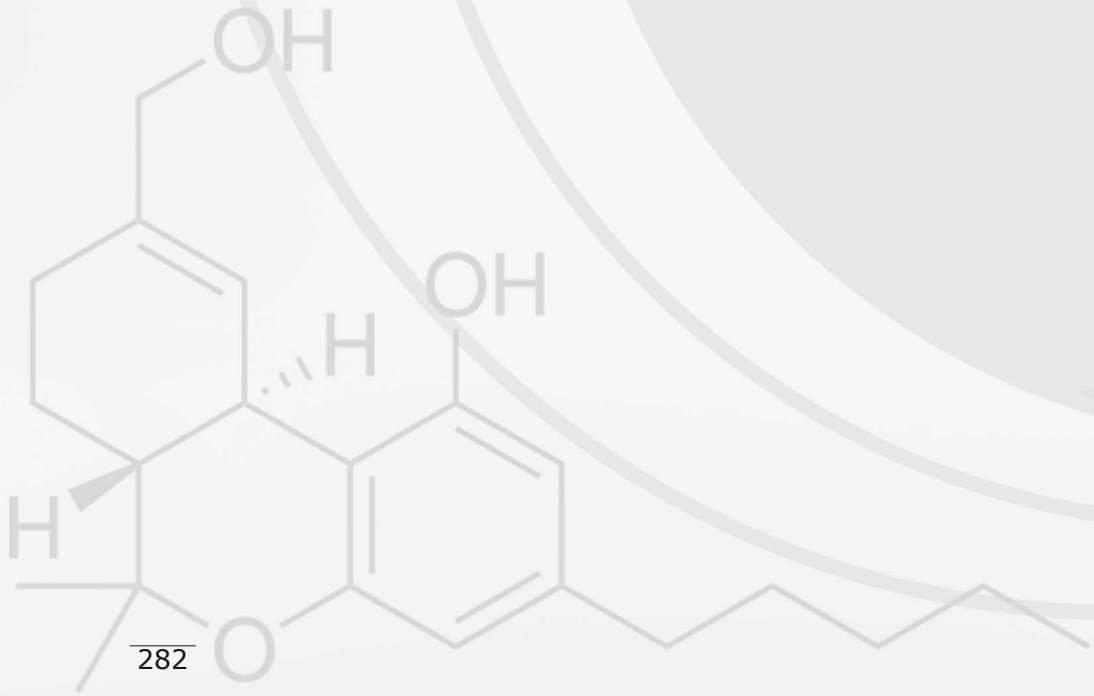

Appendix

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1. **Ahmed AI**, Wendrich-van Dael AE, Dickhoff-Evers L; Egger JI, Sachs GA, Olde Rikkert MG, van der Marck MA. Prevalence and impact of pain and pain-related behavioral problems in community-dwelling dementia patients. (Submitted)

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Curriculum vitae

Curriculum vitae

Amir Ahmed was born on 9 June 1972 in Omdurman (Sudan). In 1974, he moved with his parents to Abu Dhabi (the United Arab Emirates). In 1990, he got his high school diploma from the Abu Dhabi High Secondary School. Later that year he begun to study medicine at the Russian State Medical University in Moscow (Russia) and in 1997 he passed his doctor's exams. He then started training as a urologist at the same university.

Looking for a new challenge, Amir Ahmed moved to the Netherlands in 1998 with his wife and 3-month-old daughter, where he again studied medicine. He passed his doctor's exams in 2004 at Leiden University. Following this, he worked for 10 months as a junior doctor at the Department of Cardiology at Rijnmond Zuid Hospital in Rotterdam.

From May 2005 to May 2010, he trained in Geriatric Medicine, and from January 2010 to June 2011 he trained in Clinical Pharmacology at the Radboud University Medical Center, Nijmegen. Between 2010 and 2016, Amir Ahmed worked as a Geriatrician/Clinical Chief of the Department of Psychogeriatric Medicine at the Vincent van Gogh Hospital in Venray. There, he was also the president of the medical staff from 2013 to 2016. Amir Ahmed is connected to the Department of Geriatric Medicine/Alzheimer's Center and the Department of Pharmacology and Toxicology of the Radboud University Medical Center as a researcher. In 2011 he started his doctoral research, which has resulted in this thesis. He is assistant professor and guest speaker at various training centres.

In May 2016, Amir Ahmed set up GerCare Consulting, a Medical Company that offers medical consultancy and advice to Mental

Healthcare Institutions, nursing homes, (geriatric) rehabilitation centres and family doctors. In addition, it offers support to Healthcare Institutions in drug safety and the development of (psycho) geriatric departments and geriatric rehabilitation units. In October 2016, Amir Ahmed will start a Master of Business Administration in International Healthcare Management at the Frankfurt School of Finance & Management, Frankfurt (Germany).

Amir Ahmed is married to Youlia Ahmed (Internist-nephrologist) and father of three children: Dina, Maryam and Sami.

Curriculum vitae *(in Dutch)*

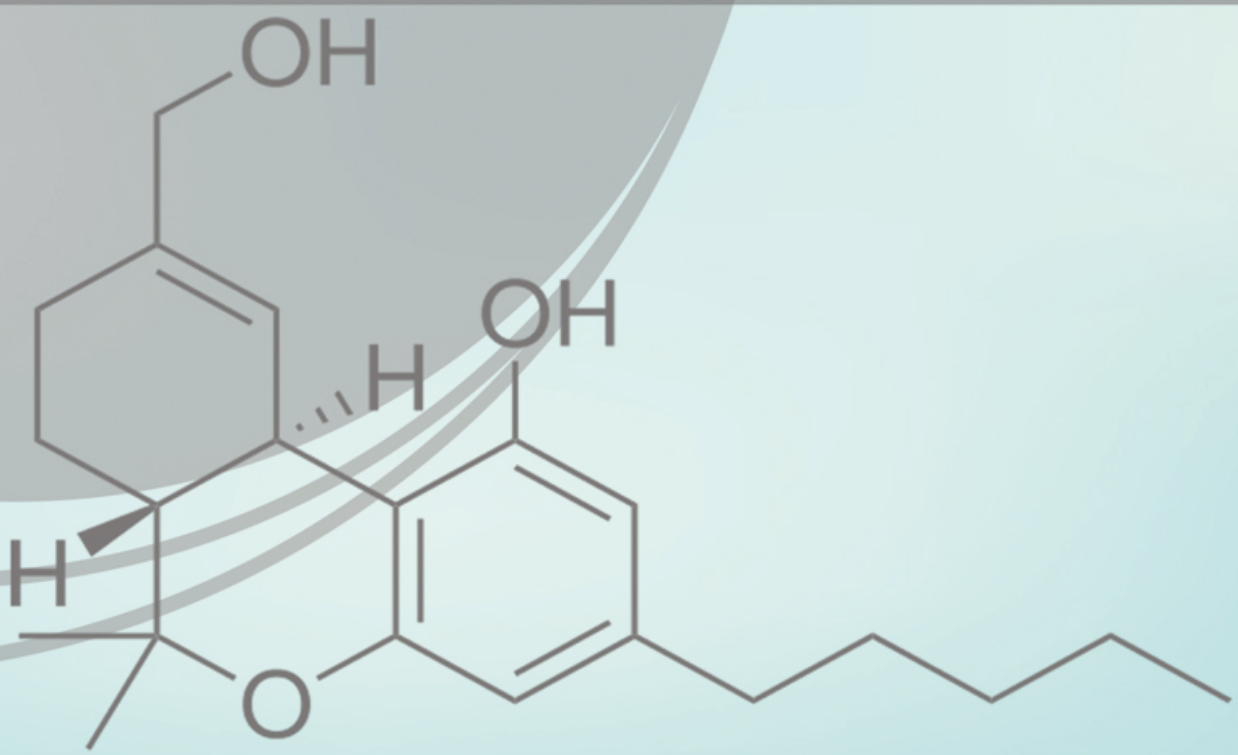
Amir Ahmed werd geboren op 9 juni 1972 in Omdurman (Soedan). In 1974, verhuisde hij met zijn ouders naar Abu Dhabi (de Verenigde Arabische Emiraten). In 1990, behaalde hij zijn High School-diploma aan de "Abu Dhabi High Secondary School". In datzelfde jaar begon hij met de studie geneeskunde aan de "Russian State Medical University" te Moskou (Rusland) en in 1997 behaalde hij zijn artsexamen. Vervolgens startte hij met de opleiding urologie aan dezelfde universiteit.

Zoekend naar een nieuwe uitdaging vertrok Amir Ahmed in 1998 met zijn vrouw en dochter van drie maanden naar Nederland, waar hij voor de tweede keer geneeskunde heeft gestudeerd. Zijn artsexamen heeft hij in 2004 behaald aan de Universiteit Leiden. Hierna is hij 10 maanden werkzaam geweest als arts-assistent cardiologie in het Rijnmond-Zuid ziekenhuis te Rotterdam.

Van mei 2005 tot en met mei 2010 volgde hij de opleiding Klinisch Geriatrie en van januari 2010 tot en met juni 2011 de opleiding Klinische Farmacologie aan het Radboud Universitair Medisch Centrum, Nijmegen. Tussen 2010 en 2016 werkte Amir Ahmed als klinisch geriater/hoofdbehandelaar afdeling Psychogeriatrie in het Vincent van Gogh te Venray. Daar was hij tussen 2013 en 2016 de voorzitter van de medische staf. Amir Ahmed is verbonden aan de afdeling Geriatrie/Alzheimer Centrum en de afdeling Farmacologie en Toxicologie van het Radboud Universitair Medisch Centrum als onderzoeker. In 2011 startte hij met zijn promotieonderzoek wat geresulteerd heeft in dit proefschrift. Hij is docent en gastspreker bij verschillende onderwijscentra.

In mei 2016 richtte Amir Ahmed GerCare Consulting op, een medisch bedrijf dat medische consultaties en adviezen biedt aan Geestelijke Gezondheidszorg instellingen, verpleeghuizen, (geriatrische) revalidatiecentra en huisartsen. Tevens biedt het bedrijf ondersteuning aan zorginstellingen bij medicatieveiligheid en het ontwikkelen van (psycho)geriatrie afdelingen en geriatrische revalidatie units. In oktober 2016 zal Amir Ahmed starten met zijn nieuwe opleiding "*Master of Business Administration in International Healthcare Management*" aan de Frankfurt School of Finance & Management, Frankfurt (Duitsland).

Amir Ahmed is getrouwd met Youlia Ahmed (Internist-nefroloog) en vader van drie kinderen: Dina, Maryam en Sami.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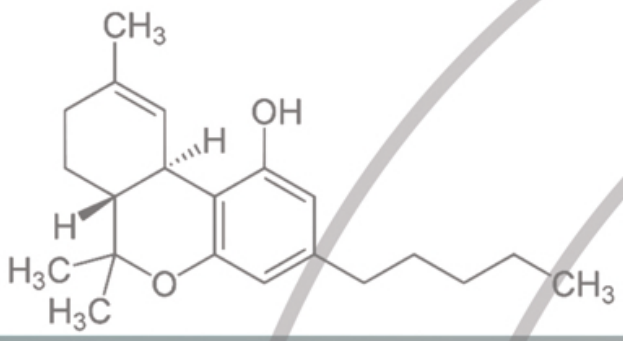
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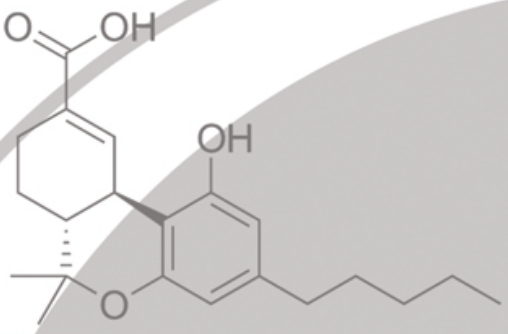
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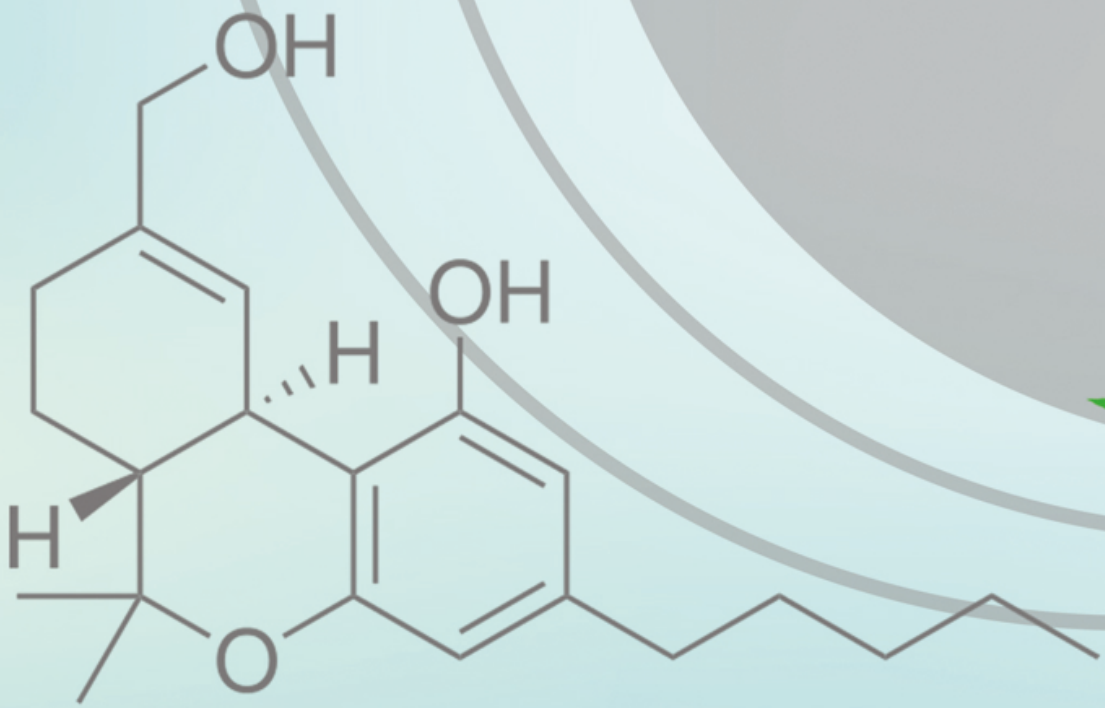
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