Tetrahydrocannabinol in the treatment of neuropsychiatric symptoms in dementia

Geke van den Elsen

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Geke Aloysia Hendrikus van den Elsen

The production of this thesis was financially supported by the department of Geriatric Medicine of the Radboud university medical center, Alzheimer Nederland, Internationale Stichting Alzheimer Onderzoek (ISAO) and Chipsoft.

Colofon

Author:	Geke Aloysia Hendrikus van den Elsen
Cover design en lay-out:	Miranda Dood, Mirakels Ontwerp
Printing:	Gildeprint - The Netherlands
ISBN:	978-90-9029499-5

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Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 4 maart 2016
om 11.30 uur precies

door

Geke Aloysia Hendrikus van den Elsen

geboren op 5 oktober 1985
te Deurne

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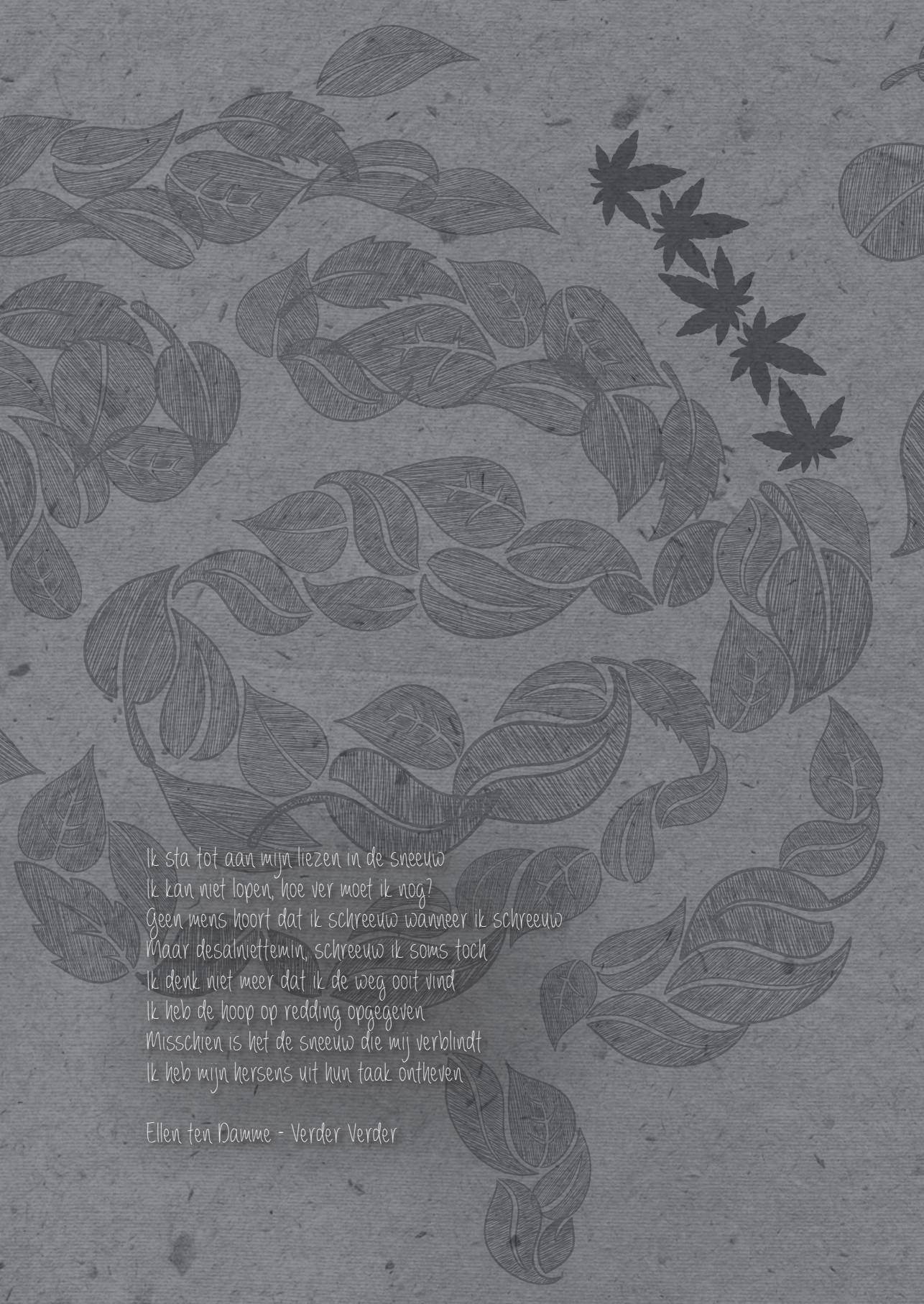

Ik sta tot aan mijn liezen in de sneeuw
Ik kan niet lopen, hoe ver moet ik nog?
Geen mens hoort dat ik schreeuw wanneer ik schreeuw
Maar desalniettemin, schreeuw ik soms toch
Ik denk niet meer dat ik de weg ooit vind
Ik heb de hoop op redding opgegeven
Misschien is het de sneeuw die mij verblindt
Ik heb mijn hersens uit hun taak ontheven

Ellen ten Damme - Verder Verder

CHAPTER 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

BOX 1

A 88-year old woman was admitted to a psycho-geriatric department of a nursing home due to progressive dementia. Her medical history included osteoarthritis and multiple depressions. She complained about abdominal pain and showed aberrant motor behavior, irritability and cursing.

After initiation of antibiotic treatment for an urinary tract infection, her abdominal pain diminished. Unfortunately, the effects on her behavior were only of short duration. She became depressed and started yelling and cried frequently. Acetaminophen was increased to 1000mg four times daily. Additionally, mirtazapine was started for alleviating her depressive symptoms. Nonetheless, her restlessness got worse and she became aggressive towards both caregivers and other patients. Light therapy was started and an occupational therapist and dietician were consulted to improve her posture and intake. None of these interventions were effective. Her physician initiated a symptomatic treatment with risperidone and oxazepam, although these interventions had to be stopped due to excessive somnolence. A psychiatrist was consulted, who prescribed carbamazepine, of which the dose was increased to 600mg daily. Unfortunately, the behavioral disturbances continued and she died shortly after due to diminished intake and physical exhaustion.

Neuropsychiatric symptoms in dementia

Although cognitive impairment is the most widely known feature of dementia, behavioral and psychological symptoms are very common as well, and often dominate the clinical presentation. Symptoms include, among others, delusions, agitation, depression and anxiety, which are referred to as 'neuropsychiatric symptoms' (NPS). NPS affect almost every individual with dementia (80-85%) at some point in the course of the disease and are particularly prevalent among nursing home patients.[1-3] Persistent symptoms lead to a significant reduction in quality of life[4] and cognitive functioning,[5] high caregiver distress[6] and may result in early institutionalization.[7] Despite the clinical relevance, the treatment of NPS is still suboptimal, as illustrated in the case report (Box 1). This imposes an enormous challenge for physicians working with dementia patients.

Non-drug based, or better called psychosocial treatments, such as person centered care, sensory interventions, and coaching of caregivers are preferred as a first line approach, although their efficacy remains only sparsely evidenced and most interventions are not easily applicable in clinical practice.[8] Therefore, to date, antipsychotic drugs (APs) are widely used in the symptomatic treatment of several dementia-related NPS.[9] Nonetheless, the scientific rationale behind this choice of drugs is limited, as the efficacy is only modest, while they are associated with relevant and serious side effects, such as falls, cardiac symptoms, cerebrovascular events and even death.[10-12] Other frequently used psychotropic drugs, such as antidepressants, anti-epileptic drugs and benzodiazepines, all have their own relevant side effects in frail dementia patients,[13] and are therefore not an appropriate alternative. This highlights the need for alternative pharmacological interventions with an improved ratio of beneficial versus adverse effects.

BOX 2
Dementia

Dementia is one of the major causes of disability and dependency among older persons worldwide.[14] It is a common syndrome, characterized by a progressive decline in various (and at least two) neuropsychological and cortical functions, including memory, orientation, language and judgment. These disturbances affect the individual's social and functional ability. Different types of dementia exist, of which Alzheimer's disease is the most prevalent (60-70%), followed by vascular dementia, while -rising with age- different types of etiology can also co-exist. Worldwide, 35.6 million people suffer from a type of dementia, of whom 250.000 are Dutch patients. This results in significant social and economical implications, which contributed to a renewed focus and financial support for scientific research on the (symptomatic) treatment of dementia patients by the Dutch government.[15]

Medical cannabinoids, towards a new pharmacological intervention for NPS?

Low dose oral tetrahydrocannabinol (THC) (Box 3) is suggested to be a promising option for the treatment of dementia-related NPS.[16, 17] THC is the main psychoactive constituent of the *Cannabis sativa L.* plant. Indeed, its psychological as well as physiological effects have

received extensive attention in the scientific field, and cannabinoids are currently used in the symptomatic treatment of patients with multiple sclerosis.[18] Additionally, several studies have been conducted regarding the efficacy of cannabinoids in a broad range of conditions, including pain, chemotherapy-induced nausea and vomiting and anorexia, but showed controversial results.[19-22] Currently, the general opinion among physicians concerning the use of medical cannabinoids is slowly changing. An increasing number of US states is legalizing the use of cannabinoids for medical purposes, which fuels the lively international debate of the advantages and disadvantages of medical cannabis among researchers and physicians.[23] Despite the above mentioned positive effects, cannabinoids, including THC, can also induce several relevant side effects, such as dizziness, fatigue and balance disturbances.[24] Especially in older, vulnerable patients, such as those with dementia, consideration for the harms of this intervention is highly important and should be addressed before widespread use.

BOX 3
The pharmacokinetic features of THC

THC is highly lipophilic and therefore rapidly distributes to fatty tissue, among which the central nervous system. It induces its effects by binding to CB_1 and CB_2 receptors, localized throughout the nervous system.[25, 26] CB receptor activation results in a depression of the pre-synaptic membrane potential, in turn reducing neurotransmission and resulting in a negative feedback loop. THC is metabolized in the liver to its metabolites 11-OH-THC and THC-COOH through several cytochroom P45 subenzymes. The onset, quantity and duration of its effects are dependent on several factors, among which route of administration, dose and several patient-related factors.

Aims of this thesis

To date, efficient pharmacological options for the treatment of behavioral disturbances in dementia patients are lacking, while these symptoms are highly prevalent, induce significant burden for both patients as caregivers and result in high healthcare costs. The overall aim of this thesis is to describe the effects of oral THC in the treatment of behavioral symptoms in patients with dementia, in order to determine whether this

intervention is appropriate in this vulnerable patient group. Specifically, we aimed to evaluate its efficacy, pharmacokinetic and pharmacodynamic properties and safety regarding adverse reactions, effects on vital signs and mobility in older patients with dementia. The studies described in this thesis are a product of a broader research project on the efficacy of Namisol® (a tablet containing THC) in the symptomatic treatment of dementia-related NPS and chronic pancreatitis, which is a collaboration between Radboud university medical center, department of Geriatric Medicine and Surgery, Clinical Research Centre Nijmegen (Nijmegen, The Netherlands) and Echo pharmaceuticals (Weesp, The Netherlands). All studies are investigator-driven and funded by the European Regional Development Fund and province of Gelderland. In none of the studies the authors nor any other member of the research team involved had conflicts of interests with the product under study (Namisol®). Initially, we planned to conduct two studies on the efficacy of Namisol® in NPS in dementia patients (described in Chapter 3 and 4). As we identified a significant gap in the knowledge of important safety aspects of oral THC formulations in older persons, including those with dementia (Chapter 2), we also conducted additional studies on the safety, pharmacokinetic properties and effects on mobility in older persons en patients with dementia (Chapter 5-7), which are described in the thesis outline.

Thesis outline

Chapter 2. Although cannabinoids are widely studied for their therapeutic potential in a broad variety of conditions, the results from young subjects cannot simply be extrapolated to older patients, especially those with cognitive disorders. This chapter describes a systematic literature search on medical cannabinoids in patients aged 65 years and older, independent of indication of use and cognitive status, providing an introduction and starting point for our clinical studies.

Chapter 3. This chapter describes the results from a randomized, placebo-controlled, crossover trial on the efficacy of two doses of oral THC in the treatment of behavioral disturbances in patients with dementia, with a focus on agitated behavior.

Chapter 4. Here, we report on the results of a second study on the efficacy of oral THC on dementia related behavioral disturbances, compared to placebo. This was a multicenter study, including community-dwelling, as well as institutionalized dementia patients. Furthermore, the effects on pain-related behavior and pain intensity are explored.

Chapter 5. Older and vulnerable persons are often excluded from intervention studies, resulting in a lack of evidence based treatments for these specific groups. Up to date, only one Phase I trial is conducted studying the safety of Namisol® in healthy young volunteers. In this study, we explored the effects of several doses of oral THC on the occurrence of adverse effects, balance and attention in a group of healthy, older persons.

Chapter 6. This chapter describes the results from a pharmacokinetic substudy of ten dementia patients treated with low dose oral THC. We report the pharmacokinetic profile of THC and its active metabolite and describe several pharmacodynamic effects, thereby contributing to optimal and safe dosing in older dementia patients.

Chapter 7. Before introducing a new psychopharmacological treatment for older patients, especially those with cognitive disturbances, effects on mobility should be explored as part of the safety evaluation. In this chapter, we describe the first study investigating the effects of THC on both balance and gait in patients with dementia, using objective and qualitative mobility assessment methods.

Chapter 8. Provides a brief summary of the studies presented in this thesis.

Chapter 9. This last chapter provides a discussion of the findings presented in this thesis.

Funding

The studies described in this thesis were made possible by a grant from the European Union, the European Fund for Regional Development, and the Dutch province of Gelderland (Grant no. 2009-019329) awarded to the consortium of Echo Pharmaceuticals, the developer of Namisol®, and the Radboud university medical center. Echo Pharmaceuticals had no role in study design, data collection, analysis, or interpretation, or writing of the manuscripts.

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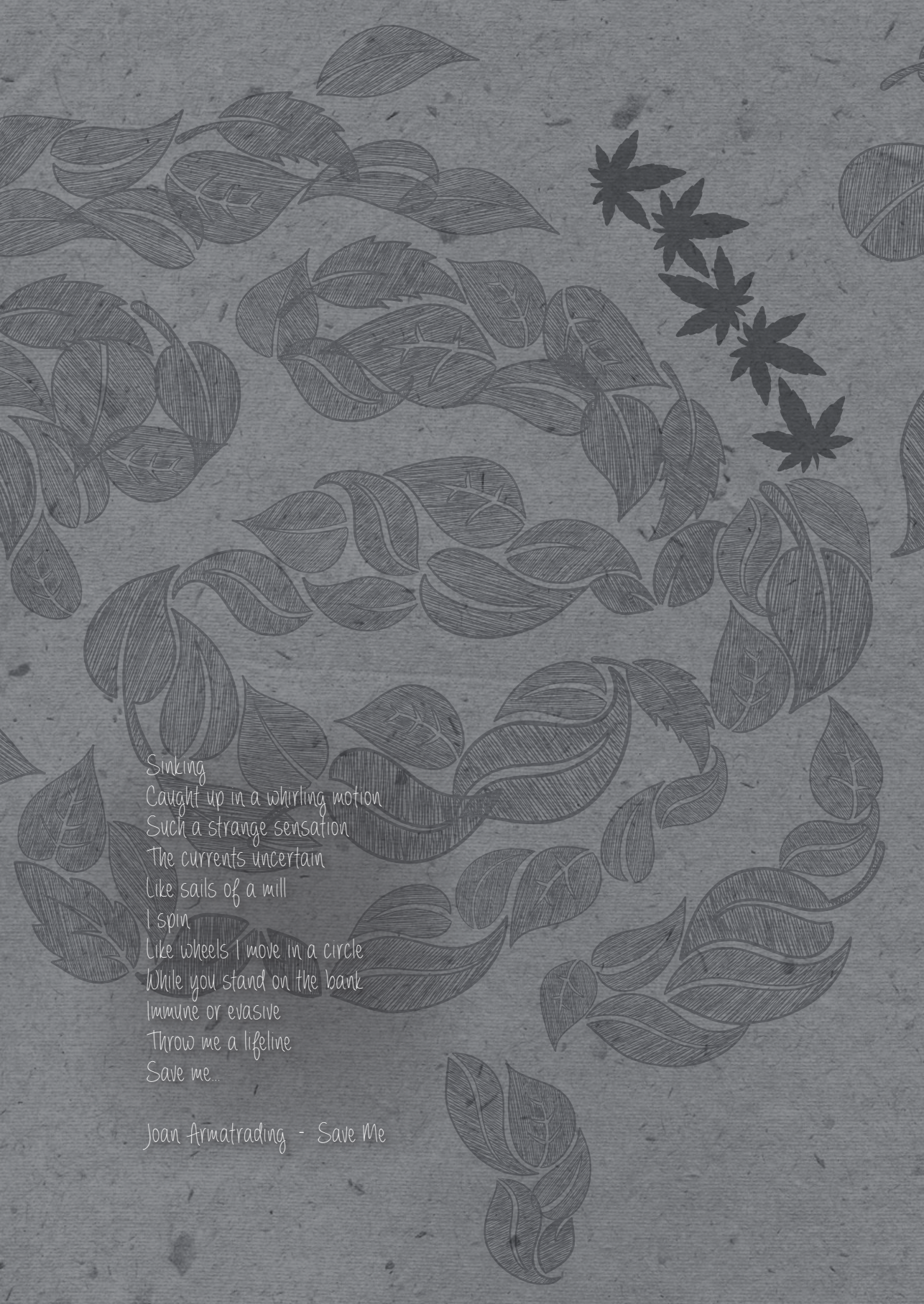

Sinking
Caught up in a whirling motion
Such a strange sensation
The currents uncertain
Like sails of a mill
I spin
Like wheels I move in a circle
While you stand on the bank
Immune or evasive
Throw me a lifeline
Save me...

Joan Armatrading - Save Me

CHAPTER 2

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

Geke A.H. van den Elsen
Amir I.A. Ahmed
Michiel Lammers
Cornelis Kramers
Robbert Jan Verkes
Marjolein A. van der Marck
Marcel G.M. Olde Rikkert

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 tetrahydrocannabinol (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 (CB_1 and CB_2) have been identified.[6, 7] These receptors are mainly located in the central nervous system (CB_1 and CB_2) and the immune system (CB_2).[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 'hasish'. 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 Organisation 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.

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.

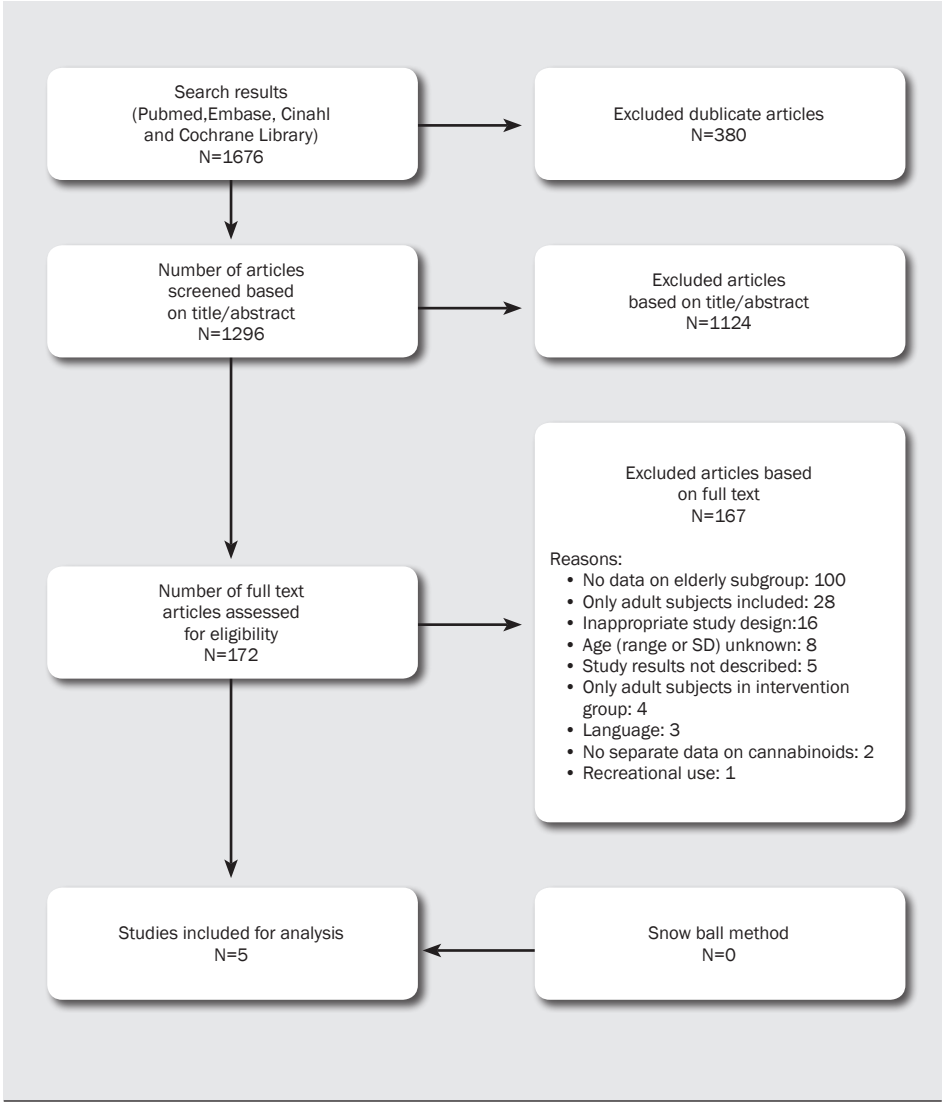

FIGURE 1
Flow diagram of the selection of studies included in this systematic review.

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 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, 21, 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.

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 - 12.5 mg five times daily	Prochlor-perazine (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 - 0.25 mg THC/kg daily	placebo	28	UPDRS Part IV (32-34), UPDRS total score
Pickering et al., 2011	RCT (crossover)	CO2 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, PetCO2, 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

Abbreviations:

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; PetCO2, 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.

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	+[a]	-[a]	-	-	-[a]	-	-	+
Carroll et al., 2004	+	+	+	+	+	+	+	+
Pickering et al., 2011	+	?	+	-	-	-	-	+
Walther et al., 2011	+[a]	+[a]	-	+[a]	+[a]	-	-	+[a]

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

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 (χ^2=2.13, NS). Furthermore, treatment with THC combined with CBD did not result in a statistical significant improvement of breathlessness in COPD[23] 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 (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 disorders.[22] 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 2.7:2.5 mg and 8.1:7.5 mg THC:CBD, respectively.[23] Another older subject with COPD developed symptoms of mild intoxication after 5.4:5 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 hours 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.

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 (0.034-0.25) 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

Abbreviations: NA, not assessed; AE, adverse event.
[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.

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 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 to 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 CB_1 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 CB_1 receptor agonism in cardiac tissue, independent of catecholaminergic ativity.[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

1. Cannabinoids [MeSH Terms]
2. Cannabinoids [tiab]
3. Cannabinoid [tiab]
4. Cannabinol [tiab]
5. Cannabidiol [tiab]
6. Tetrahydrocannabinol [tiab]
7. THC [tiab]
8. CBD [tiab]
9. 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 language

Appendix 2 - EMBASE search strategy

1. (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.
2. exp cannabinoid/
3. (frail or elder or older or elderly or aging or geriatric*).ti,ab.
4. aged/
5. 3 or 4
6. 1 or 2
7. 5 and 6
8. exp "clinical trial (topic)"/
9. 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

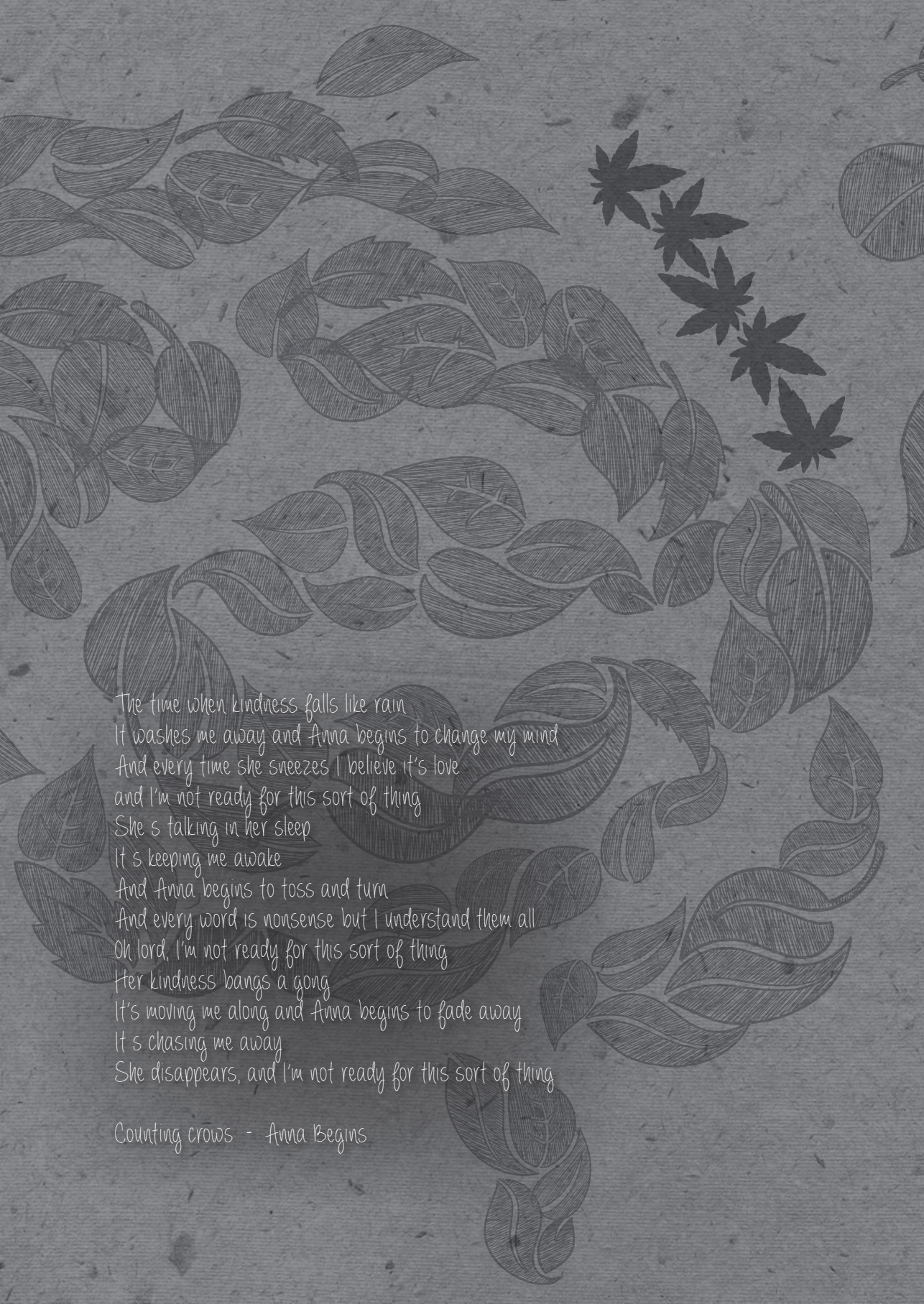
Appendix 3 – CINAHL search strategy

1. 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)

2. AB (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) 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)
3. 01 or 0201 or 02
4. (MH "Cannabis")(MH "Cannabis")
5. 03 or 0403 or 04
6. TI (frail OR elderly OR elder OR older OR aging OR geriatric*)
7. AB (frail OR elderly OR elder OR older OR aging OR geriatric*)
8. 06 or 07
9. (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

1. Cannabis
2. Cannabinoid*
3. 01 or 02
4. Elderly
5. 03 and 04



The time when kindness falls like rain
It washes me away and Anna begins to change my mind
And every time she sneezes I believe it's love
and I'm not ready for this sort of thing
She s talking in her sleep
It s keeping me awake
And Anna begins to toss and turn
And every word is nonsense but I understand them all
Oh lord, I'm not ready for this sort of thing
Her kindness bangs a gong
It's moving me along and Anna begins to fade away
It s chasing me away
She disappears, and I'm not ready for this sort of thing

Counting crows - Anna Begins

CHAPTER 3

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

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American Journal of Geriatric Psychiatry, accepted

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 (0.75mg twice daily in block 1-3 and 1.5mg 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 (NPI) score. 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.

Keywords: dementia, neuropsychiatric symptoms, tetrahydrocannabinol, randomized controlled trial.

Introduction

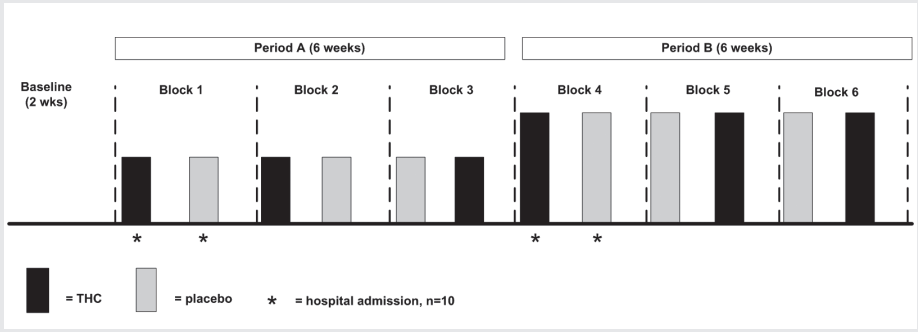
Nearly all patients with dementia experience behavioral and psychological symptoms throughout the course of the disease, including agitation, delusions and aberrant motor behavior.[1] These neuropsychiatric symptoms (NPS) result in a reduction in quality of life and cognitive functioning, are distressing 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: 18.1ms [95% confidence interval 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 0.75mg twice daily was alternated by placebo. The dosage was increased to 1.5mg 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 5mg 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: 0.75mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period. Period B: 1.5mg 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 and 1.5mg 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 (MedDRA). 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.

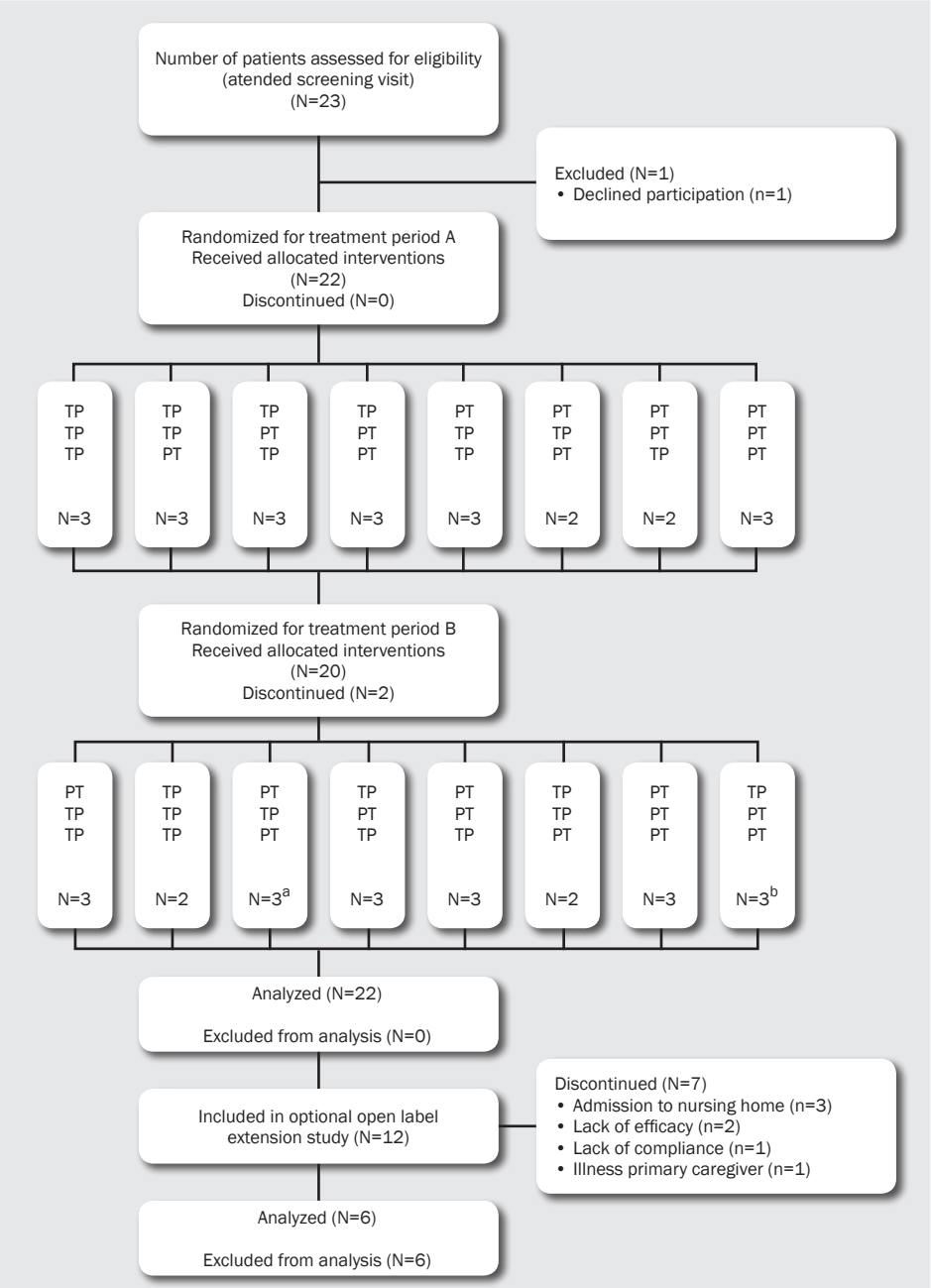
Analyses were based on the intention-to-treat principle, which means that data were analyzed according to initial treatment assignment, independent of received treatment, compliance or attrition. Data of all subjects was used in the analysis without imputation. Analyses were performed according to a 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 1.5mg 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 AEs.



Abbreviations: T, THC; P, Placebo. Period A: 0.75mg THC twice daily vs. placebo twice daily for three consecutive days, separated by a four-day washout period. Period B: 1.5mg 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, yr, *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)

Abbreviations: 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.

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).

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 (nonlinear 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).

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% Confidence Interval (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. Abbreviations: 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. Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; THC, tetrahydrocannabinol. Period A: 0.75mg THC twice daily; period B: 1.5mg THC twice daily.

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.

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.

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)	.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 *). Abbreviations: 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. [g] 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.

Conclusions

In the present study, we found no benefit of THC treatment (0.75mg and 1.5mg, 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 7.0mg 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 (incidence rate ratio [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 45mg THC daily), no direct comparison can be made with the results provided in the current study. Concerning dementia patients, previous studies report no AEs after administration of 2.5mg THC daily.[13, 34] Nevertheless, administration of higher dosages (5.0 to 7.0mg 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 AEs, as well as vital signs and mobility assessments. The lack of relevant side effects suggests that the current dosages are 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 1.5mg 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 4.5mg THC. In total, 16 AEs 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 AE occurred: a hospitalization in a specialized dementia care unit for further observation of cognition and behavior. AEs 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 1).

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

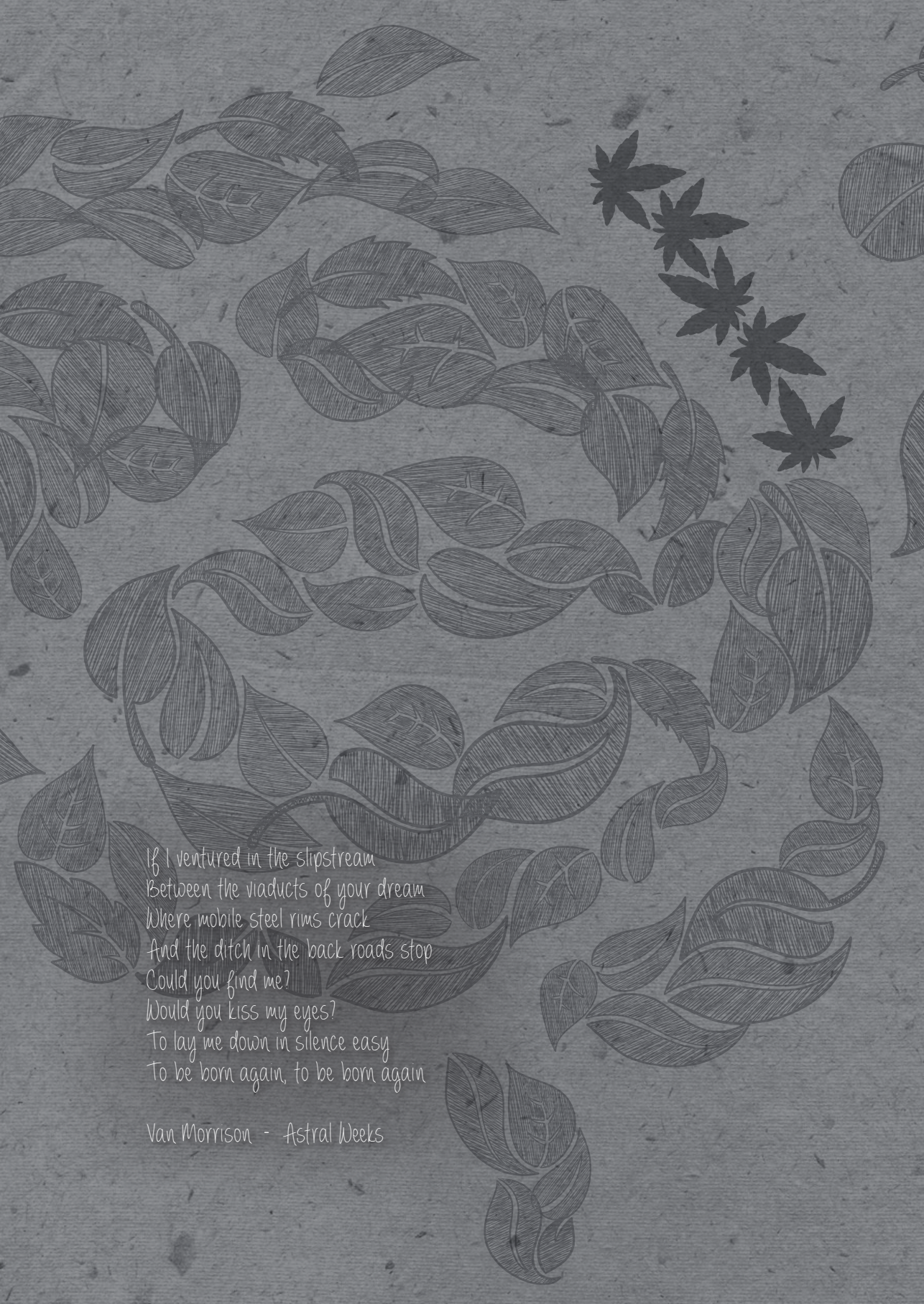
Bold numbers indicate the assessments which are used in the analyses. Abbreviations: NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory; ZBI, Zarit Burden Interview; TUG, Timed Up and Go; GR, GAITRite™; Bowdle, Visual Analogue Scale Bowdle for feeling high; ECG, Electrocardiography.
[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



If I ventured in the slipstream
Between the viaducts of your dream
Where mobile steel rims crack
And the ditch in the back roads stop
Could you find me?
Would you kiss my eyes?
To lay me down in silence easy
To be born again, to be born again

Van Morrison - Astral Weeks

CHAPTER 4

Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: a randomized controlled trial

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Neurology, 2015, 84:2338-46

Abstract

Objectives: 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 1.5mg 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 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 intervan [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 -2.6-1.6) and 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 4.5mg 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 to study whether higher doses are efficacious and equally well tolerated.

Classification of Evidence: This study provides Class I evidence that for patients with dementia-related NPS low dose THC does not significantly reduce NPS at 21 days, though it is well tolerated.

Introduction

Most patients with dementia will experience neuropsychiatric symptoms (NPS) over the course of their disease.[1] While nonpharmacologic interventions are preferred, data on their efficacy remains limited and the interventions are not easily applicable in clinical practice.[2] The pharmacological 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 suffer from clinically relevant symptoms.[7, 8] Structured analgesic treatment has recently been demonstrated to be beneficial for dementia-related NPS and in particular agitation.[9] Delta-9-tetrahydrocannabinol (THC), the main constituent of cannabis, has both psychoactive and analgesic properties,[10, 11] and might therefore serve as an alternative pharmacological treatment. Indeed, some preliminary studies suggested improvement in agitation and nocturnal motor activity in patients with Alzheimer's 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, whereas 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, ϒ-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-β clearance.[15, 16] Nonetheless, firm evidence of the efficacy and safety of THC or other cannabinoids in this vulnerable patient group is lacking and even data on older patients in general are scarce.[17] The current paper 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 (GCP), 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 south-east of The Netherlands, including geriatric outpatient clinics (n=2), psychiatric clinics (n=3), nursing homes (n=3, including in total 6 locations) and a regional network of integrated care for community-dwelling dementia patients. Written informed consent was provided at screening by the patient and closest involved proxy; the first only in case the patient was judged capable to 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 (day 2, 7, and 14). Follow up assessments by telephone were performed two weeks after study completion.

Participants

Patients diagnosed with AD, vascular or mixed dementia, according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[18] or National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche en l'Enseignement en Neurosciences[19] criteria were eligible for participation if they suffered from clinically

relevant NPS (minimal Neuropsychiatric Inventory [NPI] score ≥ 10), with symptoms reported on agitation, aggression or aberrant motor behavior, existing at least one month prior to screening. A caregiver had to be available, who was in touch with the patient at least twice a week and supervised patient's care. Exclusion criteria were current major psychiatric disorders, 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 suffering from 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 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 Appendix Table 1.

Intervention and randomization

Active treatment consisted of 1.5mg 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 1000mg acetaminophen 3 times daily in case of pain complaints, or of suspected pain in noncommunicative patients, based on physical examination at screening and information from the caregiver or physician. Study medication was administered at 9 a.m., 2 p.m., and 8 p.m. 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 centre 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 Neuropsychiatric Inventory (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 standard deviation 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 serious 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 intervals [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, centre, 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.

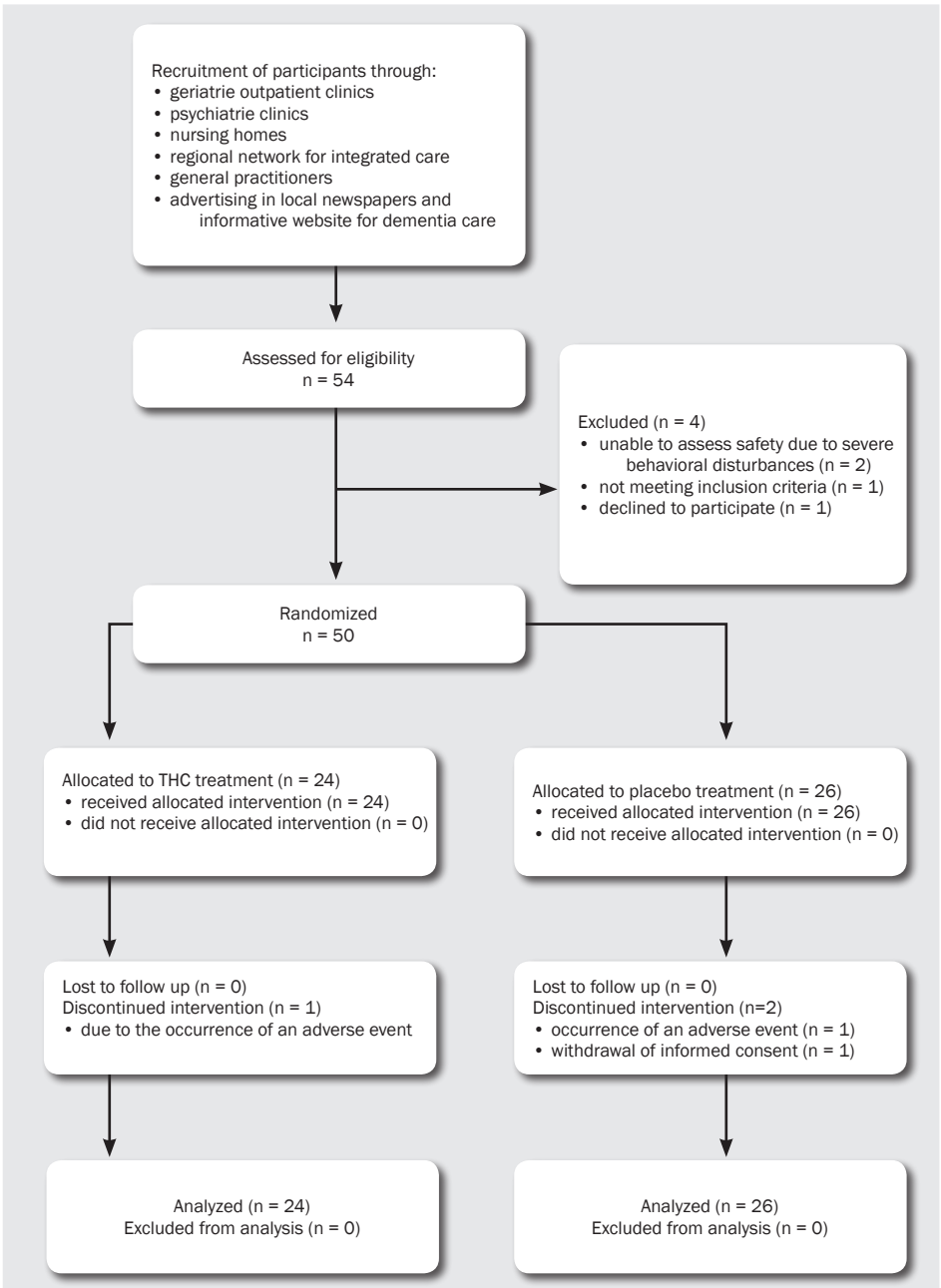
Classification of Evidence

This interventional study provides Class I evidence that oral THC of 4.5mg daily is not effective in reducing behavioral disturbances in dementia patients (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). Patient characteristics are presented in Table 1. Overall, 47 patients (94%) completed the study, while 3 patients discontinued participation due to the occurrence of adverse events (n=2) and withdrawal of informed consent (n=1).



THC = tetrahydrocannabinol

FIGURE 1
CONSORT flowchart of recruitment and selection

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/m^2, *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]	4.8 (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; NSAID, nonsteroidal anti-inflammatory drugs; THC, tetrahydrocannabinol.
[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.

Treatment compliance and concurrent medication use

Median treatment compliance, based on remaining pill count, was 98% (67 to 100%) in the THC group and 100% (94 to 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 5mg, lorazepam 1mg) and acetaminophen (500mg).

Efficacy

Study results are presented in Table 2. NPI total score decreased in both treatment conditions after 14 (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 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 Appendix Table 2), except for the domain 'eating disorders' in favor of placebo ($\Delta NPI_{eating\ disorders}$: 1.0, 95%CI 0.0 to 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) nor 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's r=0.65, p<0.001; day 21, Pearson's 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%.

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

	n	THC	n	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 [a]					
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: CCGIC, Caregiver's Clinical Global Impression of Change; CI, confidence interval; CMAI, Cohen-Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory; QoL-AD, Quality of Life-Alzheimer's Disease Scale; THC, tetrahydrocannabinol.
Group numbers are means and standard deviations (SDs). Estimates of overall mean differences over day 14 and 21 are based on linear mixed model analysis for repeated measures with correction for (subscale) NPI score at baseline, center, Clinical Demantia Rating 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).
[a] 7-point scale; 1, marked improvement; 2, moderate improvement; 3, minimal improvement; 4, unchanged; 5, minimal worsening; 6, moderate worsening; 7, marked worsening.

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 ($\chi 2$, 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 adverse 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.

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 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)

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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 4.5mg 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 very 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 suffering from 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 to 100%). This suggests a highly motivated group of participants and caregivers, in combination with the occurrence of only mild AEs. This study also 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 suffered from 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 (2.5-7mg daily) in patients with dementia.[12, 13, 21, 37] However, important methodological 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 3mg THC daily, and

did not observe a significant reduction in NPS, nor any relevant adverse events, effects on vital functions or mobility (unpublished data, 2014). Therefore, we used a dosage of 4.5mg 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 dementia patients are lacking.[40] Several pharmacotherapeutic options have been explored, such as acetylcholinesterase 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 adverse effects limit its usefulness in this vulnerable population.[34] Our current trial indicates that 4.5mg 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.

Acknowledgement

The authors thank the staff of the Department of Geriatric Medicine, Jeroen Bosch Ziekenhuis, 's Hertogenbosch; Vitalis WoonZorg Groep, Eindhoven; Liemerije, Zevenaar; Stichting LuciVer,Wijchen; Department of Elderly Care, GGNet, Apeldoorn; GGZ Breburg, Tilburg; and Hulp bij Dementie, Venray, for the recruitment of potential participants; the nursing home staff of Vincent van Gogh Institute, Liemerije, Vitalis Woon-Zorg Groep, and Stichting LuciVer; and their research assistants for their assistance in outcome assessments.

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Supplemental material

Appendix: Efficacy of THC in the treatment of pain in dementia patients with NPS.

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 behavior 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 1). 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 behavioral 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 behavior. 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.

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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)	
Day 21	4	2.3 (1.0)	9	2.3 (1.0)	-0.03 (-1.0 to 0.9)
PACSLAC-D					
Baseline	8	8.4 (5.2)	15	7.2 (4.1)	
Day 21	7	7.4 (8.0)	13	6.2 (5.5)	-0.4 (-3.8 to 3.0)

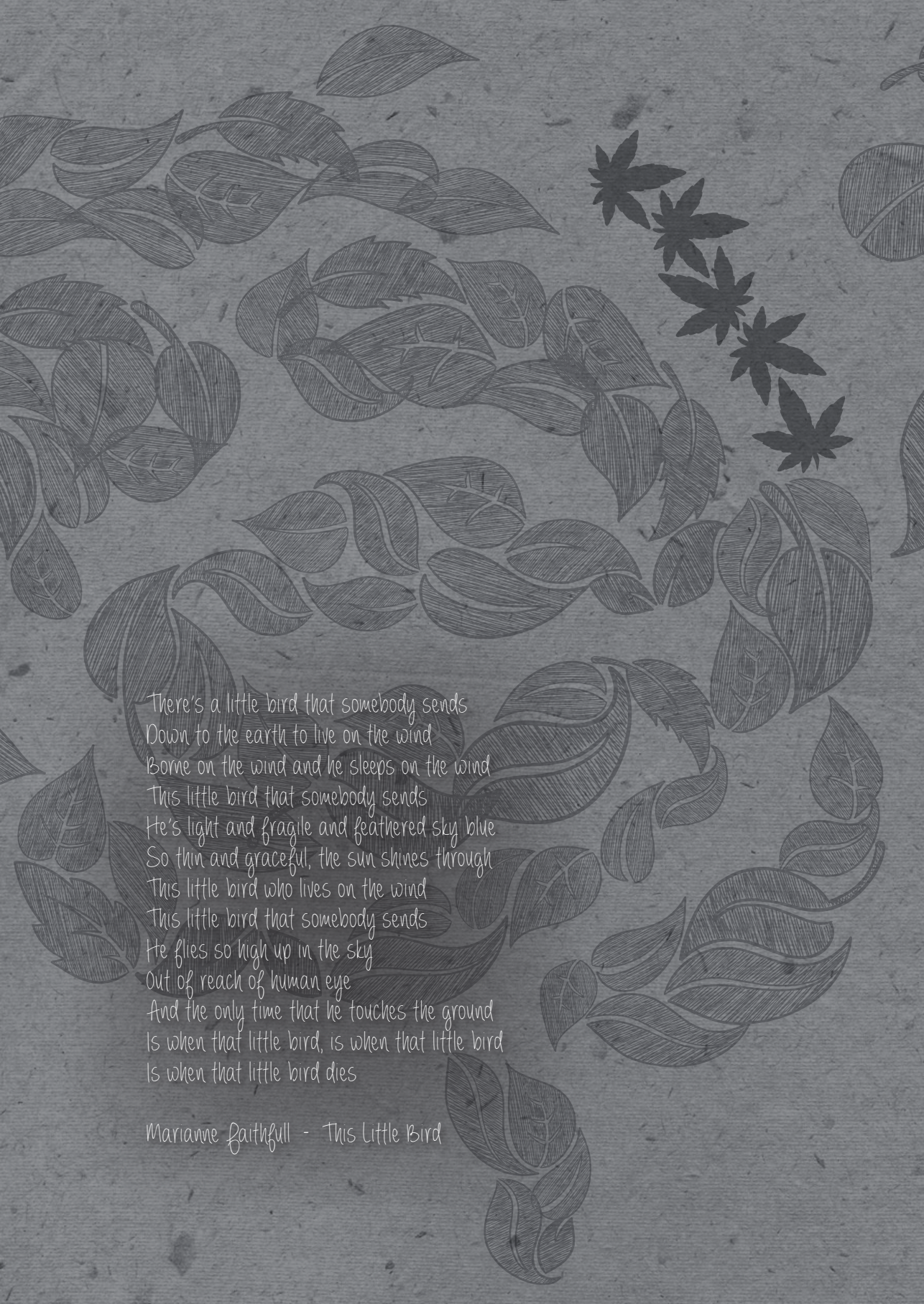
Abbreviations: PACSLAC-D, Pain Assessment Checklist for Seniors with Limited Ability to Communicate-Dutch version; VRS, Verbal Rating Scale.
Group values are means and standard deviations. Estimates of mean differences are based on linear mixed model analysis for repeated measures with participant as 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					
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 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					
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)
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.
Group values 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.



There's a little bird that somebody sends
Down to the earth to live on the wind
Borne on the wind and he sleeps on the wind
This little bird that somebody sends
He's light and fragile and feathered sky blue
So thin and graceful, the sun shines through
This little bird who lives on the wind
This little bird that somebody sends
He flies so high up in the sky
Out of reach of human eye
And the only time that he touches the ground
Is when that little bird, is when that little bird
Is when that little bird dies

Marianne Faithfull - This Little Bird

CHAPTER 5

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

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European Neuropsychopharmacology, 2014, 24:1475-82

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, crossover 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 3mg, 5mg, or 6.5mg of THC or matching placebo, in a crossover manner, on each intervention day. The data of 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 6.5mg than with 3mg (p=0.048), 5mg (p=0.034) and placebo (p=0.013). There was a wide inter-individual 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 $AUC_{0\text{-}2\ h}$ (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. CB_1, which is expressed primarily in the central nervous system, and CB_2, 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 (Sativex®), 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 ($\geq$ 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® (5mg, 6.5mg, and 8mg) 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. also reported that Namisol® was safe and well tolerated by subjects.

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 co-morbidities, 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 (3mg, 5mg, and 6.5mg) in healthy older subjects. Second, to evaluate the pharmacokinetics of THC in older people and to investigate the relationship between the drug's 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, crossover trial (ClinicalTrials.gov ID NCT01740960) was approved by the local ethics committee (Registration number: NL40591.091.12) 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 co-morbidities (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 cytochrome P450 (CYP) 2C9, 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 3mg (two 1.5mg tablets), 5mg (one tablet), or 6.5mg (one 5mg and one 1.5mg 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, 1.5mg (6 mm) and 5mg (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 biochemical 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 safety of Namisol®, which was assessed by evaluating the incidence and severity of adverse events (AEs) using a standardized THC AEs 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 telephoned 24 h after drug (active or placebo) ingestion to determine the occurrence of AEs after discharge. All AEs 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 AEs.

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 as 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 on incidence and severity of reported AEs. To explore the association between administered dose of Namisol® (3mg, 5mg, and 6.5mg) and the occurrences of AEs, Generalized Estimating Equations (GEE) were used to compare the proportion of subjects experiencing one or more AEs, and random effects analyses with non-linear mixed models (NLMIXED) to compare the number of AEs per subject per dose, assuming that AEs 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 SAS™ software (version 9.2).

Results

Baseline characteristics

Twelve healthy elderly subjects (6 male; mean age 72±5 years, range 65-85 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.

TABLE 1

Demographics and baseline characteristics of subjects randomized in the trial.

Characteristics	N=12
Male, *n (%)*	6 (50)
Female, *n (%)*	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 (%)*	11 (91.7)
≤ 2 alcoholic beverage/day, *n*	8
3-4 alcoholic beverage/day, *n*	3
BMI, mean (SD); *kg/m2*	26.4 (1.5)
Weight, mean (SD); *kg*	77.3 (9.8)
Height, mean (SD); *centimeter*	170.9 (9.2)
SBP, mean (SD); *mmHg*	134.3 (10.6)
DBP, mean (SD); *mmHg*	76.7 (6.9)
HR, mean (SD); *beats/minute*	61.3 (10.4)
MMSE-30, *mean (SD)*	29.8 (0.6)
GDS-30, *mean (SD)*	0.17 (0.4)
Number of medications used by subject, *mean (SD)*	2 (2.1)
Concomitant medications, *n (%)*[a]	
Lipid lowering	7 (58.3)
Aspirin	4 (33.3)
Beta-blockers	3 (25.0)
ACE-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)
Comorbidites, *n (%)*	
Hypertension	3 (25.0)
Hypercholesterolemia	3 (25.0)
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)

Abbreviations: BMI, body mass index; SPB, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale.

[a] Number of subjects who used one or more medications.

Safety and tolerability

The data of 11 subjects (5 men and 6 women) were included in the analysis. The data of one subject were excluded due to non-compliance to study medication. Table 2 lists all reported AEs by dose (40 in total). The first AEs were observed 20 min after dosing. All AEs 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). There were no serious adverse events (SAEs) during the trial. More subjects reported one or more AEs with Namisol® 3mg (5 subjects, p=0.036), 5mg (5 subjects, p=0.036) and 6.5mg (7 subjects, p=0.008) than with placebo (1 subject) and overall the subjects reported fewer AEs with placebo (total 1 event, p=0.013), Namisol® 3mg (9 AEs, p=0.048) and 5mg (8 AEs, p=0.034) than with Namisol® 6.5mg (22 AEs). Overall, the most frequently reported AEs 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 3mg Namisol, and 13 and 16 mm 55 and 120 min after 5mg 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 5mg 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 6.5mg 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 6.5mg Namisol®. No significant changes were found in subjects' attention 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.

Pharmacokinetic parameters

The mean THC, 11-OH-THC, and THC-COOH concentration-time curves are shown in the Figure. 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 3mg Namisol®, and in four and five subjects after 5mg and 6.5mg 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 3mg (n=10), 3.15 ng/mL (range 1.54–6.95) for 5mg (n=7), and 4.57 ng/mL (range 2.11–8.65) for 6.5mg (n=6).

TABLE 2
Overview of all 40 drug-related adverse events reported by subjects or observed by investigator during the trial.

		Placebo,		**Namisol®**		**Total**[a]
		n=11	**3mg**, n=11	**5mg**, n=11	**6.5mg**, 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)
Total number of adverse events/dose[c]		1, *p=0.013*	9, *p=0.048*	8, *p=0.034*	22, *p=1*	40
Number of subjects with one or more adverse events, *n (%)*[d]		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 pair-wise comparisons of Namisol® 6.5mg (reference) with placebo, and with the doses of 3mg and 5mg, using NLMIXED analyses.
[d] p-values based on pair-wise comparisons of each of Namisol® doses with placebo (reference), using Generalized Estimating Equations analyses.

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 (1.27-27.0)	19.3 (2.23-48.8)	26.6 (3.51-56.8)
$AUC_{0\text{-}2\ h}$ (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)**
C_{max} (ng/mL)[b]	1.42 (0.53-3.48)	3.15 (1.54-6.95)	4.57 (2.11-8.65)
T_{max} (h)[b]	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 h

Pharmacokinetic/pharmacoynamic 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 with 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 to 0.14) and 0.0081/s ($p = 0.024$; 95% CI: 0.001 to 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 to 0.13), 0.121/s ($p<0.0001$; 95%CI: 0.08 to 0.16), and 0.007 1/s ($p = 0.0087$; 95% CI:0.002 to 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 ($p = 0.84$).

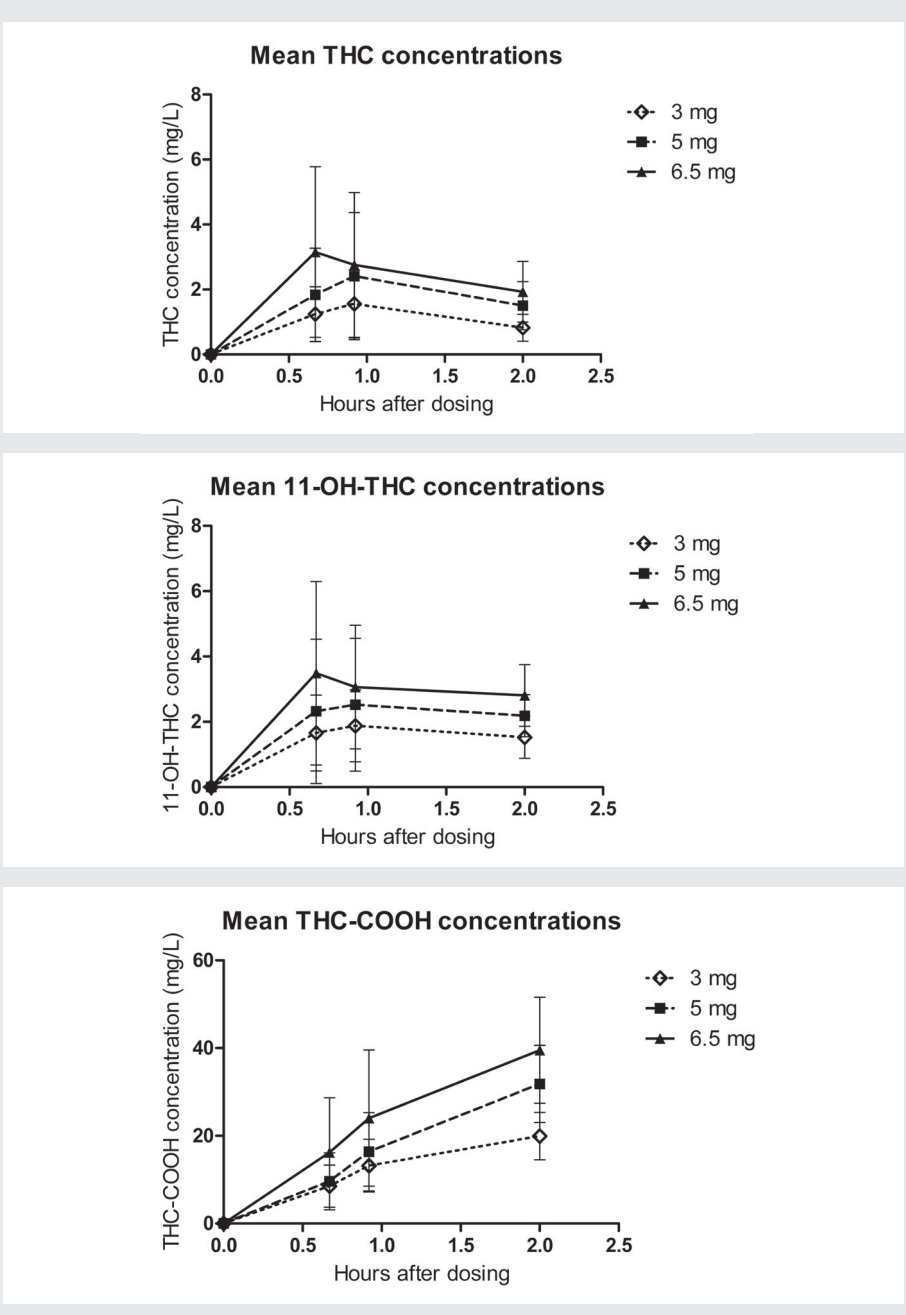

FIGURE
Mean THC, 11-OH-THC, and THC-COOH concentration-time curves.

Discussion

Safety and tolerability

Owing to the broad therapeutic application 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 I trial of the safety and pharmacokinetics of a cannabis-based medicine that included solely older individuals. Single oral doses of Namisol® of 3mg, 5mg, and 6.5mg were generally safe and well tolerated by the healthy older individuals. The 6.5mg dose was associated with more AEs than the lower doses, but there was no significant difference in the incidence of AEs between the 3mg and 5mg doses. The most frequently reported AEs were drowsiness (27%) and dry mouth (11%). All AEs were mild and resolved spontaneously within 3.5 h. There were no moderate or SAEs. 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 AE after 5mg and 6.5mg, respectively, and one subject dropped out because of drug-related syncope with the 5mg dose; all AEs were mild to moderate in severity.[7] Our findings, with zero drop-outs and 45% and 64% of subjects reporting only mild AEs with the 5mg and 6.5mg 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 an pharmacodynamic effects

Our findings showed substantial inter-individual variation 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 5mg dose and 4.57 ng/mL with the 6.5mg dose) was similar to that reported for young adults (2.92 ng/mL with 5mg and 4.43 ng/mL with 6.5mg).[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 with 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 with 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 (CB_1 and

CB_2) 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 RCT 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 co-morbidities are urgently required, as this population could benefit from the therapeutic applications of cannabinoids.

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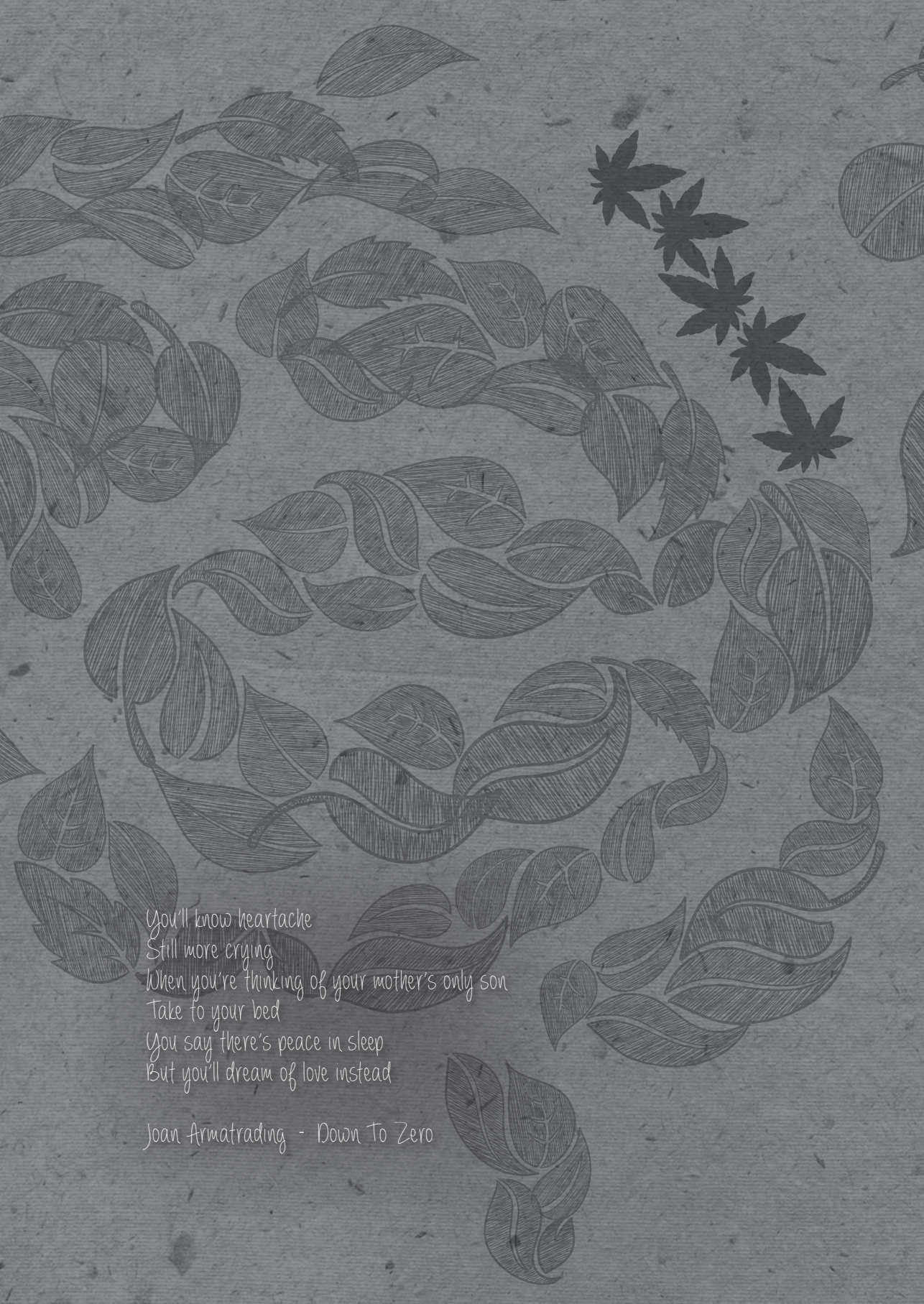

You'll know heartache
Still more crying
When you're thinking of your mother's only son
Take to your bed
You say there's peace in sleep
But you'll dream of love instead

Joan Armatrading - Down To Zero

CHAPTER 6

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

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Psychopharmacology, 2015, 232:2587-95

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, 0.75mg; weeks 7-12, 1.5mg) or placebo twice daily for three days, separated by a 4-day washout period.

Results: only six 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 0.75mg dose, VAS internal perception (0.025 units; 95 % Confidence Interval [CI] 0.010 to 0.040) and heart rate (2 beats/min; 95 % CI 0.4 to 3.8) increased significantly. Body sway-eyes-closed increased only after 1.5mg (0.59°/s; 95 % CI 0.13 to 1.06). Systolic blood pressure changed significantly after both doses of THC (0.75mg, -7 mmHg, 95%CI -11.4 to 3.0; 1.5mg, 5 mmHg, 95%CI 1.0 to 9.2). The median T_{max} was 1-2 h, with THC pharmacokinetics increasing linearly with increasing dose, with wide inter-individual 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 0.75mg dose and 1.01 (0.53-1.92) for the 1.5mg 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 inter-individual 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.

Keywords: tetrahydrocannabinol (THC); safety; pharmacodynamics; pharmacokinetics.

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: CB_1 and CB_2.[5-7] CB_1 receptors are mainly expressed in the basal ganglia, cerebellum, hippocampus, hypothalamus, and dorsal horn,[8] and CB_2 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 multi-target 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 and 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 co-morbidities, 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, NCT01302340). The study was carried out at the Radboud university medical center, Nijmegen, 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 two 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 three days, separated by a 4-day washout period. In period A, patients received 0.75mg THC twice daily, and in period B, the dose was increased to 1.5mg twice daily. Namisol® and placebo were identical in appearance and taste, and both were taken under non-fasting 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] 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 co-morbidities, 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 Regulation on Harmonization guideline for good clinical practice, the ethical principles of the Declaration of Helsinki, and relevant Dutch laws and regulations.

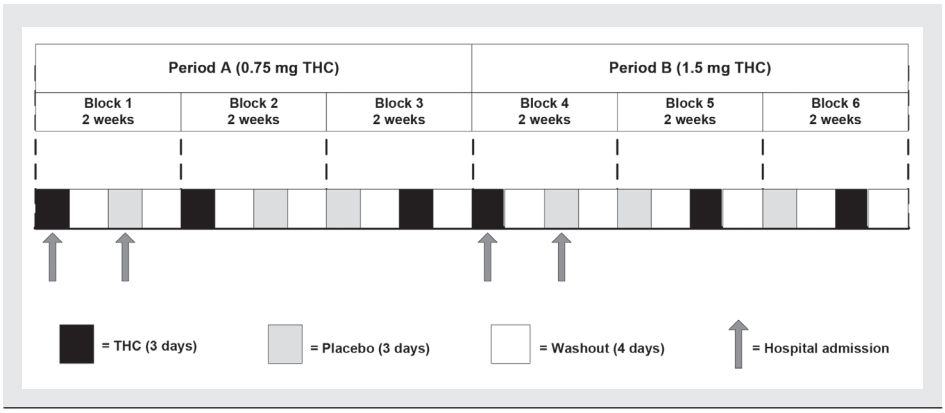

FIGURE 1
Overview of the treatment period; THC and placebo were administered at random (this is an example of random allocation of treatment)

Safety and tolerability assessments

The safety and tolerability of THC were assessed subjectively and objectively, by evaluating the incidence and severity of adverse events (AEs), 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, AEs 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, AE was clearly not related to the intervention; (2) unlikely, AE was doubtfully related to the intervention; (3) possible, AE may be related to the intervention; (4) probable, AE was likely related to the intervention; and (5) definite, AE was clearly related to the intervention. A serious adverse event (SAE) 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 AEs 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 ($AUC_{0\text{-}24\ h}$), and apparent clearance (CL/F, being the dose/$AUC_{0\text{-}24\ h}$). The following parameters were calculated for the two curves (curve 1, 0 to 6 h after the first THC dose; curve 2, 6 to 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 ($AUC_{0\text{-}6\ h}$), and AUC from 6 to 24 h ($AUC_{6\text{-}24\ h}$), using the linear-up log-down trapezoidal rule. Concentration-time graphs were plotted for the two doses. Geometric means plus 95 % confidence intervals (CI) were calculated for each pharmacokinetic parameter for each dose. The coefficients of variation (CV%) of the geometric means were calculated to describe the inter-individual variability in pharmacokinetic parameters. The geometric mean ratio (GMR) plus 90% CI of $AUC_{0\text{-}24\ h}$, CL/F, and $t_{1/2}$ of the 1.5mg dose versus the 0.75mg 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 AE 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 (anterio-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 AEs were reported during the study period. More AEs were reported with placebo (55 AEs) than with THC (43 AEs) (period A, 0.75mg THC 21 AEs and placebo 30 AEs, p=0.290; period B, 1.5mg THC 22 AEs and placebo 25 AEs, p=0.435). Thirteen (13%) of the reported AEs were considered to be possibly (n=12) or probably (n=1) related to study drugs (THC and placebo). Of these, only six AEs (6% of total AEs) were considered to be (possibly) related to THC, two with 0.75mg (dizziness and fatigue in one patient each), and four with 1.5mg (agitation in three patients and fatigue in one patient). All were mild and transitory in nature. There were no THC-related SAEs. 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 0.75mg dose, but not the 1.5mg dose, was associated with a statistically significant increase in VAS internal perception scores (0.025 units, 95% CI 0.010 to 0.040). The 1.5mg dose, but not the 0.75mg dose, significantly increased body sway with eyes closed (0.59°/s, 95% CI 0.13 to 1.06). The 0.75mg dose significantly decreased systolic blood pressure (-7.2 mmHg, 95 % CI -11.4 to 3.0), whereas the 1.5-mg dose significantly increased systolic blood pressure (5.1 mmHg, 95% CI 1.0 to 9.2). Heart rate increased significantly after

the administration of the 0.75mg dose only (2 beats/min, 95% CI 0.4 to 3.8). None of the changes in the pharmacodynamic parameters was associated with an AE.

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*	
Antidementia 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

Abbreviations: BMI, body mass index; MMSE, Mini Mental State Examination
[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 to 0.017); p=0.47	0.002 (95%CI -0.024 to 0.028), p=0.90
VAS external perception (U) [b]	0.012 (95%CI -0.005 to 0.029); p=0.16	-0.014 (95%CI -0.031 to 0.003), p=0.11
VAS internal perception (U) [b]	0.025 (95%CI 0.010 to 0.040), p=0.001[c]	-0.002 (95%CI -0.014 to 0.010), p=0.75
Body sway, eyes open (°/s)	0.37 (95%CI -1.31 to 2.10), p=0.63	0.26 (95%CI -0.91 to 1.44), p=0.67
Body sway, eyes closed (°s)	0.61 (95%CI -0.63 to 1.85), p=0.30	0.59 (95%CI 0.13 to 1.06), p<0.05[c]
Systolic blood pressure (mmHg)	-7.2 (95%CI -11.4 to -3.0), p<0.001[c]	5.1 (95%CI 1.0 to 9.2), p<0.05[c]
Diastolic blood pressure (mmHg)	0.2 (95%CI -2.0 to 2.3), p=0.86	-0.1 (95%CI -2.2 to 2.0), p=0.92
Heart rate (beats/min)	2.1 (95%CI 0.4 to 3.8), p<0.05[c]	-0.4 (95%CI -2.0 to 1.3), p=0.66

[a] All parameters are presented as mean (95% confidence intervals; p value)
[b] Log-tranformed visual analog scale (VAS) (scores in mm+2). Scores are given in units (U)
[c] Statistically significant p values (α=0.05)

Pharmacokinetic results

Pharmacokinetic parameters are summarized in Table 3 and 4. The data of one person were excluded because no blood samples were taken after the first THC dose of 0.75mg, 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 between1 and2h and was not dose-dependent. For the 0.75mg 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 1 h (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 inter-individual 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 $AUC_{0\text{-}24\ h}$ versus the 11-OH-THC $AUC_{0\text{-}24\ h}$ was 1.7 (95% CI 1.1 to 2.9) and 1.9 (95% CI 1.0 to 3.6) for the 0.75mg and 1.5mg doses, respectively. Individual

THC and 11-OH-THC AUCs are presented in Figure 3. Two participants had a high THC exposure after the 0.75mg dose. Their $AUC_{0\text{-}24\,h}$ 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 1.5mg dose. Their $AUC_{0\text{-}24\,h}$ 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 1.5mg 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).

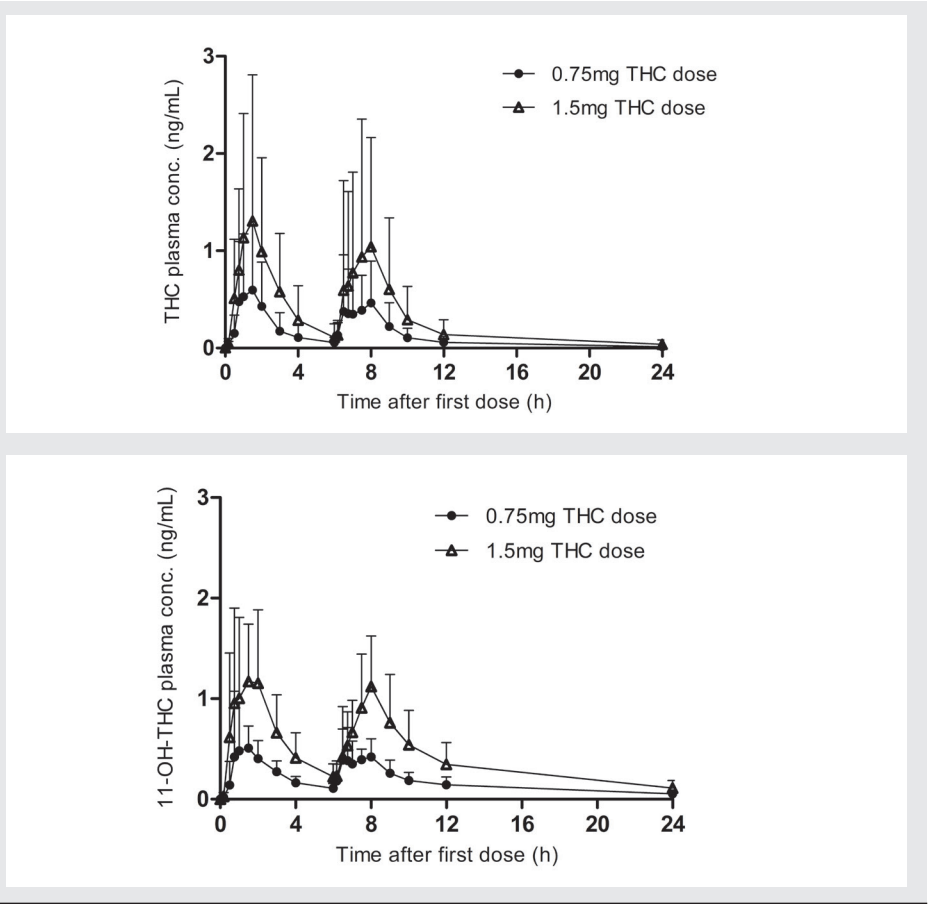

FIGURE 2
The mean concentration time profiles of THC and 11-OH-THC for both the 0.75 and 1.5mg doses over 24 h

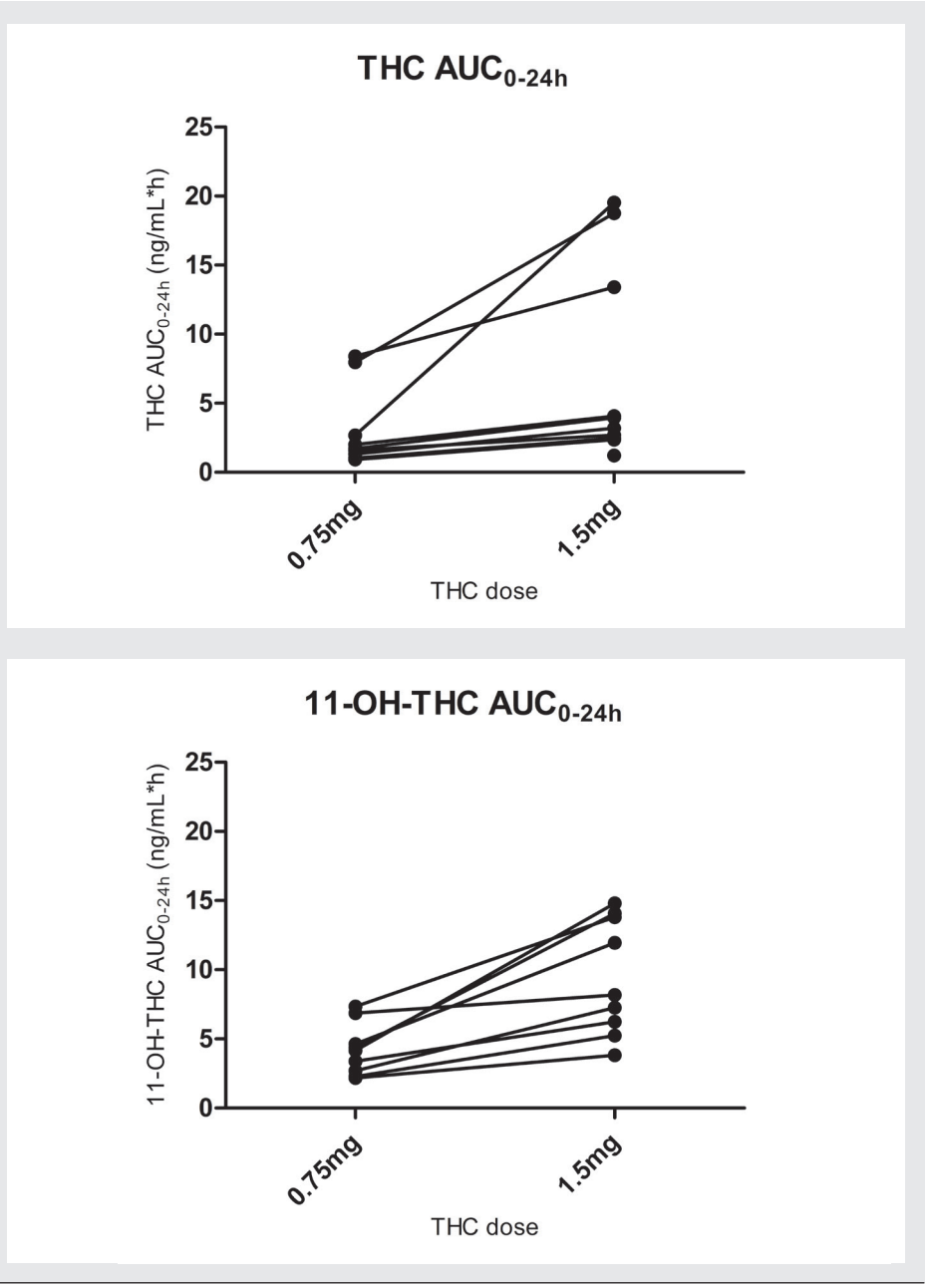

FIGURE 3
Individual pharmacokinetic parameter graphs

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

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

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

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

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

Discussion

Safety and tolerability

Older people with dementia and physical co-morbidity 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 neuroinflammation-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 1.5mg twice daily are safe and well tolerated by older individuals with dementia. Only six of the 98 reported AEs were related to THC treatment. All AEs were mild and resolved spontaneously without any intervention. Our findings are in line with previously published studies showing that THC doses up to 5mg/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 AEs, 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 AEs. 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 1.5mg. However, there was considerable inter-individual variation in plasma concentrations of THC and 11-OH-THC, which is in line with our data from a phase I 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 $AUC_{0\text{-}6\ h}$ 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 $AUC_{0\text{-}6\ h}$ was calculated).[11] A possible explanation for the discrepancies in T_{max} and $AUC_{0\text{-}6h}$ is that, in the current study, THC was taken in nonfasting state, whereas Klumpers et al. administered THC to fasting young adults. Stott et al., 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 11-OH-THC were onefold and threefold higher, respectively, in the fed state than in the fasting state.[34] 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 $AUC_{0\text{-}24}$ h was less than 1 for both doses, whereas it was almost two in the other participants. However, the sum of 11-OH-THC plus THC $AUC_{0\text{-}24}$ h was higher in these two participants than in the other participants, but this higher THC exposure was not associated with AEs.

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 1.5mg, as only six of the 98 reported AEs 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 inter-individual 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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Through the window of my eyes, I can see the rainy day
Sitting in the chair of my cool room, looking for a way to be the one who I am
It's useless to cry for the things I once have known,
thinking it will come back and reach my home

Cuby and the Blizzards - Window Of My Eyes

CHAPTER 7

Effects of tetrahydrocannabinol on balance and gait in patients with dementia: a randomized controlled crossover trial

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Abstract

Background: Oral tetrahydrocannabinol (THC) is currently studied for its possible efficacy in the treatment of dementia-related neuropsychiatric symptoms (NPS), but might lead to increased risk of falling. In this trial we evaluated the effects of THC on gait and balance in dementia patients.

Design: A randomized, double-blind, placebo-controlled, crossover study.

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

Participants: Eighteen community-dwelling patients with dementia and NPS (15 male; mean age 77 years).

Intervention: Participants received 1.5mg oral THC twice daily and placebo, in random order, for three days, separated by 4-days washout.

Measurements: Balance and gait were assessed using SwayStar™ and GAITRite™ within two hours after administration of THC or placebo in two consecutive intervention periods, under the following conditions: standing with eyes open (EO), standing with eyes closed (EC), preferred speed walking with and without performing a cognitive dual task. Adverse events (AEs) were carefully assessed.

Results: THC significantly increased sway during standing EC [roll angle 0.32(0.6)deg, p=0.05; pitch angle 1.04(1.5)deg, p=0.009; pitch velocity 1.96(3.3) deg/s, p=0.02], but not during standing EO. During preferred speed walking, THC increased stride length [4.3(5.4)cm, p=0.005] and related trunk sway in both directions [pitch angle 1.18(1.6)deg, p=0.005]. No effects were observed during dual task walking. No differences in the number and type of AEs were found and no falls occurred after administration of THC.

Conclusion: This preliminary study showed that 1.5mg oral THC has a benign adverse event profile regarding mobility and was well tolerated by community-dwelling dementia patients. Potential future studies on higher THC doses should further evaluate the effects on mobility in this vulnerable population.

Key words: mobility; fall risk; tetrahydrocannabinol; dementia; safety.

Introduction

Older patients, especially those with dementia, are susceptible to adverse drug effects, due to age-related physiological changes, cognitive disturbances, frequent co-morbidities and concurrent medication use.[1] When new drug interventions are proposed for this specific group, comprehensive safety evaluation is highly important in order to assess the benefit-to-harm ratio. This is particularly true for the introduction of psychotropic interventions, as these can lead to deterioration in cognitive and physical functioning, including an increased risk of falling. Medical cannabinoids are currently explored as a potential pharmacological treatment of dementia-related neuropsychiatric symptoms (NPS)[2] and preliminary studies suggest that low dose oral tetrahydrocannabinol (THC) reduces agitation and nighttime disturbances in patients with severe Alzheimer's disease.[3-6] Moreover, THC and other cannabinoids are more frequently administered to frail, older patients because of further liberalization of medicinal cannabis prescription for other conditions (e.g. pain and cancer related anorexia).[7] THC is the main psychoactive constituent of the *Cannabis Sativa L* plant, and binds to cannabinoid receptors localized throughout the central nervous system,[8, 9] including areas involved in movement control such as the basal ganglia and cerebellum.[10] Furthermore, THC might lead to an increased risk of falling by inducing adverse effects such as dizziness, sedation and changes in blood pressure, including orthostatic hypotension.[11-13] It is particularly important to assess effects on mobility in persons with dementia, as cognitive impairment is an independent risk factor for falling.[14] In the present article, we report on the first exploratory safety evaluation of THC with respect to balance and gait in patients with dementia, as part of a randomized controlled trial (RCT) studying low dose oral THC in the treatment of dementia-related NPS.

Methods

Study design

This study was part of a phase II, repeated crossover, double-blind RCT of 12 weeks on the efficacy and safety of two different doses (0.75 and 1.5mg twice daily) of oral THC in the treatment of dementia related NPS (registered at clinicaltrials.gov NCT01302340; accepted for publication by *American Journal of Geriatric Psychiatry*). Approval was provided by the certified ethics committee of Radboud university medical center (Radboudumc), The Netherlands. The study assessments took place between September 2011 and December 2013, at the Radboudumc Alzheimer Centre (Nijmegen, The Netherlands) and the Vincent van Gogh Institute for Psychiatry (Venray, The Netherlands). Written informed consent was provided at screening by the closest proxy and patient; the latter only in case the patient was judged capable to consent. We evaluated gait and balance effects of the highest dose of 1.5mg, as these were expected to be most pronounced. The mobility assessments were conducted during two one-week treatment periods, including 1.5mg THC or placebo for three consecutive days, separated by a four-day-washout period.

Study medication and randomization

Participants received a tablet containing 1.5mg THC (Namisol®, Echo Pharmaceuticals B.V., Weesp, the Netherlands) or matched placebo twice daily at 10 a.m. and 4 p.m. Randomization of the order of administration of study medication (THC or placebo first) was conducted by the pharmacy of Radboudumc, using a computer generated randomization list. The allocation sequence was strictly concealed from participants, caregivers and investigators and was not made available until study completion and database lock.

Study population

Eligibility criteria for the main RCT included diagnosis of possible or probably dementia type Alzheimer, vascular or mixed according to the NINCDS-ADRA[15] or NINCDS-AIREN[16] criteria, and clinically relevant and stable NPS (minimal Neuropsychiatric Inventory score ≥ 10). Exclusion criteria were current major psychiatric disorder, any severe or instable concomitant illness, frequent falling due to orthostatic hypotension, a

history of current alcohol or drug abuse and use of tricyclic antidepressants or opioids. Additionally, patients using drugs from a predesigned list of inhibitors of the cytochrome P450 enzymes (CYP): CYP2C9, CYP2C19 and CYP3A4 were excluded, as THC is metabolized in the liver through these enzymes. Patients were included in the current study on mobility when they were able to walk at least ten meters and understood simple instructions.

Mobility assessments

Quantitative balance and gait assessments were done at baseline, to familiarize the patients with the procedure and equipment, and twice during the crossover study: once after administration of 1.5mg THC and once after placebo. The assessments were carried out on the first or second treatment day within two hours after study drug administration as maximum blood concentrations were expected to occur within this time frame, according to pharmacokinetic measurements carried out in young, healthy volunteers (T_{max} of 5mg oral THC: 56.0min).[17]

Static and dynamic balance

Objective, quantitative assessments of balance during standing (static) and gait (dynamic) were done using the SwayStar™ system (BESTec-etp Freiburg GmbH, Freiburg, Germany). This accelerometer consists of a wireless device attached to the trunk at the level of the lumbar spine. The device contains two transducers to register angular velocities and displacements of the trunk in a highly sensitive manner; one in the anterioposterior (pitch) direction and one in the mediolateral (roll) direction. It has shown to be a valid method for the prediction of falls.[18-20] For analysis, the following variables were selected: pitch angle, pitch velocity, roll angle and roll velocity. Peak-to-peak ranges for all variables were used, as extreme values might be the result of exposure to THC.

Gait

Quantitative gait assessments were done using the GAITRite™ system (CIR Systems Inc, Sparta, United States); a 6.1-meter long electronic walkway containing multiple pressure sensors, connected to a computer. The GAITRite™ system has been shown to be a feasible and reliable instrument to obtain various temporal (timing) and spatial (distance) gait variables in older persons and patients with dementia.[21-26] The following

gait variables were selected for analysis as these have been shown to be best associated with an increased risk of falling in elderly or dementia patients: velocity, stride length, double support time, and variability in stride length and double support time.[25, 27-29] Furthermore, base of support was selected as a measure of gait width as this is expected to increase after administration of THC.[30]

Mobility tasks

Each assessment consisted of two stance tasks and two gait tasks. During stance tasks, static balance was assessed while patients were standing on a normal surface with their feet at comfortable distance, for the duration of 30 seconds with eyes open (EO), followed by 30 seconds with eyes closed (EC). During walking tasks, gait and dynamic balance were measured simultaneously. Patients walked at their own preferred speed; twice without a dual task and twice while performing an arithmetic, cognitive dual task, adjusted to cognitive capacity (mild dementia: continuously naming the months of the year backwards starting from December; moderate to severe dementia: continuously counting backwards from 20). In order to achieve steady-state walking, patients started walking two meters before the walkway and were instructed to keep walking until two meters behind the walkway. Use of a walking aid was allowed during the measurements when necessary, provided that it was used during both assessments. Walking aid prints were manually erased from the raw GAITRite™ data files to derive gait variables.

Assessment of adverse events

Adverse events (AEs) were solicited from patients and their caregivers at all study visits of the main RCT, using open questions and clinical observations. All reported AEs were recorded and coded following the classification of Medical Dictionary for Regulatory Activities, whether or not they were deemed to be related to study treatment.

Data analysis

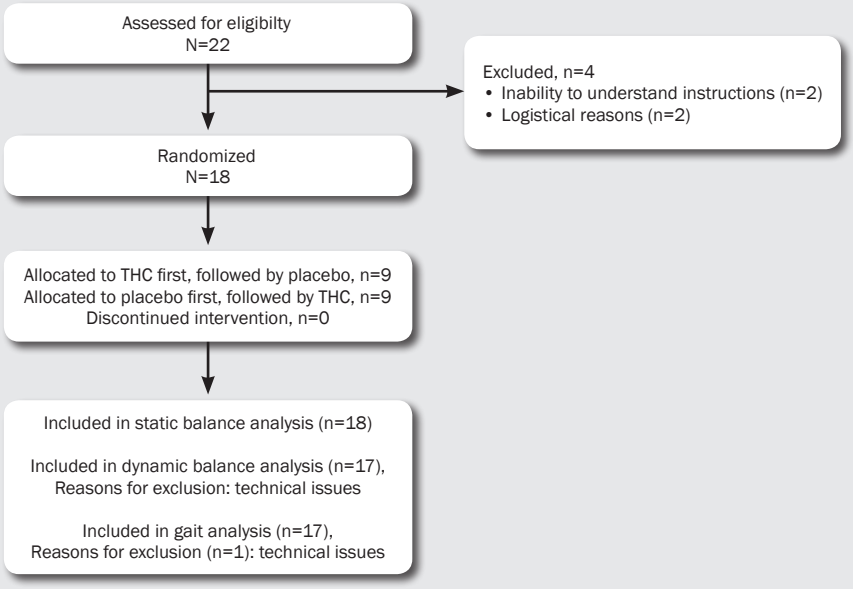
For this study, no sample size calculation was done, as these mobility assessments were part of safety assessments of a phase II trial on the efficacy of THC on dementia-related NPS (n=22). Baseline characteristics were summarized as means and standard deviations and as frequencies and percentages for categorical data. Gait tasks were performed twice and results were averaged per task for data analysis. Variability of stride length and double

support time was expressed as coefficient of variation (CoV): standard deviation/mean x 100%. Outlier evaluation by scatter plots resulted in several unrealistic extreme values in the GAITRite™ data, caused by technical errors or errors in the footfall registration process. These outliers were replaced by the means and standard deviations of individual footfalls of the same subject during the same task that were registered correctly. Values per intervention periods were expressed as means and standard deviations. Differences between THC and placebo were compared using paired t-tests. Treatment differences were also expressed as relative differences (with 95% confidence intervals [CI]), except for the CoVs of stride length and double support time. No correction for multiple comparisons was performed in this exploratory study on safety, as this correction reduces false positive results (Type II error), but may also lead to false-negative results (Type I error). Occurrence of AEs was compared between THC and placebo by non-linear mixed model analysis, assuming Poisson distribution. Additionally, AEs which were expected to influence mobility (fall incidents, dizziness, somnolence and balance disorders) were separately reported.

Results

Patient characteristics

Of the 22 patients included in the RCT, four patients were excluded for mobility assessments due to inability to understand instructions (n=2), or due to missing data because measurements could not be performed due to logistical reasons (n=2) (Figure). Hence, 18 patients were included in the mobility assessments. Baseline characteristics of these patients are presented in Table 1. For static balance tasks, complete data were available for all patients, whereas dynamic balance assessments were missing in one patient and gait assessments in another, due to technical failure of the devices.



Abbreviations: THC, tetrahydrocannabinol

FIGURE
CONSORT Flow Diagram

TABLE 1
Baseline characteristics

	All (n=18)
Men, *n (%)*	15 (83)
Age (yr), *mean (SD)*	77.0 (6)
Ethnicity, *n (%)*	
Caucasian	17 (94)
Asian	1 (6)
Type of dementia, *n (%)*	
Alzheimer	15 (83)
Vascular	1 (6)
Mixed	2 (11)
MMSE score, *mean (SD)*[a]	19.1 (6.0)
Use of cholinesterase inhibitors, *n (%)*	11 (61)
Use of psychotropic medication, *n (%)*	5 (28)
Baseline gait velocity (cm/s), *mean (SD)*[b]	91.8 (20.4)

Abbreviations: MMSE, Mini Mental State Examination.
[a] Mean MMSE score (range 0 to 30) based on 17 patients.
[b] Mean gait velocity based on 14 patients.

Static balance

Results on static balance during standing EO and EC are presented in Table 2. No differences on body sway were found between the interventions, when patients were standing with their eyes open. In the eyes closed condition, roll angle, pitch angle and pitch velocity were significantly higher after administration of THC, compared to placebo [0.32 (SD 0.6) degrees (deg), p=0.05; 1.04 (1.5) deg, p=0.009; and 1.96 (3.3) degrees per second (deg/s), p=0.02, respectively]. THC resulted in an increase of 39.1 to 49.2% in angular displacement and angular velocity.

Dynamic balance

Pitch angular displacement increased significantly after THC administration during preferred speed walking [1.18 (1.6) deg, p=0.005]. Additionally, the relative differences of all sway variables were significantly higher in the THC group compared to placebo (12.0 to 19.4%). No effects (absolute nor relative) of THC on dynamic balance were observed during walking while performing a cognitive dual task.

Gait

THC resulted in a significantly increase in stride length during walking at preferred speed [4.3 (5.4) cm, p=0.005] and a trend for increase in gait velocity (3.84 [7.8], p=0.06) (Table 3). Gait velocity during dual task walking after administration of placebo was significantly lower than gait velocity in preferred walking speed mode (77.0 cm/s vs. 89.6 cm/s, respectively; p=0.001). No effects of THC on gait were observed during walking while performing a cognitive dual task.

Adverse events

During the 12-week crossover RCT 91 AEs occurred in the THC group (0.75mg THC and 1.5mg THC twice daily), compared to 93 events in the placebo group (incidence rate ratio 0.96, 95%CI 0.7 to 1.3, p=0.77) (n=22 subjects, independent of participation in the mobility assessments). For these 22 subjects, mobility-related AEs were similarly prevalent in THC group, compared to placebo; 10 versus 9 events of dizziness, 2 versus 2 events of somnolence and 1 versus 0 events of balance disorders, respectively. More falls occurred during placebo than during THC treatment (4 versus 2 incidents) and all falls in the THC group occurred after administration of the lower dose (0.75mg THC twice daily).

TABLE 2

Results on static balance after administration of 1.5mg THC and placebo (n=18)

	Standing on two legs eyes open				Standing on two legs eyes closed			
	Placebo	**THC**	***p*-value**	**Relative difference THC vs. placebo % (95%CI)**	**Placebo**	**THC**	***p*-value**	**Relative difference THC vs. placebo % (95%CI)**
Roll angle (deg)	1.1 (0.9)	0.8 (0.6)	0.10	-4.1 (-24.0 to 15.9)	1.0 (0.7)	1.3 (1.0)	0.05	+48.2 (4.9 to 91.5)
Roll velocity (deg/s)	2.7 (3.4)	1.9 (1.1)	0.19	+7.2 (-22.8 to 37.3)	2.6 (2.6)	3.2 (3.0)	0.06	+39.1 (2.1 to 76.1)
Pitch angle (deg)	3.0 (2.1)	2.8 (1.6)	0.41	+3.1 (-19.0 to 25.2)	3.0 (1.9)	4.0 (2.0)	0.01	+49.2 (21.0 to 77.3)
Pitch velocity (deg/s)	7.9 (8.5)	5.9 (3.4)	0.22	+14.0 (-16.6 to 44.5)	8.1 (9.0)	10.1 (8.2)	0.02	+41.3 (11.1 to 71.4)

Values are means and standard deviations. Differences between intervention groups are analyzed using paired-sample t-test. Reported p-values are uncorrected.
Abbreviations: THC, tetrahydrocannabinol; deg, degrees; deg/s, degrees per second; CI, confidence interval.

TABLE 3
Results on dynamic balance and gait after administration of 1.5mg THC and placebo (n=17)

	Walking at preferred speed				Walking at preferred speed with dual task			
	Placebo	**THC**	***p*-value**	**Relative difference THC vs. placebo % (95%CI)**	**Placebo**	**THC**	***p*-value**	**Relative difference THC vs. placebo % (95%CI)**
Sway variables								
Roll angle (deg)	4.6 (1.2)	5.2 (1.1)	0.08	+16.7 (2.4 to 31.0)	5.8 (2.3)	5.7 (1.8)	0.83	+6.4 (-12.3 to 25.1)
Roll velocity (deg/s)	45.0 (11.4)	49.3 (12.4)	0.07	+12.0 (1.1 to 22.8)	45.4 (14.9)	50.6 (17.3)	0.25	+16.8 (-3.3 to 36.9)
Pitch angle (deg)	6.5 (1.2)	7.7 (1.8)	0.01	+19.4 (7.4 to 31.3)	7.7 (2.4)	8.3 (3.3)	0.33	+8.9 (-7.4 to 25.3)
Pitch velocity (deg/s)	70.4 (23.5)	73.6 (26.4)	0.57	+15.7 (6.4 to 24.9)	71.2 (24.3)	74.7 (29.5)	0.58	+8.7 (-11.3 to 28.8)
Gait variables								
Velocity (cm/s)	89.6 (20.8)	93.5 (20.9)	0.06	+5.1 (-0.1 to 10.3)	75.6 (23.1)	77.0 (23.9)	0.73	+4.3 (-8.3 to 17.0)
Stride length (cm)	108.6 (20.9)	112.9 (20.8)	0.01	+4.3 (1.3 to 7.3)	105.7 (19.9)	106.6 (21.8)	0.74	+1.1 (-4.3 to 6.5)
Stride length variability (CoV in %)	4.6 (2.3)	5.4 (3.2)	0.13	-	6.6 (2.7)	7.3 (4.3)	0.48	-
Base of support (cm)	10.3 (3.6)	10.0 (3.7)	0.38	-1.1 (-8.6 to 4.3)	10.5 (3.4)	10.2 (4.3)	0.49	-3.4 (-13.8 to 7.0)
Double support time (s)	0.30 (0.1)	0.29 (0.1)	0.33	-2.2 (-8.1 to 3.7)	0.35 (0.1)	0.39 (0.2)	0.08	+11.2 (-1.4 to 23.8)
Double support time variability (CoV in %)	14.3 (7.7)	11.9 (4.8)	0.28	-	13.8 (7.9)	25.7 (33.2)	0.15	-

Values are means and standard deviations. Differences between intervention groups are analyzed using paired-sample t-test. Reported p-values are uncorrected.
Abbreviations: THC, tetrahydrocannabinol; deg, degrees; deg/s, degrees per second; cm/s, centimeter per second; cm, centimeter; CoV, Coefficient of Variation; CI, confidence interval.

Discussion

The current study is the first to examine the effects of oral THC on mobility in patients with dementia. Our findings showed an increased body sway after administration of 1.5mg THC when patients were standing with eyes closed, but not while standing with eyes open. Furthermore, THC resulted in a higher stride length, a trend towards increase in gait velocity and consequent increase in dynamic sway during preferred speed walking. No effects of THC were observed during dual task walking.

Effects on static balance

We compared our results on static balance with the results of a previous RCT studying oral THC in healthy older volunteers (n=11, mean age 71.1 [1.4] years).[31] In this latter study, body sway during standing with eyes open and eyes closed was not affected after single administration of 3 to 6.5mg THC, compared to placebo. In comparison to these healthy volunteers, the current patient group with dementia shows an impaired static sway in the placebo condition (data of comparison not shown), which is in line with previous literature.[32]

This impaired sway, a priori, suggests that caution is required when administering higher dosages of oral THC to these vulnerable patients, as THC-related effects on sway are expected to occur in a dose-dependent manner.[17, 33] Additionally, our data showed that dementia patients were able to compensate for the effects of THC on static balance, which could not be maintained in the absence of visual feedback (eyes closed condition). This effect was expected, as the amount of sensory information is important to maintain balance, especially for older persons.[34] Nonetheless, these data suggest that dosages should be carefully and gradually increased in future studies.

Effects on dynamic balance and gait

THC resulted in a higher stride length, a trend towards increase in gait velocity and increase in dynamic sway during preferred speed walking. These effects might be due to THC-mediated cognitive disinhibition or increased alertness.[35] On the contrary, dual task walking resulted in a decreased gait velocity, which was observed in the THC group as well as the placebo group. This effect is probably a purposeful adaptation to reduce the risks of falls when performing a more complex task.[36] The changes in gait velocity

observed here are probably not clinically meaningful, as only an absolute change in velocity of 10 cm/s or more is previously determined to be clinically meaningful in older adults,[37-39] while a relative decrease of 45% or an increase of 60% are judged relevant in frail, older inpatients.[40] Unfortunately, estimates of meaningful change in stride length and postural sway are lacking.[41, 42]

Adverse events

In this study, no difference in the occurrence of AEs was observed between 1.5mg THC twice daily compared to placebo. The AEs were collected during the entire study duration of 12 weeks, and concerned all subjects in the main RCT, including the more vulnerable subjects which were excluded from the mobility assessments. Furthermore, mobility-related AEs (e.g. dizziness, somnolence and balance disorders) did not differ between the interventions. The effects observed in the quantitative balance and gait assessments were subtle and did not result in the occurrence of AEs. As such, these results suggest that low dose THC administered for short duration was well tolerated by these older dementia patients.

Methodological considerations

This study is the first to investigate the effects of THC on mobility in patients with dementia using quantitative measures of mobility. This is especially relevant as currently used drugs for NPS, such as antidepressants, benzodiazepines and antipsychotics, increase the risk of falling and are associated with impairments in postural control, especially in older persons,[43] limiting the feasibility of these interventions. Although most studies focus on the effects on postural balance,[17, 31, 33] effects on gait seem even more important, as most falls occur during walking while performing normal daily activities.[44] Therefore, the assessments performed in this study are more closely related to physical activities in daily life. Inevitable, this study also has some limitations. We assessed the effects of THC on mobility as part of an efficacy trial with a predefined design. The analyses therefore had an exploratory and descriptive character and should be interpreted as such. The data did not allow for subgroup analyses on dementia severity or concurrent psychotropic medication use. Furthermore, our study sample consisted of relatively fit dementia patients, based on their age [mean 77 (SD 6) years], cognitive status [MMSE 19.1 (6.0) points] and baseline gait velocity [91 (20.4) cm/s]. To compare, the average gait

velocity of healthy persons of similar age [80.5 (3.7) years] is slightly higher: 106 (19.3) cm/s.[45] We excluded patients with important co-morbidity such as those with severe cardiac failure and increased fall risk due to orthostatic hypotension. In comparison to our sample, nursing home residents with moderate to severe dementia show significantly lower mean gait velocity [63 (25) cm/s], stride length [76 (26) cm] and a higher mean stride length variability [9.3 (5) %].[25] Therefore, our data cannot simply be generalized to patients with more severe cognitive disturbances or those with more co-morbidity. It should be emphasized that these latter patient groups are more vulnerable and probably more suspected for THC-mediated AEs on mobility.

Clinical implications and future research

These first results suggest that low dose oral THC is well tolerated by community-dwelling dementia patients concerning mobility and risk of falling. This dose did not show benefit in the treatment of dementia-related NPS compared to placebo. The data presented here support the conduction of future higher dosing studies, provided that the dose is gradually increased. Additionally, these future studies should also address the effects of THC on mobility in more severely demented patients and patients with more co-morbidities that might affect balance and gait.

Conclusion

This preliminary study showed that 1.5mg oral THC has a benign adverse event profile regarding balance and gait and was well tolerated by community-dwelling dementia patients. Future studies are needed to evaluate the effect of higher THC doses on balance and gait in this vulnerable population.

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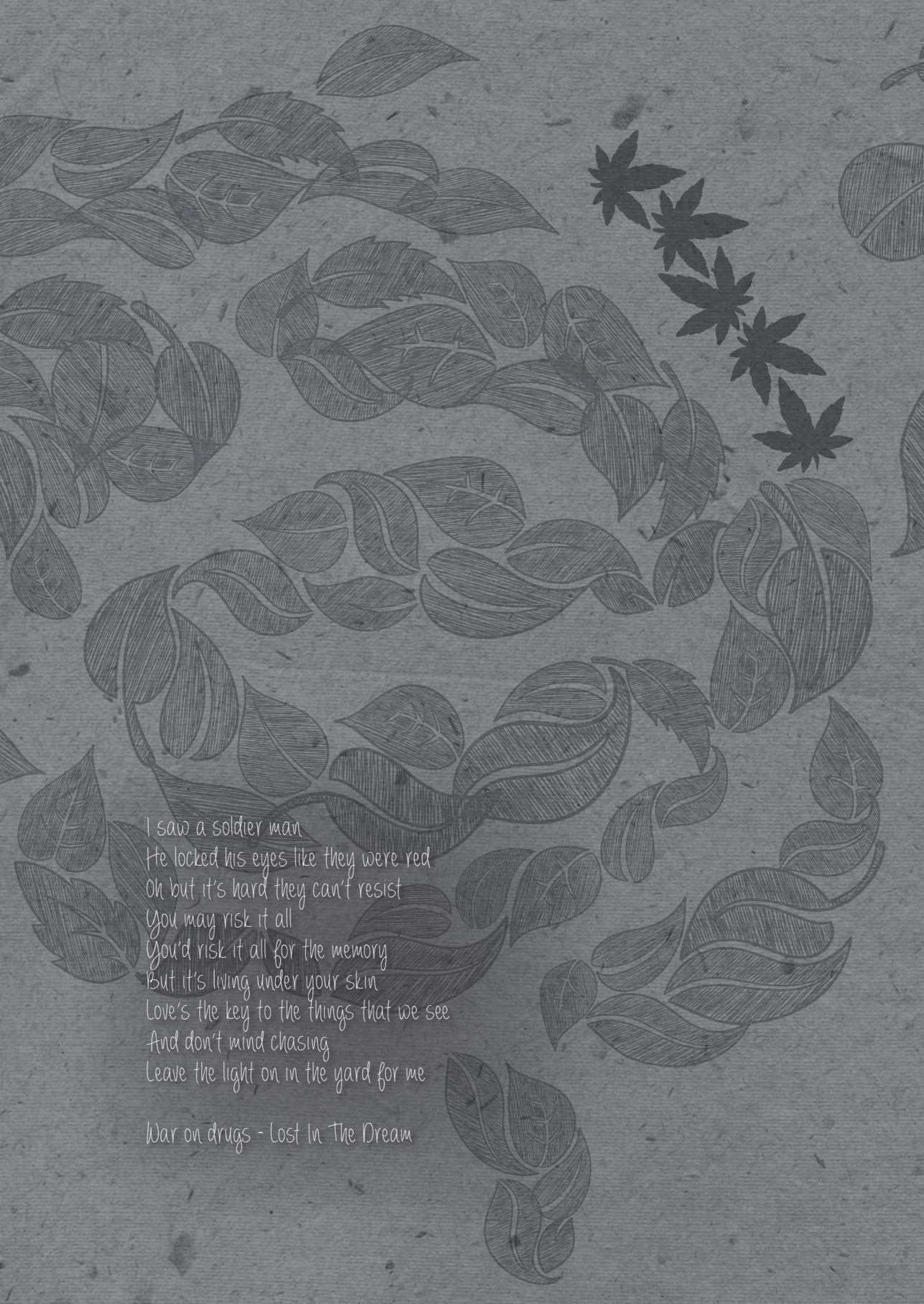


I saw a soldier man
He locked his eyes like they were red
Oh but it's hard they can't resist
You may risk it all
You'd risk it all for the memory
But it's living under your skin
Love's the key to the things that we see
And don't mind chasing
Leave the light on in the yard for me

War on drugs - Lost In The Dream

CHAPTER 8

Summary

Samenvatting

SUMMARY

The studies described in this thesis have been conducted focused on three subjects:

1. To evaluate the status of current literature on medical cannabinoids in older patients.
2. To evaluate the efficacy of oral tetrahydrocannabinol (THC) in the treatment of dementia-related neuropsychiatric symptoms (NPS).
3. To evaluate the safety or oral THC in older persons and patients with dementia.

Medical cannabinoids in older patients

In **chapter 2**, we reviewed the published reports on intervention studies with medical cannabinoids in order to summarize evidence on the indications, efficacy and safety in older participants. We developed a systematic literature search, selecting controlled intervention trials including solely participants aged 65 years and older or reporting separate data on an older subgroup. Five studies could be included that met our inclusion criteria, while 105 papers reported the inclusion of older participants, but did not provide data on this subgroup. Due to the high clinical and methodological diversity of the included studies, meta-analysis was not feasible. The studies showed no efficacy of medical cannabinoids on dyskinesia, breathlessness or chemotherapy induced nausea and vomiting, while two small, preliminary studies showed that oral THC might be useful in the treatment of anorexia and behavioral disturbances in dementia patients. Adverse events were more common during cannabinoid treatment compared to control treatments and most commonly included sedation-like effects. Two studies reported cardiac arrhythmia and seizure, although a relationship with the study medication could not reliably be assessed.

This chapter 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. Methodologically sound trials are therefore needed, as the potential symptomatic benefits of cannabinoids might be attractive for older patients with specific complaints and limited lifespan expectancy.

Efficacy of THC on reducing behavioral disturbances in dementia

In **chapter 3 and 4** the efficacy of oral THC was examined in two randomized, controlled trials. In the first trial (THC crossover study, described in **chapter 3**) 22 patients (15 men, mean age 76.4 [5.3] years) with dementia and clinically relevant NPS were randomly assigned to receive oral THC and placebo during six treatment blocks of two weeks each. In this repeated crossover study, dosages of 0.75mg and 1.5mg THC twice daily were compared to placebo. THC did not reduce Neuropsychiatric Inventory (NPI) scores, compared to placebo (low dose THC vs. placebo, 1.8, 97.5%CI -2.1 to 5.8; high dose THC vs. placebo, -2.8, 97.5%CI-7.4 to 1.8). Additionally, we found no effect on agitated behavior (NPI agitation subscale, -0.3, 95%CI -0.9 to 0.2; Cohen-Mansfield Agitation Inventory, -1.5, 95%CI -4.0 to 1.0) and caregiver burden (Zarit Burden Inventory, 0.3, 95%CI -0.9 to 1.5). THC was well tolerated; the incidence of adverse events was equal between treatment groups. Four serious adverse events occurred, of which none were related to study medication.

In the **addendum of chapter 3** we described the results of an open label extension phase, which followed the crossover trial. Twelve patients (55%) participated in this optional study, although only five (42%) completed the six month treatment period. Study discontinuation was not related to the occurrence of adverse events. Results indicated that long term treatment with low dose THC was well tolerated and did not affect cognition, mobility or weight. Additionally, no effects on behavioral disturbances or caregiver burden were observed. These results must be interpreted with caution, as the attrition rate in this phase was high (58.3%).

Chapter 4 describes a multicenter RCT aiming to evaluate the efficacy of 4.5mg THC daily in the treatment of behavioral disturbances and pain in patients with mild to severe dementia (THC parallel design study). Fifty patients with dementia and clinically significant NPS with at least agitation, aggression or aberrant motor behavior were included and randomly assigned to 1.5mg THC (n=24) or placebo tablets (n=26) three times daily for a period of three weeks. Effectiveness on NPS (using NPI) was evaluated after 14 and 21 days of treatment.THC did not significantly reduce NPI scores (THC versus placebo, + 3.2, 95%CI -3.6 to10.0), compared to placebo. Additionally no effects

on agitated behavior, daily functioning or quality of life were observed. In the subgroup of patients also suffering from pain (n=23), no treatment differences were seen concerning pain-related behavior (using Pain Assessment Checklist for Seniors with Limited Ability to Communicate, -0.4, 95%CI -3.8 to 3.0) and pain intensity (using Verbal Rating Scale, -0.03, 95%CI -1.0 to 0.9) (**Appendix chapter 4**). The number of patients experiencing one or more adverse events was equally divided among treatment groups and there were no study medication related serious adverse events.

We did not find benefit of doses up to 4.5mg oral THC daily on behavioral disturbances in dementia, compared to placebo. Nor were any differences observed concerning the secondary efficacy outcome measures, such as agitation, caregiver burden or quality of life in both studies.

Nonetheless, THC was well tolerated by these vulnerable patients. The observation that there was no biological signal of adverse events suggests that the dosages were too low, as a psychoactive drug is rarely effective without showing any side effects. Therefore, the results warrant future research using higher dosages of THC in the treatment of dementia-related NPS.

In depth safety evaluation of THC in older persons and patients with dementia

There is a great concern about the safety of medical cannabinoids in older persons, due to the lack of evidence on this specific group, while cannabinoid-related adverse effects, such as sedation, dizziness and psychoactive effects might be especially harmful in older patients. Data from young subjects cannot simply be extrapolated to an older, more vulnerable population. Therefore, we conducted a phase I, double-blind RCT with a crossover design to evaluate the safety and pharmacokinetics of single oral doses of 3, 5, 6.5mg THC and placebo in 12 healthy, older subjects (mean age 72±5 years), of which the results are reported in **chapter 5**. Data of 11 subjects were included in the analysis. THC appeared safe and well tolerated. No severe adverse events occurred. Adverse events were more common after 6.5mg THC compared to 3mg (p=0.048), 5mg (p=0.034) and placebo (p=0.013). Drowsiness (27%) and dry mouth (11%) were most frequently reported. Attention and body sway were not affected. Overall, the pharmacodynamic effects of THC were smaller than those reported in young adults. Plasma concentrations

of THC and its metabolites 11-OH-THC and COOH-THC increased dose-dependent, although a substantial inter-individual variation was observed.

While conducting the THC crossover study, described in **chapter 3**, we also collected several blood samples for pharmacokinetic analysis from 10 participating patients with dementia. The results are described in **chapter 6**. Based on the AUC and maximum concentration (C_{max}) values, THC has linear pharmacokinetics in older individuals with dementia, showing a doubling of AUC and C_{max} after administration of 1.5mg oral THC compared to 0.75mg. The C_{max} of THC after first administration of 0.75mg was 0.41 (0.18-0.90) ng/mL and for 1.5mg 1.01 (0.53-1.92) ng/mL. Median time to reach this maximum concentration (T_{max}) was 1 to 2 hours, which is longer than the reported T_{max} of oral THC in young healthy volunteers. In line with the results from the phase I study with healthy, older subjects, described in **chapter 5**, a wide inter-individual variability in pharmacokinetics of THC and its active metabolite 11-OH-THC was observed (Coefficient of variation up to 140%).

In **chapter 7** we assessed the effects of oral THC on mobility in 18 patients with dementia, as part of the safety protocol of the THC crossover study (**chapter 3**). Qualitative assessments of balance and gait were conducted within two hours after administration of 1.5mg oral THC and placebo, using SwayStar™ for assessment of postural and dynamic balance and GAITRite™ for assessment of gait during preferred speed walking with and without performing a cognitive dual task. THC significantly increased sway during standing with eyes closed [roll angle 0.32(0.6)deg, p=0.05; pitch angle 1.04(1.5)deg, p=0.009; pitch velocity 1.96(3.3)deg/s, p=0.02], but not during standing with eyes open. During preferred speed walking, THC increased stride length [4.3(5.4)cm, p=0.005] and related trunk sway in both directions [pitch angle 1.18(1.6) deg, p=0.005]. Mobility was not affected during dual task walking. No differences in the number and type of adverse events were found and no falls occurred after administration of THC.

Based on these studies, dosages up to 4.5mg THC daily appear to be well tolerated by older, dementia patients, concerning the occurrence of adverse events, vital signs and effects on mobility. Additionally, dosages up to 6.5mg THC are well tolerated by

healthy, older volunteers and static body sway was not affected. Nonetheless, our data also suggest that caution is needed with increasing dose, as the occurrence of adverse events and effects on mobility are expected to occur in a dose-dependent manner. Additionally, our data show linear pharmacokinetics of THC, although a high inter-individual variation exists. As such, future higher dosing studies can be performed, provided that the dose is gradually increased and safety is closely monitored.

Samenvatting

Probleemgedrag, zoals agressie, onrust en slaapstoornissen, komt veel voor bij patiënten met een dementie en vormt een grote belasting voor zowel de patiënt als zijn of haar mantelzorgers. Helaas is de behandeling van probleemgedrag vaak erg moeilijk; de huidige beschikbare medicatie geeft veel en soms ernstige bijwerkingen, zoals stijfheid, en een verhoogd risico op vallen en beroerte. Daarom is het belangrijk om op zoek te gaan naar nieuwe behandelmogelijkheden. Een van die opties zou medicinale cannabis kunnen zijn; eerdere, kleine onderzoeken hebben aangetoond dat een lage dosering tetrahydrocannabinol (THC), de werkzame stof uit de cannabisplant, prikkelbaarheid en onrust bij patiënten met een ernstige Alzheimer dementie verminderde. Er is een steeds toenemende interesse voor het gebruik van medicinale cannabis, waaronder THC, bijvoorbeeld in de behandeling van chronische pijn, spierspasmen en misselijkheid. Probleemgedrag, en met name agitatie en bewegingsonrust, kunnen worden veroorzaakt door niet goed behandelde pijn. Omdat THC zowel een effect heeft op gedrag als pijnstillend werkt, zou dit mogelijk een goede behandeling kunnen zijn voor probleemgedrag bij dementie.

In dit proefschrift worden meerdere onderzoeken beschreven, waarbij wij hebben geprobeerd een antwoord te krijgen op de volgende vragen:

1. Wat is er tot nu toe bekend in de wetenschappelijke literatuur over het gebruik van medicinale cannabis bij oudere patiënten?
2. Is een lage dosering THC in tabletvorm werkzaam in de behandeling van probleemgedrag bij patiënten met dementie?
3. Is een lage dosering THC in tabletvorm veilig te gebruiken bij ouderen en bij patiënten met dementie? Wat is het effect ervan op de aandacht, het geheugen en balans en lopen?

In **hoofdstuk 2** hebben wij de huidige wetenschappelijke literatuur op een gestructureerde manier onder de loep genomen en gezocht naar informatie over het gebruik van medicinale cannabis bij ouderen. Voor welke ziekten is het gebruik van medicinale cannabis bij ouderen onderzocht? Is er informatie over de werkzaamheid en veiligheid, specifiek bij deze ouderen patiënten? Uit onze zoekstrategie kwamen slechts vijf artikelen naar voren die de werkzaamheid van medicinale cannabis hebben

onderzocht bij proefpersonen die allen ouder waren dan 65 jaar, terwijl er 105 artikelen waren die oudere proefpersonen lieten deelnemen aan hun onderzoek, maar deze groep niet nader hebben onderzocht. De vijf onderzoeken bij oudere patiënten, onderzochten de werkzaamheid van medicinale cannabis voor verschillende aandoeningen: bewegingsstoornissen, kortademigheid, misselijkheid en braken na chemotherapie en probleemgedrag bij dementie. Alleen de onderzoeken bij patiënten met dementie konden aantonen dat medicinale cannabis een gunstige invloed had. Bijwerkingen kwamen echter wel vaker voor bij proefpersonen die werden behandeld met medicinale cannabis, ten opzichte van proefpersonen die placebo kregen (medicatie zonder werkzame stof). De meest voorkomende bijwerking was sufheid.

Op basis van ons gestructureerde onderzoek van de beschikbare literatuur blijkt dat er nog onvoldoende bekend is over de werkzaamheid en veiligheid van medicinale cannabis bij ouderen. Ook de studies naar probleemgedrag bij dementie waren te klein om een betrouwbaar antwoord hierop te kunnen geven. Daarvoor zijn grotere en beter opgezette studies nodig.

Werkzaamheid van THC op probleemgedrag bij dementie

In **hoofdstuk 3 en 4** beschrijven we twee onderzoeken die we hebben uitgevoerd naar de werkzaamheid van THC in tabletvorm op probleemgedrag bij dementie. Aan het eerste onderzoek, beschreven in **hoofdstuk 3**, namen 22 patiënten met dementie en probleemgedrag deel. Zij waren gemiddeld 76 jaar oud. Zij kregen gedurende 12 weken een behandeling met THC in tabletvorm gedurende drie dagen, afgewisseld met placebotabletten, eveneens gedurende 3 dagen. Na elke behandelperiode kregen zij 4 dagen geen onderzoeksmedicatie. In de eerste helft van het onderzoek kregen zij 0.75mg THC tweemaal per dag. Dit werd verhoogd naar 1.5mg THC tweemaal per dag in de tweede helft van het onderzoek. Patiënten wisten niet wanneer zij THC kregen of placebo; de behandeling was 'geblindeerd'. Ook de onderzoekers waren hiervan niet op de hoogte, zodat het onderzoek zo objectief mogelijk kon worden uitgevoerd. De ernst van het probleemgedrag werd gemeten middels een vragenlijst die werd doorgenomen met de mantelzorger: de Neuropsychiatric Inventory (NPI). Er werd geen verschil gevonden in scores op de NPI na behandeling met THC in vergelijking met placebo. Daarnaast had THC eveneens geen effect op geagiteerd gedrag of ervaren mantelzorgbelasting. Eventuele bijwerkingen werden in deze studie zorgvuldig bijgehouden. THC werd

goed verdragen door deze kwetsbare patiënten; THC gaf evenveel bijwerkingen dan de placebo tabletten.

Wanneer het onderzoek werd afgerond konden patiënten kiezen voor een eventuele vervolgstudie. Hieraan hebben 12 patiënten deelgenomen. In deze vervolgstudie kregen alle deelnemers een behandeling met THC, gedurende zes maanden. Slechts vijf van de twaalf deelnemers hebben deze behandeling in zijn geheel afgerond. De overige zeven zijn tussentijds gestopt, omdat de behandeling onvoldoende effectief was. De resultaten van dit vervolgonderzoek laten zien dat een langdurige behandeling met een lage dosering THC waarschijnlijk geen effect heeft op probleemgedrag, maar ook niet op het geheugen, het lopen of het lichaamsgewicht. Deze resultaten geven slechts een eerste indruk, omdat een groot deel van de proefpersonen het onderzoek niet heeft afgerond.

In het tweede onderzoek, dat wordt beschreven in **hoofdstuk 4**, wordt een hogere dosering THC onderzocht. In deze studie hebben wij gekeken naar de werkzaamheid van de behandeling op zowel probleemgedrag als pijn bij patiënten met een dementie. Vijftig patiënten hebben deelgenomen, waaronder zowel thuiswonende patiënten, als patiënten die in een verpleeghuis verblijven. Allen hadden zij last van probleemgedrag, met onder andere geagiteerd of agressief gedrag of bewegingsonrust. De deelnemers werden, middels loting, verdeeld over twee behandelgroepen. De eerste groep werd behandeld met 4.5mg THC per dag gedurende drie weken, de andere groep kreeg placebo-tabletten. Het onderzoek werd dubbelblind uitgevoerd; zowel de deelnemer als onderzoeker wisten niet welke behandeling een patiënt kreeg. De ernst van het probleemgedrag werd, evenals bij het eerste onderzoek, gemeten middels de NPI. Daarnaast werd ook de werkzaamheid op eventuele pijn onderzocht. Dit werd gedaan middels een vragenlijst (voor patiënten die de ernst van hun pijnklachten zelf konden aangeven) of middels observatie van pijngedrag door de onderzoeker of verpleegkundige (middels de PACSLAC-D). Na drie weken behandeling werd er een verbetering gezien op probleemgedrag in beide behandelgroepen. Daarbij werd er geen verschil gezien tussen behandeling met THC in vergelijking met placebo. Ook werd er geen verschil gezien tussen de behandelingen op pijn, functioneren in dagelijkse activiteiten of kwaliteit van leven. Ook het aantal bijwerkingen was gelijk verdeeld over de groepen. Dus ook in dit onderzoek werd de onderzoeksmedicatie goed verdragen.

Uit deze bovenstaande onderzoeken blijkt dat lage doseringen THC in tabletvorm (tot 4.5mg per dag) niet effectief zijn in de behandeling van probleemgedrag bij patiënten met dementie. Tevens konden wij geen effect aantonen op de andere uitkomstmaten, zoals geagiteerd gedrag, mantelzorgbelasting of kwaliteit van leven. Desalniettemin werd de behandeling wel goed verdragen door deze kwetsbare patiëntengroep. Het kan zijn dat de onderzochte dosering te laag was en daarom is het belangrijk om vervolgstudies te doen om de werkzaamheid van hogere doseringen te onderzoeken.

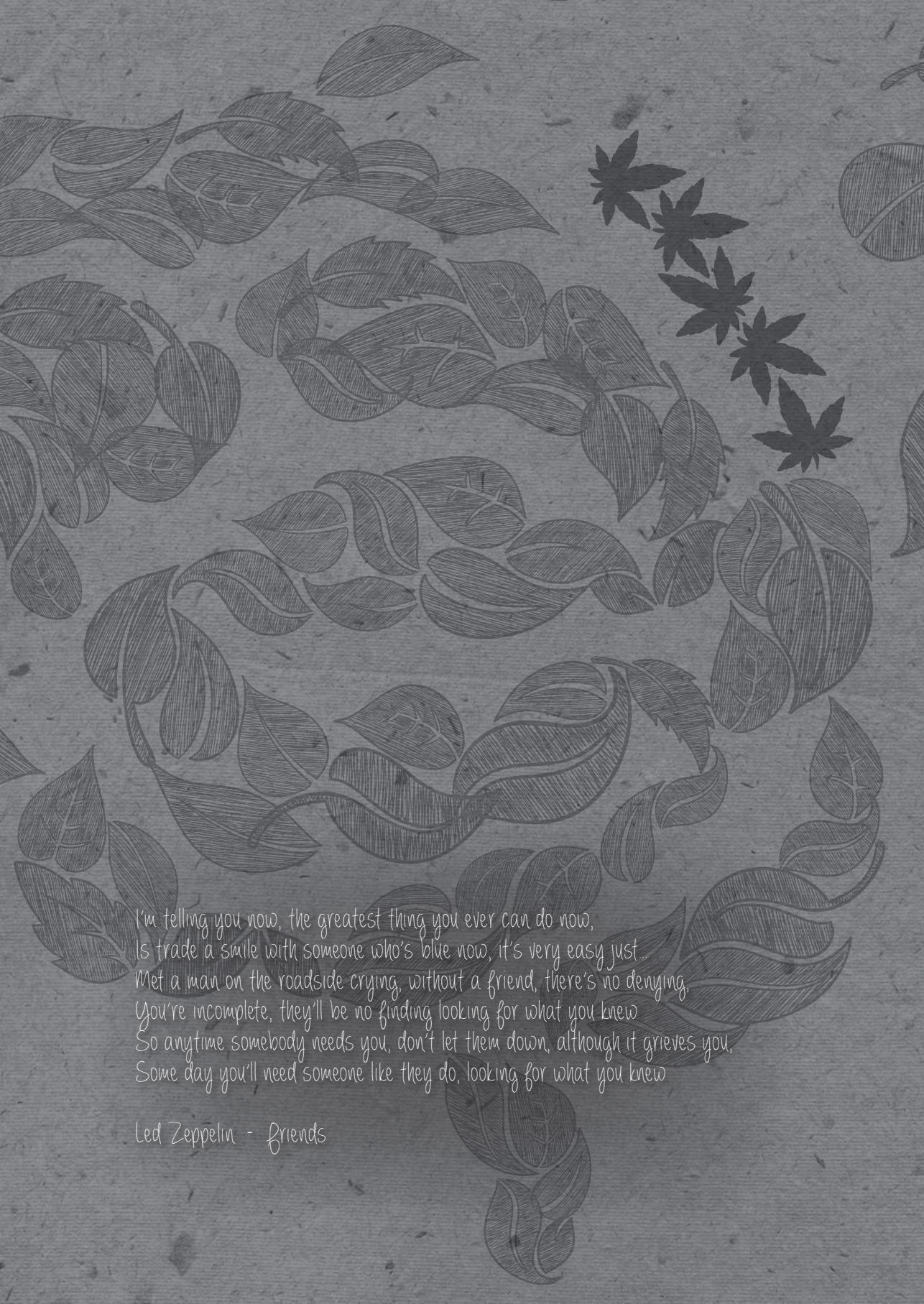
De veiligheid van THC bij ouderen en patiënten met dementie

Veel artsen zijn terughoudend met het voorschrijven van medicinale cannabis aan oudere patiënten. Dit komt enerzijds doordat er weinig bekend is van de werking bij ouderen (zoals blijkt uit ons literatuuronderzoek, beschreven in **hoofdstuk 2**), terwijl cannabis belangrijke bijwerkingen kan geven, zoals sufheid, duizeligheid en een 'high-gevoel', die vooral bij oudere patiënten tot gevaarlijke situaties kunnen leiden (bijvoorbeeld tot valincidenten). Gegevens over de veiligheid die reeds zijn verzameld bij jongeren kunnen niet zomaar worden toegepast bij een oudere en meer kwetsbare patiëntengroep, omdat veranderde lichaamssamenstelling, gebruik van meerdere medicijnen en een kwetsbaarder brein bij ouderen allen invloed hebben op de werking van een medicijn. Om de veiligheid van medicinale cannabis beter te onderzoeken hebben wij een onderzoek uitgevoerd naar de veiligheid van 3, 5 en 6.5mg THC in tabletvorm bij 12 gezonde 65-plussers (gemiddeld 73 jaar). De resultaten van dit onderzoek worden beschreven in **hoofdstuk 5** van dit proefschrift. De proefpersonen konden de studiemedicatie goed verdragen. Wel traden er na toedienen van 6.5mg THC meer bijwerkingen op vergeleken met 3 en 5mg THC en vergeleken met een placebo-tablet. Sufheid en een droge mond waren de meest voorkomende bijwerkingen. THC zorgde niet voor een verminderde concentratie of verminderde balans. Ten opzichte van een vergelijkbaar onderzoek waaraan jongeren deelnamen, lijkt THC zelfs minder negatieve effecten te hebben bij deze oudere, gezonde proefpersonen. Daarnaast hebben we bloedonderzoek gedaan om de concentraties van de werkzame stof in het bloed te bepalen. Hierbij zagen we dat de concentratie in het bloed toeneemt, wanneer een hogere dosering THC wordt toegediend. Wel viel op dat er grote verschillen bestonden in bloedconcentraties tussen de proefpersonen.

Tijdens het onderzoek dat wordt beschreven in **hoofdstuk 3**, zijn er verschillende bloedmonsters afgenomen bij 10 deelnemende patiënten met dementie, om de concentratie van werkzame stoffen van THC in het bloed te bepalen. De resultaten van dit deelonderzoek worden beschreven in **hoofdstuk 6**. Uit dit onderzoek blijkt dat bij oudere patiënten met dementie de bloedconcentraties van de werkzame stof verdubbelen, wanneer de dosering in de tablet wordt verdubbeld. Ongeveer 1 tot 2 uur na inname van de medicatie is de concentratie THC in het bloed maximaal. Dit duurt langer dan bij jonge, gezonde proefpersonen. Evenals bij oudere, gezonde proefpersonen zien we ook bij patiënten met dementie grote verschillen tussen personen in de bloedconcentraties na inname van dezelfde dosering THC.

THC kan leiden tot sufheid, duizeligheid en balansproblemen, en zou daardoor in theorie een verhoogd valrisico kunnen geven. Juist bij ouderen met dementie is het belangrijk om hier onderzoek naar te doen. Daarom hebben we bij 18 patiënten met dementie, die deelnamen aan de eerste patiëntenstudie (beschreven in **hoofdstuk 3**) uitgebreid en gedetailleerd onderzoek gedaan naar de balans en het lopen. Dit deelonderzoek wordt beschreven in **hoofdstuk 7**. Het effect van THC op het lopen werd gedetailleerd gemeten middels een ruim 6 meter lange mat met elektroden (GAITRite™), die voetstappen registreerd en daarmee de loopsnelheid, paslengte en wisselingen in het looppatroon kan berekenen. De balans werd objectief en nauwkeurig gemeten middels een bewegingssensor op de rug van de patiënt (SwayStar™). Hiermee werd de balans tijdens staan en de balans tijdens het lopen gemeten. Vergeleken met toediening van placebo, leidde 1.5mg THC in tabletvorm tot een toename van de balans wanneer patiënten stil stonden met hun ogen gesloten. De balans werd niet verstoord als patiënten hun ogen open mochten houden. Daarnaast zagen we dat THC ertoe leidde dat patiënten wat sneller gingen lopen, waarbij ook de rompbewegingen iets toenamen. THC had geen effect op het lopen, wanneer patiënten tijdens het lopen een dubbeltaak kregen. Er waren geen verschillen in het aantal of het type bijwerkingen tussen THC en placebo. Daarnaast zijn er geen valincidenten voorgekomen na toediening van 1.5mg THC.

Op basis van deze onderzoeken kunnen we concluderen dat doseringen tot en met 4.5mg THC per dag goed worden verdragen door ouderen patiënten met dementie. Daarnaast worden doseringen tot 6.5mg THC goed verdragen door gezonde proefpersonen van 65 jaar en ouder. Desalniettemin is het wel noodzakelijk om voorzichtig te zijn bij het toedienen van hogere doseringen, omdat we verwachten dat de bijwerkingen en de negatieve effecten op het lopen en de balans dan zullen toenemen. Op basis van het bloedonderzoek zien we dat er grote verschillen bestaan in bloedconcentraties tussen proefpersonen. Dit is per persoon niet goed te voorspellen. Toekomstige studies kunnen wat ons betreft worden uitgevoerd, maar de dosering van de medicatie zal langzaam moeten worden verhoogd en de veiligheid van proefpersonen moet daarbij goed in de gaten worden gehouden.



I'm telling you now, the greatest thing you ever can do now,
Is trade a smile with someone who's blue now, it's very easy just...
Met a man on the roadside crying, without a friend, there's no denying,
You're incomplete, they'll be no finding looking for what you knew
So anytime somebody needs you, don't let them down, although it grieves you,
Some day you'll need someone like they do, looking for what you knew

Led Zeppelin - Friends

CHAPTER 9

General discussion

Introduction

The treatment of neuropsychiatric symptoms (NPS) in dementia poses a significant challenge to healthcare professionals, as these symptoms are highly prevalent and can have a great impact on both patient and caregiver's lives. NPS can result from a complex interaction between biological, psychosocial and environmental factors, such as progressive brain pathology, feelings of abandonment, intercurrent diseases, pain, and confusing surroundings. Professionals should therefore always attempt to identify these triggers, in order to start a targeted intervention. When there is no underlying cause identified, non-pharmacological and comfort measures are to be preferred in the treatment of NPS, while psychopharmacological interventions should be complemented to this, to realize a so called integrated dementia care.[1]

Over the past years, a broad variety of (psycho)pharmacological treatment options have been explored. Yet, effective and safe treatment options are still lacking. Up to date, those limited drugs available that are effective in reducing NPS also cause relevant side effects in this vulnerable population. Thus, there is an urgent need for alternative pharmacological treatment options, which might be medical cannabinoids. The first preliminary studies on the efficacy of oral cannabinoids in the treatment of dementia-related NPS have been conducted circa 20 years ago, but despite positive findings hardly any follow-up studies were performed.[2] Only recently, the interest in cannabinoids for various medical applications has been growing, partly due to legalization of its use in over 30 US states.[3] Cannabinoids, including THC, are most frequently used for the treatment of pain, nausea and anorexia. In patients with dementia, suffering from NPS and agitation in particular, a structured analgesic treatment has recently been demonstrated to be beneficial.[4] Therefore, THC might serve as an alternative pharmacological treatment for dementia-related NPS, due to its psychoactive as well as its analgesic properties.

The overall aim of this thesis was to study the efficacy and safety of low dose oral tetrahydrocannabinol (THC) in the treatment of behavioral symptoms and pain in patients with dementia. Therefore, in this final chapter, the results of the individual studies will be placed in a broader perspective and recommendations for future research will be provided.

Main findings

This thesis describes the efficacy and safety of oral THC, the main psycho-active component of the cannabis plant, in the treatment of dementia-related NPS. Below, the main findings are summarized:

- Although trials studying medical cannabinoids include older subjects, there is a lack of evidence of its use specifically in older patients (**chapter 2**).
- No benefits of oral THC in daily doses up to 4.5mg were observed in the treatment of behavioral disturbances in dementia patients, compared to placebo (**chapter 3 and 4**).
- The effect of oral THC on pain intensity and pain behavior remains unclear, as the group of patients suffering from persistent pain was small and pain assessments did not appear to be feasible in our study (**chapter 4**).
- Daily dosages up to 4.5mg THC can be safely used for a duration up to three weeks in this frail and cognitively impaired patient group (**chapter 3, 4 and 7**).
- 1.5mg oral THC twice daily increases body sway in dementia patients when standing with eyes close, but does not negatively affect balance or gait while performing several mobility tasks with eyes open (**chapter 7**).
- Dosages up to 6.5mg oral THC are safe and well tolerated in healthy, older volunteers (**chapter 5**).
- In older patients with dementia, low dose oral THC shows rapid absorption, dose-linear pharmacokinetics, although with considerable inter-individual variation (**chapter 6**).

Efficacy versus safety of oral THC in dementia

Efficacy

Our results show that oral THC up to 4.5mg daily does not have a beneficial effect on behavioral disturbances in dementia patients, compared to placebo (**chapter 3 and 4**). This finding is in contrast with previous literature on medical cannabinoids in the treatment of dementia-related NPS (see also Chapter 2, Section Efficacy). All previous studies reported a positive effect of oral THC in patients with severe dementia. There are several factors that might have caused this discrepancy in findings. First, the previous studies have important methodological drawbacks, possibly leading to an overestimation of the treatment effect; two randomized controlled trials (RCTs) analyzed only a small number of patients (n=2; n=12),[5, 6] while the other studies had a retrospective or uncontrolled design.[7, 8] And second, there are also factors that can be appointed in our studies that might have diminished the likelihood of finding a treatment effect. For the first study (**THC crossover study, chapter 3**) we chose relatively short treatment periods in a repeated crossover design, in order to conduct a methodologically valid trial, including only a relatively small number of patients. The length of the treatment episodes and washout were based on the pharmacological profile of one single oral dose of 5mg Namisol® (purified THC)[9]; a half life ($T_{1/2}$) of 71.9 ± 17.3 minutes for THC and 196 ± 65.1 minutes for its active metabolite 11-OH-THC. Furthermore, this study showed that the pharmacodynamic peak effects were reached approximately 1 to 2 hours after dosing.[9] Therefore, a treatment period of three days and washout period of four days was judged to be sufficient for both the plasma concentration and the pharmacodynamic effect level. We acknowledge that these short treatment periods might have led to a reduced change of finding a treatment effect, as neuropsychiatric symptoms might not be continuously present. Furthermore, it is imaginable that there were carry-over effects, which may have been influenced by non-pharmacological factors. We observed a significant increase in behavioral disturbances and caregiver burden over the course of the study, which might have been caused by caregivers' attributions, regarding a high experienced burden of participation or a failure to observe an expected treatment effect.

On the contrary, we observed a remarkable improvement in NPS in the intervention group of our second patient study, (mean decrease NPI: -9.6 points), while patients receiving placebo treatment improved even more (mean decrease NPI: -11.5 points) (**THC**

parallel design study, chapter 4). This placebo-effect is striking, but similar substantial improvements in dementia trials have been reported before[10, 11] and may be due to the so called 'Hawthorne effect', in which factors including attention and support by the study team, improved standard care, rater's expectations about scoring, as well as patients' and caregivers' expectations concerning the potential treatment effects - specifically with regard to cannabinoids -, together might contribute to a temporarily change in behavior.[12] Another known factor that might have diminished the likelihood of detecting a treatment effect is the heterogeneity of the studied populations. Previous studies on the efficacy of THC in NPS all included severely demented patients. In contrast, we included a more heterogeneous patient group, ranging from community-dwelling to nursing home patients, which has possibly led to a high variability in symptoms, disease progression and outcomes. This was also represented by the larger standard deviation in the baseline NPI total score, which was larger than we had expected based on the literature (16.5 vs. 8.1)[13] (**chapter 3**). Previous positive findings in other studies might suggest that more severely demented (in)patients benefit more from THC than less affected patients do, although adequate evidence lacks to confirm this.

Despite these possible shortcomings that might have confounded the estimates of the treatment effects, our studies were the largest, prospective trials evaluating the efficacy of oral THC in dementia patients, using randomized, placebo-controlled designs with valid and rigorous methods, including adherence to masking and blinded outcome assessment, and thereby setting a standard for possible future studies on this subject.

Safety

In this thesis we report on a broad range of safety aspects regarding oral THC in older and cognitively impaired subjects, including the occurrence of adverse events and effects on vital signs, cognition and mobility (**chapter 3 to 7**). The consistent findings over these studies lend credibility that dosages up to 4.5mg THC daily can be safely administered for a short duration to dementia patients, as we observed no THC-mediated adverse events in our trials (**chapter 3 and 4**), while effects on mobility were small with a limited clinical relevance (**chapter 7**). It must be stated though, that the results of these latter mobility assessments are preliminary and should be researched more extensively.

In retrospect, we could have administered higher doses. The results of our phase I study indicate that single dosages up to 6.5mg oral THC are well tolerated by older persons (**chapter 5**). This study also showed that THC-related adverse events occur in a dose-dependent manner, as significantly more patients reported the occurrence of at least one adverse event after administration of 3, 5 and 6.5mg oral THC, compared to placebo. Additionally, 6.5mg THC resulted in more adverse events than did 3 or 5mg, including drowsiness, dry mouth and coordination disturbances. This is a relevant finding, as these types of adverse events can induce significant health problems, especially in frail, older patients with cognitive disturbances. As such, future studies on THC in the treatment of dementia-related NPS should evaluate higher dosages (with respect to effectiveness), yet, caution is needed when administering dosages of 3mg and more related to possible side-effects and doses should therefore be gradually increased.

Why should future studies be conducted?

We did not find a benefit of low dose oral THC on dementia-related NPS in our studies (**chapter 3 and 4**). The fact that we observed clinically relevant improvement, as well as clinical relevant worsening or no meaningful change in behavioral disturbances in a similar number of patients (**chapter 3**) suggests that 1) changes in NPS were random and not a consequence of the intervention, and 2) for individual patients NPS can change over time, independent of an intervention. As such, severity and frequency of NPS is a challenging outcome measure when evaluating the efficacy of an (pharmacological) intervention in a research setting. The evaluation of our assessment measures will be described below.

Nonetheless, we assume that the dosages used in our trials were too low, as no biological signal of adverse events was observed, while rarely a psychopharmacological intervention is effective without showing any side effects. In light of the preliminary evidence on medical cannabinoids in dementia, negative findings on efficacy in combination with absence of adverse reactions, makes it worthwhile to first examine the efficacy of higher doses, before conclusions can be drawn on ineffectiveness of the compound for this specific indication.

Selecting the appropriate dose

When studying a new pharmacological intervention, selection of the optimal dose is challenging, especially when it concerns the administration to a vulnerable and heterogeneous patient group. After performing a review of the literature (**chapter 2**), we concluded that previous scientific results on medical cannabinoids in older patients, including those with dementia, are extremely scarce. Other trials on medical cannabinoids for various indications, such as pain, multiple sclerosis and anorexia, used strikingly high doses (up to 60mg oral THC daily) with a large between-study variation.[14-16] Preliminary trials on NPS in dementia patients showed positive effects of 2.5 to 5.0mg synthetic THC daily.[5, 7, 8] We contacted the corresponding authors and asked for their motivation on the selected dose in their studies, and received the following answers:

Researcher #1: *"We have chosen the low dosage of 2.5mg because of the literature on the use of oral dronabinol in dementia and pain. We were aware that particularly in pain or Tourette's syndrome dosages up to 20mg daily were administered. However, as we were piloting the trial and were concerned about potential side effects and negative publicity, we chose to stick to the lowest reported dosage. We didn't want any headlines about serious side effects in elderly put on cannabis..."*

Researcher #2: *"We selected the dose for our study because it was the recommended dose for treatment of anorexia in patients with AIDS. I agree that it may be possible to use higher doses because we did not find any serious side effects except for one case of seizure"*

Both researchers had to base their choice on very limited evidence and selected a relatively low dose to prevent serious side effects. Several factors, such as age-related pharmacokinetic changes, frequent concomitant illnesses, concurrent medication use, and difficulties in outcome assessments with regard to reliability and burden, probably all contribute to an increased risk of adverse effects and need to be considered when designing a trial to determine the optimum dose in older patients.

In line with Researcher #1, we also chose a conservative approach in our dose selection. The Investigational Medical Product (IMP) used in our studies, which is Namisol®, was never administered to this patient group before. Only data from a Phase I trial on healthy, young volunteers (mean age 21.4 years) were available at that time.[9] As

Namisol® is not registered for clinical application, the knowledge of its effects regarding different patient characteristics is limited. Namisol® contains purified, natural THC, opposite to the products that were used in previous studies with dementia patients, which were all synthetic (dronabinol). To get the best possible reasoning for the dose, we compared the mean maximal concentration of THC and 11-OH-THC of 5mg oral Namisol® in young adults to pharmacokinetic data on 20mg oral Marinol® (dronabinol) (5), assuming linearity of the parameters. Based on these data 2.5mg Marinol® equals 1.25mg Namisol®. Taken into account the lack of high quality studies, the vulnerability of this patient group, the controversy concerning the intervention (which also exists in The Netherlands), and the inexperience concerning Namisol®, we selected relatively low doses to investigate a dose-dependent increase of effects or adverse events (studying 1.5, 3.0 and 4.5mg THC daily). In this strategy, we complied to the generally accepted principle in all guidelines for pharmacological interventions in frail older patients which recommends "to start low, and go slow" in increasing dosages, in line with the general medical principle "to first do not harm" and the more critical pharmacodynamics in older patients.

To conclude, the chosen doses used in our studies might have been higher in retrospect, but the tolerability of a higher dose would not have been based on available evidence. In order to obtain additional data on this IMP and its tolerability in older patients, we also conducted a pharmacokinetic sub-study (**chapter 6**) and performed structured safety assessments, including short-term effects on vital signs, adverse event monitoring and effects on balance and gait (**chapter 3, 4 and 7**). As a result, we now provide this evidence, with which our study contributes valuable and solid information to the scarce literature on this subject.

Challenges to clinical research in dementia

Older patients, including those with dementia, represent a rapidly growing patient population, necessitating targeted interventions. This imposes significant challenges to the scientific evaluations of new interventions in this specific group. We faced some methodological and practical difficulties while conducting our studies and will address some of the lessons learned.

Recruitment

With 22 and 50 participants in our patient studies these should be considered small. Nonetheless, they are the largest prospective trials on THC in dementia to date. Recruitment issues played an important role in the conduct of both our studies, which is not uncommon in dementia studies. These issues resulted in a prolonged recruitment period in our THC crossover study and failure to enroll the planned number of patients in the THC parallel design study (**chapter 3 and 4**).

Despite comprehensive recruitment efforts, there were several factors that negatively influenced the recruitment rate, which were associated to the complexity of the studied population and intervention. Potential participants were recruited through physicians from collaborating memory clinics, nursing homes and general practices. Although many physicians and informal caregivers recognized the importance of conducting an intervention study for behavioral disturbances, they still seemed reserved. Our trials were time consuming, included several hospital admissions (crossover study only) and frequent assessments, introducing a significant burden for the patient as well as the caregiver and probably leading to selection bias (especially in the crossover study), resulting in the inclusion of relatively healthy and less severe impaired patients.

Several efforts were made to lower the burden of participation and to minimize the attrition by optimizing the benefit-to-burden ratio. First, home visits and telephone calls were performed, avoiding travel problems and reducing the burden to participate. Second, despite an overall positive attitude towards THC, the restricted short-term availability of study medication was one of the major reasons for patients and caregivers not to participate. Therefore, we included an optional open label extension phase, following the THC crossover trial in case of positive preliminary effects (so called *'compassionate use'*). Unfortunately, it was not possible to incorporate 'compassionate use' in our THC parallel design trial, as an open label extension phase because of lack of ethical and license approval. Third, many patients and informal caregivers appreciated the social interaction with the research staff. To provide continuity of care as much as possible, one researcher conducted all study visits for one patient. These actions probably have contributed to the very low attrition rates of our trials (under 9%).

Choice of outcome measures

Assessment of behavioral disturbances and agitation

The primary outcome measure in our efficacy studies was the *Neuropsychiatric Inventory* (NPI),[17] which is a frequently used tool for the assessment of NPS in clinical research. The NPI evaluates 12 behavioral domains, of which the frequency and severity is scored by the caregiver. The NPI total scores is the sum of all domain scores. By using this scale, our results can be easily compared to other intervention trials. Furthermore the scores are solely based on the caregiver's input and the NPI is therefore suitable for assessment in an ambulatory setting, and does not warrant extensive observation periods by the researchers. Nonetheless, the NPI also has its methodological shortcomings. First, assessment by the caregiver makes the measurements subject to several confounding factors, such as their expectations, burden and continuation of care, etc. Second, the total NPI score may not reflect a change in behavior, despite a reduction in individual domain scores. For this reason, we conducted additional analyses on the NPI subdomains of our interest (including agitation, aggression and aberrant motor behavior), but we did not find any group differences in these specific symptoms (**chapter 4**).

Furthermore, we evaluated several available alternative outcome measures. The *Pittsburgh Agitation Scale* (PAS) assesses the severity of aberrant vocalization, motor agitation, aggression and resisting care by direct observation of the patient and is especially useful in assessment of NPS in patients with severe dementia.[18] It has been suggested that the PAS may also allow assessment of pain in non-communicative patients with dementia.[19] Unfortunately, this assessment method is not developed for assessment of NPS in community-dwelling patients with mild to moderate dementia.

The *Neurobehavioral Rating Scale* (NBRS), which was initially developed for assessment of NPS in patients with traumatic brain injury, has been used in several relevant trials studying dementia-related NPS.[10, 20] It is a 28-item observer-rated instrument of which the reliability has also been assessed in the use in dementia patients.[21] Unfortunately, both the PAS and NBRS are not available in Dutch. Additionally, the NPI proved to have the highest sensitivity in detecting improvement in agitated behavior in dementia, compared to the *Empirical Behavioral Rating Scale* (E-BEHAVE-AD) and NBRS,[22] and is therefore to be preferred.

When assessing agitated behavior in particular, the *Cohen-Mansfield Agitation Inventory* (CMAI) can also be a valuable option and was implemented in our trials as a secondary outcome measure. The CMAI is an internationally validated instrument, and mostly used in nursing homes.[23] Additionally, a large validation study supports construct validity of the CMAI Dutch version across different settings and severity of dementia.[24]

In conclusion, up to date, the NPI and CMAI are to be preferred when studying the efficacy of an intervention on behavioral disturbances and in agitation in particular, as they are both frequently used in clinical trials, are well validated, sensitive to change and both available in Dutch. Other outcome measures, such as quality of life, activities of daily living or caregiver burden should, in our opinion be used as contributing, secondary assessments, though not as a primary outcome measures when studying dementia-related NPS.

Pain assessments

No benefit of THC was found in the treatment of pain in patients with dementia (**chapter 4**). However, the number of available pain assessments in our study was low, resulting in preliminary data which must be interpreted with caution. Assessment of pain in dementia is challenging, especially in patients with severe cognitive disturbances, due to loss of judgment, abstract thinking and language skills. As our study sample size was expected to be heterogeneous, by including patients with dementia ranging from mild to very severe and by conducting assessments in various settings, we selected two pain assessments measures: 1) assessment by self-report and 2) an observational instrument. Self-reporting of pain is often referred to as 'gold-standard',[25] but requires the capability of understanding the task and communicate the experienced sensation. Studies have demonstrated that mildly to moderately demented patients are capable in using self-report scales to assess pain intensity.[26] Although the Verbal Rating Scale (VRS) is one of the most commonly used assessment methods, only 13 (57%) of patients in our pain subgroup included in our study, were able to use the VRS.

The Pain Assessment Checklist for Seniors with Limited Ability to Communicate – Dutch version (PACSLAC-D) was assessed as an observational instrument for pain-related behavior. Although this instrument is commonly used in nursing homes, it has some limitations regarding the use in this study. First, the PACSLAC-D was not feasible for assessment of pain in community-dwelling patients with mild dementia, who were

able to adequately report their complaints and did not express pain through exaggerated behavior. And second, no single item on the PACSLAC-D is an exclusive marker for pain and can overlap with behavioral symptoms due to dementia itself. Future studies on the efficacy of an analgesic treatment in dementia, which THC might still be, should focus on a more homogeneous patient group, in whom one outcome assessment regarding pain is feasible.

Missing data

In the THC parallel design study, a relatively high rate of missing data was observed, leading to limitations in the analysis of some outcome measures, such as for episodic memory, quantitative mobility assessments, pain-related behavior and pain intensity (**chapter 3 and 7**). Missing data can bias results and limit the statistical power to detect significant effects. Factors contributing to missing data in our studies are: 1) specific assessments, such as episodic memory testing and self-reporting of pain intensity, were only feasible for patients with a mild dementia severity and resulted in missings in the more severely demented subjects, 2) there were missing values due to patients' unwillingness to cooperate or severe behavioral disturbances, and 3) data collection was sometimes prioritized for assessment of main outcome measures to reduce participants burden when patients were at risk to be lost to follow-up (resulting in missing secondary outcomes). These factors are highly related to the participants characteristics, as all were suffering from cognitive disturbances, co-morbidities and behavioral disturbances, and thereby were a challenge for traditional research methods, which are not developed for, and not very well fitting this vulnerable and functionally impaired group of individuals.

In the current studies, missing data were therefore often nonrandom, as more severe demented participants were not able to complete the abovementioned assessments due to severe cognitive impairments, behavioral disturbances or fatigue.

To prevent high numbers of missing data, we selected proxy-directed questionnaires and observational assessments (NPI, CMAI, ZBI, Barthel Index, QoL-AD, PACSLAC-D) as primary and secondary efficacy outcome measures. Furthermore, burdensome assessments such as extensive physical examination, blood sampling, cognitive and mobility assessments were kept to a minimum. Nonetheless, a certain amount of missing data could not be prevented and were most common in patients with severe dementia or severe behavioral disturbances.

Patient and caregiver participation

Participating in a trial may easily overburden dementia patients and their caregivers. Involvement of patients or their representatives in the design of a new study will probably provide valuable information on the benefit-to-burden ratio and can result in studies that are more suited to the needs, possibilities and wishes of those participating, probably stimulating recruitment and retention rates. The THC crossover study was judged to be burdensome, due to its multiple hospital admissions, blood sampling and weekly visits (which was also reflected in the increasing NPI scores over the study period). Therefore, we implemented 'patient participation' in the design phase of the THC parallel design study, resulting in a simple study design, with a limited number of outcome assessments, limited number of outcome assessments, often assessed by a caregiver

Future directions

Future directions in the clinical practice

Behavioral disturbances in dementia can be various and highly prevalent, affecting both community-dwelling and institutionalized patients. Momentarily, psychotropic drugs, such as antipsychotics, benzodiazepines and antidepressants are not registered for the treatment of behavioral disturbances in dementia, although these interventions are mentioned in the Dutch guidelines and can be prescribed 'off-label'.[1]

Atypical antipsychotics are probably the most extensively studied and used psychotropic drugs in the treatment of dementia-related NPS. The best evidence is for the atypical antipsychotics risperidone and aripiprazole, specifically regarding the treatment of agitated and aggressive behavior.[27-29] Nonetheless, treatment duration of the studies is often short, the effects tend to be limited and many studies had potentially important methodological limitations. Studies on the long-term effects are lacking.[28] The adverse effects of antipsychotics in this frail patient group are well known among physicians and include sedation, mobility disorders, falls and fall-related injuries. Less common, but more severe adverse effects are an increased risk of cerebrovascular events and death (OR for mortality: 1.54).[30] The evidence for other treatment options is limited, although some positive findings have been reported on carbamazepine and memantine.[29] Furthermore, there is a growing interest in the use of antidepressants for this indication. A recent

trial studying the efficacy of high dose citalopram in patients with Alzheimer's disease, reported a significant reduction in agitation and overall behavioral disturbances.[10] This latter finding was reflected by a group difference of six points on the NPI after nine weeks of treatment. Unfortunately, relevant adverse effects on falls and cardiac conduction raise concerns on the safety of this treatment and limits its use in this vulnerable patient group.

Based on the results of this thesis, we cannot yet recommend the use of oral THC in the treatment of dementia-related NPS. The benign adverse-event profile observed in our studies warrants further research on the possible efficacy of higher doses.

Future directions in research

Despite centuries of experience on the medical application of cannabinoids, evidence on its efficacy and safety in older patients is lacking (**chapter 2**). Future studies should evaluate the benefit to risk ratio of higher dosages. In this section, we provide some directions on the most appropriate design, setting and dose that can be incorporated.

Study design

The studies described in this thesis underline that it is possible to conduct a methodological valid trial, even when studying a vulnerable patient group. To minimize bias, future studies should at least be randomized and placebo-controlled, with blinded outcome assessment. Based on our experience after the THC parallel design study, we suggest to keep future studies as simple as possible, regarding both the design and type and number of assessments and include patient and proxy participation in the phase of design development. In this way, patients' and caregivers' burden can best kept to a minimum, which reduces the change of drop-outs and missing data. To correct for a possible substantial placebo response, which was observed in our parallel design study, it is probably worthwhile to implement an individual crossover design including two treatment periods, in which a participant serves as his or her own control. This will probably also reduce the reluctance of patients and their caregivers to participate, as every participant will receive active treatment. To optimize the chance of finding a treatment effect, the treatment periods should be extended to approximately six weeks in a future phase II trial. Phase III studies should evaluate the intervention for a longer period, which should be at least three months, to monitor treatment beyond the timeframe of the Hawthorne effect.

Participants

An important limiting factor in the THC parallel design study (**chapter 4**) was the large variation in NPI scores between participants and relatively low mean agitation subscore at baseline. The NPI total score of our population was 35.0 points, which is comparable to or higher than the scores reported in other intervention trials on behavioral disturbances in dementia.[10, 11] As stated before, the NPI is a sum of various and heterogeneous symptoms, and does not necessarily imply that agitated behavior is present at a clinically relevant level. The overall baseline severity of agitated behavior of our population, which is represented by the NPI agitation/aggression score of 4.1 and CMAI score of 58.3, was lower than reported in other intervention trials (Porsteinsson et al., NPI agitation/aggression score 7.9; Fox et al., CMAI score 68.0; Howard et al., CMAI score 62.5, NPI agitation/aggression score not provided).[10, 31, 32] Therefore, we suggest that future studies include patients with clinically relevant agitation, represented by a NPI agitation/aggression subscore of 4 points or more.

The wide range of cannabinoid-mediated receptor actions and interaction with various neurotransmitters, such as acetylcholine, dopamine, serotonin and opioid peptides,[33] in combination with the first positive clinical study effects on oral THC on behavioral disturbances suggests that patients suffering from more severe dementia will probably benefit most from treatment with THC. [2-4] Unfortunately, subgroup analysis in our parallel study showed no benefit of THC in community-dwelling patients ($NPI_{THC\ versus\ placebo}$ 5.0, 95%CI -1.8 to 11.7) or inpatients ($NPI_{THC\ versus\ placebo}$ 1.5, 95%CI -10.0 to 13.1), representing patients with mild and moderate to severe dementia, respectively. Our results therefore cannot confirm this statement (**chapter 4**). The baseline scores by patient subgroup for dementia severity (rated by Clinical Dementia Rating, CDR) are provided in the Table, in order to select the most appropriate patient group for future studies, with regard to baseline severity scores of behavioral disturbances and between subject variation.

TABLE
Assessment scores by dementia severity (data from the TCH parallel design study on the efficacy of THC in NPS in dementia)

	CDR 1[a] (n=11)	CDR 2[b] (n=19)	CDR 3[c] (n=20)
NPI total score	32.7 (12.2)	34.6 (12.1)	40.3 (14.4)
NPI agitation/aggression subscore	5.2 (4.5)	5.3 (4.1)	6.9 (3.7)
CMAI total score	56.1 (15.5)	59.6 (16.1)	63.2 (19.5)

Values are means and standard deviations.
Abbreviations: CDR, Clinical Dementia Rating; NPI, Neuropsychiatric Inventory; CMAI, Cohen-Mansfield Agitation Inventory. [a] CDR 1, mild dementia. [b] CDR 2, moderate dementia. [c] CDR 3, severe dementia.

In line with the treatment intensity, the severity of NPS and agitation is highest in patients with severe dementia (CDR 3). For NPI agitation/aggression subscore the variability of scores in this subgroup was also the smallest. This makes this subgroup favorable for a future intervention trial. To be able to recruit sufficient participants a future multicentre trial is preferred, including nursing homes and specialized psychiatric dementia care units. Nonetheless, rigorous national regulations on medical cannabinoids limited a rapid and easy implementation of the study in the participating clinics of our study. Therefore, future studies should take into account these time consuming regulatory requirements prior to study conduct.

Dose

Future studies should evaluate higher doses, as 4.5mg oral THC daily appeared to be safe and without clear biological effects when administered for a short duration. Our phase I study showed that single doses up to 6.5mg oral THC were well tolerated by healthy elderly volunteers, and that adverse events occurred in a dose dependent manner (**chapter 5**). Future studies should increase the dose gradually. Nonetheless, based on our findings, we suggest that doses up to 5mg THC twice daily can be safely studied in dementia patients. Considering the large variety in symptoms, concurrent morbidities and treatment response of dementia patients, in combination with the substantial inter-individual variation in pharmacokinetics of oral THC (**chapter 6**), it might be worthwhile to implement an individually tailored dose titration from a low initial dose.

Conclusion

The work included in this thesis describes the largest randomized controlled trials on the efficacy and safety of oral THC in the treatment of dementia-related neuropsychiatric symptoms and thereby adds to the scarce literature on this subject to date. The results show no benefit of doses up to 4.5mg oral THC daily in NPS in dementia patients, although comprehensive safety results, including occurrence of adverse events, effects on vital signs, gait and balance and pharmacokinetics suggest that the intervention is well tolerated by this frail population and offers an evidence base for future research on this topic. The emerging international consideration for cannabinoids in the treatment of various conditions, in combination with these preliminary results offer chances to future research concerning its applicability in neuropsychiatric symptoms, and offers hope for patients with dementia and their caregivers, who are in urgent need for better treatments.

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Dans les yeux de ma mère
Il y a toujours une lumière
Dans les yeux de ma mère
Il y a toujours une lumière
L'amour je trouve ça toujours
Dans les yeux de ma mere

Amo - Les Yeux De Ma Mère

Dankwoord

List of publications

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Dankwoord

In de afgelopen vijf jaar ben ik getraind in het maken van korte en bondige formuleringen, maar aangezien het dankwoord, het meest gelezen hoofdstuk van dit proefschrift, geen *word limit* kent, wil ik deze kans niet onbenut laten om uit te pakken.

Allereerst wil ik mijn **proefpersonen** én **hun mantelzorgers** danken. Zonder hen is klinisch onderzoek niet mogelijk. Ik ben ontzettend onder de indruk van de betrokkenheid, enthousiasme en hun doorzettingsvermogen. Ik realiseer me goed dat ik veel van hen heb gevraagd; onder andere opnames in het ziekenhuis, wekelijkse huisbezoeken en héél erg veel bloedafnames en vragenlijsten. Het is een voorrecht te mogen ervaren dat de deur altijd open stond en zij bereid waren zowel de leuke als moeilijke gebeurtenissen met me te delen.

Dit proefschrift is het resultaat van de jarenlange inspanning van een heel team. Helaas blijft dat vaak onzichtbaar op de publicaties. Daarom wil ik iedereen bedanken met wie ik in de jaren heb mogen samenwerken om de studies en dit proefschrift tot een succes te maken, allereerst het promotie team:

Beste **Marcel**, deze promotie begint en eindigt bij jou; je hebt me de kans gegeven deze onderzoeken op te zetten en uit te voeren, en me tot en met de afronding fantastisch begeleid. Ik bewonder je creatieve geest, razendsnelle correcties en positieve blik (in tegenstelling tot die van mij, is jouw glas altijd half vol!). Heel erg bedankt!

Beste **Marjolein**, wat heb je ontzettend veel tijd in dit project gestoken! Ik ben je eerste promovendus, maar ik had me geen betere co-promotor kunnen wensen. Niet alleen heb ik ontzettend veel geleerd van je management skills, je kritische blik en je vermogen om zelfs de kleinste foutjes uit mijn artikelen te halen, maar ik heb ook erg genoten van je gezelligheid.

Beste **Robbert-Jan**, in dit team begonnen als co-promotor, maar inmiddels ben ook jij gepromoveerd (zij het met een iets grotere prestatie dan die van mij). Jouw frisse blik en onderzoekservaring vanuit de psychiatrie is van grote meerwaarde geweest voor het

project. Ik waardeer je rust en je oprechte interesse voor alles wat met wetenschap te maken heeft.

Beste **Kees**, je bent wat later betrokken geraakt bij mijn promotie. Natuurlijk kende ik je al als docent vanuit de opleiding geneeskunde en ik vind het een eer om met je samen te mogen werken. Dank voor je kritische bijdrage aan dit proefschrift. Ik kijk ernaar uit om nog veel meer van je te leren tijdens mijn stage interne geneeskunde.

Leden van de manuscriptcommissie: **prof. dr. Koopmans**, **prof. dr. van Marum** en **prof. dr. Vernooij**, hartelijk dank voor het beoordelen van dit manuscript op zijn wetenschappelijke inhoud.

Dear **dr. Paul Rosenberg**, thank you so much for your important contribution to this thesis. It was an honor to meet you at the AAIC Conference in Washington D.C. I wish you all the best in conducting more research on this fascinating and important topic.

Beste **Amir**, dank voor je bijdrage aan de studies, je positieve instelling en het feit dat je op elk moment van de dag bereid was voor overleg. Succes met de laatste loodjes van je eigen proefschrift!

Lieke, **Michiel**, **Caspar**, **Vera**, **Janny**, **Esther** en **Peter**, allen heel erg bedankt! Ongelofelijk hoeveel werk jullie hebben verricht binnen dit project! Daarnaast de lieve onderzoeksverpleegkundigen van de afdeling Geriatrie: **Willemien**, **Lucia**, **Johan**†, **Nanda**, **Loes**, **Willy**. Jullie hebben met veel enthousiasme, precisie en geduld zo'n 120 opnamedagen tot een groot succes gemaakt. Ik wil **Ton Feuth** bedanken voor het verrichten van de statistische analyses en het iets begrijpelijker maken van wat voor mij complete abracadabra was. Eveneens had ik in het begin niet veel kaas gegeten van *Good Clinical Practice, SOPs, delegation logs* en *drug accountability***.** Dankzij het **Clinical Research Centre Nijmegen** heb ik deze onderzoeken kunnen uitvoeren volgens de hoogste kwalitatieve standaarden, wat zelfs een audit van de Inspectie voor de Gezondheidzorg heeft overleefd. Mijn speciale dank gaat uit naar **Hettie Maters**, mijn monitor, maar vooral ook steun en toeverlaat. Je bent een fantastisch mens! Medewerkers van de apotheek, wat hebben jullie een werk gehad aan de Namisolstudies. Het is bewonderenswaardig hoe

jullie je door de administratie, het verpakken, herverpakken, nogmaals herverpakken en de inspectiebezoeken heen hebben gevochten. **Saskia van de Velde**, **Marieke Welzen** en **Nienke Lankheet**, bedankt voor de fijne samenwerking. Daarnaast wil ik **Angela Colbers** danken voor het heldere licht dat ze heeft geworpen op de farmacokinetische data en analyses. Leden van **het Consortium** (o.a. **Harry**, **Marjan**, **Tim**, **Venesa**, **Joyce**, **Dagmar**, **Emanuel**, **Luuk**, **Dyonne**); met vallen en opstaan en vechten tegen de achterblijvende rekruteringscijfers hebben we, volgens mij, een prachtig project neergezet. Ik vond het een eer om hier deel van te mogen uitmaken.

Alle arts-assistenten en klinisch geriaters, en met name **Marianne** en **Jurgen**, die me ook tijdens mijn onderzoeksperiode vaak uit de brand hebben geholpen; dank voor jullie interesse, ondersteuning en vooral relaxte overgang terug naar de klinische praktijk.

William, jouw charmes, grijze haren en vlotte babbel hebben menig vrouwelijk patiënt het hoofd op hol gebracht. Niet alleen heb je hart voor je patiënten, je hebt ook een wonderbaarlijk talent voor rekruteren van proefpersonen. Jouw bijdrage is onbetaalbaar geweest.

Dankzij alle onderzoekers van de afdeling Geriatrie heb ik een fantastische tijd gehad! Een superleuke groep, waarmee menig koffiepauze, pubquiz en nacht van de professoren volledig uit de hand kon lopen! In het bijzonder wil ik mijn kamergenootjes **Gerrita**, **Sharon**, **Daan**, **Saskia**, **Marit**, **Lonneke**, **Lotte, Linda, Kim en Sondra** bedanken voor de ontzettend leuke tijd die ik met ze heb gehad en voor het geduld dat ze af en toe voor mij moesten opbrengen.

Lieve **Aisha**, mijn maatje van het eerste uur. Ondanks dat we ongeveer opgesloten zaten in ons 'hokje' op de afdeling, heb ik me geen moment verveeld dankzij jou! Ik bewonder je openheid, oprechtheid en natuurlijk je onderzoekstalent. Wat ben je ongelofelijk slim. Menig maal heb je me uit de brand geholpen toen ik als ware alpha weer ruzie had met SPSS. Ik zie je minder vaak dan ik zou willen, maar ik wens je al het geluk in je onderzoekscarrière en natuurlijk met je prachtige gezinnetje.

Lieve **Annelien**, je begon als onderzoeksassistent, maar transformeerde je als snel tot onderzoeker, projectmanager, rekruterings-kampioen, 'personal assistant' (sorry) en bovenal mijn vriendin. Het leukste gedeelte van dit promotietraject was de tijd dat jij onderdeel van het team uitmaakte. Je voelt me haarfijn aan en bent niet zo snel onder de indruk van mijn gezeur en uitspattingen. Natuurlijk is sushi-candy niet voldoende om je hiervoor te bedanken. Je bent geweldig! ZTWK!

Ook mijn vrienden en familie wil ik bedanken: voor het aanhoren van mijn frustraties en mijn gebedel om onnodig schouderklopjes (ik ken mezelf), maar vooral voor het allernoodzakelijkste waarmee je een promotietraject heelhuids door komt: afleiding!

Natuurlijk de gezelligste mensen van Nijmegen Atletiek: **Leonie**, **Evelien**, **Debby**, **Jeanine en Freek N** en in het bijzonder mijn marathon buddies **Freek**, **Jan** en **Yves**; ik zou met plezier zelfs de Dijkenloop marathon lopen, als het maar met jullie is!

Lieve **Lotti**, **Maud, Eefje** en **Myrte**, mijn vriendinnen vanaf de kleuterschool. Het is mooi dat we ieder onze eigen kant op zijn gegaan en we toch altijd weer bij elkaar terugkomen. Fijn dat jullie ook bij deze belangrijke gebeurtenis in mijn leven aanwezig willen zijn.

Lieve **Lonneke**, **Saskia**, **Lindy** en **Ronne**, dank jullie wel voor ruim tien jaar vriendschap. Wat hebben we in die jaren veel meegemaakt. Van mooie (studenten)feestjes tot koophuizen en baby's. Fijn dat jullie altijd in de buurt zijn. **Lonnie**, wat vind ik het een eer dat je mijn paranimf wilt zijn.

Mijn lieve broers, **Len** en **Ron**, dank voor jullie onvermoeide pogingen mij met beide benen op de grond te laten staan. Af en toe had en heb ik jullie nuchtere commentaar nodig. Met jullie voelt het altijd fijn om thuis te komen.

Lieve **Albert**, mijn maatje. Jij weet me altijd op te vrolijken met je enthousiaste en grappige verhalen. Als jij ergens bent straalt de kamer van de energie. Ik bewonder jouw levenslust, doorzettingsvermogen en discipline. Dankjewel dat je me al die jaren hebt ondersteund, geadviseerd en gestuurd als dat nodig was. Je bent lief.

Lieve **Pap** en **Mam**, al die jaren hebben jullie me ondersteund en mijn frustraties, geklaag en enthousiasme aangehoord. Heel erg bedankt voor jullie interesse in alles wat ik doe. Papa, terwijl Mama al mijn verhalen aanhoort en mij van advies voorziet, steun jij me door het feit dat je er altijd bent als ik je nodig heb en door mij te wijzen op fantastische muziek en concerten. Deze muzikale opvoeding is een rode draad in mijn leven. De lyrics in dit proefschrift heb ik voor jullie uitgekozen. Ik hou van jullie.

List of publications

Listed in this thesis

Geke A.H. van den Elsen, Amir I.A. Ahmed, Michiel Lammers, Cornelis Kramers, Robbert Jan Verkes, Marjolein A. van der Marck, Marcel G.M. Olde Rikkert. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. *Ageing Research Reviews* 2014, 14:56-64.

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* Shared first authorship

Geke A.H. van den Elsen, Lieke Tobben, Amir I.A. Ahmed, Robbert-Jan Verkes, Cornelis Kramers, Radboud M. Marijnissen, Marcel G.M. Olde Rikkert, Marjolein A. van der Marck. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: a randomized controlled crossover trial. *Submitted.*

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Amir I.A. Ahmed, Marjolein A. van der Marck, Geke A.H. van den Elsen, Marcel G.M. Olde Rikkert. Cannabinioids in late-onset Alzheimer's disease. *Clinical Pharmacology and Therapeutics* 2015, 97(6):597-606.

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Curriculum vitae

Geke van den Elsen was born October 5th 1985 in Deurne and grew up in Asten, The Netherlands. In June 2004, she graduated from pre-university secondary school (Varendonck College, Asten). Thereafter, she studied medicine at the Radboud University Nijmegen. During her study, she worked at the department of Psychiatry of the Radboud university medical center (Radboudumc), as a research assistant on a study project on the early diagnosis of ADHD. Furthermore, Geke performed a scientific internship at the Miami Project to Cure Paralysis at the University of Miami (Florida) focusing on the effects of obesity on energy expenditure of wheelchair propulsion in patients with spinal cord injury. In December 2010, she received her medical degree (MD) and started as a PhD student at the department of Geriatric Medicine at Radboudumc. Up to June 2014 she performed the studies presented in this thesis under supervision of prof. Marcel Olde Rikkert and prof. Robbert-Jan Verkes. Since October 2014 she has been working as a resident in geriatric medicine.

Geke van den Elsen werd geboren op 5 oktober 1985 in Deurne en groeide op in Asten. In 2004 behaalde zij haar atheneum diploma aan het Varendonck College te Asten, waarna ze startte met de opleiding geneeskunde aan de Radboud Universiteit Nijmegen. Tijdens deze studie heeft zij als onderzoeksassistent gewerkt op de afdeling psychiatrie van het Radboud universitair medisch centrum (Radboudumc), binnen een onderzoek naar vroegtijdige diagnosestelling van ADHD. Daarnaast heeft Geke een wetenschappelijke stage gelopen aan het Miami Project to Cure Paralysis van de Universiteit van Miami (Florida), waar zij onderzoek deed naar de effecten van overgewicht op het energieverbruik van patiënten met een dwarslaesie. De opleiding geneeskunde heeft ze in december 2010 afgerond, waarna zij heeft gewerkt als promovendus op de afdeling Klinische Geriatrie van het Radboudumc. De studies die ze daar uitvoerde, onder begeleiding van prof. Marcel Olde Rikkert en prof. Robbert-Jan Verkes, hebben geresulteerd in dit proefschrift. Vanaf oktober 2014 is zij in opleiding tot klinisch geriater.

Donders Graduate School for Cognitive Neuroscience Series

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