Efficacy and safety of delta-9-tetrahydrocannabinol (delta-THC) in behavioural disturbances in dementia

Published: 13-03-2012
Last updated: 26-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39470

Source
ToetsingOnline

Brief title
delta-THC in dementia

Condition

- Other condition
- Dementia and amnestic conditions

Synonym
Alzheimer's disease, Dementia

Health condition

probleemgedrag

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: EFRO subsidie + Provincie Gelderland&Overijssel subsidie

Intervention

Keyword: Cannabis, Dementia, Neuropsychiatric symptoms, Pain

Outcome measures

Primary outcome

Primary study parameter: Neuropsychiatric Inventory (NPI)

In the current study, the neuropsychiatric inventory (NPI) is selected as the primary outcome measure, as this tool has been accepted as the standard measure of NPS in most clinical trials, due to high validity, good inter-rater reliability, high internal consistency and its sensitivity to drug treatment effects. In clinical practice as well as clinical research the NPI is the most commonly used instrument to assess behavioral changes. The NPI evaluates 12 behavioral domains (e.g. agitation/aggression and motor disturbance). The frequency and severity of these behaviors is scored by the caregiver. The product of frequency and severity of each of the domains is used as the final score and ranges from 0 to 144 (with a maximum of 12 points per domain). A decrease in 4 points in NPI-baseline score is regarded as minimum clinically important difference (MCID).

Secondary outcome

Secundary study parameters

1. Behaviour

- Cohen Mansfield Agitation Inventory (CMAI): validated instrument, specifically developed to measure agitation and agressive behaviour in people with dementia

2. Pain:

- Pain Assessment Checklist for Seniors with Limited Ability to Communicate Dutch version (PACSLAC-D): a observation scale for assessment of pain behavior.
- Verbal Rating Scale (VRS): a self-reporting scale for assessment of pain intensity. It's a six point scale consisting of a list of phrases that describes increasing levels of pain intensity. The subject selects the phrase best characterizing their pain at that moment.

3. Other outcome measures

- Quality of Life-Alzheimer*s Disease Scale (QoL-AD): a 13 -item scale using four-point Likert-scales, completed by a caregiver interview. It is developed for assessment of quality of life in subjects with mild to moderate severe dementia.
- Barthel Index: an easy to conduct, 10-item scale which scores several primary activities of daily living.
- Caregiver Clinical Global Impression of Change (CCGIC): this a 7-point Likert scale that assesses global change from baseline by the caregiver.
- Paired Associates Learning test (PAL WMS-R): a verbal cognitive test for the assessment of episodic memory

4. Safety

Among other outcome measures: vital signs, physical examination, ECG,

hematology and biochemistry and adverse event checklist.

Study description

Background summary

The prevalence of Alzheimer*s disease (AD) is estimated to exceed 35 million worldwide and this will increase to 42 million by 2020. With this increasing prevalence, there will also be a substantial increase in patients with dementia who suffer from behavioural disturbances, such as agitation, aggression or aberrant motor behaviour. These symptoms are summerized as neuropsychiatric symptoms (NPS). NPS reduce patient's cognitive functioning and quality of life and increase caregiver's burden. NPS are often treated with antipsychotic drugs (APs). APs have only a modest efficacy and important side-effects, which result in extrapiramidal symptoms and increased risk of morbidity and mortality. Persistent pain can cause NPS. Due to a decreased cognitive and communicative ability, pain is often expressed in behavioural changes, such as repetitive movements, vocalizations and wandering. Alterations in pharmacokinetics, pain perception, communication and concurrent medication asks for an adequate and safe drug treatment in these older and frail patients.

There is evidence that THC has a positive effect on NPS. Unfortunately, there are only few trials studying the efficacy of THC in dementie patients. The cannabinoid agonist dronabinol (containing THC) was first found to improve agitation and appetite in dementia. Furthermore, several clinical studies show that cannabinoids are effective in treatment of neuropathic pain and spasticity in patients with Multiple Sclerosis (MS). Unfortunately, to our knowledge, no previous studies have been conducted to assess the efficacy of cannabinoids on pain in dementia patients.

The high prevalence of behavioural disturbances in persons with dementia, a clear interaction with persistent pain, the lack of appropriate drugs for treating this problem and the positive suggestions from preliminary clinical studies with THC directly fuel the study presented here. This will be a phase II study in which the efficacy and safety of Namisol® (a tablet with THC) behavioural disturbances in dementia patients will be evaluated. Secondarily, we will evaluate the effiacy on persistent pain in a subgroup of particpants.

Study objective

The primary objective is to evaluate the efficacy of Namisol® in the management of behavioural disturbances in patients with dementia.

Secondary objectives are:
- To evaluate the efficacy of Namisol® on secondary outcome measures, such as quality of life and functioning.
- To evaluate safety of Namisol® in this subject group, as assessed with physical examination and adverse event monitoring.
- For the subgroup of subjects suffering from pain: to evaluate the efficacy of Namisol® pain intensity.

It is hypothesized that Namisol® will lead to more reduction in NPS than placebo, as assessed with the neuropsychiatric inventory (NPI), especially on the domains agitation/aggression and motor disturbance. We expect this to be primarily due to psychoactive effects of Namisol® and secondary to a reduction in pain sensation. It is expected that behavioural disturbances will lead to better functioning in daily living and quality of life.

Study design

This is a randomized placebo-controlled double-blind parallel-group multicentre study

Subjects who appear to fulfill the eligibility criteria are informed about the study. After signing informed consent, a screening visit will take place. Subjects who are eligible for participation enter a wash-out period, for discontinuation of their own analgesic medication (only if applicable). Acetaminophen (PCT) 1000 mg three times daily will be started in this wash-out period, independent of the occurrence of pain complaints. Subjects will be randomly allocated to receive one of the two interventions (Namisol® 1.5 mg and PCT 1000 mg three times daily, or placebo and PCT 1000 mg three times daily) for a double-blind intervention period of three weeks. After two weeks treatment (day 14) the NPI and CCGIC will be assessed by telephone interview with the caregiver. Subjects and their caregivers visit the site twice (at baseline (day 0) and after three weeks treatment (day 21)) for assessments of the outcome parameters. For the purpose of compliance and safety, there will also be three phone calls, performed by the researcher during the intervention period. After completion of this intervention period subject*s own analgesic treatment will be restarted (if applicable). A follow up phone call will follow two weeks after last study medication intake for assessment of adverse events and pain complaints.

Intervention

Intervention phase:
first study arm: delta-9-THC (Namisol®) 1.5 mg three times daily +

acetaminophen 1000 mg three times daily for a period of three weeks
second study arm: placebo (tablet) three times daily + acetaminophen 1000 mg three times daily for a period of three weeks

Study burden and risks

THC is already widely used, among other indications as a registered analgetica in MS patients. THC is also used as study drug in dementia patients, which has resulted in a therapeutic effect in this patient group. Due to the current extensive knowledge of THC, it can be stated that the drug related risks are limited. Moreover, the current study will use significantly lower dosages of THC compared to the conducted studies.
Possible side effects (as described in the Investigator Brochure) are:
- dizziness
- somnolence
- tachycardia
- euforia
- changes in blood pressure (not specified)
It should be noted that older people are likely more sensitive to the psychoactive effects and effects on blood pressure.

Subjects and caregiver's burden mainly consists of several visits to the outpatient clinic. During this visit, mainly questionnaires will be conducted. During treatment at home, the subject will be asked to report their medication intake, side effects and pain intensity daily. The caregiver will be asked to assist the subject. The burden is believed to be proportional in relation to the considered problem for which this trial is instituted.
The burden of behavioural problems in dementia can be very large, for both patient and caregiver. This leads to a high disease related distress.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Subject has possible or probable dementia, type AD, VaD or AD/VaD, according to the criteria of NINCDS-ADRDA/NINCDS-AIREN or based on an expert panel decision.;- Clinical Dementia Rating (CDR) score 1 to 3 (mild to severe dementia).;- Clinically relevant behavioural disturbances existing at least one month prior to screening, defined as a score of >= 10 on the NPI, including presence of the domain agitation/aggression or motor disturbance.;- if applicable: subject agrees with temporarily stopping analgesic drugs for the duration of the study;- Informed consent by the subject and subject*s informal caregiver.

Exclusion criteria

- Dementia other than AD, VaD or AD/VaD;- Major psychiatric disorder ;- History of, or current drug abuse.;- Current alcohol abuse or unwillingness to use no more than 2 alcoholic consumptions daily ;- Severe (and/or unstable) concomitant or intercurrent illness;- Clinical or biochemical evidence of liver disease (ALT or AST >= twice the upper limit of normal) or known allergy to acetaminophen.;- Use of tricyclic antidepressants (TCA), carbamazepine or fluoxetine.;- Changes in dosage of antipsychotics, benzodiazepines or cholinesterase inhibitors within 2 weeks prior to intervention.

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-11-2012
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Namisol
Generic name:	delta-9-tetrahydrocannabinol (delta-9-THC)

Ethics review

Approved WMO Date:	13-03-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-05-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2013

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005289-39-NL
ClinicalTrials.gov	NCT01608217
CCMO	NL38617.091.12