The CanISleepinMS Study: Effect of cannabidiol (CBD) on sleep quality in patients with multiple sclerosis, a series of 15 randomised, placebo-controlled N-of-1 trials

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This study has been transitioned to CTIS with ID 2024-518280-35-00 check the CTIS register for the current data. To investigate the effect of CBD on MS patients with impaired sleep quality.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56335

Source
ToetsingOnline

Brief title
Effect of CBD on sleep quality in MS

Condition

- Other condition

Synonym
Sleep quality

Health condition

Slaapkwaliteit

Research involving
Human

Sponsors and support

Primary sponsor: Wageningen Universiteit
Source(s) of monetary or material Support: Nationaal MS Fonds

Intervention

Keyword: cannabidiol, multiple sclerosis, N-of-1 trials, sleep

Outcome measures

Primary outcome

Insomnia Severity Index (ISI) score

Secondary outcome

Diary measurements (sleep-related outcomes: number of awakenings (NA), Sleep Onset Latency (SOL), Sleep Efficiency (SE), Wake time After Sleep Onset (WASO), Total Sleep Time (TST); non-sleep outcomes: changes in number of nocturnal voidings, number, type, and severity of adverse events (AEs);

Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Checklist Individual Strength Fatigue-subschaal (CIS-F);

Keystroke features of the Neurocast® App, a 24/7 digital measure of fatigue, rest and activity patterns, and daily functioning based on dynamics of keyboard key strokes on personal smartphones; furthermore answers on daily pop-up questions for Numeric Rating Scale (NRS) scores for pain, spasms, and fatigue;

Study description

Background summary

The high prevalence of impaired sleep quality in multiple sclerosis (MS) has an impact on the patient*s quality of life and disease burden. Therapeutic options include cognitive behavioural therapy and the use of hypnotics. The former is considered a cornerstone but is not widely available and is labour-intensive.The use of hypnotics can be problematic as their long-term use can be associated with tolerance, dependence and side effects.Data from pre-clinical studies and reports from case-studies - albeit of varying quality - have attracted the attention of patients and practitioners to use cannabis products as an alternative option. A medicinal cannabis preparation, registered as Sativex® containing tetrahydrocannabinol (THC) and cannabidiol (CBD) is already available as additional treatment of specifically spasticity in MS. Reports from patients, patient organisations and health care professionals, underlined by patient surveys consistently suggest widespread use of uncontrolled cannabis products - inevitably of varying quality - by MS patients, with the aim of improving their sleep quality. To date, there is no substantial evidence of cannabinoid effectiveness on human sleep quality. Furthermore, the THC component of cannabis has psychoactive, cardiovascular, and addictive properties.12 In contrast, the non-psychoactive CBD component has a considerably better safety profile next to the potential to improve several physiological conditions, including sleep.Therefore, we want to investigate the effect of CBD on sleep quality in MS patients in the present study.

Study objective

This study has been transitioned to CTIS with ID 2024-518280-35-00 check the CTIS register for the current data.

To investigate the effect of CBD on MS patients with impaired sleep quality.

Study design

A series of 15 N-of-1 trials investigating the effects of CBD in MS patients with chronic impairment of sleep quality. Each N-of-1 trial will consist of two crossover studies performed in a single patient. Within a crossover, the interventions with either CBD or placebo are randomised and double blinded. After a run-in period of 2 weeks, there will be 4 treatment periods of 3 weeks, separated from each other by a washout of 1 week.

Intervention

In week 1 of the treatment phase, trial participants take either a solution of CBD (10% w/v) in almond oil for oromucosal administration at a dose of 150 mg once daily or a placebo, 30 minutes before going to bed at night. In weeks 2 and 3 of the treatment phase, trial participants take either a solution of CBD (10% w/v) in almond oil for oromucosal administration at a dose of 300 mg once daily or a placebo, 30 minutes before going to bed at night.

There are 4 treatment periods of 3 weeks, separated by a wash-out period of 1 week.

Study burden and risks

With respect to patient burden the following key figures are of relevance. The total study duration for a single participant will be 18 weeks consisting of a run-in period of 2 weeks, 4 treatment periods of 3 weeks which are separated by a washout period of 1 week, and a last contact moment in week 18. There will be a first physical appointment in the Rijnstate Hospital for screening, and blood will be taken. Halfway through the study and at the end there will be another two physical appointments for blood sampling.
Furthermore, during the 16 week-lasting intervention phase the participant is required to collect measurements as planned in the protocol, which will take time and effort. First, each day a participant is required to record sleep- and non sleep-related outcomes in a digital diary. Once a week the diary recordings have to be sent to the research assistant. Subsequently, the participant will be contacted by telephone by the research assistant about these recordings to discuss and, if desired, further elaborate on the experiences and to check how the participant is doing. In addition, the participant will be provided with questionnaires by the study nurse weekly. The participant will also be required to install a 24/7 digital recording app (NeurokeysR) on his/her mobile phone which monitors keyboard key stroke patterns. Sometimes it takes some time to get used to this keyboard . The data recorded will be extracted by the study nurse at the end of the run-in period and after each treatment period.
Another element of patient burden is that the participant should be willing to comply with the requirements of the study protocol, among which being willing to take a purified CBD product or a placebo once daily, 30 minutes before going to bed in the evening.

Risks associated with participation are minimal. CBD is considered non-toxic, non-psychoactive, and non-addictive. Adverse effects reported in animal studies are associated with doses far exceeding those recommended for humans. The maximum dose foreseen in our study of 300 mg CBD once daily is also substantially lower than the maximum dose of twice daily 10 mg/kg body weight of an approved medicinal CBD preparation to control seizures, Epidiolex® (in an 80-kg person this corresponds to 800 mg twice daily). Of relevance would be a risk of CBD- drug interactions to occur as CBD is known for its inhibitory effects on some cytochrome P450 (CYP450) and UPGT-enzymes (glucuronidation) next to serving as a substrate of CYP450 enzymes itself.A change in effectivity of drugs respectively CBD may be the consequence. In Appendix C1 an overview is given of medications interacting with CBD.Before final enrolment of a patient, the potential risk of interactions will be evaluated by the study pharmacist.

This study will create more insights into the effects of CBD on sleep quality in MS. The results This study may benefit sleep quality of the individual participants and prevent them from experimenting with freely available cannabis

products of varying quality, which may lead to unexpected side effects because of the high prevalence of impaired sleep quality accompanied with daytime consequences in the MS population. Thus, this study may create more insight into the effects of a safe CBD product on sleep quality of MS patients.

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

• A diagnosis of MS confirmed by a neurologist, based on the revised 2010 or 2017 McDonalds criteria • Relapsing-remitting or primary or secondary progressive MS • Expanded Disability Status Scale (EDSS) score < 7.5 • No relapse for at least 6 months before the screening visit • No changes in immunomodulating therapy stable for at least 3 months before the screening visit; no changes in use of other medications used for chronic conditions for

at least 6 weeks before the screening visit (e.g. anti-depressant drugs, antidiabetics) • Age minimally 18 years at the time of screening • Body Mass Index (BMI) < 35.0 kg/m2 at the moment of screening. • Elevated levels of transaminases (ALAT, ASAT) until twice the Upper Limit of Normal (2x ULN) are allowed, as elevation of these levels is a common finding in MS patients. • No plans to (be involved in) getting pregnant during the trial. • No breast feeding during the trial • A complaint of chronic impairment of sleep quality, leading to a diagnosis of insomnia by an MS neurologist and an experienced somnologist. In this context, insomnia is defined as difficulties initiating and/or maintaining sleep or too early awakenings, despite adequate opportunity and circumstances for sleep, resulting in some form of daytime impairment. Causes include psychophysiological insomnia, insomnia due to mental disorders like depression, and insomnia secondary to other MS-related symptoms like spasticity, pain or nocturnal voidings. Diagnosis will be based on fulfilment of the ICDS-3 criteria of insomnia and an ISI score of minimally 15 (threshold for clinical insomnia). • Continuation of pharmacological treatments will be at the discretion of the study physicians. • Willing and able to refrain from new, sleep-facilitating pharmacological treatments until the end of the treatment phase of the study • Willing and able not to use any other cannabis product until completion of the study • Willing and able not to use any supplement that could promote sleep (e.g. L-tryptophan, valerian, melatonin) during the treatment phase of the study. • Continuation of non-pharmacological treatments will be at the discretion of the study physicians. • Willing and able to refrain from new, sleep-facilitating non-pharmaceutical interventions until the end of the treatment phase of the study. Lifestyle should be kept as stable as possible. • Willing and able to give informed consent • Willing and able to fill in a daily digital diary during the treatment phase, to send this to the study nurse or research assistant once a week, and to be contacted by the research assistant minimally twice a week during the treatment phase of the study • Willing and able to use the Neurokeys app (thus mobile phone) daily • Willing to have blood sampled at the screening visit and have another two blood draws during the treatment phase of the study • Willing and able not to drive a car or operate machinery within 8 hours after intake of the investigational product until the end of the treatment phase of the study • Willing and able not to do evening/night shift work and not to cross time zones until the completion of the study • Willing and able to refrain from excessive use of excessive use of caffeine (> 1 cup of coffee or 1 serving of energy drink) and alcohol (> 1 serving) in the evening, 6 hours before going to bed • Willing and able to refrain from (products of) grapefruit, Seville oranges (used in marmalade), limes and pomelos during the treatment phase of the study. • Willing and able to refrain from experimenting with timing and type of diet, and beverages during the treatment phase of the study. A participant*s dietary intake pattern should be kept as stable as possible during the treatment phase as there are numerous dietary components other than furanocoumarins that may influence CBD bioavailability

Exclusion criteria

• Circadian rhythm sleep-wake disorders, sleep related breathing disorders (such as moderate to severe obstructive sleep apnea, central breathing disorders during sleep, or sleep-related stridor that require prompt specific treatment), current delayed sleep phase syndrome where wake up time is regularly later than 8.00 a.m., or a sleep problem fulfilling the ICSD3 criteria of parasomnias • Good response to initial treatment for the assessed sleep disorder • Use of a benzodiazepine or other sleep medication, unless the patient has tapered off the sleep medication before the moment of inclusion • Liver disease or blood levels of transaminases (ALAT, ASAT) above 3x ULN, as long term administration of high doses of CBD may affect (although reversible) liver function • History of severe psychiatric comorbidity • Increased risk of suicidal thoughts or behaviour • History of drug or alcohol abuse • Known or suspected hypersensitivity to cannabinoids or to excipients of the formulation of the investigational product - almond oil • History of use with CBD oil prepared by pharmacy Clinical Cannabis Care • Structural or recreational use of a cannabinoid product < 2 months before screening • Whether the use of any of the following medications is a reason for exclusion will be at the discretion of the study physicians and delivery pharmacist. o drugs with risk of liver injury; the decision of exclusion will be made in consultation with the MS neurologists and the pharmacist that provides the CBD product. o drugs with risk of interaction with CBD. Data on the potential drug-CBD interactions below are based on mechanistic and clinical studies: • Drugs of which their biotransformation is primarily dependent on the cytochrome P450 enzymes CYP2C19 and CYP3A • Drugs that are inducers or inhibitors of enzymes of which CBD is a substrate: CYP2C19, CYP3A4.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-07-2024
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	20-11-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-08-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2024
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
EU-CTR	CTIS2024-518280-35-00
EudraCT	EUCTR2022-002372-36-NL
CCMO	NL83212.091.22