THE IMPACT OF PSILOCYBIN ON PAIN IN FIBROMYALGIA PATIENTS: A MULTICENTER TRIAL

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This study has been transitioned to CTIS with ID 2024-516890-63-00 check the CTIS register for the current data. Primary Objective: The primary objective is to assess the effects of low psilocybin doses on pain perception in FM patients and their…

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

Summary

ID

NL-OMON55974

Source
ToetsingOnline

Brief title
THE IMPACT OF PSILOCYBIN ON PAIN IN FIBROMYALGIA

Condition

- Other condition

Synonym
Fibromyalgia

Health condition

Fibromyalgia

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: fibromyalgia, pain, psilocybin

Outcome measures

Primary outcome

Primary outcomes will be subjective and objective measures of pain endurance

and pain threshold (i.e.,Pressure Pain Threshold Cold, Pressor Test, BPI).

Secondary outcome

Secondary measures will assess the effects that placebo and psilocybin will

have on mood, cognition and psychedelic experience. The employed tests will be

the following:

Visual Analogue Scale (VAS), Profile of Mood States (POMS), Clinical

Administered Dissociative States Scale (CADSS), Brief Symptoms Inventory (BSI),

Altered States of Consciousness (5D-ASC), Ego Dissolution Inventory (EDI),

Blood pressure (BP), Heart rate (HR), Multifaceted Empathy Test (MET),

Alternate Use Test (AUT), Digit Symbol Substitution Test (DSST), Psychomotor

Vigilance Task (PVT), Brief Pain Inventory (BPI).

Study description

Background summary

Serotonergic psychedelics are substances whose primary mechanism of action is the activation of the serotonin 5-HT2A receptor (1-5). They are considered safe when administered in appropriately controlled settings (6,7) and are used for

recreational and spiritual purposes because of their effects on consciousness (8). Recent clinical studies suggest clinical effectiveness in treating a range of conditions such as treatment resistant depression (9,10), anxiety and depression in end-of-life settings (11,12), tobacco addiction (13,14), alcohol addiction (15).

The earliest attempt at testing these agents to treat pain dates back to the *60s and involved patients suffering from neuropathic, ischemic or cancer-related pain (16). In a prospective non-randomised trial, authors compared the efficacy of 0.1 mg of LSD with hydromorphone HCl, 2 mg., and meperidine HCl, 100 mg. Results showed greater analgesic action of LSD compared to the other drugs. Shortly after, another case series involving 128 terminal patients treated with the same dose resulted in immediate and sustained (3 weeks) pain reduction (17). In a pre-post, no control group clinical study with 60 cancer patients, Grof et al. (18) observed that LSD-assisted psychotherapy led to improvements in pain ratings. Fanciullacci et al. (19) investigated the effects of a sub-hallucinogenic dose of LSD (25 µg) in a case series populated by 7 patients suffering from phantom limb pain, and reported improvements in 5 of them. Furthermore, patients experienced rare, transient and mild psychic reactions.

As in other areas of application, these kinds of studies were halted for political reasons as a consequence of the Controlled Substances Act of the Comprehensive Drug Abuse Prevention and Control Act and it is only in the last decade that we witnessed a resurgence of interest in psychedelic research (20). A retrospective survey recruiting 53 individuals who met the International Classification of Headache Disorders-2 criteria for cluster headache and who reported psilocybin or LSD use to self-medicate, provided preliminary evidence on the potential of such agents (21). More specifically, participants reported that a single non-hallucinogenic dose of LSD or three non-hallucinogenic doses of psilocybin were often sufficient to abort attacks, induce the termination of episodes and extend the duration of remission periods. Analogous results were obtained via the Clusterbuster.org survey (22), a larger cross-sectional retrospective survey aimed at characterizing the effects of conventional and complementary therapies for cluster headaches. The survey included data from 496 responders and results indicated that psilocybin and LSD were comparably or more efficacious than conventional treatments. More specifically, participants - who were recruited through cluster headache websites and headache clinics - reported that the serotonergic agents caused cluster periods to shorten, aborted attacks and led chronic cluster headaches into remission. Interestingly, even infrequent sub-hallucinogenic doses of psilocybin were described as efficacious. Again, similar results were found in a smaller sample survey (23). A recent randomised, double-blind, placebo-controlled, within-subjects study with healthy volunteers showed immediate (1.5h after administration) and stable (5h after administration) improvements in pain tolerance and ratings of unpleasantness after the administration of 20µg of LSD (24). Effects sizes were medium to large and were comparable to those obtained after the administration of oxycodone (25) or morphine (26). Earlier research (27) suggests that these analgesic effects may outlast the 5h time window that

was considered in the study. Patients reported small increases in anxiety, somatisation, amnesia, depersonalisation, derealisation and dissociation ratings. Taking into account recent studies indicating that 26µg of LSD tartrate does not affect or mildly affects cognitive function, mood, perception and state of consciousness (28,29), authors suggest that such effects would not interfere with daily functioning.

Recent hypotheses maintain that the effectiveness of psychedelics in various areas of clinical relevance is based on an enhancement of neuroplasticity (30) and, consequently, of environmental sensitivity (31,32). A possible correlate of this phenomenon is the increase in suggestibility that was observed in individuals who took LSD (33). While evidence seem to indicate that hypnotic suggestions may lead to a certain degree of relief in patients suffering from both procedural and chronic pain (34,35), such techniques were never tested as potential tools to improve the effectiveness of psychedelics in both the fields of psychiatry and pain management.

Fibromyalgia (FM) is a syndrome characterised by widespread pain, fatigue, sleep disturbances and cognitive impairment that imposes a considerable burden on patients* quality of life (QOL) (36,37) along with high direct and indirect costs (38-40). Comorbid depression is common (41,42) as well as high anxiety (43). With a prevalence between 0.2% and 6.6% (44) in the general population, it is the second most common rheumatological disorder (45) and its diagnostic criteria have changed in recent years. Current guidelines require the fulfilment of 3 conditions (46): a) Widespread Pain Index >= 7 and Symptom Severity Score >= 5 or Widespread Pain Index between 3-6 and Symptom Severity Score >= 9; b) Symptoms have been present at a similar level for at least 3 months; c) The patient does not have a disorder that would otherwise sufficiently explain the pain. While multifocal pain is considered the primary manifestation of the condition, its other clinical features led to its inclusion in a group of diagnoses called central sensitivity syndromes which contain irritable bowel syndrome, chronic fatigue syndrome and temporomandibular joint dysfunction among others (47). More specifically, current consensus holds that FM results from augmented sensory and pain processing as evidenced from lower thresholds for pain, heat, cold, electrical and auditory stimuli (45). Its primary causes are considered to reside in dysfunctions of both descending and ascending neural pathways resulting in decreased pain inhibitory functions and facilitated pain signalling (48,49). Among other factors responsible for the pathogenesis of FM, evidence points to mechanisms related to peripheral neuro-inflammation (50) that may be triggered by trauma and/or psychological stress, oxidative stress (51), poor sleep quality (52) and vitamin deficiency (53-56). Recent evidence emphasises the role of factors such as resilience (57), psychological trauma (58), auto-immune reactions (59), gut microbiome (60), neuromuscular efficiency (61,62) and neuroendocrine dysregulation (63).

Twin studies suggest that half of the risk of developing fibromyalgia is due to genetic factors (64). More specifically, genes responsible for the serotonin receptor 2A region of chromosome 13, the serotonin transporter gene regulatory region, and the HLA region of chromosome 6 (65) along with polymorphisms of

catecholamine methyltransferase (COMT), dopamine-D-3 receptor and adrenergic receptor genes (66).
Multiple treatments have been proposed for FM including exercise (67), electrotherapy (68), pharmacological therapies (69), cognitive-behavioural therapy (70), mindfulness (71,72) and mindfulness-based stress reduction (73), attachment-based compassion therapy (74) and acupuncture (75). Despite the variety of options, a recent meta-analysis reveals that only some of these therapies are associated with small improvements in pain ratings and QOL and concludes that evidence is still lacking for most of them (76).
Given the current need of effective treatments for FM and the analgesic potential that low, non-hallucinogenic doses o

Study objective

This study has been transitioned to CTIS with ID 2024-516890-63-00 check the CTIS register for the current data.

Primary Objective: The primary objective is to assess the effects of low psilocybin doses on pain perception in FM patients and their association with BDNF levels.

Secondary Objective(s): The secondary objective is to assess the impact of low psilocybin doses on mood, cognition, personality, autobiographical memory functioning and psychedelic experience. We will also test whether hypnotic suggestions can moderate the potential effects of psilocybin on pain perception and tolerance. Finally, we will test whether the plasma levels of inflammatory biomarkers (IL-1α, IL-1β, IL-6, IL-8, and TNF-α, C-reactive protein (CRP)) will decrease in response to psilocybin administration.

Study design

The study will use a double-blind, placebo controlled, design. 35 FM patients will receive placebo and 2 different doses of psilocybin (5 or 10 mg) in a randomized design. Effects on pain perception, mood and cognitive performance will be repeatedly measured throughout the study day. Data will be collected in two collaborating centres: 1) the department of Neuropsychology and Psychopharmacology, FPN (Maastricht) and the department of Anaesthesiology, LUMC (Leiden).

Intervention

35 FM patients will receive placebo and oral doses of 5 mg or 10 mg of psilocybin in a double-blind, randomized, placebo-controlled design. All participants will receive a brief hypnotic induction aimed at producing analgesia before the second administration of CPT.

Study burden and risks

Prior to participation, subjects will have to sign the informed consent form, after which they will be requested to fill out a drug and medical questionnaire. Eligible subjects are invited for a physical examination (including medical examination, medical history anamnesis, ECG). Routine laboratory blood tests (10ml) are performed at the screening examination including creatinine, ASAT, ALAT, hemoglobin, hematocrit, white blood cell count, red blood cell count, and platelet cell count. Urine tests for urine drug screens as well as pregnancy tests in women will be performed. The recruitment process will be supervised by Prof. Albert Dahan MD who has clinical experience in diagnosing and treating patients suffering from FM. When there is no medical objection for participation, subjects will be included into the study and invited to a training session during which they will be familiarized with the study procedures, questionnaires and trained on the cognitive tasks. In case of incidental medically relevant findings, the study physician will contact the subject and discuss further steps. All participants will then be advised to contact their general practitioner (GP). FM patients* GPs will be directly informed of the participation by the researchers. Participants will also be informed about and familiarized with the study procedures, used questionnaires will be explained, and they will be trained on the cognitive tasks.

Each of the 3 test sessions lasts for 7h. Subjects will arrive at 9 AM at the test site. Subjects are requested to have a light breakfast at home (no caffeine). Pregnancy, drug, and alcohol screens will be performed first, using a urine pregnancy and drug test and breathalyzer. In case of a positive screen for pregnancy or cannabis, cocaine, alcohol, opiates, benzodiazepine, methamphetamine or amphetamine, subjects will be sent home to return to the laboratory at a later time. In case tests are negative, an indwelling intravenous catheter will be inserted into a subcutaneous vein of the forearm and baseline measures will be obtained. Psilocybin or placebo will be administered at 10 AM. Outcome measures will repeatedly be assessed during the study session.

For pharmacokinetic analyses, venous blood samples (8x5 ml, Lithium Heparin, per study day) will be collected at baseline, and at regular times after treatment to determine psilocin plasma concentration (see Table 1). IL-1α, IL-1β, IL-6, IL-8, and TNF-α plasma concentrations will be determined using bead-based multiplexing technology using a XMAG- Luminex assay (Bio-Rad, Hercules, California, USA) (Bio-Plex Pro Human Cytokine Kit Panel). Blood samples for plasma concentration and analysis of inflammatory biomarkers will be centrifuged and plasma will be frozen at -20°C until analyses for pharmacokinetic assessments. Whole blood samples will be taken to measure brain-derived neurotrophic factor (BDNF; 4x 5ml, EDTA blood per study day) and the analysis of microRNA expression levels in brain derived extracellular

vesicles (BDEVs; 3x 5ml EDTA blood per study day). BDNF and microRNAs expression levels in BDEVs will be measured 4 times per study day (see Table 1). EDTA plasma samples will be centrifuged and stored at -80°C until biochemical analyses are performed. For the complete study we will collect 225 mL of blood which is about half a blood donation. These samples will be sent to the analytical lab in several batches during the study.

Subjects will be under continuous medical supervision until 6h after drug administration and if necessary, will be additionally supervised until any alterations of consciousness have completely subsided (<10% of maximum effects on the VAS). There will be a washout phase of at least 5 days between each study day. The risk of lasting psychological and physical harm is considered low. The most important acute adverse effects of a high dose of psilocybin are anxiety and panic attacks, and with regard to somatic effects increased heart rate.

The risk of lasting physical and psychological harm is considered low (87,91-96). With regard to subjective distress after psilocybin, experiencing an altered state of consciousness may produce transient anxiety and some tolerable adverse effects (86). FM participants may experience reductions in pain perception. Experiencing the altered state of consciousness under psilocybin reportedly has lasting positive effects (103) such as decreased depression (105) and anxiety (106); improved openness, social relations, altruism (107,108), mood (8,88,109,110), mindfulness (111) and quality of life (8,112,113). Furthermore, based on other studies with psilocybin, subject will mostly experience pleasure and positive alterations in their state of mind (103). Subjects may also participate because they have an interest in this specific experience which is expected to be of some personal value (103).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Age between 18 and 65 years
• Normal weight, body mass index (weight/height2) between 18 and 30 kg/m2
• Fulfilment of the American College of Rheumatology criteria for FM diagnosis
• A minimum NRS pain score of 5 out of 10
• Proficient knowledge of the Dutch or English language
• Written Informed Consent
• Understanding the procedures and the risks associated with the study
• No use of regular use of psychotropic medication such as opiates, antidepressants, muscle relaxants, anticonvulsants, sleep aids, benzodiazepines. Non pharmacological regimens will be allowed along 1 rescue therapy such as acetaminophen <=4,000 mg/day, ibuprofen <=1,200 mg/day, naproxen <=660 mg/day, or ketoprofen <=75 mg/day. Use of paracetamol (PCM) and non-steroidal anti-inflammatory drugs (NSAIDS) will be allowed and monitored.
• Willingness to refrain from taking psychoactive substances during the study.
• Willingness to drink only alcohol-free liquids and no coffee, black or green tea, or energy drinks after midnight of the evening before the study session, as well as during the study days
• Willingness not to drive a traffic vehicle or to operate machines within 24 h after substance administration

Exclusion criteria

Fibromyalgia Patients:

• Presence of any other painful condition such as inflammatory rheumatic diseases, migraines or headaches and of other chronic or acute medical conditions
• Presence of any other psychiatric condition such as primary major depressive

disorder, anxiety disorders or substance use
disorder.
• Have a history of psychotic or bipolar disorders

• Previous experience of serious side effects to psychedelic drugs (anxiety or
panic attacks)
• Tobacco smoking (>20 cigarettes per day)
• Excessive drinking (>20 alcoholic consumptions per week)
• Psychotic disorder in first-degree relatives
• Pregnancy or lactation
• Hypertension (diastolic >90 mmHg; systolic >140 mmHg)
• History of cardiac dysfunctions (arrhythmia, ischemic heart disease*)
• For women: no use of a reliable contraceptive

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2022
Enrollment:	35
Type:	Anticipated

Ethics review

Approved WMO

Date:	22-12-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-01-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-04-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-06-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	CTIS2024-516890-63-00
EudraCT	EUCTR2021-002909-10-NL
CCMO	NL78008.068.21