RESEARCH PROTOCOL

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

PROTOCOL TITLE : The impact of psilocybin on pain in fibromyalgia patients: a multicentre trial.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

5D-ASC	**5 Dimensions of Altered States of Consciousness**
AE	**Adverse Event**
AR	**Adverse Reaction**
AUT	**Alternate Use Test**
BDNF	**Brain-Derived Neurotrophic Factor**
BFI	**Big Five Inventory**
BPI	**Brief Pain Inventory**
CEQ	**Credibility Expectancy Questionnaire**
COMT	**Catecholamine Methyltransferase**
CPT	**Cold Pressor Task**
DSMB	**Data Safety Monitoring Board**
DSST	**Digit Symbol Substitution Test**
ECG	**Electrocardiogram**
EudraCT	**European Drug Regulatory Affairs Clinical Trials**
FIQ	**Fibromyalgia Impact Questionnaire**
FM	**Fibromyalgia**
IRI	**Interpersonal Reactivity Index**
LSD	**Lysergic Acid Diethylamide**
MET	**Multifaceted Empathy Test**
METC	**Medical Research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)**
MODTAS	**Modified Tellegen Absorption Scale**
NSAIDS	**Non-steroidal anti-inflammatory drugs**
NRS	**Numeric Rating Scale**
POMS	**Profile of Mood States**
PCM	**Paracetamol**
PPT	**Pressure Pain Threshold**
PVT	**Psychomotor Vigilance Task**
QOL	**Quality of Life**
SAE	**Serious Adverse Events**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
TEC	**Treatment Expectations in Chronic Pain Scale**

VAS	**Visual Analogue Scale**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Recent evidence shows that Lysergic Acid Diethylamide (LSD), even when administered in low, non-hallucinogenic doses, can produce analgesic effects and improve pain tolerance in a sample of healthy volunteers. Such results complement what was already observed with other serotonergic psychedelics such as psilocybin: survey studies and case series indicate that its use may lead to improvements in chronic pain conditions such as migraines, cluster headaches and phantom limb pain even at low, non-psychedelic doses. These effects have however not yet been investigated and confirmed in clinical populations under controlled experimental conditions.

Fibromyalgia (FM) is a chronic condition characterised by widespread pain, hyperalgesia, anxiety, disturbed sleep patterns, impaired cognitive functioning and comorbid mood disorders. It has high direct and indirect costs and it is considered challenging to treat. Most suggested therapies, in fact, are only associated with small improvements in pain ratings and quality of life. Currently, there is no data concerning the effectiveness of serotonergic psychedelics in improving pain ratings in fibromyalgia patients.

Objective: The present study will explore the effects that the administration of a placebo and 2 low psilocybin doses (5 mg or 10 mg) will have on pain perception in a group of fibromyalgia patients.

Study design: The present study uses a double-blind, randomized, placebo-controlled design. All participants will receive a placebo and 2 doses of psilocybin (5 mg or 10 mg) and will undergo the Cold Pressor Test (CPT) and the Pain Pressure Threshold Task (PPT) o test its analgesic effects.

Study population: 35 fibromyalgia patients aged 18 to 65 years.

Intervention: Placebo, 5 mg or 10 mg of psilocybin in randomized order.

Main study parameters/endpoints: Primary outcomes will be subjective and objective measures of pain perception. Secondary measures will assess the effects that placebo and psilocybin will have on mood, cognition and psychedelic experience. Finally, participants will take part to an additional CPT after receiving hypnotic suggestions of analgesia to test whether such intervention may moderate pain ratings of individuals who took small doses of psilocybin.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will visit the research lab 5 times during 5 weeks. Before the first study day, subjects will come for a screening visit during which they will also be familiarized with tests and study procedures. This includes a medical screening by a licensed physician (medical history review, laboratory screening, electrocardiogram

recording). The study visits will consist of taking the study treatment (5 mg or 10 mg of psilocybin or placebo), taking part to the experimental tasks, taking blood samples, completing computer tasks and filling out questionnaires. Finally, participants will take part to a final online visit to administer post-study questionnaires.

1. INTRODUCTION AND RATIONALE

Serotonergic psychedelics are substances whose primary mechanism of action is the activation of the serotonin 5-HT_{2A} 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 of serotonergic psychedelics have shown in surveys, clinical studies and controlled experiments recruiting healthy volunteers, we present a proposal to investigate the effects that such agents may have on improving pain perception in FM patients. Furthermore, since psychedelics seem to increase blood levels of brain derived neurotrophic factor (BDNF) (77,78) and this increase has been hypothesised to play a role in determining clinical outcomes (77,78), we will determine its concentration across the

study days and to test its association with the potential analgesic effects of psilocybin. Finally, since recent studies showed that psilocybin has anti-inflammatory properties (167) and have proposed its use to reduced peripheral neuroinflammation, we will assess its acute and persisting effects on inflammatory markers associated with FM and psychiatric conditions

2. OBJECTIVES

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.

Primary Hypothesis: We hypothesize that psilocybin will induce significant analgesic effects at 5 mg and 10 mg compared to placebo as measured by subjective measures and the outcomes of the PPT and CPT. We also hypothesize that these potential effects will be associated with variations in BDNF levels.

Secondary Hypothesis: We hypothesize that 5 mg and 10 mg of psilocybin will have mild to no effects on mood, cognition, and psychedelic experience compared to placebo as measured by the outcomes of the Digit Symbol Substitution Test (DSST), Psychomotor Vigilance Task (PVT), Multifaceted Empathy Test (MET), Interpersonal Reactivity Index (IRI), Alternate Use Test (AUT), Story writing, Profile of Mood States (POMS), 5 Dimensions of Altered States of Consciousness (5D-ASC), Clinical Administered Dissociative States Scale (CADSS), Brief Symptom Inventory (BSI), Ego Dissolution Inventory (EDI), Autobiographical Memory Test (AMT), Autobiographical Recollection Test (ART) and of a VAS. Additionally, given the recent interest on the effects that psychedelics have on personality, we will administer the Big Five Inventory (BFI) and the Interpersonal Reactivity Index (IRI) at the beginning and end of the study. Finally, we expect to find an interaction between psilocybin and hypnotic suggestions and hypothesize that participants undergoing CPT after receiving hypnotic suggestions will report lower pain intensity and show greater pain tolerance.

3. 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).

4. STUDY POPULATION

4.1. Population (base)

Potential male and female volunteers (18 to 65 years of age) will be recruited from the general population. Volunteers will have to fulfil a number of general inclusion and exclusion criteria before being admitted to the study. Initial screening includes a questionnaire on medical history and a standard medical screening. Volunteers will then undergo a psychiatric history screening (including use of medication, alcohol, nicotine, and other drugs) and medical screening including an electrocardiogram, blood biochemistry and haematology, urinalysis for drug screening and pregnancy (in women of childbearing potential), and a routine medical examination including vital signs. In total, 35 volunteers will be selected for participation. Volunteers will be treated according to the international convention governing drug studies in human volunteers; i.e. the declaration of Helsinki and its amendments (World-Medical-Association, 2013).

4.2. Eligibility

In order to be eligible to participate in this study, volunteers must meet all of the following criteria:

4.2.1. Inclusion Criteria

- Age between 18 and 65 years
- Normal weight, body mass index (weight/height^2) between 18 and 28 kg/m^2
- Fulfilment of the American College of Rheumatology criteria for FM diagnosis (43)
- 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 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

4.2.2. Exclusion Criteria

- Presence of any other painful condition such as inflammatory rheumatic diseases, migraines or headaches and of other chronic or acute medical conditions
- Presence or history of any other psychiatric condition such as primary major depressive disorder, anxiety disorders or substance use disorder as determined by the medical questionnaire, drug questionnaire and medical examination
- Previous experience of serious side effects to psychedelic drugs (anxiety or panic attacks)
- Tobacco smoking (>20 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

4.3. Sample size calculation

The primary outcome is pain perception (pain tolerance time in seconds) in the 3 different treatment conditions: placebo, 5 mg or 10 mg of psilocybin. While there are no other studies in clinical settings investigating the role of psilocybin on pain perception, a recent work focused on the analgesic effects of another serotonergic psychedelic: LSD (79). Results show that 20 µg led to significant improvements (η^2=0.09). Considering these findings, a total sample size of 28 individuals be sufficient to achieve a power of 95% (α = 0.05). Since

we expect about 20% of participants to drop out of the study, we plan to recruit 35 participants in total.

5. TREATMENT OF SUBJECTS

5.1. Investigational product/treatment

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.

5.2. Use of co-intervention (if applicable)

Participants will be asked to refrain from any drugs, except PCM and NSAIDS 5 days, before the first study day and during the whole study period. Subjects will not be allowed to use alcohol on the day prior to an experimental session.

5.3. Escape medication

NA

6. INVESTIGATIONAL PRODUCT

6.1. Name and description of investigational product(s)

Psilocybin will be administered to study its effects on pain perception, mood, cognition and psychedelic experience in FM patients. Along with psilocin, it is the primary psychoactive compound of *psilocybe* mushrooms and its effects are mediated by the $5HT_{2A}$ as well as the $5HT_{1A}$ and $5HT_{2C}$ serotonin receptors (2,3). Subjective effects are mostly blocked by the $5\text{-}HT_2$ antagonist ketanserin (80–82) and psychedelic effects occur at doses above 15 mg (83). Participants will receive two doses of psilocybin (5 mg or 10 mg) on two different occasions while in a third occasion they will receive microcrystalline cellulose (MCC) as a placebo.

6.2. Summary of findings from non-clinical studies

Psilocybin is the prodrug of the tryptamine psilocin (4-hydroxy-dimethyltryptamine), the primary hallucinogenic component of magic mushrooms. Psilocin exerts its effects through the serotonergic system, with pharmacodynamic research indicating that its psychedelic mechanism of action is through agonism on the serotonin 2A (5-HT2A) receptor (84). However, some of psilocin's psychoactive effects may also be due to downstream effects on other neurotransmitter systems, like glutamate and dopamine (85).

Psilocybin has variable psychological effects depending on the dose and the personal conditions such as experience with the drug and mood. Use of psilocybin leads to closed-

eye hallucinations, in which individuals see multicolored geometric shapes and imaginative sequences (85). Further subjective effects consist of intended feelings of relaxation, euphoria, giddiness, joy, uncontrollable laughter, disorientation, and in some cases anxiety or paranoia (86).

The physical effects of psilocybin may include increased heart rate, dilation of pupils, dizziness, weakness, muscle aching, shivering, and nausea and abdominal pain (87). However the latter are thought to be due to the recreational consumption of mushrooms, and not attributed to psilocybin itself. These effects are temporary and disappear a few hours after use. Additionally, previous research has demonstrated that psilocybin affects both subjective and physiological parameters in a dose-dependent manner (85,88–90).

Early and modern non-clinical research shows that psilocybin, if administered in appropriately controlled environments, shows a good safety profile (6,7,91), low toxicity (87,92,93) and bears no risk of engendering dependence or addiction (92,94,95). Furthermore, its use in recreational settings is associated with a lower rate of required emergency medical treatment compared to substances such as alcohol, cannabis or methamphetamine (96). Further evidence shows that lifetime use of psychedelics such as psilocybin is not associated with the risk of developing mental health conditions or decreased cognitive function (93,94,97–99). The analgesic potential of psilocybin and LSD (both 5-HT receptor agonists) was investigated in 3 surveys addressed to patients suffering from cluster headaches (21–23). More specifically, participants from all three surveys reported that both psilocybin and LSD aborted attacks, induced their termination and extended the duration of remission periods even when took in low, non-hallucinogenic doses. A recent study on healthy volunteers who received microdoses of LSD showed that 20 µg improved pain tolerance and ratings of unpleasantness with a medium to large effect size (24). The magnitude of this improvement is comparable to what was observed in studies employing opioids (25,26). Furthermore, this dosage caused only small increases in anxiety, somatisation, amnesia, depersonalisation, derealisation and dissociation ratings. Earlier studies show that a similar dose (26 µg of LSD) has no or little effect on cognitive function, mood, perception and state of consciousness (28,29) and its impact on subjective experience and functioning seems smaller than that of other pain management compounds such as cannabis or ketamine (100).

6.3. Summary of findings from clinical studies

Most clinical evidence on the effectiveness of 5-HT receptor agonists on pain comes from early studies employing LSD and involving patients affected by life-threatening conditions. More specifically, a prospective non-randomised study showed that a 0.1 mg dose of LSD

was more effective than hydromorphone HCl, 2 mg., and meperidine HCl, 100 mg in reducing pain in a sample of patients suffering from neuropathic, ischemic or cancer-related pain (16). A subsequent case series involving terminal patients treated with equal doses showed immediate pain reductions that remained stable at the 3-week follow up (101). Similarly, a pre-post, no control group clinical study on a sample of 30 cancer patients, showed that LSD-assisted psychotherapy was associated with improvements in pain ratings (18). Sub-hallucinogenic doses of LSD led to improvements in pain measurements in 5 over 7 patients suffering from phantom limb pain in a case series study (19).

Psilocybin has been shown in two double-blind, placebo-controlled, crossover trials to produce rapid and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress (88,102).

A study by Ross et al. (102) included 29 patients, each receiving a single-dose of psilocybin (0.3 mg/kg). Researchers reported that no pharmacological interventions were needed, no participants became addicted to psilocybin, and there were no cases of prolonged psychosis. The most common psychiatric adverse effects were transient anxiety (17%) and transient psychotic-like symptoms (7%). The most common medical adverse events (AE) were non-clinically significant elevations in blood pressure and heart rate (76%), headaches (28%), and nausea (14%).

The study by Griffiths et al. (12) included 51 patients, each receiving a low dose (3 mg/70 kg) and a high dose (30 mg/70 kg) of psilocybin. The most common psychiatric adverse effects were transient anxiety (15% in the low-dose, 26% in the high-dose) and psychological discomfort (12% in the low-dose, 32% in the high-dose). The most common medical AE were non-clinically significant elevations in systolic (17% in the low dose, 34% in the high-dose) and diastolic (2% in the low-dose, 13% in the high-dose) blood pressure.

Neither aforementioned study reported serious adverse effects. Furthermore, patients in both studies reported immediate and sustained improvements in anxiety and depression, spiritual wellbeing, attitude toward death, and increased quality of life. At the 6 months follow up, psilocybin was further associated with enduring positive effects in 80% of the participants.

6.4. Summary of known and potential risks and benefits

Psilocybin is considered to be safe when administered in appropriately controlled settings (87,91–96) and can incite feelings of relaxation euphoria, giddiness, and joy, and lead to altered perception of reality. These sensory distortions may be coupled with negative effects like restlessness, anxiety, and a sense of unreality. Thus, the most important acute adverse effects are anxiety and panic attacks, and with regard to somatic effects, increased

heart rate. However a recent survey among 600 subjects showed that the drug effects of psilocybin were considered beneficial with a relatively low harm potential (86).
Carbonaro et al. (103), considering the totality of research related administrations (n. 380) of full doses of psilocybin at Johns Hopkins Hospital Center for Psychedelic and Consciousness Research, reported that instances of behaviours that could have potentially put participants or staff members at risk occurred in 0.9% of cases (uncommon events according to the MedDRA international guidelines). Examples of such behaviours are vigorous movements and disorientation. Furthermore, in 0.9% of cases, subjects reported psychological distress potentially caused by psilocybin that eventually encountered spontaneous remission or were found to be related to a yet undiagnosed case of hyperthyroidism. Comparable rates of AE were reported in another paper by Studerus et al. (104) who pooled data of 110 participants from several studies.
Under controlled and supportive conditions, the psilocybin experience reportedly had 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 QOL (8,112,113).

6.5. Description and justification of route of administration and dosage

The study will use low doses of psilocybin (5 mg or 10 mg), all given orally. These low doses (114) are justified by the intent to achieve greater pain tolerance in the absence of psychedelic effects. These doses are smaller than others used in previous studies (115–118) and that were shown to be well tolerated.

6.6. Dosages, dosage modifications and method of administration

Psilocybin will be administered in the form of 1 or 2 5 mg capsules. In the 5 mg condition participants will take 1 psilocybin capsule and 1matching placebo capsule; in the 10 mg condition participants will take 2 psilocybin capsules; in the placebo condition participants will take 2 matching placebo capsules.

6.7. Preparation and labelling of Investigational Medicinal Product

Psilocybin is obtained as 5 mg capsules and will be provided by the Usona Institute (www.usonainstitute.org) along with matching placebo.

6.8. Drug accountability

LUMC's pharmacy will import the study medication from Almac Clinical Services, blind the treatments and prescribe them to Prof. Albert Dahan. Half of the treatment batch will be then sent to MUMC pharmacy that will prescribe the treatments for the Maastricht site to Dr. Cees van Leeuwen. In the trial master files, a drug accountability log will be kept where

information about distribution and return will be registered. An import licence will be obtained.

7. NON-INVESTIGATIONAL PRODUCT

7.1. Name and description of non-investigational product(s)

Subjects will receive identical MCC capsules serving as placebo.

7.2. Summary of findings from non-clinical studies

NA

7.3. Summary of findings from clinical studies

NA

7.4. Summary of known and potential risks and benefits

None

7.5. Description and justification of route of administration and dosage

Capsules identical to the psilocybin ones will be provided to participants.

7.6. Dosages, dosage modifications and method of administration

Subjects will receive identical MCC capsules serving as placebo.

7.7. Preparation and labelling of Non Investigational Medicinal Product

Identical MCC capsules will be used.

7.8. Drug accountability

In the trial master file, there will be drug accountability log where information about distribution and return will be registered.

8. METHODS

8.1. Study parameters/endpoints

8.1.1. Main study parameter/endpoint

- Pressure Pain Threshold (PPT)
- Cold pressor task (CPT)
    - Pain tolerance time (in seconds)
    - Subjective pain ratings (Visual Analogue Scale)
- Brief Pain Inventory - Short Form (BPI)

8.1.2. Secondary study parameters/endpoints (if applicable)

- Subjective effects
    - 5 Dimensions of altered states of consciousness (5D-ASC)
    - Profile of mood states (POMS)
    - Visual analogue scales (VAS)
    - Ego Dissolution Inventory (EDI)
    - Clinical Administered Dissociative States Scale (CADSS)
    - Brief Symptom Inventory (BSI)
- Cognitive performance
    - Digit Symbol Substitution Test (DSST)
    - Psychomotor Vigilance Task (PVT)
    - Multifaceted Empathy Test (MET)
    - Alternate Use Test (AUT)
    - Story Writing
- Autobiographical memory
    - Autobiographical Memory Test (AMT)
    - Autobiographical Recollection Test (ART)

8.1.3. Other study parameters (if applicable)

- Treatment expectancy
    - Credibility/Expectancy Questionnaire (CEQ)
    - Treatment Expectations in Chronic Pain (TEC)
- FM Pain and impact
    - Fibromyalgia Impact Questionnaire (FIQ)
- Personality
    - Big Five Inventory (BFI)

- Modified Tellegen Absorption Scale (MODTAS)
- Interpersonal Reactivity Index (IRI)

- Depression
  - Beck Depression Inventory – II (BDI-II)

8.2. Randomisation, blinding and treatment allocation

Each participant will receive 2 different doses of psilocybin and a matching placebo on three separate occasions.

With these 3 treatment conditions there will be a total of 6 possible treatment orders which will be allocated to 35 subjects. Blinding will be handled by the LUMC pharmacy and order and allocation of the treatment to each participant will be completely randomized. This setup ensures that neither the participant nor the experimenter running the test day will be aware of the contents of the capsule.

Following completion of all data collection, the study will be fully unblinded. If necessary, e.g. in cases of emergency, the principal investigator will break the blind on a study day. It is not possible that the code can be broken by accident or technical issues.

8.3. Study procedures

Screening: 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 ample 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.

8.4. Schedule of experimental session:

Table 1 shows the schedule of events for each experimental session. Each of the 3 test sessions lasts for 7h. Subjects will arrive between 9 AM and 10 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. All participants will always take 2 identical capsules in each condition (2 MCC capsules for the placebo condition, 1 psilocybin capsule and 1 MCC capsule for the 5mg condition, 2 psilocybin capsules for the 10 mg condition). Outcome measures (see below) will repeatedly be assessed during the study session. 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. An additional online visit will be performed 1 week after the last study day to administer post study measures.

8.5. Measurements:

			10.00	10.30	11.00	11.30	12.00	12.30	13.00	14.00	15.00	16.00
Table 1. Schedule of events for each session												
Relative Time		-1	0	0.5	1	1.5	2	2.5	3	4	5	6
Substance Administration												
	Psilocybin/Placebo		X									
Pain												
	PPT					1				2		
	CPT					1		2*		3		
	BPI											1
Psychometrics												
	VAS	**0**	0	1	2	3	4	5	6	7	8	9
	POMS	**0**			1		2		3		4	
	CADSS, BSI	**0**										1
	5D-ASC, EDI											1
Autonomic Measures												
	BP, HR	**-1**	0	1	2	3	4	5	6	7	8	9
Blood samples												
	Substance concentration	**0**		1	2	3	4		5	6		7
	BDNF	**0**					1			2		3
Computer tests												
	ART										1	
	MET				1							
	Story Writing						1					
	AUT							1				
	AMT										1	
	DSST, PVT					1				2		
	Visual Analogue Scale (VAS), Profile of Mood States (POMS), Clinical Administered Dissociative States Scale (CADSS), Brief Symtpoms 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), Pressure Pain Threshold (PPT), Cold Pressor Task (CPT), Brief Pain Inventory (BPI), Autobiographical Recollection Test (ART).											
	* CPT plus suggestion											

Pressure Pain Threshold (PPT)

We will use the FPN 100 N Algometer (FDN 100, Wagner Instruments Inc., Greenwich, CT, USA) (119) to deliver pressure pain on a skin area of 1 cm2 between thumb and index finger. The FDN 100 has a force capacity (± accuracy) of 100 ± 2 N (10 ± 0.2 kgf) and graduation of 1 N (100 gf), respectively. A gradually increasing pressure is manually applied and the subjects are asked to indicate when the procedure becomes painful (pressure pain threshold, PPT, in kPa).

Cold Pressor Task (CPT)

The Cold Pressor Task (CPT) (120) will be used to induce a painful sensation. A water tank will be filled with water that was cooled to 3°C. Participants will be informed that the procedure could be painful and that they will be able to stop the task at any point without

consequences. The instructions before immersion will be as follows: “The aim of the task is to submerge your right hand in this cold water tank for as long as possible until you cannot take it anymore. When you cannot take it any longer, you are allowed to remove your hand from the water. Try, however, to hold on as long as possible.” The immersion duration will be set to 3 min. Participants will not be aware of this time limit. If the 3 min maximum will be achieved, the experimenter will signal the participant to remove the hand from the water. Dependent measures of the CPT include pain tolerance (seconds), i.e. the number of seconds until withdrawal of the hand from the water tank, and subjective ratings of painfulness, unpleasantness and stress as assessed on 10cm visual analogue scales. Water temperature at onset and completion of the CPT will be assessed as control measure. The CPT will be administered repeatedly throughout the day (Table 1) after the PPT with a 5 minutes interval between the two. At the 2.5 hours mark (between the first and last CPT), participants will receive an additional CPT plus hypnotic suggestions. Before the second CPT session, participants will listen to a 10-minute-long audio recording of a hypnotic induction structured to promote analgesia. The script will be structured in 4 parts: a) induction phase to focus attention inward, b) imagery suggestions aimed at reaching a comfortable place, c) suggestions evoking strength, confidence, resistance to cold, dissociation of the hand and relaxation while doing the CPT, d) alerting. The structure of the script will be developed by a trained hypnotherapist and will be based on recent studies investigating the analgesic potential of hypnosis in enduring experimental pain-related tasks (121,122).

Subjective Effects

Visual analogue scale (VAS)

A visual analogue scale measuring the subjective drug effects will be repeatedly used to assess the drug effect over time. The visual analogue scale will be presented as 100 mm horizontal lines marked with “not at all” on the left and “extremely” on the right. VAS scales will be administered repeatedly during the study day (Table 1).

Altered states of consciousness questionnaire (5D-ASC)

The 5 dimensions of altered states of consciousness (5D-ASC) scale is a visual analogue scale consisting of 94 items (123,124). The instrument is constructed of five scales and allows the assessment mood, anxiety, derealization, depersonalization, changes in perception, auditory alterations, and reduced vigilance. The scale is well-validated and has

been used across different groups with various psychedelic substances (4,85,88,125). The 5D-ASC scale will be administered once at the end of the session and subjects are instructed to retrospectively rate peak alterations during the study session. Each item of the scale is scored on a 0-100 mm VAS. The 5D-ASC will be administered once at the end of the day (Table1). The 5D-ASC will be administered once at the end of the day (Table 1).

Profile of mood states (POMS)

The profile of mood states (POMS) questionnaire (126) is a self-assessment mood questionnaire that will be used to assess mood before and after drug intake. It consists of 32 visual analogue scales of 100mm. It will be administered repeatedly to assess the different states of mood over time. The questionnaire allows quantification of eight mood states (anxiety, depression, anger, vigour, fatigue, confusion, friendliness, and elation), as well as two composite scales (arousal and positive mood). The POMS will be administered repeatedly throughout the day (Table 1).

Clinician Administered Dissociative States Scale (CADSS)

The Clinician Administered Dissociative States Scale (CADSS) (127) comprises 19 subjective items, ranging from 0 ‘not at all’ to 4 ‘extremely. It is divided into 3 components: 1) depersonalization, 2) derealization and 3) amnesia. Summed together, these subscales form a total dissociative score. The CADSS is specifically designed to be a standardized measure of present-state dissociative symptomatology. The CADSS will be administered repeatedly throughout the day (Table 1).

Ego dissolution inventory (EDI)

The Ego-Dissolution Inventory (EDI) (128) is a self-report scale that will be used to assess ego-dissolution after drug intake. The questionnaire consists of 8-items in which participants have to rate retrospectively, including: I experienced a dissolution of my “self” or ego; I felt at one with the universe; I felt a sense of union with others; I experienced a decrease in my sense of self-importance; I experienced a disintegration of my “self” or ego; I felt far less absorbed by my own issues and concerns; I lost all sense of ego; All notion of self and identity dissolved away. The EDI will be administered once at the end of the day (Table 1).

Brief Symptom Inventory (BSI)

The Brief Symptom Inventory (129) is a shortened version of the widely used Symptom Check List 90. The BSI18 contains only the three six-item scales somatization (SOMA),

anxiety (ANX), depression (DEPR), and the global Scale Global Severity Index (GSI). It will be administered twice, on arrival and at the end of the day.

Personality

The Big Five Inventory (BFI)

Personality traits are known to affect subjective responses to psychoactive substances (130,131). The Big Five Inventory (BFI) (132) is a 44-item inventory that measures an individual on the big five factors (dimensions) of personality, including extraversion, agreeableness, conscientiousness, and openness. Each of the factors is then further divided into personality facets. The BFI will be used to assess personality traits, their potential modulatory effects on the responses to low doses of psilocybin and to test its stability after the 3 experimental sessions. It will be therefore administered at baseline and at the end of the study.

Interpersonal Reactivity Index (IRI)

The Interpersonal Reactivity Index IRI (133) is a 28-item questionnaire consisting of 4 discrete seven-item scales i.e. 'Fantasy', F (tendency to imaginatively transpose oneself into fictional situations), 'Perspective-Taking', PT (tendency to spontaneously adopt the psychological viewpoint of others), 'Empathic Concern', EC (taps the respondents' feelings of warmth, compassion and concern for others), and 'Personal Distress', PD (assesses self-oriented feelings of anxiety and discomfort resulting from tense interpersonal settings). The IRI will be used to assess interpersonal reactivity, its potential modulatory effects on the responses to low doses of psilocybin and to test its stability after the 3 experimental sessions. It will be therefore administered at baseline and at the end of the study.

Modified Tellegen Absorption Scale (MODTAS):

The Modified Tellegen Absorption Scale (MODTAS) was derived from measures of hypnotic susceptibility and assesses the tendency to be deeply involved (absorbed) by the object of the experience and was derived from measures of hypnotic suggestibility (134). The author further defined it as a disposition to surrender - in appropriate circumstances - active, realistic, voluntary and relatively effortful planning, and decision making and goal directed behaviour in favour of an effortless, non-volitional quality of deep involvement with the objects of consciousness (135). The MODTAS scale will be administered at baseline and 1 week after the last experimental session.

Cognitive effects:

Multifaceted empathy test (MET)

The Multifaceted Empathy Test assesses cognitive and affective empathy by inferring the mental state of a person in a scene and rating the intensity of how much they were feeling for each individual in a scene or how much they were aroused by each scene. The MET is a reliable and valid task to assess the cognitive and emotional aspects of empathy (136). The MET has been shown to be sensitive to oxytocin (137), MDMA (138,139), LSD (140), psilocybin (141). The computer-assisted test consists of 40 photographs that shows people in emotionally charged situations. To assess cognitive empathy, the participants are required to infer the mental state of the subject in each scene and indicate the correct mental state from a list of four responses. Cognitive empathy is defined as the percentage of correct responses in the total responses. To measure emotional empathy, the subjects are asked to rate how much they are feeling for an individual in each scene (i.e., explicit emotional empathy) and how much they are aroused by each scene (i.e., implicit emotional empathy) on a 9 point scale. The latter rating provides an inherent additional assessment of emotional empathy, which is considered to reduce the likelihood of socially desirable answers. The three aspects of empathy are each tested with 20 stimuli with positive valence and 20 stimuli with negative valence, resulting in a total of 120 trials. The test requires about 15 minutes. The MET will be administered once during the study day (Table 1).

Alternate Use Test (AUT)

In the AUT (142) participants are asked to list as many possible uses for three everyday household items and are given three minutes per item for this task. Responses are scored afterward by two independent raters who are blind to the treatment condition. Dependent outcome variables are Fluency, Originality, the ratio of Fluency and Originality, Flexibility, and Elaboration, and they all convey information about the level of divergent thinking of the participant. Fluency is defined as the total number of alternate uses produced by the participant. Each response will be rated for uniqueness or ‘originality’ by awarding points between 0-2—higher scores signal higher originality. A ‘2’ indicates that the same response was given by only 1% of the sample, a ‘1’ will be awarded when the response will be given by 5% of the sample, and when the response will be given by more than 5% of the sample, a ‘0’ will be awarded. Originality is the sum of the originality points. The ratio of Originality and Fluency is calculated as a genuine index of divergent thinking to correct Originality for the number of responses that were generated. If a participant would give two responses of ‘medium’ originality, which is worth one point, and another participant would give only one

highly original response, which is worth two points, Originality would be awarded two in total for both. Even though the scores are the same, the quality is not. The ratio reflects this difference in quality with the first participant in the example having Ratio '1' and the second participant Ratio '2'. The ability to generate a diversity of responses 'Flexibility' will be assessed by clustering the responses into categories; the sum of categories will be the dependent variable. The amount of detail in the responses, 'Elaboration' was scored by summating the number of details. The interrater reliability will calculated before averaging the ratings. Statistics are reported below before findings are presented. Parallel versions will be used on separate test days.

Story Writing

At the beginning of the test day, participants will be given three words and the instruction that at noon they will have to write a story with no restrictions on the type ((non-)fiction) or emotional tone (happy/sad). In order to assess the level of divergent thinking or creativity of the story, two independent raters will assign a creativity score between zero ('not creative at all') to five ('extremely creative') to the stories. The creativity criterion and scoring will be similar to the procedure described by Wolfradt and Pretz (143) that was based on the 'consensual assessment technique' (144) in which raters use their own subjective definition of novelty and originality to rate creativity. The interrater reliability will be calculated before averaging the creativity ratings. This average creativity score will be one of the dependent variables in this task. Statistics are reported below before findings are presented. Next to that, the written stories will be scored on creative and social content in an automated way using a 'standard dictionary approach' using a computer program called Linguistic Inquiry and Word Count (LIWC) (145,146). LIWC reports word use in percentages indicating the number of words used in a particular category, relative to all the words used by a particular participant per generated story. Next to that, there are a number of 'summary' variables that are standardized composites that have been converted to percentiles based on the information included in the LIWC database (145,146). We will focus on a selected number of categories related to psychological and social processes: Emotional Tone (summary variable), Family, Friends, Positive Emotion, Negative Emotion, Anxiety, Anger, Sad, Authentic (summary variable), Analytical thinking, and a general measure, Word Count ('Fluency'). Pennebaker et al. (147) provide definitions for the summary variables. A high number on Emotional Tone is associated with a more positive, upbeat story style; a lower number reveals more significant anxiety, sadness, or hostility; a number around 50 suggests either a lack of emotionality or different levels of ambivalence. A higher number

of Authentic is associated with a more honest, personal, disclosing text; lower numbers suggest a more guarded, distanced form of discourse. A higher number of Analytical thinking reflects formal, logical, and hierarchical thinking, whereas lower numbers reflect more informal, personal, here-and-now, narrative thinking. Participants will not be explicitly instructed to be creative and will receive fifteen minutes to complete this task. Parallel versions of this task will be used on separate test days.

Digit Symbol Substitution test (DSST)

The DSST (148) is a computerized version of the original paper and pencil test taken from the Wechsler Adult Intelligence Scale. The participant is shown an encoding scheme consisting of a row of squares at the top of the screen, wherein nine digits are randomly associated with particular symbols. The same symbols are presented in a fixed sequence at the bottom of the screen as a row of separate response buttons. The randomization procedure is chosen such that symbols never appear at the same ordinal position within both rows. The encoding scheme and the response buttons remain visible while the participant is shown successive presentations of a single digit at the centre of the screen. The task is to match each digit with a symbol from the encoding list and click the corresponding response button. The number of digits correctly encoded within 3 minutes is the performance measure. The DSST will be administered repeatedly throughout the day (Table 1).

Psychomotor vigilance task (PVT)

The psychomotor vigilance task assesses (149) the reaction time in response to a visual stimulus. The visual stimulus will be a counter in the center of a computer screen that will run in 1 min from 0 to 60 with a fixed inter-stimulus interval of 1 ms. The counter will start at random intervals between 2 and 10 s, and the subject will have to react to the onset of the counter as quickly as possible by pressing a response button. Duration of the task will be 10 min. This task has often been used to assess the impact of sleep loss on performance. The PVT will be administered repeatedly throughout the day (Table 1).

Autobiographical memory:

Autobiographical Memory Test (AMT)

The Autobiographical Memory Test (AMT) (165) is the most widely used instrument for studying the specificity of autobiographical memories. In the written version of the AMT, participants report autobiographical memories in response to (emotionally charged) cue

words, and these memories can then be coded for, e.g., specificity, emotional valence, or pain-related content. In this study, the AMT will be used to explore the effects of psilocybin on the autobiographical remembering of the participants, especially on the specificity, emotional valence, and pain-related content of their memories, and whether any such acute or post-acute effects are linked to less experience of pain or pain-related distress, or other improvements in mental health and well-being. The AMT will be administered once during the test day (Table 1).

Autobiographical Recollection Test (ART)

The Autobiographical Recollection Test (ART) (166) assesses individual differences in how well people think they remember personal events. The ART comprises seven theoretically motivated, empirically supported, interrelated aspects of recollecting autobiographical memories: reliving, vividness, visual imagery, scene, narrative coherence, life-story relevance, and rehearsal. It consists of 21 likert scale items that range from 1 (strongly agree) to 7 (strongly disagree). The ART will be administered at baseline and follow up.

Expectations:

Credibility/Expectancy Questionnaire (CEQ)

The Credibility/Expectancy Questionnaire (150) is the most widely self-report measure of treatment credibility and expectancy. The scale was developed to be used in clinical outcome studies and has good psychometric qualities and is divided into two sets of items. The credibility set includes 3 9-point likert scale items and 1 item graded on a scale from 0% to 100%. The expectancy set includes 2 9-point likert scale item and 1 item graded on a scale from 0% to 100%. The CEQ will be administered to FM patients at baseline.

Treatment Expectations in Chronic Pain (TEC)

The Treatment Expectations in Chronic Pain (151) is a reliable and valid self-report scale developed for use in clinical trials to investigate the role of treatment expectations in patients suffering from chronic non-cancer pain. It measures both ideal and predicted improvement by means of two sets of 9 items each, graded on a 5-point likert scale (1 = *I strongly disagree*; 5 = *I strongly agree).* The TEC will be administered to FM patients at baseline.

Fibromyalgia Pain and Impact:

Fibromyalgia Impact Questionnaire (FIQ):

The Fibromyalgia Impact Questionnaire (FIQ) (152) was developed to measure the components that are most affected by the condition such as physical impairment, feeling good, missing work, doing work, pain, fatigue, restfulness, stiffness, anxiety, and depression. It has good psychometric properties and it shows responsiveness to change (153–155). The FIQ will be administered at baseline and 1 week after each experimental session.

Brief Pain Inventory – Short Form (BPI):

The Brief Pain Inventory – Short Form (BPI) (156) is a valid and reliable self-report measure (157) that assesses pain severity (BPI-S) and pain interference (BPI-I) on 0-10 numeric scales. The BPI will be administered at baseline, at the end of each experimental session and 1 week after the last experimental session.

Depression

Beck Depression Inventory-II (BDI-II):

The Beck Depression Inventory-II (BDI-II) (158) is widely used to screen for depression, is composed by 21 questions, each scored 0 to 3, asking about the presence of depressive symptoms in the pas 2 weeks. Scores between 0 and 13 indicate minimal depression, between 14 and 19 mild depression, between 20 and 28 moderate depression and between 29 and 63 severe depression. The BDI-II will be administered at baseline.

Blood samples:

Blood samples for laboratory safety will be collected at screening (2x5 ml). 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). Blood samples for plasma concentration 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). BDNF will be measured 4 times per study day (see Table 1). For the complete study we will collect 190 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.

8.6. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.7. Replacement of individual subjects after withdrawal

Any volunteer dropping out of the study will be replaced by a volunteer receiving the treatment. About 4 of drop-outs are foreseen i.e. there will be spare medication for the extra subjects. Any test day on which a subject has been administered study medication and on which tests cannot be conducted, due to unforeseeable technical failures (e.g. computer malfunction) that occurred after drug administration, can be repeated on the next visit of the subject using spare medication.

8.8. Follow-up of subjects withdrawn from treatment

In case a subject withdraws or is withdrawn from the study due to an AE or SAE the usual procedures will be followed as stated in chapter 9 of this protocol.

8.9. Premature termination of the study

Premature study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study subjects.

9. SAFETY REPORTING

9.1. Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2. AEs, SAEs and SUSARs

9.2.1. Adverse events (AE)

Adverse events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to psilocybin. All AE reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2. Serious adverse events (SAEs)

A serious adverse event (SAE) is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAE will be reported within a period of maximum 15 days after the sponsor has first knowledge of the SAE.

9.2.3. Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

In case of a SUSAR blinding will be broken to allow for reporting.

9.3. Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4. Follow-up of adverse events

All AE will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5. Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable to this study.

10. STATISTICAL ANALYSIS

Statistical analyses will be performed by the means of the latest available version of the statistical programs SPSS. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical variables.

10.1.Primary study parameters

Two GLM repeated measures ANOVAs will be conducted with Treatment (0, 5 or 10 mg of psilocybin) and Time (1.5 and 5 hours after treatment administration) as within subject factors.

In case of an overall effect, subsequent analyses for comparing Treatment, Time after administration carried out using posthoc tests.

10.2.Secondary study parameter(s)

Statistical analyses of subjective dependent variables VAS and POMS will be conducted using a GLM repeated measures ANOVA, consisting of the within-factors Treatment (0 mg, 5 mg or 10 mg of psilocybin) and Time after administration (11 timepoints for VAS and 5 timepoints for POMS).

Statistical analyses of subjective dependent variables CADSS and BSI will be conducted using a GLM repeated measures ANOVA, consisting of the the within-factors Treatment (0 mg, 5 mg or 10 mg of psilocybin) and Time (before administration, end of session).

Statistical analyses of the subjective dependent variables 5D-ASC and EDI) will be conducted using a GLM repeated measures ANOVA, consisting of the the within-factors Treatment (0 mg, 5 mg or 10 mg of psilocybin).

In case of overall effects, subsequent analyses investigating potential interactions will be carried out using posthoc tests. Bonferroni correction will be applied to correct for multiple comparisons and all outcomes with effect sizes and measures of precision will be included to prevent the risk of selective reporting.

Data of the VAS and POMS will be checked for normality using Shapiro-Wilks tests. In case of normality, Pearson correlations will be used for correlation of mood changes (increase or decrease as change from placebo and baseline) with changes in cognitive performance and plasma concentrations. Spearman correlations will be used in cases of non-normality.

Statistical analyses of a selection of the cognitive tests (MET, Story writing task, and AUT) will be conducted using a GLM repeated measures ANOVA, consisting of the within-subject factor Treatment (0 mg, 5 mg or 10 mg of psilocybin). For DSST and PVT the within-subject factor Time after administration (2.5 hours and 4 hours) will be included.

In case of a main effect of Treatment, or a Treatment by Time interaction exploratory analyses will be carried out using posthoc tests. Bonferroni correction will be applied to correct for multiple comparisons and all outcomes with effect sizes and measures of precision will be included to prevent the risk of selective reporting. Data of the cognitive tests will be checked for normality using Shapiro-Wilks tests. In case of normality, Pearson correlations will be used for the correlation of performance change (change from placebo and baseline) with mood change (change from placebo and baseline) and plasma concentrations. Spearman correlations will be used in cases of non-normality.

10.3.Other study parameters

Plasma concentrations and subject expectations will be used as potential covariates in the above-mentioned analyses to test the influence of these variables on outcome measures.

10.4.Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1.Regulation statement

This study will be conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This implies that all subjects will participate voluntarily and will be fully informed of all procedures, possible adverse events to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. All subjects shall give their informed consent, in writing, and the individual subject's anonymity shall be maintained in all communications from the project. Approval for the studies shall be obtained from the Academic Hospital and University's Medical Ethics committee.

All data will be treated confidentially using codes and only the researchers involved in the study will have access to the data. An independent physician is at the subjects' disposal for additional information. Subjects are offered the possibility to be informed about the results of the study.

11.2.Recruitment and consent

Participants will be recruited via advertisements which will be put up in university buildings and published online or in local newspapers. When potential subjects react to the advertisement, they will receive the subject information sheet, which they are requested to read carefully.

The researcher will discuss questions with the potential participant. The individual subjects' pseudonymity shall be maintained in all communications on the project. They will then have one week to decide whether they want to participate. If they so wish and after the reflection period has expired, they will be invited for a medical screening. During this screening, they will be fully informed of all procedures, possible adverse events to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without consequences. They will also be given the opportunity to ask the investigator any question they may have and the investigator will check whether prospective participants have understood what participation entails. Only then, if still willing to participate, they will sign the informed consent at the presence of the investigator and will be included in the study. Once the consent is signed, participants will fill in the medical questionnaire and drug questionnaire before taking part to the medical examination. After all (laboratory) results are obtained, one of the researchers and the medical doctor will check if all in- and exclusion criteria are met. Subjects are subsequently informed whether

they fulfil the criteria or not. In case of an incidental medically relevant finding the study physician will contact the subject and discuss further steps. The subject will then be advised to contact his/her general practitioner. If during screening participants are deemed not suitable for participation, they will be regarded as dropouts.
After consent has been given, data will be collected by experimenters and will be encoded. All collected and encoded urine and blood samples will be destroyed after analysis.

11.3.Objection by minors or incapacitated subjects

Not applicable

11.4.Benefits and risks assessment

Potential benefits to society: The present study will provide data to clarify the potential role that psilocybin may have in treating symptoms in FM, a disabling condition that is currently considered hard to treat.
Potential benefits to participants: Should this study consolidate earlier results obtained in non-clinical studies, FM participants may experience reductions in pain symptoms. 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).
Risk/benefit Ratio: The risk of lasting psychological and physical harm is considered low (86,87,91–96,103,104). On the other hand, FM patients may experience reductions in pain symptoms, a pleasant alteration of their state of mind and a personally significant experience (8,88,103,105–108,110–113). Furthermore, the benefits will include increased information that will be of benefit for the society.

11.5.Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6.Incentives

Subjects will be compensated for their participation by means of a monetary reward. Participants will receive € 225 for their participation in the study. This is based on € 10/hour, plus € 15 bonus when they participate in all conditions. In case of premature termination of the study, compensation will be based on number of participated hours. In addition, their tickets for using public transport and parking fees to come to the test site and to return home will be reimbursed.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1.Handling and storage of data and documents

All data is provided with a code that consists of the following information:

- Project number (intern): P137
- Subject number: assigned based on order of inclusion
- Test day: test day 1 is labelled A; test day 2: B; test day 3: C
- In case a test is repeatedly administered on a test day, the repetitions will be labelled: 1-….

All data is collected in electronic and paper format. Data from the questionnaires is collected on paper. These (paper) source data are saved in maps which are stored in a locked cabinet which. Only researchers and the monitoring involved in the project have access to the source data. In case of inspection by national authorities, the inspectors will be granted access. Electronic source data is stored on a partition of a server (hosted in the University Building) which is only accessible to the principal investigator. The key code is safeguarded by the local principal investigator: Prof. Johannes G. Ramaekers for the Maastricht site and Prof. Albert Dahan for the Leiden site. Data will be kept for 25 years for further analyses regarding this study or future studies on the effects of psychedelics on mental and physical health. Body material will be destroyed once analyses are complete. Data will be accessible by the research team, interns supervised by the principal investigators, Stefan Toënnes who is responsible for laboratory analyses, Rafael de la Torre who is responsible for the BDNF analysis. The handling of data will be in accordance with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (UAVG). As part of the contract with the Usona Institute, the supplier of the psilocybin, anonymised safety data will be shared with said Institute. The data will be used to monitor the substance safety.

12.2.Monitoring and Quality Assurance

Monitoring of the study will take place. The monitor, Anita van Oers, will conduct three visits in which she will (for details see monitoring plan):

- do the verification of the source documentation
- check the drug accountability plan
- check the trial master file
- discuss the results of the visit and write a report

12.3.Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4.Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, SAE/ serious adverse events, other problems, and amendments.

12.5.Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient’s last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. The reasons for premature termination prevail over the texts in the protocol.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6.Public disclosure and publication policy

All results from this research will be disclosed unreservedly in a scientific paper aimed for publication in a peer reviewed scientific journal. Research data collected in the current study will be owned by Maastricht University. The publication conditions prevail over the texts in the research protocol.

13. STRUCTURED RISK ANALYSIS

13.1.Potential issues of concern

a. Level of knowledge about mechanism of action

Psilocybin is the prodrug of the tryptamine psilocin (4-hydroxy-dimethyltryptamine), the primary hallucinogenic component of magic mushrooms. Psilocin exerts its effects through the serotonergic system, with pharmacodynamic research indicating that its psychedelic mechanism of action is through agonism on the serotonin 2A (5-HT2A) receptor (84). However, some of psilocin's psychoactive effects may also be due to downstream effects on other neurotransmitter systems, like glutamate and dopamine (85).

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

The effects of psilocybin have been investigated previously (4,12,85,102,117,118,159) in studies using similar or higher doses to observe its effects on behavioral and biological measures similar to our study.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

No, we are specifically interested in changes in human behaviour.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Psychological Effects: Safety concerns regarding psilocybin are primarily psychological. Transient anxiety, restlessness and paranoia may occur in some subjects (86). These reactions are expected to be rare (given the small administered dose) and to resolve spontaneously with supportive care by the investigators (7,103,104). At the doses of

psilocybin used in the present study, subjects are expected to retain most of their thought control and will remain aware of the transient state of the drug-induced experience. Rare events of more pronounced anxiety, panic attacks or agitation under psilocybin may be treated with benzodiazepine administration if needed. Additionally, the study physician can be contacted for assistance.

Physiological effects: The effects of psilocybin may include increased heart rate, dilation of pupils, dizziness, weakness, muscle aching, shivering, and nausea and abdominal pain (7,87). However, the latter are thought to be due to the recreational consumption of mushrooms, and not attributed to psilocybin itself. These effects are temporary and disappear a few hours after use.

Additionally, previous research has demonstrated that psilocybin affects both subjective and physiological parameters in a dose-dependent manner (85,88–90).

Abuse liability: psilocybin possesses little if any abuse liability. LSD is not self-administered by animals and there is no human psilocybin dependence syndrome (92,94,95).

Neurotoxicity: Psilocybin is not neurotoxic (87,92,93).

e. Analysis of potential effect

The given dose is expected to be well tolerated in participants and will induce effects such as relaxation, euphoria, giddiness, and joy, and lead to mild alterations in the perception of reality. 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.

f. Pharmacokinetic considerations

After oral administration, psilocybin is detectable in significant amounts in the plasma within 20-40 minutes, its active metabolite, psilocin, is detectable at about 30 minutes, with maximum concentrations found around 80 minutes (92). The terminal elimination half-life is around 160 minutes (160).

g. Study population

Participants will be FM patients aged between 18 and 65 years. All subjects will be medically screened. In- and exclusion criteria are mentioned under section 4.2 and 4.3.

h. Interaction with other products

Participants are not allowed to use any psychoactive medication during the study. Use of drugs like painkillers (e.g. ibuprofen, aspirin, paracetamol) and oral contraceptives will be allowed during the study. Therefore, there will be no risk of drug interactions.

i. Predictability of effect

At the doses of psilocybin to be used in the present study, subjects are expected to retain their thought control and will remain aware of the transient state of the drug-induced experience. Given the results of previous research, we expect a reduction in pain tolerance and painfulness ratings in the psilocybin conditions. Effects such as relaxation euphoria, giddiness, joy, lightly altered perception of reality and anxiety are to be expected.

j. Can effects be managed?

Noticeable effects will disappear as the drug is eliminated from the body. Any long-term effects are regarded as positive. No harmful side effects are expected. If a person experiences unwanted effects, the medical supervisor will be contacted immediately and is in charge for detecting the cause and the seriousness of the complaints, and to provide a solution.

13.2.Synthesis

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).

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