Efficacy and safety of minidosing lysergic acid diethylamide (LSD) for chronic cluster headache: a randomized placebo-controlled study

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This study has been transitioned to CTIS with ID 2024-520305-39-00 check the CTIS register for the current data. Primary objective: to evaluate the efficacy of LSD 25µg every 3 days for 3 weeks in cCH. Additional objectives:- To evaluate the safety…

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

Summary

ID

NL-OMON57258

Source
ToetsingOnline

Brief title
LSD to Improve Cluster headache Impact Trial (LICIT)

Condition

- Headaches

Synonym
cluster headache

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Chronic cluster headache, LSD, Placebo-controlled, Psychedelics

Outcome measures

Primary outcome

Mean change in weekly attack frequency in the third treatment week compared to the 4-week baseline, across treatment groups.

Secondary outcome

- Response: 100% reduction (remission rate) in number of weekly attacks in the third treatment week compared to the 4-week baseline.

- Response: >=50% reduction (50% responder rate) in number of weekly attacks in the third treatment week compared to the 4-week baseline.

- Response: >=30% reduction (30% responder rate) in number of weekly attacks in the third treatment week compared to the 4-week baseline.

- Response: 100% reduction (remission rate) in number of weekly attacks across weeks 4-8 compared to the 4-week baseline and for each week separately.

- Response: >=50% reduction (50% responder rate) in number of weekly attacks across weeks 4-8 compared to the 4-week baseline and for each week separately.

- Response: >=30% reduction (30% responder rate) in number of weekly attacks across week 4-8 compared to the 4-week baseline and for each week separately.

- Mean change in weekly attack frequency across weeks 4-8 compared to the 4-week baseline and for each week separately.

- Mean change in weekly attack frequency in the entire 3 week treatment period compared to the 4-week baseline.

- Mean change in mean headache attack duration (minutes) and severity (1-10) in week 3 and across weeks 4-8 compared to the 4-week baseline.
- Mean change in weekly number of all acute medication to treat CH attacks in week 3 and across weeks 4-8 compared to the 4-week baseline.
- Proportion of subjects who required additional prophylactic treatment and/or GON-block during weeks 4-8, across treatment groups (denominator: randomized subjects who received at least two doses of study drug).
- Correlation between individual pharmacokinetics of LSD and relative change of weekly attack frequency (PK-PD modelling).
- Patient Global Impression of Change (PGIC) at weeks 3 and 8.
- Change from baseline in EQ-5D-5L Visual Analogue Scale (VAS) at weeks 3 and 8.
- Change from baseline in Adapted Cluster Headache Quality of Life Questionnaire (CHQ) 3 and 8.
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) at weeks 3 and 8.
- Efficacy of treatment masking at week 1 and 3, measured as perceived treatment assignment on a 5-point scale (likely verum/possibly verum/don*t know/possibly placebo/likely placebo).
- Change in rsMRI hypothalamic-diencephalic functional connectivity, comparing before and after the three weeks of treatment.
- Correlation between change in hypothalamic-diencephalic functional connectivity and change in weekly cluster headache attack frequency in the third week of the treatment period compared to baseline.
- Correlation between individual pharmacokinetics of LSD and change in

treatment-related rsMRI hypothalamic-diencephalic functional connectivity

(PK-PDimaging modelling).

- Cost-effectiveness analysis (CEA) from a societal perspective comparing the

LSD intervention with usual care.

Study description

Background summary

Cluster headache (CH) is the most painful and disabling primary headache disorder with a population
prevalence 0,124%. The desperation in this patient population is exemplified by approximately half of
patients reporting self-injurious behavior during attacks and many resorting to unproven complementary
remedies and illicit drug use in an attempt to treat their condition. CH has a major impact on quality of life,
socioeconomic functioning and use of healthcare resources.
Treatment of CH consists of acute remedies for attacks (mainly 100% O2, sumatriptan), transitional
treatment for temporary frequency reduction (subcutaneous steroid injection at the greater occipital nerve
(GON block), oral steroids or frovatriptan) and prolonged prophylaxis (e.g. verapamil, lithium, topiramate).
Although the latter compounds have shown some efficacy in reducing the attack frequency, the evidence
for their effect is weak. Moreover, all are used off-label, may have side effects and safety issues limiting
their utility, and efficacy may not persist over time. Some 15% of patients suffer from chronic CH (CCH),
when (near) daily attacks persist for more than * of the year; 10% of them are medically intractable4. To
control ongoing disease activity, prophylactic treatment is the current treatment standard for CCH, despite
considerable impact of drawbacks. Invasive, expensive treatments like hypothalamic deep brain
stimulation, occipital nerve stimulation and sphenopalatine ganglion stimulation are last resort options.
Recently, an expensive monoclonal antibody targeting CGRP received FDA approval for episodic CH
(ECH), but was shown to be ineffective in CCH. Thus, there is a considerable

unmet need for effective
treatments for CH that are better tolerated, safe and affordable, potentially
through repeated administration
of safe transitional treatments in the long-term control of disease activity.
In this study, we will assess the efficacy of interval treatment with a
psychedelic in CCH. LSD is probably
best called a mixed 5-HT2/5-HT1 receptor partial agonist and shares some
receptor properties with
methysergide, a compound that has been used in CH until its withdrawal from the
market. The
mechanism of action of LSD in CH is unknown, but probably mediated through its
affinity for serotonin
receptors, similar to other accepted treatments (ergotamine, triptans). Formal
evidence for the
efficacy of LSD in CH is currently lacking. However, several lines of
circumstantial evidence provide strong
indications that LSD may have potential for cluster headache prophylaxis

Study objective

This study has been transitioned to CTIS with ID 2024-520305-39-00 check the CTIS register for the current data.

Primary objective: to evaluate the efficacy of LSD 25µg every 3 days for 3
weeks in cCH.

Additional objectives:
- To evaluate the safety of LSD 25µg every 3 days for 3 weeks in cCH.
- To explore the exposure-response relationship of 25µg LSD in cCH.
- To assess the effect of treatment with 25µg LSD on hypothalamic functional
connectivity in patients with cCH, using resting state functional magnetic
resonance imaging (rsMRI).
- To explore cost-effectiveness of treatment with LSD in cCH.
- To evaluate the efficacy of LSD on health-related quality of life.

Study design

Randomized, double-blind, placebo-controlled, 1:1 parallel group, 12-week trial
comparing oral LSD 25µg to
placebo
Baseline phase: eligibility, 4-week baseline headache observation
Treatment phase: 3-week double-blind 1:1 treatment phase (LSD 25µg vs.
placebo); pre- and post-treatment funcional MR imaging of the brain
Follow-up phase: 5-week post-treatment safety and prolonged efficacy follow-up

Intervention

1-ml LSD base 25 microgram (dissolved in ethanol 96%) orally once per 3 days for 18 days (7 doses) versus placebo (ethanol 96%)

Study burden and risks

Number of physical visits: 4

Number of phone visits: 5

Investigative tools:
E-Diary: daily during the entire study
Questionnaires: Adapted Credibility/Expectancy Questionnaire (once); Patient Global Impression of Change (PGIC) (twice); EQ-5D-5L (three times), adapted Cluster Headache Quality of Life Questionnaire (CHQ) (three times); Hospital Anxiety and Depression Scale (HADS) (three times); iMCQ (once); iPCQ (once); Efficacy of Treatment Masking (twice)
MRI (twice)

Physical examinations: two
Laboratory sampling: 5 drawings, and one urine sample

ECG: two

Risk of investigational treatment: The minimal recognizable dose of LSD in humans is about 25 µg p.o. and side effects are dose dependent. At this dose, a positive mood effect and notably only very small and nonsignificant ego dissolution, with no anxiety, may be expected. As a member of the ergot alkaloid superfamily, development of retroperitoneal fibrosis must be monitored and left-sided cardiac valve dysfunction, although this has not been published.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male and female subjects 18-70 years of age at screening with CCH according to ICHD-3
- At screening: stable weekly attack frequency in the 4 weeks prior to screening (assessed retrospectively), averaging at least 8 per week and each week within a 40% window around the average
- At randomization: average of at least 8 attacks per week and no absence of attacks on more than two consecutive days during baseline

Exclusion criteria

- Use of excluded concomitant treatment at screening (lithium; other prophylactics if not on a stable dose for less than one month; steroids/GON block within 2 months before screening; sphenopalatinum block, neurostimulation (stimulator on) or botulinum toxin within 3 months before screening) and during the double-blind phase
- Use of LSD(-derivatives) (other than investigational drug), psilocybin, ketamine or cannabis within 3 months prior to screening and throughout the study (except study drug)
- Lifetime and/or family history (first degree relatives) of psychotic or bipolar disorder, suicidal intention or attempt
- A score of 6 or more on the *Ervaringenlijst* (PQ-16) to exclude subclinical

susceptibility to
psychosis
- Actual abuse of alcohol and/or recreational drugs
- Lifetime history of cardiac valvular disease
- History or evidence of cognitive disorder at screening
- Positive urine drug screen at screening
- Females: Pregnancy, lactation, no acceptable contraceptive use

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2023
Enrollment:	52
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Geen
Generic name:	D-lysergic acid diethylamide

Ethics review

Approved WMO

Date:	14-01-2025
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-01-2025
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-520305-39-00
EudraCT	EUCTR2022-003272-16-NL
ClinicalTrials.gov	NCT05477459
CCMO	NL82754.091.22