# A randomized, parallel, double-blind, placebo controlled trial to investigate HPA-axis activation before and after electro-convulsive therapy in patients with a major depressive episode using an orally administered 5-HTP challenge test

Published: 25-03-2009
Last updated: 06-05-2024

Primary:1. to investigate the serotonergic HPA-axis activation (cortisol, ACTH, prolactin) in patients with a major depressive episode, using a newly developed oral 5-HTP-challenge administered before the first ECT treatment.2. to investigate the...

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| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Mood disorders and disturbances NEC |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON33643

**Source**
ToetsingOnline

**Brief title**
5-HTP challenge in patients with a major depressive episode.

### Condition

- Mood disorders and disturbances NEC

**Synonym**
depression, depressive disorder

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Centre for Human Drug Research
**Source(s) of monetary or material Support:** Centre for Human Drug Research;Leids Universitair Medisch Centrum

## Intervention

**Keyword:** 5-HTP, depression, ECT, serotonin

## Outcome measures

### Primary outcome

Primary study endpoints

• Plasma ACTH

• Serum total and free cortisol

• Serum prolactin

• Saliva free cortisol

• Bond and Lader Visual Analogue Scale (VAS) for alertness, mood, calmness and

nausea.

• Adverse Event reporting (AE*s).

### Secondary outcome

Secondary endpoints:

Pharmacokinetics:

• plasma 5-HTP concentrations.

Psychometric parameters:

• Brief Symptom Inventory (BSI);

• Comprehensive Psychopathological Rating Scale (CPRS)

Safety:

• Blood pressure, Heart Rate, Body temperature, electrocardiogram

# Study description

**Background summary**

The relevance of assessment of serotonergic stimulation of HPA-axis in major unipolar or bipolar depressive disorder.
There is compelling evidence that among the biological factors predisposing a person to major depression, alterations in presynaptic 5-HT activity, alterations in postsynaptic 5-HT2 and 5-HT1A receptors in the brain, and reciprocal relationships between dysfunctions in these systems and the hypothalamus-pituitary-adrenal (HPA)-axis play an important role. Major depression is characterized by an increased number, affinity, or responsivity of central postsynaptic 5-HT2 receptors. This is associated with an increased HPA-axis (cortisol, ACTH) response to 5-HT precursors L-TRP and 5-HTP. Although oral administration of 5-Hydroxytryptophane (5-HTP) is a commonly used serotonergic challenge of the HPA-axis, there is little standardization of 5-HTP-challenge tests, and its use has been hampered by unclear pharmacokinetics. Furthermore, a narrow window exists between neuroendocrine responses and side effects, which limits its usefulness in patient studies.

The need for the development of a reproducible well-tolerated 5-HTP-challenge
Recently, several studies were performed in healthy volunteers at CHDR to develop a reproducible well-tolerated serotonergic challenge of the HPA-axis. This oral challenge test consists of several drugs:
-the serotonin precursor 5-hydroxytryptophan (5-HTP) at a dose of 100 mg, to stimulate serotonergic activity of the central nervous system
-the L-aromatic decarboxylase-inhibitor carbidopa at two doses of 100 and 50 mg, to inhibit peripheral conversion of 5-HTP with the aims of reducing peripheral gastrointestinal and cardiovascular adverse effects, enhancing brain exposure and diminishing the doses of 5-HTP
-the selective 5HT3-antagonist granisetron at a dose of 2 mg, to prevent nausea and vomiting

Recently a challenge test consisting of 5-HTP 100 mg, 200mg and 300mg combined with CBD 100 mg + 50 mg (5-HTP100/CBD100+50) was investigated and found to produce a reliable dose-dependent release of cortisol. Its pharmacokinetics were predictable and variability was acceptable, but its applicability was limited due to the frequent occurrence of nausea and vomiting. Therefore, maximal stimulation of the serotonergic system was precluded. Since suboptimal stimulation of central serotonergic pathways may lead to minimilization of

differences between treatment effects (eg. healthy volunteers vs. patients) this challenge was combined with an anti-emetic. 5-HTP 200 mg combined with CBD 100mg + 50mg (5-HTP200/CBD100+50) challenge test was combined with 2 mg granisetron and found to be effective in curbing its side-effects (figure 2) with maintenance of a predictable serum cortisol response and pharmacokinetics.

This challenge test was found to produce reproducible stimulations of the HPA-axis, evidenced by dose-dependent increases in (both plasma and salivary) cortisol and (more variably) of ACTH. The challenge did not lead to any increases in prolactin (contrary to 5-HTP-challenges without granisetron) and limited nausea without vomiting.

Other serotonergic challenges (like mCPP, 5-HTP alone, or SSRIs) are often characterized by low tolerability, poor reproducibility and/or limited HPA-axis stimulation. This 5-HTP-challenge developed at CHDR offers the most balanced serotonergic challenge that is available today.[3-5] This makes this challenge suitable for studies in patients, where assessment of serotonergic activation can provide important pathophysiological information about abnormalities of the HPA-axis in (subsets of) disease, and responses to treatments. Restoration from HPA-axis abnormalities with clinical responses to treatment has been documented, particularly in depressed patients who underwent electroconvulsive therapy (ECT). Commonly, HPA-axis abnormalities and their restoration after treatment is assessed with the dexamethasone suppression test (DST) or the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test. Currently there are no studies available that evaluate HPA-axis function before and after ECT treatment with a challenge of endogenous serotonergic activity. This study aims to apply this newly developed challenge in patients with major depressive disorder, before and after ECT.

**Study objective**

Primary:
1. to investigate the serotonergic HPA-axis activation (cortisol, ACTH, prolactin) in patients with a major depressive episode, using a newly developed oral 5-HTP-challenge administered before the first ECT treatment.
2. to investigate the effects of an ECT course on serotonergic HPA-axis activition (cortisol, ACTH, prolactin) in patients with a major depressive episode, using a newly developed oral 5-HTP-challenge administered before the first and after the last ECT treatment.
3. to investigate the tolerability of a newly developed oral 5-HTP-challenge in patients with a major depressive episode (Visual Analogue Scales).
4. to investigate the safety of a newly developed oral 5-HTP-challenge in patients with a major depressive episode (in terms of Adverse Events).

Secondary:
1. to investigate the kinetics of 5-HTP in patients with a major depressive episode.

2. to investigate the autonomic effects (temperature, blood pressure, heart rate) of a newly developed oral 5-HTP-challenge in patients with a major depressive episode
3. to explore the relationship between plasma and salivary cortisol profiles in patients with a major depressive episode receiving a newly developed 5-HTP challenge.
4. to explore the relationship between clinical response (CPRS) and neuroendocrine 5-HTP-challenge response (ACTH, cortisol, prolactin) before and after a course of ECT.

Pilot study:
In order to assess practical feasibility of the study and the burden of the study procedures for the patients, a pilot study (consisting of the first 5 patients or the first 6 months of study duration, whichever comes first) will be performed. The results will be presented to the ethics committee for review, prior to execution of the rest of the study

**Study design**

Randomized, parallel, double-blind, placebo controlled administration of an oral 5-HTP challenge test before and after electroconvulsive therapy (ECT).

The trial will consist of two parts separated by an interim analysis:

Part 1: Randomization in the first part will be asymmetrical with a 2:1 ratio of active:placebo treatment. 10 patients will receive 5-HTP and 5 patients will receive placebo.

Part 2: Randomization for the second part will be performed after the interim analysis. If decided to proceed with the second part, 10 more patients will receive 5-HTP and 5 more patients will receive placebo.

At the start of part 1 of the trial, a pilot study will be performed with 5 patients or during 6 months (whatever occurs first). The randomisation ratio of active:placebo treatment is 2:1, so after inclusion of 5 patients, at least 3 patients will have received the active treatment.

The results of the pilot study will be submitted to the Medical Ethics Committee of Leiden University Medical Centre prior to continuing the study. This will include the burden to patients, adverse events, the number of screened patients and the percentage of excluded patients after screening will be calculated, to evaluate the feasibility of the study. Based on the results of this interim analysis and the subsequent evaluation by the Medical Ethics Committee, the trial will either cease, continue or an amendment will be submitted before continuing in the case of change in the ethical nature of the original protocol.

**Study burden and risks**

- 2 days prior to the first and 1 day after the last ECT treatment patients will receive either a 5-HTP challenge or a placebo challenge.
- Patients are medication free since they are indicated for electroconvulsive therapy (ECT)
- Questionnaires are administered as part of routine patient care and do not signify additional burden to the patients.
- The 5-HTP challenge has been developed at CHDR and the PD effects, PK characteristics and safety have been studied well in at least 5 healthy volunteer trials.
- During the challenge patients are required to remain on bed (in total 4.5 hours).
- Patients receive an intravenous cannula on each study day for blood sampling.
- Patients may develop self limiting and short lasting nausea as side-effect of orally adminsitered 5-HTP.

# 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 or female sex
• Age of 18-75 years (extremes included);
• Diagnosed with a major depressive episode according to DSM-IV by attending psychiatrist;
• Scheduled for an ECT course;
• Signed Informed Consent;

## Exclusion criteria

• Severe hallucinations, delusions,or disorganized behaviour that could interfere with study compliance and/or provision of informed consent as to judgment of the psychiatrist;
• Suicidal intent or behaviour that may render participation dangerous to the patient and/or to the staff as to judgment of the psychiatrist;
• Severe cognitive impairment could interfere with study compliance and/or provision informed consent as to judgment of the psychiatrist or a MMSE score < 19;
• Use of prescribed drugs with a known effect on the serotonergic system. A minimum of 7 days medication-free days prior to the first challenge will be maintained except for drugs requiring a longer washout period due to kinetic properties. Specifically the use of serotonergic antidepressant drugs (SSRI*s, SNRI*s, TCA*s, MAOI*s, Lithium and atypical antipsychotic) are prohibited for the mentioned periods;
• Use of prescribed drugs with a known effect on the HPA-axis within 2 weeks of the first challenge. Specifically current oral corticosteroid use is prohibited.
• Comorbid post-traumatic stress disorder (PTSD);
• Clinically significant neuroendocrine disorders, specifically previous or current diagnosis of Cushing*s disease, Addison*s disease or adrenalectomy;
• Any other clinically significant concomitant disease which may negatively influence the study objectives or affect the patients* compliance to study procedures;
• Known history of adverse reactions to 5-HTP, carbidopa or granisetron.
• Use of illicit drugs within two weeks prior to the first challenge;
• Pregnant or breast feeding female patients;
• Previous use of MDMA or ecstacy;
• Blood donation according to the limits of the blood donation service prior to the first challenge.
• Participation in an investigational drug study within 90 days prior to the first challenge, or participation in four studies (or more) in the year prior to the first challenge.

# Study design

## Design

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| Study type: | Observational invasive |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Placebo |
| Primary purpose: | Diagnostic |

## Recruitment

NL

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| Recruitment status: | Will not start |
| Enrollment: | 30 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Product type: | Medicine |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 25-03-2009 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 07-07-2009 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO | |

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|---|---|
| Date: | 07-10-2009 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 10-12-2009 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 28-04-2010 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2008-007089-46-NL |
| CCMO | NL25767.058.09 |