SAMe as an epigenetic treatment of depression in people with childhood trauma, a double blind placebo-controlled trial

Published: 12-04-2018
Last updated: 15-04-2024

Primary objective is to compare changes in depression ratings in patients with childhood trauma receiving SAMe with patients receiving a placebo over a 12 week follow-up period. A number of secondary objectives will be investigated: 1. Comparing the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON55549

Source
ToetsingOnline

Brief title
SAM study

Condition

- Mood disorders and disturbances NEC

Synonym
depression in patients with childhood trauma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw en hersenstichting (hersenstichting via ZonMw in kader van PTO)

Intervention

Keyword: childhood trauma, depression, DNA methylation, S-adenosyl-L-methionine

Outcome measures

Primary outcome

The main study outcome is the difference in response rates according to Hamilton Depression ratings, between the treatment and placebo group from baseline to 12 week follow up. Response is defined as 50% reduction or more on the HAM-D.

Secondary outcome

1. The treatment group will be compared to the placebo group regarding changes in:

1.1 Montgomery-Åsberg Depression Rating Scale scores (measured weekly over the 12 week intervention period and at 6 month follow-up).

1.2 Relation between plasma levels of SAMe, genome-wide DNA methylation and KITLG methylation (measured before and after the 12 week intervention).

1.3 Inventory of Depressive Symptomatology (IDS) scores and Altman mania scores (monthly over a 6 month follow-up period).

1.4 Altered stress resilience (weekly during 12 weeks intervention and monthly during 6 month follow-up) using APL.

2. Measure SAMe plasma and serum levels and validate the DNA methylation

changes in separate cell types and whole blood expression for better

understanding of their biological relevance of identified methylation marks.

Study description

Background summary

The global burden of depression is increasing and progress in treatment discovery is disappointing. It is therefore important to capitalize on the recent insight that epigenetic mechanisms play a role in the increased risk to depression after childhood trauma. We have evidence for a consistent epigenetic maladaptation to childhood trauma in bipolar disorder and therefore propose to target these epigenetic abnormalities for treatment
of depression in patients with high levels of childhood trauma. To this end, we will use S-Adenyl-Methionine (SAMe) that influences DNA methylation. We have shown that SAMe changes a prominent DNA methylation mark of childhood trauma in vitro, and previous studies have shown efficacy in depression and cancer treatments. We investigate whether the epigenetic changes that are related to childhood trauma provide a treatment target for successful treatment of depression with SAMe.

Study objective

Primary objective is to compare changes in depression ratings in patients with childhood trauma receiving SAMe with patients receiving a placebo over a 12 week follow-up period. A number of secondary objectives will be investigated:
1. Comparing the treatment group with the placebo group regarding changes in continuous and long-term depression scores, measured weekly over a 12 week period and at 6 month follow-up.
2. Comparing the treatment group with the placebo group assessing changes in DNA methylation on a genome-wide scale, including the KITLG gene.
3. Investigate the relation between changes in plasma levels of SAMe and treatment response as well as DNA methylation (pertaining to the question whether there is a dose response relation of SAMe with methylation changes as well as treatment response)
4. To collect and store RNA, serum, plasma and sorted cells in order to measure SAMe plasma and serum levels and validate the DNA methylation changes in separate cell types and whole blood expression for better understanding of their biological relevance of identified methylation marks.
5. Comparing the treatment group with the placebo group regarding changes in stress resilience (changed symptom response on stressors).

Study design

12-week double-blind randomized placebo controlled add-on clinical trial with 6 months follow up. SAMe or placebo is added to trauma therapy and medication.

Intervention

For 12 weeks, 50 patients receive once daily 3 x 400mg of SAMe and 50 patients receive daily three placebo capsules which is added to 12 weekly individual sessions of trauma therapy.

Study burden and risks

Using SAMe carries a risk of rare side effects, the most common of which gastrointestinal symptoms and headaches. Manic switching in patients with bipolar disorder has been reported in case studies with the use of intravenous administration (but rates were not compared to switch rates in untreated patients not using SAMe). In this proposal we use oral administration of SAMe and do not expect an increased rate of manic switching. However (as part of good clinical practice) we will monitor participants closely for signs of elation and (hypo)manic symptoms. There is no additional risk associated with the study procedures. The pragmatic study design intends to minimize additional time investment from participating subjects. Permission to collect laboratory and medication history from available databases including their pharmacy and laboratory will be requested. Potential individual benefits are substantial: a decline of depressive symptoms and better adjustment to stressful experiences.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Diagnosis of current depressive episode as defined by DSM-IV-R as determined by the SCID.
2. Age 18 -65 years.
3. Stable medication use (in the last month and during study, meaning: no changes in: mood stabilizer, antidepressants and antipsychotics; dosage changes are allowed).
4. High levels of childhood trauma (as defined by above moderate to severe cutoff scores for any of the subscales; 13 for emotional abuse, 10 for physical abuse, 8 for sexual abuse, 15 for emotional neglect, and 10 physical neglect using the CTQ (Bernstein et al., 2003).
5. About to receive traumatherapy.

Exclusion criteria

1. Compulsory admission or treatment under Dutch law (BOPZ)
2. Major somatic disorder interfering with treatment or diagnosis
3. Pregnancy or breastfeeding or the intention to get pregnant in the near future
4. Rapid cycling (4 or more mood episodes in the previous year).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2019
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	S-Adenosyl-L-Methionine
Generic name:	S-Adenosyl-L-Methionine

Ethics review

Approved WMO Date:	12-04-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-002097-38-NL

Register	ID
CCMO	NL62020.041.17
Other	NTR, TC= 6302

Study results

Date completed:	31-05-2023
Actual enrolment:	31

Summary results
Trial ended prematurely