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Minimizing nocebo effects by conditioning with verbal suggestion

Submission date	Recruitment status	[_] Prospectively registered
16/10/2016	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/10/2016	Completed	[X] Results
Last Edited	**Condition category**	[X] Individual participant data
08/11/2023	Signs and Symptoms	

Plain English summary of protocol

Background and study aims
In common conditions associated with chronic (long-term) itching, the effects of treatment are usually small and vary between patients. Patients' expectations about treatment may contribute to this variation. Placebo effects are favorable treatment effects that are caused by patients' positive expectations about a treatment. Nocebo effects are unfavorable treatment effects that are caused by patients' negative expectations. Placebo and nocebo effects can be caused by verbal suggestion and conditioning. Verbal suggestion consists of providing verbal or written information about clinical improvement or aggravation, such as potential side effects. Conditioning consists of learning via experiencing. Placebo and nocebo effects have been investigated mainly in studies that focus on pain. Recent research has shown that verbal suggestion and conditioning can also induce placebo and nocebo effects on itching. This is highly relevant for the development of treatments for patients suffering from chronic itch, but first needs to be tested in healthy volunteers with itching stimulated either electrically or with the chemical histamine. The main aim of this study is to determine whether nocebo effects for electrical itch stimuli can be reduced by creating positive expectations, resulting in less itching. The other aims are to explore the effects of expectation on scratching behavior, and the role of characteristics like personality traits and genes.

Who can participate?
Healthy volunteers between 18 and 35 years old

What does the study involve?
The study consists of three parts. In part I, negative expectations regarding electrical itch stimuli are created. In the learning phase, two colored lights are displayed on a computer screen. Participants are instructed that one light indicates an increase in the itch stimulus and the other light indicates no change in the itch stimulus. Itch stimuli of high intensity are applied along with the first light and itch stimuli of medium intensity along with the other light. In the testing phase, participants are again told that the different lights indicate increased or non-changed itch stimuli, but only itch stimuli of medium intensity are applied.
In part II, participants are randomly allocated to one of three groups. In group 1 positive expectations are created by instructing participants that one light indicates a decrease in the itch stimulus and the other light indicates no change in the itch stimulus. Itch stimuli of low

intensity are applied along with the first light and itch stimuli of medium intensity along with the other light. In group 2 negative expectations are created using the same procedure as Part I. In group 3 no verbal suggestion is provided and only itch stimuli of medium intensity are applied. In the testing phase only itch stimuli of medium intensity are applied for all three groups. The levels of itching and scratching behavior caused by the different stimuli are measured to find out whether the nocebo effects created during Part I of the study can be changed by creating positive expectations (group 1), resulting in lower itch scores.
In part III, the same verbal suggestions are given to each group as in part II and then a single histamine itch stimulus is given.

What are the possible benefits and risks of participating?
Participants are reimbursed with money or research credits. No risks are involved with participation in this study, only an investment of time. Sensations of itch are induced using frequently used and tested stimuli of short duration which are not burdensome.

Where is the study run from?
Leiden University (Netherlands)

When is the study starting and how long is it expected to run for?
September 2013 to July 2015

Who is funding the study?
Innovation Scheme (Vidi) Grant of the Netherlands Organization for Scientific Research

Who is the main contact?
Prof. Dr Andrea WM Evers
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NL47084.058.14

Study information

Scientific Title
Can nocebo effects on itch be modified by a positive expectation induction? A randomised controlled trial

Study objectives
The primary objective of the study is to determine whether induced negative expectation effects for electrical itch stimuli can be modified. It is hypothesized that levels of itch (measured on a numerical rating scale; NRS) will be reduced after positive expectation induction in comparison to control groups in which either continued negative expectations are induced or an extinction procedure is applied. Exploratively, also expectancy effects on scratching behavior and generalization of expectancy effects to another itch stimulus (histamine iontophoresis) are studied. It is explored whether scratching will be reduced after positive expectation induction in comparison to the control groups, and that levels of itch as well as scratching will also be reduced when histamine iontophoresis is applied.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leiden University Medical Centre ethics committee (Commissie Medische Ethiek [CME]), 26/02 /2014, ref: P14.019

Study design
Single-centre three-arm randomized controlled single-blind study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied

Experimentally induced itch in healthy subjects

Interventions
Participants visit Leiden University once for approximately 4.5 hours. Expectations regarding itch stimuli are induced by conditioning and verbal suggestion procedures with respect to purple and yellow colored cues being displayed on a computer screen. For half of the participants, the purple cue is the conditioned cue and the yellow cue is the neutral cue, and visa versa for the remaining participants.

In part I during the learning phase, negative expectations for itch are induced in all participants by instructing them that the conditioned cue will indicate an increase in the itch stimulus. Accordingly, itch stimuli of high intensity are applied along with the conditioned cues and itch stimuli of medium intensity along with the neutral cues. In the testing phase, the same suggestions are provided, but only itch stimuli of medium intensity are applied.

In part II, participants are allocated to one of three groups through stratified random allocation to ensure equivalent numbers of male and female participants in each group. The participants were blinded for allocation to these groups, but it was not possible to blind the experimenter since the experimenter provided different verbal suggestions for the different groups.
1. In group 1 (experimental), positive expectations are induced by conditioning and verbal suggestion. Participants are now instructed that the conditioned cue will indicate a decrease in the itch stimulus and accordingly itch stimuli of low intensity are applied along with the conditioned cues and itch stimuli of medium intensity along with the neutral cues.
2. In group 2 (control), the negative expectation induction is continued as in Part I
3. In group 3 (control), an extinction procedure is applied in which no verbal suggestion is provided and only itch stimuli of medium intensity are applied.
In the testing phase of part II only itch stimuli of medium intensity are applied for all three groups.

In part III, the same verbal suggestions are provided for each group as in part II and then a single histamine itch stimulus is provided.

Intervention Type
Behavioural

Primary outcome measure
Level of itching, measured using an NRS score, induced by each electrical stimulus

Secondary outcome measures
1. Scratching behavior, induced by each electrical stimulus. Scratching behaviour is assessed by videotaping the participants during the experiment. Frequency, duration and localization of scratching behaviour are scored by an experimenter who is blinded for the randomization of groups and colored cues.
2. Level of itching (NRS rating) and scratching behavior induced by histamine iontophoresis

Overall study start date
04/09/2013

Completion date
16/07/2015

Eligibility

Key inclusion criteria
1. Healthy human volunteers
2. 18 - 35 years old
3. Both male and female
4. Fluent in Dutch language

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
35 Years

Sex
Both

Target number of participants
99

Total final enrolment
129

Key exclusion criteria
1. Severe morbidity (e.g., multiple sclerosis, diabetes mellitus, heart or lung diseases)
2. Psychiatric disorders (e.g., depression)
3. Use of pacemaker
4. Color blindness
5. Diagnose of histamine hypersensitivity
6. Chronic itch or pain complaints
7. Pregnancy

Date of first enrolment
10/09/2014

Date of final enrolment
16/07/2015

Locations

Countries of recruitment
Netherlands

Study participating centre
Leiden University
Wassenaarseweg 52
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Sponsor information

Organisation
Leiden University

Sponsor details
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Sponsor type
University/education

ROR
https://ror.org/027bh9e22

Funder(s)

Funder type
Government

Funder Name
Nederlandse Organisatie voor Wetenschappelijk Onderzoek

Alternative Name(s)
Netherlands Organisation for Scientific Research, Dutch National Scientific Foundation, Dutch National Science Foundation, Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek), NWO:Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), Dutch Research Council, Dutch Research Council, Netherlands, NWO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Netherlands

Results and Publications

Publication and dissemination plan
It is intended to publish the results in December 2016.

Intention to publish date
01/12/2016

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		14/09/2017	29/01/2019	Yes	No
Results article		05/11/2018	29/01/2019	Yes	No
Dataset		14/09/2017	08/11/2023	No	No
Protocol (other)		14/09/2017	08/11/2023	No	No