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PARTICIPANT INFORMATION SHEET
Cognitive-behaviour therapy and losartan

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You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take a moment to read the following information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?
Cognitive-behavioural therapy (CBT) is an effective talking treatment for anxiety disorders, but courses are long and difficult to access. However, we have recently shown that even a single session of CBT already has an effect on anxiety. On the other hand, research has shown that a simple blood pressure medication called losartan can improve cognition and memory. In this study, we would like to test whether combining a single-session of CBT with losartan can improve effects on anxiety, and what the underlying brain mechanisms of such an enhancement effect are. We would like to test two groups of people with panic attacks: one who receives CBT after having taken a single capsule of losartan, and one who receives CBT after having taken a placebo capsule. In particular, we would like to monitor your anxiety throughout the study and measure how your brain processes emotional information on the day after treatment. It is hoped that the knowledge gained from this study will contribute to the improvement of treatment for people who experience distressing panic attacks and anxiety disorders.

What is losartan?
Losartan is a medication for high blood pressure which has had UK market authorisation for 20 years. Recent research suggests that this drug can also improve cognition and the effects of learning experiences. As a side effect, some participants experience symptoms such as drowsiness, muscle weakness, low blood sugar, headaches, hypotension or allergic reactions. However, if you are randomised to the losartan condition you will only be asked to take a very low, single dose of 50mg, which is equivalent to what you would be prescribed daily if you had high blood pressure. Recent studies have shown that taking such doses is very unlikely to cause side effects.

Why have I been chosen?
You have been chosen because you have reported to experience panic attacks.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide to take part you will be given a paper copy of this information sheet to keep and a consent form to sign. You will still be free to withdraw at any time and without giving a reason. Withdrawal will not affect your clinical care.

What will happen to me if I take part?
If you decide to volunteer, we will establish your general eligibility over the phone or via email. You will then be asked to come to the Department of Psychiatry/ Warneford Hospital on five occasions over 6 months (see study flow chart). Before your Treatment Visit, you will be randomised to receiving a capsule before your CBT that will either be:

- a placebo capsule (not containing any medication)
- a 50mg losartan capsule.

Randomisation is a procedure that is often used in these kinds of studies and is comparable to tossing a coin. Until the end of your study participation, neither you nor the experimenter will be aware which treatment you have received.

We will have to ask you to refrain from taking benzodiazepine or beta-blockers 48 hours before your Treatment and Testing visits and your Follow-up visits, as these drugs are known to have an additional impact on the brain and symptom measures we are interested in.

1. Visit 1: Screening

Your first visit will be a screening session where we will make sure that it is safe for you to take part, and that you are suitable for this particular study. We will also give you the chance to ask any questions you might have. This session will involve asking you to:

- sign a consent form
- give us some information about your medical history
- answer some detailed questions about your current and previous psychological well-being
- complete a series of questionnaires asking about symptoms such as anxiety or low mood

The psychiatric interview can raise sensitive or upsetting personal issues. To minimize the chance of distress, these will be carried out by an experienced clinical psychologist in a private room, and you will be given breaks whenever needed.

Previous work has also suggested that normal variations in certain genes may influence how the brain responds to emotional information. We would like to measure this using a quick and painless genetic test, which is a cheek swab. This will be optional - you will be asked in the consent form if you agree to the collection and analysis of this sample for this study, and if you agree for your sample to be kept for future use.

The screening visit will take about 1 ½ to 2 hours.

2. Visit 2: Treatment

This visit will take place no later than 1 month after your Screening Visit. At the beginning, we will ask about your mood. You will then be participating in a testing session lasting about 1.5 hours. During this time, we will measure your speed and accuracy in simple reaction tasks on the computer, including responding to photographs of faces with different expressions, or categorizing words on the screen. Afterwards, you will receive a capsule that will either be a placebo capsule or a 50mg losartan capsule. After 1 hour, during which we will ask you to wait at the department (you will be allowed to read or work during this time), you will receive a single session of CBT. This will involve detailed individual information about the factors maintaining your anxiety and an exercise demonstrating how maintaining versus dropping these factors impacts on your anxiety. For the purpose of quality control, parts of this session might be audio taped but this will be anonymised and will not be published or made available to anyone outside of the research team. The researcher will make you aware of when this is happening and ask for your consent. This session will take 4 hours.

3. Visit 3: Testing

On the day following your treatment, we will ask you to answer some more questions about your mood and to work on a battery of computer tasks. The total time of your Testing Visit is approximately 2 hours.

4. Visit 4 and 5: Follow-ups

One month and 6 months after your treatment, we will assess your mood, using questionnaires and a brief interview. Each of these sessions will take about 1 hr.

Study flow-chart:

Visit 1: Screening (1 ½ hours)

Information and consent, medical and psychiatric screening, questionnaires

1 day to 1 month later:
Visit 2: Treatment (4 hours) Computer tasks Randomisation to receive either Losartan (50mg) + CBT Placebo +CBT
24 – 48 hours later:
Visit 3: Testing (2 hours) computer tasks, questionnaires
28- 40 days after visit 3:
Visit 4: 1-month Follow-up (1/2 hour) Questionnaires
180-200 days after visit 3:
Visit 5: 6-month Follow-up (1/2 hour) Questionnaires

What is Cognitive Behaviour Therapy (CBT)?
CBT is a form of psychotherapy based on the concept that the way we think about things affects how we feel emotionally. Thus, it aims at helping people to modify the way they think and the way they act. The underlying assumption is that learning processes play an important role in overcoming anxiety. Previous research suggests that this type of therapy is very effective in the treatment of anxiety disorders. In this study, we will only be able to offer one session of CBT. Full CBT treatment for panic disorder typically involves around 6-10 sessions, thus we do not expect that you will necessarily be free of all your symptoms after the brief intervention. Nevertheless, our previous work suggests that the majority of people experience a significant improvement in their symptoms at this point.

Inclusion Criteria
- Willing to give informed consent for participation in the study and to comply with all study requirements
- Male or Female, aged 18 years or above
- Experience of panic attacks and some life style changes as a results of those attacks

Exclusion Criteria
You will not be able to participate in this study if you:
- have a history of epilepsy or another neurological disorder, or other severe diseases such as kidney, liver, heart or respiratory problems, renal insufficiency, systemic infection, or intravascular fluid depletion
- have a history of a psychotic disorder, bipolar disorder, alcohol or substance abuse
- are pregnant or breast-feeding
- are taking blood pressure or other heart medication, especially a drug called aliskiren, or beta blockers, on a daily basis
- have been on antidepressant medication during the last 6 weeks
- have received the very specific psychological treatment we are using in this study in the last 3 months
- Participated in another study involving certain medication during the last 6 weeks
- will not be able to refrain from benzodiazepines or beta-blockers for 48 hours before the treatment or testing sessions

Please do not hesitate to contact us if you are unsure as to whether you fulfil criteria for study participation.

Are there any risks in taking part in this study?
For the doses used here, no side effects have been reported in previous studies. However, as a safety measure we will encourage you not to drive or cycle for two hours after study participation on your Testing Visit Day and instead walk or use public transport to get home.

What are the possible benefits of taking part?
Based on our previous experience it is likely that patients in both treatment groups will experience a decrease in anxiety and panic as well as agoraphobic avoidance. In addition, participants will be given the opportunity to make a contribution to our scientific

understanding of how the combination of acute losartan intake in combination with a single session of cognitive–behavioural therapy affects clinical anxiety and emotional processing to help understand the mechanisms underlying successful treatment.

Expenses and payments
If you take part in this study, you will be paid £70 for participation, and we are happy to reimburse reasonable travel expenses. In addition, you will receive one session of CBT for your panic symptoms, and we hope that you will find this useful.

What will happen if I do not want to carry on with the study?
Even after you have signed the consent form, you are absolutely free to withdraw from the study at any point without giving any reason and without medical care/legal rights being affected. Any identifiable data will then be destroyed.

What would happen if there is a problem?
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr. Andrea Reinecke, on (01865) 226471, email: andrea.reinecke@psych.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk. The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact PALS@oxfordhealth.nhs.uk or telephone 0800 328 7971

Will my taking part in this study be kept confidential?
Any information collected about you during this study would be kept strictly confidential and must be kept securely in paper or electronic form for at least 5 years following its completion. Any electronic data will be anonymised with a code. All such data are kept on firewall and password-protected computers and any paper information (such as your contact details and any research questionnaires) would be stored safely in lockable cabinets in a swipe-card secured building and would only be accessed by the research team. Responsible members of the University of Oxford, the Oxford Health NHS Foundation Trust or regulatory authority may be given access to anonymised data for monitoring and/or audit of the study to ensure we are complying with regulations. Sometimes, new methods to analyse data become available after a study has ended. Therefore we would ask for your permission to use your anonymised data in future studies, and to share data with other researchers both inside and outside the European Union. Research is a task that we perform in the public interest. The University of Oxford, as sponsor, is the data controller. This means that we, as University of Oxford researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will destroy most identifiable information about you as soon as possible after the study has finished. However, we will keep your consent form, which contains your name, for 5 years after the study has finished. We will store this securely at the University of Oxford and separately from your research data.
With your consent, we will keep your personal information on a secure database in order to contact your for future studies. If your treatment has been audio taped, these will be stored anonymously and will be deleted as soon as quality control has taken place (to confirm that the treatment has been delivered according to protocol). Audio taped information will never be published in direct quotes.
Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/]
You can find out more about how we use your information by contacting andrea.reinecke@psych.ox.ac.uk.

What will happen to the results of the study?
Anonymised results may be published at conferences and in scientific journals. However, no information which could be used to identify any individual participant will be published. Prior

to study participation, we will ask for your consent to use your anonymised data in future studies if new research questions emerge. However, you can opt out of agreeing to this, and this will not affect your study participation. At the end of the study, you will receive a lay report of the results if you are interested.

What will happen to my DNA samples?
Should you agree to have DNA samples taken these will be anonymised and stored in the laboratory freezer. We would also like to have your permission to store any remaining DNA. This will allow us to carry out similar work in the future on any genes that are subsequently identified to be potentially involved in anxiety and investigate how people's individual variations in these genes can affect their response to the measures used in this study. Ethical approval will be obtained for all such future projects. If you do not want to provide a DNA sample and/or do not wish us to store it we will note this on your consent form. If you do decide to take part in this part of the study, you can withdraw at any time without giving a reason, up to the point where samples are anonymised. If you withdraw from the study, your samples will be destroyed. The results of our research may eventually allow us to identify functional effects of the different types of brain receptors. However, many other factors are also likely to be involved and individual results will be very difficult to interpret. For this reason, we do not inform individual participants of their results from this part of the study.

Who is organising and funding the research?
The University of Oxford is Sponsor of the research and it is being funded by MQ: Transforming Mental Health.

Who has reviewed the study?
This study has been reviewed and given favourable opinion by South Central – Oxford A Research Ethics Committee.

Contact details
For further information on the study, or if you have any concerns, please contact Dr Andrea Reinecke. Email: andrea.reinecke@psych.ox.ac.uk or telephone: 01865 618320.

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