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PARTICIPANT INFORMATION SHEET FOR 18-20 YEAR OLDS
Losartan and emotional processing in healthy adolescents

Central University Research Ethics Committee Approval Reference: R79545/RE004
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We would like to invite you 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 time to read the following information carefully and discuss it with friends, family, or your GP if you wish. If there is anything that you do not understand, or if you would like more information, please ask us. Please take time to consider whether you wish to take part.

1. What is the purpose of the research?

One in five teenagers suffer from an anxiety disorder. However, even the most effective adult treatment – cognitive-behaviour therapy – only works in less than half of the younger patients. Neuroscientists suggest that teenagers' reduced response to treatment has to do with the brain still maturing during adolescence, particularly in brain areas that are important for good treatment response. Research in our and other labs in adults has recently shown that a single dose of a licensed blood pressure medication called Losartan can help improve function in exactly these brain areas. This could mean that taking Losartan before cognitive-behaviour therapy might help more teenagers benefit from treatment.

In this study, we are exploring how a single dose of Losartan affects learning in young people aged 16 to 20 years. We are particularly interested in aspects of learning that we know are important for psychological therapy to work well. For instance, it is thought that the ability to learn from positive feedback makes it more likely that a person responds well to anxiety treatment. To measure such aspects of learning, you will be working on a battery of simple computer tasks. In one of these tasks, you will for instance try and earn as many points as possible by correctly "betting" on one of two cards, and we will record which card you have chosen. We would like to test two groups of people: one who receives a single dose of Losartan, and one who receives placebo (a pill not containing any medication). Your allocation to one of these groups will be decided at random by a computer program. We hope that the knowledge gained from this study will eventually contribute to the improvement of anxiety treatments for teenagers.

2. Why have I been invited to take part?

We would like 60 people aged 16-20 years to take part.

Exclusion criteria: You may not be able to participate in this study if you:

- are younger than 16 or older than 20 years
- have a body weight below 35kg
- have extremely low blood pressure (we will assess this for you)
- are smoking more than 5 cigarettes a day
- are pregnant or breast-feeding
- have a close family member with a history of a severe psychiatric disease
- have ever had a severe psychological disorder such as psychotic disorder, bipolar disorder, alcohol or substance abuse
- have impaired kidney function or very high levels of potassium in your blood (we will assess these with a blood test)

- have a history of epilepsy or another neurological disorder such as ADHD or autism, or other severe diseases such as kidney, liver, heart or respiratory problems, systemic infection, or intravascular fluid depletion
- have been on certain medication that influences the central nervous system (e.g. antidepressants) during the last 6 weeks
- are currently taking blood pressure or other heart medication, especially a drug called aliskiren, or beta blockers
- participated in another study involving central-nervous-system-active (CNS)-active medication during the last 6 weeks
- have significant loss of hearing that is not corrected with a hearing device
- have insufficient written and/or spoken English skills
- are unable or not willing to provide GP contact details
- are unable to attend appointments in Oxford without occurring extreme travel costs

3. Do I have to take part?

No. It is up to you to decide if you want to take part in this research. Even after you have signed the consent form, you are free to withdraw from the study at any time without giving any reason, and without your withdrawal having any impact on your medical or legal rights, by advising us of this decision. If you are a student at the University of Oxford or Oxford Brookes, there would be no academic penalty if you decide not to take part in this study, or if you decide to withdraw at any point. Any personal data will be destroyed.

4. What will happen to me if I take part?

PRE-SCREENING ONLINE/PHONE (5 mins)

If you decide to participate, there will be an initial pre-screening: we will email you an online link to a few screening questions for you to complete (for instance, your age, weight, current medication and health, history of severe psychiatric illness for you or a close family member). You can complete this pre-screening online, or you can arrange a phone appointment with us. If you are ineligible and excluded from the study, all screening data will be destroyed. Once we have established your general eligibility, we will invite you to the Department of Psychiatry, Warneford Hospital, for two appointments: a brief *Screening Visit* and the *Testing Visit*.

SCREENING VISIT (1 hour)

This visit will involve:

- A chance to discuss this information sheet and any further questions
- Signing a consent form
- Asking you for some sociodemographic information (e.g. gender, level of education)
- Asking you for your GP's contact details so that we can inform them of your study participation
- Asking some detailed questions about your current and previous psychological well-being in an interview and a battery of questionnaires
- Asking some detailed questions about your current and past medical health, about medications you have been taking in the last 6 weeks, checking your weight, and taking your blood pressure.
- If you are female, we will ask you whether you might be pregnant during this visit.

If the above information suggests that you are ineligible to take part in the study, all your data will be destroyed. If you are eligible to go ahead, we will take a small blood sample (1ml, which is the equivalent to about 20 drops) from the crook of your elbow, to make sure that your kidneys are functioning normally. This will feel similar to having a blood sample taken at your GP practice, with potential brief discomfort when the needle goes in.

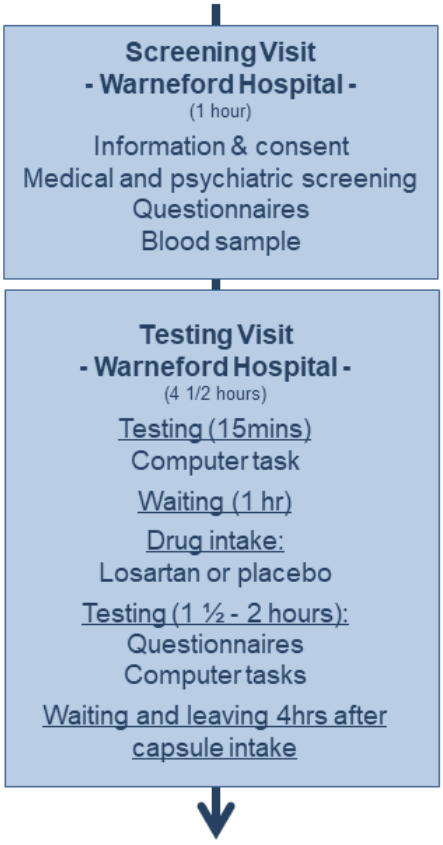
TESTING VISIT (4 ½ hours)

At the beginning of this visit, we will ask you whether anything has changed since your screening visit in terms of medication you are taking, physical health, and mental wellbeing. If you are female, we will also ask again whether you might be pregnant, and we will offer you a pregnancy test if you are unsure. Following this, you will work on a "*Threat" Processing Task* (15mins). You will be shown geometric shapes on a computer screen, with some of them being followed by a brief, moderately unpleasant tone (a scraping sound). We will ask you how pleasant or unpleasant you find the shapes, and we will measure galvanic skin response. Galvanic skin response is a pain-free measure of the electric characteristics of the skin and thought to indicate physiological or psychological agitation. It is measured using two probes that will be attached to your palm. We will also measure heart rate, by placing a cap on your index finger.

You will then receive a capsule that will either be:

- a placebo capsule (not containing any medication; main ingredient: microcrystalline cellulose)
- a capsule containing Losartan (50mg if you weigh over 50kg, 25mg if you weigh 35-50kg).

Which one of these treatments you will receive will be randomised, and until the end of your study participation, neither you nor the researcher will be aware which treatment you have received. Losartan has been tested in similar studies before, and it has been shown that single-doses like the one you might be receiving are unlikely to cause any side effects. We will ask you for physical symptoms before and after you have taken the capsule using questionnaires, and we will monitor your blood pressure.



One hour after having taken the capsule, you will be participating in another computer testing session lasting about 1 ½ to 2 hours. Again, we will be presenting stimuli on the computer screen and over headphones, and we will measure your choices, reaction times, and galvanic skin response. One of these tasks will be another "*Threat" Processing Task*, similar to the one you complete at the beginning of this session. Other tasks include a *Gambling Task* where you will try and earn as many points as possible by choosing one of two cards, or a *Memory Task* where you will indicate whether you have seen an item presented on the screen in a previously presented sequence.

You will be able to have breaks or stop the research at any point. Once you have completed the computer tasks, you will stay at the department until 4 hours have passed since you have taken the capsule. This is to make sure that your blood pressure is stable and that you are safe to go home. During this time, you will be able to read, eat, or do light work.

5. What is Losartan

Losartan is a medication for high blood pressure which has had UK market authorisation for over 20 years. Recent research in adults suggests that the medication can also improve cognition and the effects of learning experiences. Losartan has a good safety profile for use in adolescents, and the risk of side effects with a single dose is minimal.

6. Are there any risks in taking part?

We believe the risks associated with this study are minimal, but here is some more information on aspects of the study that you might be worried about:

i) Taking a drug: Half of the participants in this study will be taking one dose of Losartan, either 25mg (if weight 35-50kg) or 50mg (if weight at least 50kg). This is the equivalent to the dose

your GP would start you on if you had high blood pressure. Losartan has been tested and considered safe in children as young as 1 year. As a side effect, some patients who use Losartan daily for their blood pressure experience symptoms such as headaches, dizziness, tiredness, or drowsiness. In very rare cases, regular use of Losartan can lead to severe side effects such as kidney failure. However, before including you in the study, we will take a small blood sample from you to make sure your kidneys are working okay. Also, if you are randomised to the Losartan condition, you will only be asked to take a single dose. Others' and our own recent research in young adults have shown that taking such doses is very unlikely to cause any side effects.

Although we believe this is a very safe study, we will maximise your safety by:

- Screening you carefully for any criteria that might put you at risk (e.g. kidney dysfunction, heart disease, pregnancy, or lithium intake)
- Informing your GP of your study participation
- Monitoring you for 4 hours after capsule intake
- Having a doctor on site during your visit
- Having an independent data monitoring and safety board in place that will review the study on a regular basis.

In designing this study protocol, we have worked closely with world-leading experts to ensure the safety of our young participants. These include:

- Dr. Alexander Jones (University of Oxford), Consultant Paediatric Cardiologist and researcher with great expertise in the long-term use of Losartan in young children,
- Prof. Eric Storch (Baylor College of Medicine, Texas), a clinical psychologist with great expertise in pharmacological-psychological combination treatments for adolescents, and
- Prof. Anthony James (University of Oxford), CAHMS Consultant Adolescent Psychiatrist with a daily routine of prescribing medication and monitoring the safety of adolescents. Prof. James will be on site during your Testing Visit.

ii) Having blood taken: You will also be asked to provide a small blood sample during this study, to make sure it is safe for you to take Losartan. Blood will be taken by a trained and experienced researcher. However, as with all blood tests, this can lead to slight discomfort or bruising where the needle goes in.

iii) Psychological interview: As part of the screening session, we will be asking about your mental health. For instance, we will ask whether you have ever experienced a time in your life where you felt very low in mood, whether you have experienced or witnessed any traumatic events (i.e. a life-threatening event such as a traffic accident or fire), or whether there are any situations you feel very anxious in. Such questions could be upsetting. However, these interviews will be performed by experienced researchers who are closely supervised by a clinical psychologist.

iv) Data confidentiality: All information collected about you during this research will be kept strictly confidential. Any electronic data will be pseudo-anonymised and kept on firewall and password-protected computers. Any paper information (such as your consent form, contact details) will be stored safely in lockable cabinets in a swipe-card secured building and would only be accessed by the research team.

7. Are there any benefits in taking part?

While there are no immediate benefits for those people participating in the project, it is hoped that this research will contribute to the improvement of anxiety treatments for teenagers.

8. Expenses and payments

If you take part in this study, you will be given £100 for participation via bank transfer upon completion of the testing visit. We will also cover reasonable travel expenses.

9. What will happen to any samples I give?

As part of this study, we will take a small blood sample. These samples will be sent to the Haematology Department of the John Radcliffe Hospital on the same day using the hospital blood transport system. There, they will be analysed within 48 hours to make sure that your kidneys are working okay. No other tests will be performed on your sample. Once the samples have been analysed, they will immediately be disposed of by the laboratory.

Once we have taken your sample, it will immediately be pseudo-anonymised by a participant ID. This means it will not contain your name but only a unique study identifier. Only the researchers involved in the study will be able to link the sample code to your name.

10. What information will be collected and why is the collection of this information relevant for achieving the research objectives?

As part of this study, we will collect some **personal information** from you, meaning you are identifiable from it. This includes:

- Consent forms, where you sign that you feel informed and content to take part in the study. These forms will be kept in a locked filing cabinet only accessible by the study researchers. They will be stored for 5 years after the end of the study, separate from all other data, and then destroyed by shredding.
- Your contact details (name, phone number, email address) will be kept on a password-protected university server to be able to contact you throughout the study. This information will only be accessible by named researchers, and it will be destroyed at the end of the study.
- Link list: A list linking individual participant IDs to personal information will be held by the study researchers on a password-protected university server that will be accessible by named researchers only. This list will be destroyed at the end of the study.
- Reimbursement forms: Your name, home address, and bank details will be shared with the finances team of the Department of Psychiatry, who will issue the reimbursement for your time and travel. This information will be emailed to the finances team in a password-protected excel file and then deleted on the researcher's computer.

We will also collect **pseudo-anonymised data** from you, meaning that instead of your name, we will use a unique study code to label this data. While the study is running, the involved researchers will be able to link your code to your name, using the link list. This link list will be destroyed at the end of the study. Your data will then not be identifiable. The following data will be taken this way:

- Screening information will be collected including your age, gender, and level of education, to make sure the two groups we are comparing (the Losartan and the placebo group) are comparable with respect to these measures. We will also assess your medical and psychological history, to make sure you fulfil inclusion criteria for the study and are safe to take Losartan. This information will be collected on a paper form and transferred to a digital data sheet (similar to an Excel table), using only the unique participant code rather than personal information. If screening indicates a participant as non-eligible or a participant does not return for the testing session, all paper and electronic data will be destroyed for that participant.
- Questionnaire data will be collected to demonstrate that the two groups we are comparing (the Losartan and the placebo group) are comparable with respect to levels of anxiety, depression, and information processing styles. This data will be collected on a computer using survey software and then extracted into a digital data sheet. After extraction, your data will be deleted from the survey software.
- Computer task data, including choices, reaction times, accuracy, heart rate and galvanic skin response (the pain-free measure of the electric characteristics of the skin) recorded while you are working on the computer games. These tasks assess how you process certain emotional information, such as rewarding feedback or unpleasant sounds, and the data will allow us to explore how Losartan compared to placebo affects these parameters. After testing, this data will be transferred from the testing laptop to the university server and will then be deleted from the laptop.

At the end of the study, the code linking your personal information to your screening, questionnaire, and computer task data will be destroyed, so that data is no longer identifiable. This anonymised electronic data will be stored on a password protected university server with a secure firewall and stored for a minimum 5 years. With your permission, anonymised data collected during the course of the study may be used in future research.

11. Will the research be published? Could I be identified from any publications or other research outputs?

The findings from the research may be presented at academic conferences and may be written up in academic publications and a DPhil thesis. A copy of a DPhil thesis will be deposited both in print and online in the Oxford University Research Archive where it will be publicly available to facilitate its use in future research. You will not be identifiable from the outputs.

12. Data Protection

The University of Oxford is the data controller with respect to your personal data and, as such, will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest. Further information about your rights with respect to your personal data is available here: https://compliance.admin.ox.ac.uk/individual-rights.

13. Who has reviewed this study?

This study has received ethics approval from a subcommittee of the University of Oxford Central University Research Ethics Committee. (Ethics reference: R79545/RE004).

14. Who is organising and funding the research?

This study is organised by Dr Andrea Reinecke, Principal Investigator at the Department of Psychiatry, University of Oxford. The research is being funded by an award from the Oxford University John Fell Fund.

15. Who do I contact if I have a concern about the research or I wish to complain?

If a participant in research is ever considered to have suffered harm through their participation, the University has arrangements in place to provide for compensation. If you have a concern about any aspect of this study, please contact the principal investigator in this study, Dr Andrea Reinecke, email andrea.reinecke@psych.ox.ac.uk, telephone 01865 618320, and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) at the University of Oxford who will seek to resolve the matter as soon as possible: Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Boundary Brook House, Churchill Drive, Oxford OX3 7GB.

16. Further Information and Contact Details

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

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