Participant Information Sheet

Predicting **R**elapse after **A**ntidepressant **D**iscontinuation using **A**cute tryptophan depletion and **M**agnetoencephalography (PRADAM)

PRADAM is a research study. It will examine what happens when antidepressants are stopped. The study may in the future help us decide who can stop antidepressants safely, and who should continue taking them. me

It is important that you understand **why** the research is being done and **what it will involve**. Please take time to read the following information carefully **before you decide** whether to take part. You may wish to discuss it with relatives, friends, and colleagues. Please tell us if anything is not clear or if you would like more information. Take time to decide whether you wish to take part.

Overview

Why are we doing this study?

We would like to **help people stop antidepressant medications safely**. Research has shown that around one in three people who stop their antidepressants will have another episode of depression. PRADAM will develop measurements of brain function to understand this and predict, ahead of time, who will relapse.

Who can take part in the study?

People who would like to stop their antidepressant medication and who are no longer depressed. You have to have a GP in the UK, be between 18 and 64 years, and live within 1-2 hours of central London.

People cannot take part if they are still depressed. Women who are pregnant, breast-feeding, or planning pregnancy cannot take part.

Why have I been invited?

If you have received a letter from your GP, then this is because we have asked local General Practitioner (GP) surgeries and NHS services who often see people with depression to help us find suitable study participants by inviting some of their patients to take part. You will have been contacted if you have had an antidepressant prescription relatively recently or if you have discussed coming off the antidepressant with your GP or prescriber.

Do I have to take part?

No. It is completely up to you. Please read this information sheet carefully and think about any questions you may have. If you agree to talk to someone from the research team on the phone or by video call, we can discuss the study in more detail with you and answer any questions or concerns you may have. If you decide to take part, we will ask you to sign a consent form to show you have agreed to take part and you will be given a signed copy to keep. If you decide not to take part, you do not have to give a reason, and you will continue to be looked after by your GP.

Who do I contact if I want to take part?

If you are interested in taking part, you can enter your details on the study website at www.pradam.org or you can ask your GP or service provider to refer you to the study. You can also scan the QR code which will take you to the website.

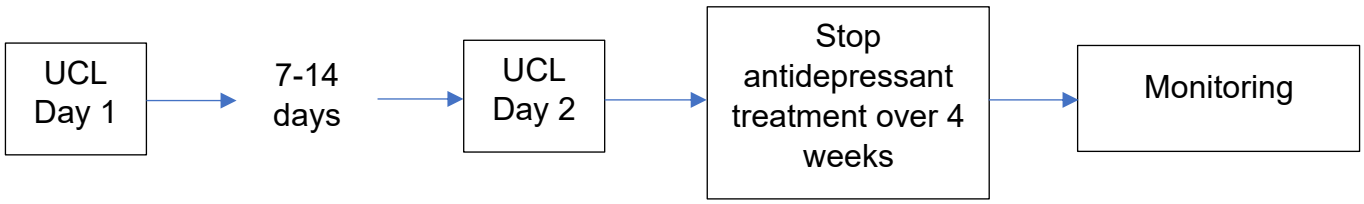
What will happen if I change my mind and want to stop taking part in the study?

You are free to withdraw from the study at any time, without giving any reason. You can tell us that you no longer want to participate, or you can simply stop responding.

What does the study entail?

What will happen to me if I take part?

Here is what participating in the study will look like:



You will be attending University College London (UCL) in central London for **two whole days**, each around 9 hours long. On each of these days, you will be having two **brain scans**. You will also have to **fast (not eat anything, but you can drink water)** from 8pm the evening before and will receive a very **specific diet** for the day. We will have to take two blood samples on each day. After these two days, you will slowly reduce and then **stop your antidepressant** medication. Once you have stopped the medication, we will **monitor** your mood. You will do tasks on a computer online and we will then contact you regularly for six months for signs of depression returning. If you have another depressive episode, we will let your GP know and you can decide with your GP what steps to take.

Stopping antidepressants. As part of the study, you will be stopping your antidepressant medication gradually over about four weeks. You should only participate in the study if you want to stop your antidepressant medication anyway, and have discussed this with your GP or psychiatrist. The medication tapering will be led by your GP or psychiatrist.

Brain Scan: The brain scan is called magnetoencephalography, or MEG for short. MEG measures magnetic signals that exist naturally in your brain. It does not interfere in any way with brain function and is not invasive. You will have two brain scans on each of the two visits to UCL, so four in total. During each of the brain scans, you will do a variety of tasks on a computer in front of you. Each brain scan lasts around 40 minutes. You will have to sit upright and keep your head very still during the scans. You will need to remove all hearing aids, cochlear implants, dental braces and any other metal before the scan. Here is an example video of what a MEG scan typically looks like https://www.youtube.com/watch?v=uwxR3wEeZnM.

Fasting and diet on UCL visit days: On the two brain scan days you will have to fast from 8pm the night before, i.e. refrain from eating anything. You can still drink water. You will be provided with food at UCL. The diet you will receive on the UCL days is called Acute Tryptophan Depletion or ATD for short. On one of the two UCL days (chosen randomly), the diet you receive will lack one specific amino acid called tryptophan. This will induce a drop in the serotonin levels in your body and in your brain within 2-3 hours. In some people, this can temporarily bring back symptoms of depression. At the end of both UCL days, everybody will get food that includes tryptophan. Any symptoms of depression resolve again within 2-3 hours after this. People who fast for religious reasons can participate outside their fasting period.

Monitoring: During the period when you reduce your antidepressants, and for six months after that, we will monitor you regularly. This will involve **eight emails or phone/video calls which take approximately 2-5 minutes per contact** and two approximately one-hour **sessions of tasks and questionnaires on your own computer at home**. In addition, we will ask you to complete a 15-minute recognition task on two occasions. You will access a website to complete the tasks. The tasks are a bit like games. They allow us to measure learning processes in the brain. After 6 months, we will call you to complete a final diagnostic assessment and questionnaires which together take approximately 40 minutes.

Total amount of time: The total time for participating in the study is anticipated to be around 2 whole days initially, and then another 3.5 to 4 hours spread out over six months.

Detailed overview of study activities

Initial assessment (35 minutes): You will be invited to talk to a researcher by phone or video call. If you agree to take part in the study, you will be asked to sign a consent form electronically. The researcher will then ask you questions to determine eligibility. The questions will be about your medical history, current medications, women's menstrual cycle (period), age, gender, marital status, ethnicity, education, finances and living arrangements. These questions help us ensure that people from diverse backgrounds are included. You will also be asked to complete questionnaires and practise a task on your computer at home.

Pregnancy test: If you are a woman who might get pregnant, we will send you a urine pregnancy test by post and will need you to tell us the result is negative before you can take part in the study.

GP contact: We will inform the GP that you are planning to stop your antidepressant medications as part of this study. We will give them time to contact us should they have concerns about this.

Online task instructions (20 minutes): After you have been invited to take part in the study, you will need to complete a set of online task instructions on a computer at home. These instructions are a simplified version of some of the experimental tasks that you will perform during the study. At the end of the session, you will also be asked to complete several questionnaires. Please note that all online parts of this study must be completed on a computer and cannot be completed on a tablet or smartphone.

Online training (65 minutes): Exactly three days before your UCL MEG visit, you will need to complete a set of online training tasks. This training session must be completed on that day.

Fasting: Stop eating at 8pm the night before UCL visit days, and only drink water from then until you visit UCL. We will then provide you what you eat and with drink during your days at UCL.

UCL visit day (whole day): On each of your two UCL visit days, you will arrive at UCL either at 8am or 10am (we will confirm the time). You will be met by a researcher and a psychiatrist. After a welcome, we will start with brief questionnaires (around 20 minutes total), followed by a first blood sample. You will then take the ATD diet. Neither you nor the researcher will know whether it contains tryptophan or not. There is then a waiting period until the diet takes its effect. During this waiting period, you will be offered food that does not interfere with the ATD diet, a selection of movies to watch, and will also do a few brief computer tasks. We will then take you to the MEG scanner. Around 3 hours after the diet intake, there is another blood sample and then you will start your first MEG session, which will last one hour, with some breaks. During MEG scanning, you will again do tasks on a computer in front of you. You will be sitting comfortably in a chair and be asked to try to move your head as little as possible. There is then a one-hour break and then the second MEG scan. After the second scan, you will have some more tasks to do on the computer before receiving a repletion diet which contains tryptophan. We will ask you to complete some additional questionnaires at different points during the day to monitor the effects of ATD diet. As soon as you are ready to go you will be free to leave.

	Early Schedule	Late Schedule
08:00	*Blood sample*, monitoring questionnaires **Diet intake**	
09:00	*Questionnaires (full)*	
10:00	Movie + brief computer tasks	*Blood sample* + Monitoring questionnaires, **diet intake**
11:00	Movie + brief computer tasks	*Questionnaires (full)*
12:00	B*lood sample* + Monitoring Questionnaires	Movie + brief computer tasks
13:00	**MEG scan 1**	Movie + brief computer tasks
14:00	Break	*blood sample*
15:00	**MEG scan 2**	**MEG scan 1**
16:00	Monitoring questionnaires Computer tasks	Break
17:00	**Repletion diet** Monitoring questionnaires	**MEG scan 2**

18:00	Monitoring questionnaires, Computer tasks
19:00	**Repletion diet**
20:00	Monitoring questionnaires

Learning task assessments (1 hour each): Around one week after discontinuing your antidepressants, we will ask you to do tasks on your computer at home. You will have three days to complete the whole set. You will repeat this once more at the very end of the study. In one of the learning tasks, you will try to find out which of two or more pictures produces more points if clicked on. Other tasks involve simply pressing one of two keys on your keyboard when you detect an arrow pointing one direction or the other.

Diagnostic assessment: After 6 months or whenever the monitoring suggests you may again have depression, we will perform a more in-depth diagnostic assessment.

Risks and benefits

What are the possible benefits of taking part?

There are no guaranteed direct benefits from participating in this research. However, you may benefit from being monitored carefully during the period where you stop antidepressants. Some people feel more comfortable trying to stop their antidepressant medication with this monitoring as it would allow them to react in good time if their depression started again. You may find it rewarding to take part in medical research. The results of this study may improve treatment and increase understanding of treatments for future patients, but this won't apply to you as we need to finish the study first.

Will I be paid for taking part?

Yes. There are three types of payments in the study. We will only be able to pay you for the parts of the study you complete. Payment will be through Love2Shop vouchers

Compensation: As a token of appreciation, we will compensate you for participating as follows:

- Each UCL study day: £100
- Monitoring time: £20

Reimbursement: We will reimburse standard class travel to UCL. If you travel by car, mileage will be reimbursed according to HMRC rates.

Bonus rewards: You can earn up to £30 in bonuses in the computer-based tasks, both online and during the MEG recording. This will be clearly indicated to you during the tasks.

Hence, in total, we can pay you up to a maximum of £250.

In addition to the payment, participants will receive a video clip of their own brain activity recorded during the MEG scans as a token of appreciation.

What are the risks and possible disadvantages of taking part?

Depression relapse and discontinuation symptoms: Stopping antidepressants increases the risk of a relapse of depression. Stopping too quickly also increases the risk of withdrawal symptoms. This is why we ask that you reduce medications slowly, and why we will monitor for relapse.

Acute Tryptophan Depletion: Some people find the diet we have to give you to reduce tryptophan levels unpleasant. Rarely, people even experience nausea and vomiting. In these cases, you may be withdrawn from the study. After taking the diet without tryptophan you may like you felt when you were depressed, with low mood and even with suicidal thoughts coming back. These symptoms resolve rapidly when you take tryptophan again. To manage this, a psychiatrist will always be looking after you during the UCL visit days. They will also ensure any further treatment or support is engaged quickly in the unlikely event that this should be required.

Magnetoencephalography (MEG) scanning: MEG is a non-invasive procedure and poses no known physiological risk. The most common barrier to MEG scanning is mild claustrophobia suffered by some people when enclosed in the magnetically shielded room (which is about the size of a large freight elevator). All participants are provided with a squeeze bulb that they can activate at any time in order to alert experimenters to stop the scanning and allow them to leave the room.

Pregnancy: Pregnancy is a period of high risk for depression. Stopping antidepressants while pregnant increases the risk of a relapse. Episodes of depression can have adverse effects both on the mother and the baby. If you become pregnant, please tell us and your GP immediately.

Psychological distress: Some of the questions on the questionnaires may make you feel upset. If you become distressed at any point during the study we can provide details of organisations you can contact for support. It is also possible to take breaks when completing the questionnaires.

Disclosure of information: If we are worried about your safety, or the safety of others, we may have to tell your GP. We will always try to speak with you before doing this. Very rarely, we might have to pass information to your GP without your agreement. We would only do this if we had urgent concerns for your welfare, or the welfare of others. For example, if you told us that you were having thoughts of harming yourself or someone else. There is a very small risk that information we hold is disclosed by accident, for instance due to criminal activity or due to a major failure of computer systems.

What happens if the research stops?

Very rarely a study is stopped early. If this happens, the reasons will be explained to you and arrangements made for your GP to continue your care as usual.

Your data

How will we use information about you?

We will need to use information from you for this research project. This information will include your initials, name, date of birth, NHS number, address, and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

UCL is responsible for looking after your information. We will not share your information related to this research project with any other organisations. We will keep all information about you safe and secure by:

- keeping data that can be used to identify you on a highly secure UCL server
- keeping this research data separate from other research data
- transferring data from the tasks and questionnaires you complete online to UCL servers
- recording MEG data on university computers and securely transferring it to UCL servers.

International transfers

We may share or provide access to data about you outside the UK for research related purposes to:

- enable other researchers to use the research data to examine any questions this data could be helpful for. This is to ensure that the research data is put to best possible use and to ensure any findings based on these data can be openly and transparently tested by others.

If this happens, we will only share the data that is needed. We will also make sure you can't be identified from the data that is shared where possible. This may not be possible under certain circumstances – for instance, if you have a rare illness, it may still be possible to identify you. If your data is shared outside the UK, it will be with the following sorts of organisations:

- any organization or individual interested in the data

We will make sure your data is protected. Anyone who accesses your data outside the UK must do what we tell them so that your data has a similar level of protection as it does under UK law. We will make sure your data is safe outside the UK by doing the following:

- We will anonymize data before sharing it. This means no identifiable information about you will be shared, and that data will only be shared in a form that minimises the risk that you could be identified.

How will we use information about you after the study ends?

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. We will

keep your study data for a maximum 5 of years. The study data will then be fully anonymised and securely archived or destroyed.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. You have the right to ask us to access, remove, change or delete data we hold about you for the purposes of the study. You can also object to our processing of your data. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this.

Where can you find out more about how your information is used?

You can find out more about how we use your information at **www.hra.nhs.uk/patientdataandresearch**, by contacting the UCL Data Protection Officer at data-protection@ucl.ac.uk, by going online and accessing the UCL research privacy notice: https://www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice or by asking one of the research team.

What will happen to my blood samples?

Your samples will be stored in a freezer on secure UCL premises until they are sent to the laboratory to measure the level of tryptophan and other amino acids in your blood. After that, the samples will be destroyed.

Confidentiality

We need to tell your GP that you are participating in this study and intent on stopping your antidepressant medication.

The study will hold sensitive data about you. There are strong safety precautions in place, but there is a very small risk that sensitive medical information about you may become public, for instance if the computers are hacked.

We respect confidentiality but cannot keep it a secret if anyone is being harmed or is at risk of any harm. If this arises, you will be informed that confidentiality cannot be maintained in that regard, and the appropriate personnel will be informed.

Certain individuals from the research team, UCL and regulatory organisations may occasionally look at your medical and research records to meet legal, ethical and safety requirements. All individuals who have access to data will be bound by strict data protection and confidentiality rules. The researchers who analyse the study information will not be able to identify you or see your name, NHS number or contact details.

What will happen to the results of the research study?

Publication of results: We will publish the results in scientific journals and where possible on our laboratory website (www.acplab.org). Interested participants will be provided with a lay summary of the results.

Publication of research data: To allow other researchers to build on the findings of this study and verify them, the research data will be published in anonymised form. This means that the data will be openly accessible to anybody, but only in a form that minimises the risk that you could be identified. Personal details that can be used to identify you will never be published under any circumstances.

Other important details

Contact

Please contact the study team on pradam@ucl.ac.uk for further information.

What if there is a problem?

Every care will be taken during this study. However, in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor's (University College London) or site's negligence, then you may be able to claim compensation. After discussing with your study doctor, please make the claim in writing to Prof Quentin Huys (q.huys@ucl.ac.uk) who is the Chief Investigator for the study and is based at University College London. He will then pass the claim to the Sponsor and on to Sponsor's Insurers. If you have a claim, then it might be helpful to consult a lawyer. Participants may also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your study doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the study, the normal National Health Service complaints mechanisms are available to you (https://www.england.nhs.uk/contact-us/feedback-and-complaints/complaint/). Please ask your study doctor if you would like more information on this. Details can be obtained from the NHS website. You can also contact your local PALS (Patient Advice and Liaison Service) to make a formal complaint.

Who is funding the research?

The funder of this research is the Wellcome Trust (grant number 221826/Z/20/Z).

Who is responsible for the study and the data overall?

UCL is the sponsor for this study based in the United Kingdom. UCL will act as the data controller for this study. This means that UCL is responsible for looking after your information and using it properly.

Who has reviewed the study?

All proposals for research using human subjects are reviewed by the Health Research Authority (HRA) and an Ethics Committee before they can proceed. This proposal was reviewed by the East Midlands - Leicester South Research Ethics Committee.

Appendix

ATD drink mixtures

Balanced drink (TRP+)		Depletion drink (TRP-)	
Amino Acid	Gram	Amino Acid	Gram
L-isoleucine	6.0	L-isoleucine	6.0
L-leucine	10.1	L-leucine	10.1
L-lysine	6.7	L-lysine	6.7
L-methionine	2.3	L-methionine	2.3
L-phenylalanine	4.3	L-phenylalanine	4.3
L-threonine	4.9	L-threonine	4.9
L-valine	6.7	L-valine	6.7
L-tryptophan	3.0	L-tryptophan	-
Total:	44g		41g

Study flowchart