Summary

This is only a summary of the study. Please do read the full Participant Information Sheet that follows this summary if you are interested in the study.

Why me?

You are being invited because you have told your GP or another NHS service that you experience low mood.

What is the purpose of the study?

We don't know which antidepressant drug works best for whom. This means that we often have to try out different drugs before we finally find one that works. We would like to be able to tell in advance which drug will work best for any one person. This study is part of a research effort working towards that goal.

Do I have to take part?

No, you don't have to take part. It is entirely up to you whether you want to take part. Take your time to decide. You won't be treated any differently by the NHS or your GP if you choose not to.

What will taking part involve?

We will first assess whether you can take part in the study. We will need to know things like whether you have depression, and whether you can take antidepressant drugs safely.

Taking part in the actual study will mainly involve two things:

- taking one of two antidepressant drugs for 6 months
- doing tasks and answering questionnaires on your computer at home

The two antidepressant drugs are called escitalopram and bupropion. For the first 8 weeks, you will not know which drug you are taking. For the first 2 weeks, you might even be taking a placebo, i.e. no antidepressant drug at all.

The tasks are a bit like games, and allow scientists to measure learning processes in the brain. You will play them before starting to take the drugs, and then again after 2 weeks and after 4 weeks. The tasks and questionnaires will take around 2 hours to do each time. All together, the study could take up to 7 hours of your time in the first month, and another 1 hour over the next 6 months. We will reimburse you for your time.

There are also some other, optional study activities you can do if you want to. These involve a brain recording ("EEG") and doing the tasks and questionnaires again at the end of the study.

Are there benefits?

Through the study, you could be getting bupropion, which is not usually prescribed by GPs but by specialists. You can also earn a small monetary bonus in the tasks.

Are there any risks? Yes, there can be risks when taking medications. We will check that the medications are safe for you to take. You cannot take part if you are pregnant or planning a pregnancy.

Participant Information Sheet

REinforcement **L**earning **ME**chanisms of pharmacological treatments for **D**epression (RELMED)

RELMED is a research study. It will examine how different antidepressants work. This research could help doctors make more personalised decisions on which antidepressant to prescribe to a particular person.

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 want to understand how different antidepressant drugs work. Research has shown that antidepressants can change learning processes in the brain. However, we do not know if this is how antidepressants work in treating depression. We also do not know if different antidepressants affect different learning processes. To study learning processes, scientists use **computer-based tasks**. This study uses tasks to examine whether different antidepressants change different learning processes in our brains.

Who can take part in the study?

People aged 18 or above who have depression and are under the care of a participating GP in the UK can take part.

People cannot take part if they have taken an antidepressant in the past six weeks or if they cannot take bupropion or escitalopram for medical reasons. Women who are pregnant, breast-feeding, or planning pregnancy and who do not wish to use effective contraception cannot take part.

Why have I been invited?

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 recently discussed low mood with the GP or your local service provider/organisations.

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.relmed.ac.uk or you can ask your GP or service provider to refer you to the study.

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. However, it is important that you do not stop taking the study medication suddenly. You will need to gradually reduce your dose, and we will guide you on how to do this.

What does the study entail?

What will happen to me if I take part?

Medication: As part of the study, you will be given one of two antidepressant drugs **for 6 months**. Both are equally good at treating depression. The antidepressant **escitalopram** is licensed in the UK for treating depression. The antidepressant **bupropion** is used widely across the world to treat depression. In the UK, it is licensed to help people stop smoking, but it is used by specialists to treat depression.

Random allocation: A computer will randomly assign you to one of four groups:

- Group 1: People in this group take the antidepressant escitalopram.
- Group 2: People in this group take the antidepressant bupropion.
- Group 3: People in this group take a placebo (a pill without active ingredients) for two weeks, then the antidepressant escitalopram.
- Group 4: People in this group take a placebo for two weeks, then the antidepressant bupropion.

For the first 8 weeks, neither you nor the research team will know which group you are in. After 8 weeks, we will tell you which medication you are on. If there is an emergency, there is a procedure in place to find out which medication you are taking.

Tasks on the computer: You will **do tasks on your own computer at home**. 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. You will do the tasks before starting to take the drugs, and then again after 2 weeks and after 4 weeks. You will also fill in some questionnaires. The tasks and questionnaires will take around 2 hours to do each time. However, you always have three days to complete all the tasks and questionnaires. We will additionally ask you to fill in questionnaires on your computer after 6 and 8 weeks, which will take around 10 minutes each time.

Total amount of time: The total time for participating in the study is anticipated to be around 7 hours in the first month, and 1 hour spread over the next 6 months.

Detailed overview of study activities

Initial assessment (1 hour): 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, menstrual cycle (period) in women who can get pregnant, 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 about anxiety and quality of life. Finally, you will practise the learning tasks on your computer.

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 before you can take part in the study.

GP contact: Where there is uncertainty the study team will contact your GP to confirm that there are no known medical reasons why you should not take part in the study.

Learning task assessment 1 (2 hours): We will then ask you to complete the first 2-hour session of the online learning tasks at home. This will also include a set of questionnaires about aspects of depression and anxiety. You will have 3 days to complete the online learning task and the questionnaires. You do not have to complete it all in one go.

Random assignment and medication start: If you are suitable for the study, you will be randomly assigned to one of the four trial groups. The study medication will then be posted to you via 24 hour tracked mail. We will tell you when the medication has been posted. You will need to sign to receive this when it arrives. For the first eight weeks, you will not know which medication you are taking. The research team also will not know.

Taking the medication: You will receive four boxes of medication. Each box contains the medication for a specific time period. We will call you to tell you which box to use when. During these calls, we will also ask you to count the number of tablets left in the bottle. We will also ask if you have experienced side effects.

Learning task assessments 2 and 3 (2 hours each): After two weeks, you will do the learning tasks and questionnaires again. This should again take two hours. You will do this on your computer at home. You will have three days to complete the whole set. After another two weeks have passed (week 4), you will repeat this once more.

Questionnaire assessments (10 min each): After 6 and 8 weeks of medication, we will ask you to fill in the same questionnaires as before.

Finding out which antidepressant you are taking: After 8 weeks, you will receive your medication for the next 18 weeks. You and the research team will now find out which medication you are taking.

End of treatment: After 24 weeks, you will start to slowly reduce the dosage of medication. The aim will be to stop the medication by 6 months under medical guidance. If you wish to continue to take the medication, you will need to discuss this with your GP. In this case the GP would continue prescribing the medication.

1-year follow-up (10 min): After 1 year, we will ask you to fill in the same questionnaires as before one last time even if you have stopped the medication after 6 months.

Optional study components

Optional EEG recording

You may choose to take part in an additional study. This will involve measuring brain activity using electroencephalography (EEG). EEG measures electrical signals in the brain using small sensors placed on your head. EEG is painless. The EEG assessment will take about 3 hours and requires an in-person visit to the local university site. We will not share any details about the EEG with you or your GP. If you agree to take part in the EEG study, you will have an EEG session before starting to take the drugs and we will invite you back for another EEG session three weeks later. During the EEG, we will also ask you to do the learning task on the computer. You will be reimbursed for travel to the EEG site and receive additional compensation for doing this.

Optional additional computer learning tasks and questionnaires at the end of treatment

After 6 months, the medication will normally be stopped unless your GP and you agree to continue with the medication. When the medication is stopped, you can choose to participate in another optional component of the study. This will involve repeating the online computer learning tasks once just before you stop the medication, and one more time two weeks after that. You will obtain additional compensation for doing this.

Risks and benefits

What are the possible benefits of taking part?

You have a 50% chance of being treated with bupropion. Bupropion is usually only prescribed by specialists. Both escitalopram and bupropion are expected to improve your symptoms of depression. We cannot promise that there will be any other direct benefits to you from this research. However, the results of this study may improve treatment and increase understanding

of treatments for future patients. Some people find it rewarding to take part in medical research and appreciate the additional monitoring and contact with the researchers.

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.

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

- Main study participation: £50
- Optional EEG component participation: £50 + artistic rendering of your brain waves
- Optional discontinuation component participation: £25

Reimbursement: We will reimburse standard class travel to the EEG recording site if you participate in the optional EEG component.

Bonus rewards: You can earn bonuses in the computer-based tasks, both online and during the EEG recording. For each session, you will be able to earn up to £5 depending on your choices. This will be clearly indicated to you during the tasks. There are a total of 3 task sessions in the main study, 2 in the EEG component, and 2 in the discontinuation component.

What are the risks and possible disadvantages of taking part?

Pregnancy: Escitalopram and Bupropion may harm unborn babies and may be passed through breast milk. There may be harm to your baby if you become pregnant while taking this medication during the trial. If you become pregnant during the trial, **you must inform the study team immediately**. The study medication will be stopped. We will discuss referral for specialist counselling on the possible risks to yourself and your unborn baby. To better understand the effects the medications may have on the developing foetus, we will ask you to allow us to monitor your pregnancy. We will give you detailed information on this and you can choose whether to take part or not. If you take part, we will monitor the pregnancy until 6 weeks after the due date.

Contraception: To take part, women who can get pregnant must agree to use an effective method of contraception. Effective methods are either treatments like the “pill” or barrier methods (such as condoms) or not having any sex at all.

Side effects: Escitalopram and Bupropion can cause side effects. Only some people get them. People taking higher doses are more likely to feel side effects. Both medications can have serious side effects if you suffer from certain illnesses, or if they are taken in combination with certain other medications. We will check your medical history and what medications you take before including you in the study. When you start taking the study medication, you will take a lower dose in week 1 to mitigate possible side effects. If you experience side effects when you take the study medication, it is possible to reduce the dose. Some of the most common side effect for Bupropion include: Abdominal pain; anxiety; lack of concentration; constipation; dizziness; dry mouth; fever; digestive system disorders; headache; excessive sweating; hypersensitivity; difficulty falling asleep (reduced by avoiding dose at bedtime); nausea; skin reactions; taste altered; tremor; vomiting. For Escitalopram these include: Sinus infection; Anxiety; abnormal appetite; irregular

heartbeat; joint pain; unusual fatigue; lack of concentration; confusion; constipation; depersonalisation; diarrhoea; dizziness; drowsiness; dry mouth; fever; gastrointestinal discomfort; unusual bleeding or bruising; headache; excessive sweating; malaise; memory loss; menstrual cycle irregularities; muscle ache; enlarged pupils; nausea (dose-related); palpitations; pins and needles; changes in heart rhythm; sexual dysfunction; skin reactions; sleep disorders; taste altered; ringing in ears; tremor; urinary disorders; visual impairment; vomiting; weight changes; yawning. A detailed list of all the side effects including less common and rare one along with contraindications for the medications can be found at the end of this document.

Random allocation: You cannot choose which of the two antidepressants you receive. Your allocation will be decided by chance. For the first eight weeks, neither you, your GP, nor the research study team will know which treatment you are taking. Please do not try to find out yourself. After eight weeks you will find out what medication you have been receiving. We will provide your doctors with a way of finding out which medication you are taking if this is medically required.

Withdrawal effects: You can stop taking the study medication at any time. Stopping suddenly increases the risk of withdrawal symptoms. If you stop taking the medication, you should reduce it gradually, under medical guidance. If the medication improved your symptoms, then stopping it may also increase the risk of having a depression relapse.

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.

EEG (optional): There is a small chance that people with sensitive skin might experience some redness or irritation where the EEG sensors touch. This usually goes away within a day. Otherwise, EEG is safe.

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.

We will keep all information about you safe and secure. Data that can be used to identify you will be kept on a highly secure server at University College London (UCL). It will be kept separate from any other research information we collect. The data from the tasks and questionnaires you complete online will be transferred directly from your browser to UCL servers. If you participate in the optional EEG study, the EEG data will be recorded on university computers and securely transferred to UCL servers.

Only authorised members of the research team will have access to your information though we will need to pass on your name, address and contact details to the pharmacy who will send you the study medication through the post and we will need to provide your name, phone number and email address to the company managing the login system for the study website. If you would like to receive tracking updates from Royal Mail about the trial drug delivery and coordinate scheduling of the delivery, the pharmacy can share your mobile phone number and your email address with Royal Mail for this purpose with your consent.

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.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports so that no one who takes part in the study can be identified.

Confidentiality

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.

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.

What will happen to the results of the research study?

Publication of results: We will publish the results in scientific journals. Summaries of the results will appear on the study website www.relmed.ac.uk.

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.

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. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

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.

Other important details

Contact

Please contact the study team 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 clinical trial/ 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. 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 226790/Z/22/Z).

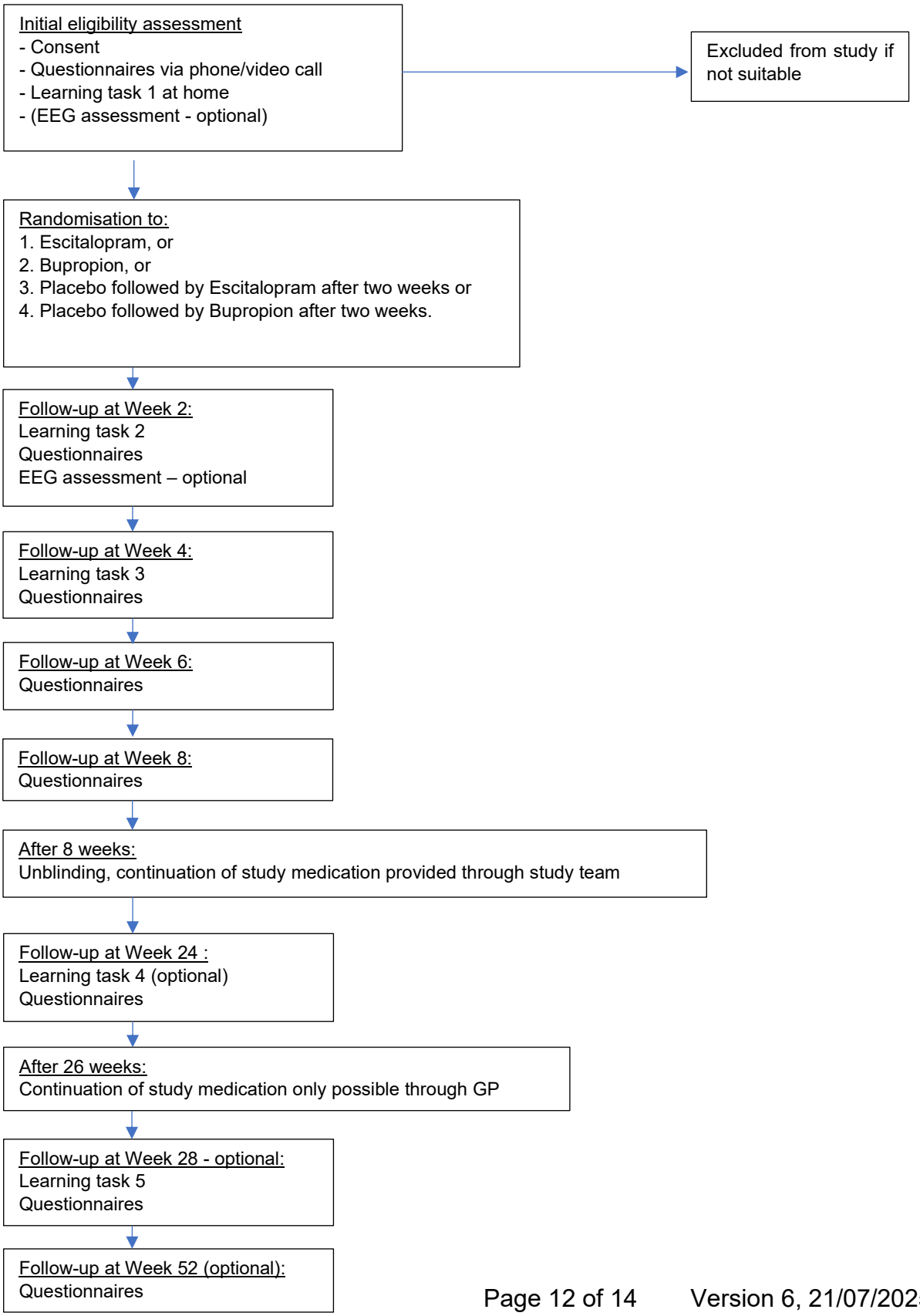
Who is responsible for the study and the data overall?

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 South Central - Berkshire Research Ethics Committee.

Study flowchart



Appendix - Bupropion side effects and contraindications

Side effects

Common (occurring in at least 1 in 100 people) or very common (occurring in at least 1 in 10 people)
Abdominal pain; anxiety; difficulty concentrating; constipation; dizziness; dry mouth; fever; gastrointestinal disorder; headache; hyperhidrosis (excessive sweating); hypersensitivity; insomnia (reduced by avoiding dose at bedtime); nausea; skin reactions; altered taste; tremor; vomiting

Uncommon (occurring between 1 in 100 to 1 in 1000 people)
Decreased appetite; asthenia (feeling weak); chest pain; confusion; tachycardia (heart beating faster than normal even at rest); tinnitus (ringing in ears); vasodilation (widening of blood vessels which could cause low blood pressure and flushes); visual impairment

Rare (occurring in up to 1 in 1000 people) or very rare (occurring in up to 1 in 10,000 people)
Angioedema (swelling under the skin); arthralgia (joint pain); abnormal behaviour; bronchospasm (sudden tightening of airways); delusions; depersonalisation; dyspnoea (difficulty breathing); hallucination; hepatic (liver) disorders; irritability; memory loss; movement disorders; muscle complaints; palpitations; paraesthesia (pins and needles); parkinsonism (shaking); postural hypotension(feeling dizzy when standing up); seizure; sleep disorders; Stevens-Johnson syndrome; causing painful rashes and peeling skin; syncope (fainting or temporary loss of consciousness); urinary disorders

Frequency not known
Anaemia; hyponatraemia (low salt levels in the blood); leucopenia (low white blood cell count); psychosis (hallucinations or delusions); suicidal behaviours; thrombocytopenia (low blood platelet count)

Contraindications

Acute alcohol withdrawal; acute benzodiazepine withdrawal; bipolar disorder; central nervous system tumour; eating disorders; history of seizures; severe hepatic cirrhosis.

Appendix – Escitalopram side effects and contraindications

Side effects

Common (occurring in at least 1 in 100 people) or very common (occurring in at least 1 in 10 people)
Sinusitis (sinus infection); Anxiety; abnormal appetite; arrhythmias (irregular heartbeat); arthralgia (joint pain); asthenia (unusual fatigue); difficulty concentrating; confusion; constipation; depersonalisation; diarrhoea; dizziness; drowsiness; dry mouth; fever; gastrointestinal discomfort; haemorrhage (unusual bleeding or bruising); headache; hyperhidrosis (excessive sweating); malaise; memory loss; menstrual cycle irregularities; myalgia (muscle ache); mydriasis (enlarged pupils); nausea (dose-related); palpitations; paraesthesia (pins and needles); QT interval prolongation (changes in heart rhythm); sexual dysfunction; skin reactions; sleep disorders; altered taste; tinnitus (ringing in ears); tremor; urinary disorders; visual impairment; vomiting; weight changes; yawning

Uncommon (occurring between 1 in 100 to 1 in 1000 people)
Oedema (swelling usually in the legs or hands); Alopecia (hair thinning); angioedema (swelling under the skin); abnormal behaviour ; hallucination; mania; movement disorders; photosensitivity (skin reacting to sunlight causing rashes); postural hypotension (feeling dizzy when standing up); seizure; suicidal behaviours; syncope (fainting or temporary loss of consciousness)

Rare (occurring in up to 1 in 1000 people) or very rare (occurring in up to 1 in 10,000 people)
Galactorrhoea (unexplained milk production from the breasts even if not pregnant or breastfeeding); hepatitis; hyperprolactinaemia (high level of the hormone prolactin); hyponatraemia (low salt levels in the blood); serotonin syndrome caused by too much serotonin in the brain which could lead to agitation and confusion; severe cutaneous adverse reactions (SCARs) which are skin rashes that may require urgent medical attention; syndrome of inappropriate antidiuretic hormone(SIADH) a condition where the body makes too much of a hormone that controls water balance which could potentially lead to swelling; thrombocytopenia (low platelet count)

Frequency not known
Withdrawal syndrome

Side-effects, further information
Symptoms of sexual dysfunction may persist after treatment has stopped.

Contraindications

QT-interval prolongation (change in heart rhythm); poorly controlled epilepsy; SSRIs (the family of drugs Escitalopram belongs to) should not be used if the patient enters a manic phase.