Study protocol

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SSRIs and active placebo: treatment of social anxiety disorder studied with brain imaging

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Abbreviations used in the Protocol

ANOVA – analysis of variance
ANCOVA – analysis of covariance
APL – Apoteket production and Laboratories LTD
ATC – Anatomical Therapeutic Chemical Classification
BAI – Beck Anxiety Inventory
BOLD – blood-oxygen-level-dependent
CBT – cognitive behavioral therapy
CGI – Clinical Global Impression-Improvement
CRF – Clinical Report Form
DSM-IV – Diagnostic and Statistical Manual of Mental disorders, 4th ed.
fMRI – functional magnetic resonance tomography
GCP – Good Clinical Practice
IMP – Investigational medicinal product
KSP – Karolinska Scale of Personality
LSAS – Liebowitz Social Anxiety Scale
MADRS-S – Montogmery Åsberg Depression Rating Scale
MRI – magnetic resonance imaging
NEO-PI – Neuroticism Extraversion Openness Personality Inventory
NK1 – neurokinin 1
PET – Positron Emission Tomography
QOLI – Quality of Life Inventory
SCID IV – Structured Clinical Interview for DSM-IV Axis I disorders
SIAS – Social Interaction Anxiety Scale
SPM – Statistical Parametric Mapping
SPS – Social Phobia Scale
SPSS – Statistical Package for the Social Sciences
SPSQ – Social Phobia Screening Questionnaire
SSRI – selective serotonin reuptake inhibitors
STAI-T/STAI-S – Spielberger's trait/state anxiety inventory
VBM – voxel based morphometry

Synopsis

The overall aim of this project is to investigate the neural mechanisms underlying successful treatment with SSRIs and to evaluate the role of psychological expectations both for the clinical and the neural treatment outcome in SSRI treatment of social phobia. The project investigates brain structure and functional activations, as well as availability of serotonin and dopamine transporters, both before and after completing the SSRI treatment (escitalopram, 9 weeks) in 48 subjects diagnosed with social anxiety disorder.

The study is a randomized, controlled trial. All subjects will receive packages containing the SSRI (escitalopram) from the project's psychiatrist. The subjects will be randomized into two treatment groups corresponding either to normal high (positive) or low (negative) expectations of improvement. One group will receive accurate information of the labeled drug. The other group will get the drug encapsulated, and these participants will be informed that they are given active placebo treatment with a previously tested neurokinin-1 (NK1) antagonist. Accurate information will be given after the treatment period, and both groups are also offered 9 weeks of Internet-based cognitive – behavioral therapy after the SSRI period. The procedure has been approved by the Regional Ethics Committee Uppsala (application No. 2013/184). When starting the SSRI treatment, all subjects in both groups will be given dosing instructions i.e., the first week's oral dose will be 10 mg escitalopram which is then stepped up to 20 mg for the remainder of the treatment period.

Structural and functional brain imaging will be performed using magnetic resonance imaging (MRI/fMRI) prior to and upon completion of the SSRI treatment, thus being associated either with positive or negative expectations about therapeutic improvement. In addition, assessment of serotonin and dopamine transporter availability (binding potential) in the brain, using positron emission tomography (PET), will be undertaken. The study also aims at examining differences between men and women regarding the neural and clinical outcome measures, as well as to relate the differences in brain anatomy and monoamine related gene polymorphisms to different outcome measures. The study is scheduled to begin in January to March 2014 and be completed during the spring of 2015.

Summary flow chart

			PET	fMRI	Forms	Medical-contact
Data Collection (A)						
SSRI + normal high expectation	n = 12	Baseline		x	x	x
		Treatment				x
		Post measurement		x	x	x
		12-months follow-up			x	
SSRI + low expectation	n = 12	Baseline		x	x	x
		Treatment				x
		Post measurement		x	x	x
		12-months follow-up			x	
Data Collection B						
SSRI + normal high expectation	n = 12	Baseline	x	x	x	x
		Treatment				x
		Post measurement	x	x	x	x
		12-months follow-up			x	
SSRI + low expectation	n = 12	Baseline	x	x	x	x
		Treatment				x
		Post measurement	x	x	x	x
		12-months follow-up			x	

The study normally involves 5 visits for participants in data collection A and 7 visits for data collection (B). See also the information for participants.

Background

Social anxiety disorder, or social phobia, is one of the most common psychiatric illnesses. Research suggests that over 12% of the population, at least in the West, meet the criteria for social anxiety disorder at some point in life, and the disorder is typically chronic and disabling.[1] Besides a great deal of suffering for the individual, social anxiety disorder also causes high costs to society due to its impact on work absence and sickness rates.[2,3] Consequently, it is of great importance to increase our understanding of this anxiety condition and to develop more effective treatments. With this project we aim to investigate the neurobiological mechanisms that may explain the effectiveness of treatment with anxiolytic drugs. Brain imaging studies have shown that the amygdala, located in the temporal lobe, a key brain region for fear learning and processing, is crucially involved in the neuropathology of social anxiety disorder.[4] Pharmacological research on selective serotonin reuptake inhibitors (SSRIs), considered to be the first-order drug treatment for social anxiety disorder, has demonstrated that successful treatment outcome is associated with reduced neural activity in the amygdala.[5] The SSRIs are believed to enhance neurotransmission of serotonin in the brain by inhibiting the serotonin transporter protein. This leads to both a decreased reabsorption and increased accumulation of serotonin in the extracellular space, which increases the magnitude and duration of serotonergic influence on pre- and postsynaptic receptors.[6] But in spite of the widespread use of SSRIs, it is well documented that a high proportion of patients do not achieve a sufficient therapeutic effect with this type of medication.[7.8] An obvious limitation in the majority of SSRI brain imaging studies is that they have not studied the neurofunctional profiles associated with poor or insufficient therapeutic response. Brain imaging studies can provide increased understanding of how neurochemical changes after SSRI treatment correspond to changes in brain activity patterns and, at the behavioral level, sufficient of insufficient reduction of clinical anxiety.

Although SSRIs are considered to be the pharmacological treatment of choice in anxiety disorders and depression, there has recently been a lively debate about the clinical effectiveness and benefits of these drugs. It has then been discussed how much of the SSRI effect can be explained by the placebo effect or expectations.[9-11] The placebo effect can be defined as a beneficial treatment effect that occurs in the patient even though the treatment itself lacks specific activity as it has no pharmacological components that could have an impact on the medical condition, and the treatment effect can therefore be attributed to the patient's positive expectations. Controversial results from meta-analyses of depression treatment suggest that the relative efficacy of SSRIs can be explained by the placebo effect, and that the small difference in improvement that is often attributed to the SSRIs actually could be due to a heightened placebo effect in patients who received the drug due to the side effects associated with SSRIs.[12] Because of side effects, the patients could often correctly guess that they have been assigned to SSRI treatment, which is in turn may increase their expectancies to be helped by treatment. The term "active placebo" has been introduced to describe drugs that provide significant physiological effects or side effects, thus influencing expectations, although they lack specific action for the condition being treated. The placebo effect is considered to be an important element of any medical treatment. Nowadays, our knowledge of the effect of expectancies on physiological processes has increased significantly and the role of expectancies in medical treatments has become a field of research in itself.[13] By manipulating expectations, it has been proved that it is possible to initiate healing processes and even to block the actual effects of active pharmacotherapy. For example, with regard to benzodiazepines, it has been reported that "open" administration of the anti-anxiety medication diazepam resulted in significantly lowered anxiety levels whereas "hidden" administration of the same drug was proved ineffective. This suggests that the beneficial effects of diazepam to high degree is attributable to positive expectancies rather than the pharmacological components.[14] Or at least that expectations are important when pharmacological components exert their effects.[15] This is in line with results from meta-analyses of depression treatment, which have suggested that pharmacotherapies used (including SSRIs) may not be more beneficial than active placebo.[12] This underscores the important role of expectancies in clinical practice and the need to understand the

mechanisms of action in the brain underlying these effects. Although the clinical usefulness of SSRIs has been questioned in the ongoing debate, there is still no brain-imaging study that has examined how manipulation of expectancies can influence SSRI treatment outcome.

Randomized controlled trials have found relatively strong placebo effects in the treatment of social anxiety disorder.[16] Our research group has previously reported that anxiety reduction after 8 weeks of placebo treatment of social anxiety disorder, was associated with a reduction of amygdala reactivity only in patients who were homozygous for G-allele of TPH2 G703-T polymorphism.[17] This indicates that serotonin has a modulating function in placebo-induced anxiety reduction. We have also previously observed the largest decrease of amygdala activity in patients who responded well to treatment (i.e. responders), both after SSRI- and placebo treatment, which may suggest that expectations of improvement play an important role in both treatment modalities.[18] In other words, it seems likely that SSRI-efficacy not only depends on a specific pharmacodynamic or neurophysiological effect but also on psychological factors, such as positive expectancies, which traditionally have been associated with the placebo effect.

In order to further clarify the influence of expectancies on treatment outcome, the present study will manipulate expectancies in adult subjects with social anxiety disorder in the context of an SSRI treatment. The study will evaluate the effects of manipulation of expectancies both on clinical efficacy and neurofunctional changes. By examining the role that expectations play in the response to SSRI treatment, the underlying neural mechanisms (activation patterns and transmission systems in the brain) and genetic markers, we aim to sort out the specific factors behind therapeutic improvement and distinguish them from non-specific factors unrelated to symptom improvement. This may have important consequences not only for the treatment of social anxiety, but also for other anxiety disorders and depression. Knowledge of this kind is important for treatment theory as well as for clinical practice.

Objective

The overall objective of this research study is to examine the clinical and neural effects of psychological expectations within the context of an SSRI treatment for social anxiety disorder, as well as to examine the effects of genetic markers and to distinguish specific pharmacodynamic mechanisms. More specifically, the study aims at evaluating the neurofunctional mechanisms underlying the therapeutic response to SSRI treatment and the importance of expectations for treatment outcome and neural activity, as measured by functional magnetic resonance imaging (fMRI), as well as serotonin and dopamine transporter availability, as measured with positron emission tomography (PET). We will also examine the brain functions that overlap and separate treatment responders either with normally high (positive) or low (negative) expectations of improvement. Based on previous research, as described above, we anticipate that high expectations of improvement with SSRI treatment will result in anxiety reduction while low expectations will not, even though the SSRI-treatment is exactly the same for all participants in the study. By investigating the importance of expectations for SSRI efficacy, we will get a good opportunity to clarify the contribution of psychological vs. pharmacodynamic factors for a successful treatment outcome. The primary research questions are:

1), Will SSRI treatment (escitalopram) with normally high (positive) as compared to low (negative) expectations of improvement result in different clinical outcomes? Will low (negative) expectation of improvement abolish the anxiolytic SSRI effect?

2) Which are the brain mechanisms underlying effective and ineffective SSRI treatment with normally high (positive) or low (negative) expectations of improvement? Brain mechanisms refer to neural activations as measured by magnetic resonance imaging (fMRI), as well as the availability of serotonin and dopamine transporter measured with PET.

3) How much of the therapeutic effect observed in SSRI-responders can be explained by a positive expectancy effect?

4) How do monoaminergic gene variants exert their effects on clinical (behavioral) and neural treatment outcome?

Timetable

Assessments in the study are expected to commence as soon as the appropriate permissions have been obtained. The study is already approved by the regional ethical review board in Uppsala (May 29th, 2013, Reg. No. 2013/184). Start of treatment is planned to March 2014. The study will last throughout 2014 and is scheduled to be completed in the spring of 2015.

Study type

The study is a randomized controlled trial. Subjects with social anxiety disorder will be randomized to 9 weeks of treatment with escitalopram that is associated either with normally high or low expectation of therapeutic improvement.

Study population and recruitment

The general study logistics will be essentially the same as in a recently completed PET/fMRI-study of SSRI treatment of social anxiety (see MPA reg. No. 151:2011/958; EU-number 2010-023007-10). A total of 48 individuals with social anxiety disorder are to be recruited as participants, of which 24 are women and 24 men. Subjects will be randomized, stratified by gender, into either SSRI+normally high expectations, or SSRI+low expectations.

Inclusion criteria:

1. Social anxiety disorder, according to DSM-IV,[19] must be the main diagnosis as assessed with the structured clinical interview for DSM-disorders (SCID). [20]
2. Otherwise somatically healthy
3. Age 18-65 years
4. The subject's own consent to participate in the brain imaging/provocation study

Exclusion criteria:

1. Treatment for social anxiety within three months before the start of the study
2. Other serious psychiatric disorder (such as psychosis, depression, bipolar disorder)
3. Suicide risk
4. Chronic use of such medication that can affect the results (e.g., antidepressants or anti-anxiety drugs, beta blockers, some sleeping pills and health food preparations like St. John's wort
5. Abuse and/or addiction to alcohol or drugs
6. Pregnancy or planned pregnancy during the study period
7. Entered menopause
8. Past PET scan (for data collection (B) in the flowchart)
9. Factors arguing against MRI examination (e.g., implants, or other metal objects in the body, as well as surgery in the head or heart)
10. Contraindication to treatment with escitalopram are present
11. Coronary artery disease, recent myocardial infarction or pronounced failure

Recruitment and consent to participation

The subjects will be recruited through advertisements in the media and public billboards of institutions. Persons who meet the above inclusion criteria, and not any exclusion criterion, will be asked to participate in the study.

Information about the study is given prior to and at the first screening visit, as well as on the project's website. Consent to participate in the study is collected at the first visit. Prospective volunteers have the opportunity to read the information without stress, in the comfort of their homes, and decide on participation in the study.

A CRF will be created for all of the subjects participating in the study.

Representativeness

The recruited study population will consist of people who indicated interest in participating in a research study. Recruitment via advertisements will likely lead to the recruitment of mostly people from Uppsala and surrounding areas. This, however, should not lead to specific limitations in generalizability.

Ethical considerations

The study has been approved by the regional ethical review board in Uppsala (reg. No. 2013/184). The subjects are participating voluntarily in the study. The procedure with a "cover story" for individuals randomized to SSRI+low expectations entails special considerations (discussed below). Firstly, the following ethical risks have been identified:

Being in an MRI scanner may be perceived as movement restraining, but it is hardly any risk. The images shown during fMRI assessments, even if they contain emotional stimuli, cause only a limited discomfort. Discomfort when preparing and delivering a short oral presentation, in association with fMRI assessments, is itself a feature of social anxiety disorder and thereby one of the targets of the treatment. This short-term discomfort, however, should be balanced against the possibility to achieve long-term improvement with the treatment offered in this study.

PET means that a small amount of a radioactive tracer substance is injected, which means that the subject is exposed to ionizing radiation. There is a connection between ionizing radiation and the risk of injury. The radioactive isotopes used decay quickly, however, and have largely disappeared from the body about 2 hours after the completion of investigation. The injected dose is reviewed, before the study, by a radiation safety committee. Our previous PET treatment study of social anxiety disorder, which has recently been completed (MPA reg. No. 151:2011/958; EU-number 2010-023007-10) used the same radiotracers as described here.

The risk involved with voluntarily providing a blood sample (10 ml) and saliva sample is considered small. To provide blood and saliva samples for analysis of genes may be perceived as intrusive and it is therefore emphasized that no participants or individual values will be possible to identify for others. The biological material is surrounded by the necessary confidentiality. The samples are encrypted, and the participants are informed that anyone working with the samples must keep research data and results secret. The subjects will be informed that the results of the analyses are not disclosed to any other party, including family members, doctors, insurance companies or employers, unless it is required legally. Subjects are also informed that genetic data are only collected for research purposes and not used for any other purpose.

Structural clinical interviews and completion of self-report questionnaires can hardly be perceived as unpleasant, but obviously they take some time to complete.

Another risk is that subjects in need of specialized medical investigations may be included. At the slightest suspicion of unclear symptomatology, subjects will be asked to seek medical advice. We will also inform that the project is not suitable e.g., for individuals suffering from a severe depression or having suicidal thoughts. Individuals who are excluded from the study may perceive this negatively. All excluded individuals will be given recommendations on how and where to seek help, and, when appropriate, relevant self-help literature will be suggested.

When it comes to the drug treatment, subjects will be informed of the precautions and the most common side effects of the SSRI (escitalopram). These are according to FASS, among others, nausea, affected appetite, affected sexual desire or ability, nasal congestion, weight gain, sweating, tremor, dizziness, muscle aches, diarrhea or constipation. However, SSRIs are generally well tolerated and it is not certain that the person will be experiencing side effects.

Regarding the pharmacological treatment, as described earlier, incorrect information will be given to subjects that they may be randomized to treatment with "active placebo" consisting of an NK1 antagonist, and prior to initiation of treatment they will be informed about which of the treatment groups they have been allocated to. However, no "active placebo" will be given as all subjects, regardless of treatment group, will receive the SSRI, although only one group gets to know this in advance. We are aware that the study may lead to an ethical dilemma as the person is given incorrect information during the initial treatment period. The risk of using deceitful information, however, is expected to be small. This is because all participants will be treated with an SSRI, which constitutes the best existing pharmacotherapy for social anxiety disorder, and participation in the study requires that consent is given by all to be treated with the SSRI. The study drug, escitalopram, is approved for social anxiety disorder and has been given the highest evidence rating by the Swedish agency for Health Technology Assessment of Social Services, SBU. In addition, all subjects, directly after SSRI treatment (9 weeks), will be offered an effective CBT treatment, free of charge, which should reduce the risk of discomfort or loss of privacy. In addition, the subjects will also have the opportunity to continue treatment under supervision of the project's psychiatrist.

During the treatment period, there is no need to unblind the study regarding the treatment allocation, e.g. in the event of serious adverse reaction, as all participants receive the same treatment. All subjects in both groups will be individually informed about the study's real purpose and its research questions (debriefing) but only after the drug treatment and postassessments are completed in its entirety, in order not to threaten the integrity of the study. Each subject will, at the time this information is revealed, be given the opportunity to ask questions and get the study's purpose clear. All will also, where appropriate, be given the opportunity to later pose questions to the research team by e-mail and/or phone. Similarly, all will be informed that they at anytime during or after the study may refuse further participation and to request that their data are destroyed. All research ethics principles issued by the American Psychological Association (APA) and Humanities and the Social Sciences Research Council in Sweden have carefully been taken into account regarding the requirements of confidentiality, voluntariness, informed consent, and no commercial use of the data collected. Also that information and debriefing is given to all participants due to the design with deception and that no physical damage is imposed. We believe that all these ethical principles have been met in our design and that the risks of discomfort or other concerns have been minimized. Given that the study primarily aims at examining the importance of the subjects' expectations, and how these affect clinical and neural treatment outcomes, the deceitful information included in the "cover story" is regarded as necessary. It is central to investigate the degree to which the SSRI-effect is driven by initial expectations, which is a very important and so far unanswered scientific question.

Blinding

Because the study design involves manipulation of expectations of the participants, a traditional pharmaceutical double-blind design, where also the project's staff do not know the research question or the intervention allocation, is partly abandoned. To minimize the risk of reactivity or the risk that the project staff expectations could affect outcomes, the following will apply: 1. Neuroimaging with fMRI and PET, as well as initial assessment will be carried out before the clinical intervention allocation; 2. The personnel carrying out the initial screening interviews, responsible for bookings/scheduling and keeping regular contact with participants are blinded (not informed about the main research question); 3. The personnel carrying out fMRI/PET will not have access to the randomization list and therefore they do not know what group (escitalopram or active placebo) the

participant belongs to; 4. Estimates of the primary outcome measure LSAS and secondary clinical outcome measure of the study is conducted online, from the participant's own computer at home, to prevent that reactivity from the study staff will affect responses. The online version of LSAS (LSAS-SR) will be regarded as the main outcome measure. The estimates of the online LSAS-SR will be compared with the clinician administered LSAS to evaluate reactivity.

Patient number and power calculation

The number of participants will be 48 subjects allocated to treatment with SSRI+normally high expectations or to SSRI+low expectation. In each treatment group 12 women and 12 men are planned to be included. The project, however, will not have the resources to perform PET scans of all subjects in the study, but these scans are carried out in half the sample. The participants undergoing PET are 12 random people selected from the randomization list (6 women/men from each treatment arm) from the spring data collection and 12 people from the autumn data collection.

The number of participants is the same as in our recently completed study (MPA reg. No. 151:2011/958; EU-number 2010-023007-10) and justified by recommendations in published power analyses in functional brain imaging, as well as our previous studies where we've found significant group differences both for behavioral and brain data, and significant correlations between them.

Previous studies with functional brain imaging methodology suggest that the statistical power increases when research participants are added up to 12 people in each group, but that the statistical power thereafter is harder to increase. We want to include a larger number of subjects, mainly when it comes to fMRI data, because we would additionally be able to detect differences between genetic subgroups.

Previous medication

Chronic use of medication that can affect the results will be an exclusion criterion. This concerns, for example, antidepressants or anti-anxiety drugs, beta blockers, some sleeping pills and health food preparations like St. John's wort. Otherwise, changes will not be made of the subjects' usual treatment.

Study drug – dosage and method of administration

IMP

The subjects will be randomized to nine weeks of treatment either with escitalopram associated with normally high (positive) expectations or escitalopram associated with low (negative) expectations. The chosen method of administration, dosage and dose intervals are based on the regular dosage information as described in FASS (of Cipralex). This is equivalent to 10 mg for the first week and 20 mg in the rest of the treatment period. The doses will be packaged in such a way that the subjects take one capsule a day.

Escitalopram is obtained from APL (Pharmacy production and Laboratories LTD.), Prisma vägen 2, SE-141 75, Stockholm, Sweden (www.apl.se). For the group escitalopram+positive expectation, open labelling will be used i.e., containers bearing the text "Escitalopram". Regarding the group escitalopram+negative expectation, the encapsulated medicine is marked, on the container, with "Escitalopram/active placebo". Detailed additional information regarding encapsulation and the capsules' contents and labelling will be submitted when APL have implemented and completed their initial tests and pharmaceutical documentation (scheduled for fall 2013).

<u>Escitalopram + positive expectation: (exact pharmaceutical documentation provided by APL)</u>

Content: Escitalopram (as oxalat salt), 10 or 20 mg, Microcrystalline Cellulose, colloidal silicon dioxide, talc, croscarmellose sodium, magnesium stearate, hypromellose, Macrogol 400, titanium dioxide (E 171).
ATC code: N06AB10
Manufacturer: Lundbeck
Delivery: APL, Stockholm
Suggested use: one tablet daily for nine weeks containing 10 mg of escitalopram for the first week and 20 mg in the rest of the treatment period. APL also delivers two weeks extra supply since the last dose must fit in with the PET/fMRI-postassessments, which can vary slightly. The drugs left over from these two additional weeks will be used for tapering off the SSRI in order to avoid abrupt discontinuation.

Escitalopram + negative anticipation: (exact pharmaceutical documentation provided by APL)
Content: Escitalopram (oxalatsalt), 10 or 20 mg, Microcrystalline Cellulose, colloidal silicon dioxide, talc, croscarmellose sodium, magnesium stearate, hypromellose, Macrogol 400, titanium dioxide (E 171).
ATC code: N06AB10
Manufacturer: Lundbeck
Encapsulation and delivery: APL, Stockholm
Dosage: one capsule daily for nine weeks containing 10 mg of escitalopram for the first week and 20 mg in the rest of the treatment period. APL also delivers two weeks extra supply since last dose must fit in with the PET/fMRI-postassessments, which can vary slightly.

Other permitted treatments
Except for the exclusion criteria regarding treatment and medication that may affect the results of brain imaging, there are no restrictions on which drugs the subjects may use during the study.

Non-IMPs
Safety documentation for PET-ligands 11C-DASB and 11C-PE2I is attached to the protocol. These have previously been used in humans in a large number of studies, including in our recent treatment study (MPA reg. No. 151:2011/958; EU-No. 2010-023007-10).

Patient code, patient identification lists and randomization
At baseline, all subjects are to be assigned a unique patient code. The patient identification lists will be kept by the sponsor and kept together with the subjects' other documents (CRF).

Randomization

Allocation of the subjects into the two treatment groups is implemented through randomization stratified on the basis of sex. The randomization list will be prepared by APL, Stockholm, and retained by the clinical pharmacy at Uppsala university Hospital together with the sealed opaque envelope that contain the randomization code registered for each trial subject. The envelope will be broken only if a serious side effect occur during the study. The date and reasons for breaking the randomization code for a single subject will be recorded.

Patient data
Data are recorded and maintained in accordance with GCP standard. Each subject will, after inclusion, receive a patient code that is then used for recording data and for dispensing. The patient code aims to protect the subject's anonymity. All data (lab samples, physical findings, results of questionnaires, rating scales) are recorded or stored in a patient form (CRF) marked with the subject's code. The sponsor handles the patient identification lists and the subjects' CRFs are kept locked in the study sponsors' lab until completion. After the study ended, the data will be stored for 15 years.

Packaging and labelling

See the pharmaceutical documentation from APL for marking on each package. The labels will indicate "clinical trial", EudraCT number and number of capsules/tablets. Furthermore, the administration day (1-7, 8-63 or extra supply day 64-77) is indicated. The randomization number, principal investigator, sponsor and dosage information is shown, as well as the batch number, expiry date and manufacturer. For the treatment group escitalopram+positive expectation, open label escitalopram is to be given. For the group escitalopram+negative expectation packages of encapsulated medicine will be marked Escitalopram 20 mg/Active placebo (10 mg the first week).

Supplying medicinal products

Drugs are handed to the treating psychiatrist (principal investigator) from the hospital pharmacy. The psychiatrist records that drugs are received in accordance with the number of participants. Drugs for the first week's treatment are given by the psychiatrist to the subjects during the visit before trial start. At a revisit after a week, medicine for the remaining treatment period (8 weeks + 2 weeks of extra supply) is given.

Storage

Preparations will be stored in locked cabinets, protected from light, heat and humidity.

Methods for effect registration

All prospective subjects will initially answer structured clinical interviews, screening questionnaires and undergo a physical health examination. Subjects first answer two self-reports: the Social Phobia Screening Questionnaire (SPSQ)[21] and the Montgomery-Asberg Depression Rating Scale (MADRS).[22] Subjects included will meet the criteria for social anxiety disorder, according to the international classification system Diagnostic and Statistical Manual of Mental disorders, 4th edition (DSM-IV). This is determined initially by the SPSQ-instrument that has been shown to have good sensitivity and specificity in comparison with structured diagnostic interviews. In addition, an interview is thereafter conducted with questions based on Structured Clinical Interview for DSM-IV Axis I disorders (SCID) regarding social phobia. The subjects also undergo a medical check-up after a week of treatment.

Availability of serotonin as well as dopamine transporters will be studied using positron emission tomography (PET) at the PET Centre, Uppsala University (former Uppsala Imanet AB). Half of the study's subjects will undergo two PET scans, carried out both before and after treatment. The subjects remain in the PET scanner for approximately 1 hour for each survey so that the accumulated trace binding is representative of the binding to the serotonin and dopamine transporter respectively. For the serotonin transporter, the 11C-DASB will used whereas 11C-PE2I is used for evaluation of dopamine transporter availability.

At a separate occasion, the subjects will be invited to the MRI Department at Uppsala University Hospital. At this time they will be exposed to four paradigms in the MR scanner, conducted in cooperation with Prof. Elna-Marie Larsson. There is an anatomical imaging of brain structure and functional paradigms where subjects look at emotionally relevant images. The subjects will also be investigated when they prepare an oral presentation, the actual presentation takes place, however, outside the scanner for technical reasons. Brain activity during the speech preparation will be compared to a resting state. In addition, the fMRI session includes a cognitive condition in which subjects respond to attention-demanding tasks presented on a computer screen. Evaluation of blood-oxygen-level-dependent signal (the BOLD signal) is made with a 3.0 Tesla scanner. The total time for the MRI session is estimated to be about 1 hour and 15 minutes.

Statistical analysis of brain imaging data is made mainly with Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8).

All subjects will be asked if they are willing to provide a voluntary blood sample (10 ml) or saliva sample for genotyping. Genetic analyses will be carried out by professor Elias Eriksson, Dept. of Pharmacology, University of Gothenburg, also saving the samples in a BioBank database at the Sahlgrenska Academy. After treatment, a blood sample is taken for determination of drug concentration/pharmacokinetic information, carried out in collaboration with Dr Margaret Reis, Dept. of Medicine and Health sciences, Linköping University (only for analysis, samples are not saved).

Measurements of brain functions are carried out before and after SSRI treatment.

Before and after treatment, subjects fill out self-report instruments. In addition to the SPSQ and MADRS-S, these consist of: the Liebowitz Social Anxiety Scale (LSAS),[23] Social Interaction Anxiety Scale (SIAS),[24] Social Phobia Scale (SPS),[24] Beck Anxiety Inventory (BAI),[25] and Quality of Life Inventory (QOLI).[26] Before treatment, subjects also fill out the Karolinska Scale of Personality (KSP),[27] the personality inventory NEO-PI,[28, 29] and Spielberger's scale for trait and state anxiety (STAI-T and STAI-S).[30] All these scales are internationally established, having good psychometric properties.

Postassessments are conducted in connection with the last brain imaging session after 9 weeks of SSRI treatment, and self-report forms are to be re-administered after the voluntary CBT treatment following the SSRI-period. Follow-up assessments, using the same self-report scales, are conducted 12 months after the completion of CBT treatment. The latter is done to evaluate the long-term effects of treatment and in comparison with the short-term effects. Pre, post, as well as follow-up measurements will be made with the same established international instruments (see above). At posttreatment, the subjects will also meet the treating psychiatrist again and assessment of clinical improvement will be conducted using the CGI-I (Clinical Global Impression-Improvement) scale.[31] Subjects have the opportunity to discuss, with the psychiatrist, about continued drug treatment once the project has been completed.

The primary outcome measure of treatment efficacy is the self-rated LSAS, online version, (also called the LSAS-SR). Other self-report and clinician administered measures are secondary. Genotypes and drug levels/metabolites are also regarded as secondary measures.

Adherence to treatment

Adherence to treatment is evaluated by control questions at the posttreatment visit, and indirectly as subjects return leftover medicines, and through pharmacokinetic analysis of drug concentration (blood test).

Methods for safety registration

Recording and reporting of suspected adverse drug reactions

Adverse events are defined as all harmful and unintended reaction or events that a subject can experience during a clinical trial, whether these are directly related to the study drug or not. All side effects of the treatment reported spontaneously or observed by the principal investigator/psychiatrist or other staff in the project will be recorded using a special form. The severity of symptoms will be estimated according to the following scale:

Mild	*Experiencing discomfort that does not lead to disruption of normal daily activities.*
Moderate	*Experiencing discomfort to the degree that it reduces or affects normal daily activity.*
Severe	*Inability to work or carry out normal daily activities.*

For each adverse event, its relationship to the study drug (certain, probable, possible, unknown, none) will be evaluated by the principal investigator. Any action taken, in connection with side effect, is also recorded. Side effects which are potentially fatal, life-threatening, disabling, or which leads to hospitalization, will be described as severe adverse reaction.

Suspected serious unexpected adverse reactions will, at the latest within 15 days after they have come to the sponsors attention, be reported to the Swedish MPA. Side effects that are fatal or life-threatening are reported as soon as possible and at the latest within 7 days, followed by relevant follow-up information within an additional 8 days. It is the sponsor's responsibility that reporting is done.

The sponsor will make a compilation of all suspected serious adverse reactions and, on the basis of these, do a safety analysis. This report will be sent to the MPA and the Regional Ethics Committee.

Monitoring of adverse reactions
After the event, the subject will be followed until the symptoms disappear.

Interruption of study
The subjects have the right to terminate their participation in the study. Reasons for termination of the study will be recorded as well as the time of termination.

If a medical condition, that could pose a risk to the subject, is evolving and association with the study drug cannot be excluded, the treating psychiatrist must ensure that the subject interrupts the study. Grounds for termination, due to this reason, will also be recorded.

If a subject does not come to the revisit, the reason for this must, as far as possible, be made clear. The information provided by the subject will be recorded in his/her CRF.

Subjects that interrupt the study after randomization will not be replaced with new subjects.

Follow-up of subjects leaving the study
Subjects leaving the study before it is terminated will be asked regarding the reason for this. If the subject terminates the study due to an adverse event or reaction, he/she will be monitored until this remits or can be assessed. According to the intention-to-treat "policy", people aborting treatment prematurely, will be asked to take part in the subsequent evaluation of the treatment outcome, with the last assessment point 12 months after the final CBT-period.

Patient information and obtaining consent to participate
The written information to subjects is attached. Information to subjects is given in several steps. Initial information about the study is provided on the project website. Information is also provided in oral and written form before and at the first screening visit. Informed consent is obtained in connection with the first doctor's visit. Consent to participation in the study is documented in the subject's medical records.

Monitoring of the trial
The study has a limited budget and lacks sponsorship from pharmaceutical companies. Monitoring will be done by nurse Ingrid Lindquist, who has adequate GCP training, extensive experience, and is currently employed as a monitor of the company Crown. Lindquist is also employed part-time at Dr.

Walhstedt's clinic in Uppsala, assisting in clinical trials. She will otherwise not be involved in the current trial, i.e., she is not involved in the subjects' treatment or in other parts of the study.

The monitor will continuously carry out the usual checks, such as verifying that the subjects are enrolled, that informed consent has been signed before any study-specific action is carried out and that the study's main outcomes and safety reports are handled correctly. The monitor will also ensure that trial protocols are followed and that the basic documents are complete according to good clinical practice. Furthermore, the monitor will make sure the CRFs, are in accordance with the protocol and source data. Source data in the patient's medical records will include the name, randomization trial number, date of informed consent, information about inclusion/exclusion criteria, information about the diagnosis, the ingestion of investigational medicinal product, the date of termination or, if applicable, interruption of the study. The monitor will also check that information and, if necessary, training, has been given to the personnel involved in the study. The subjects will be required to provide written consent for the quality review.

Disposal after the end of the trial

At the end of the drug treatment period, after 9 weeks, the principal investigator/psychiatrist meets subjects for a final interview during which continuing treatment is discussed. The discussion on continued treatment is based on the subjects' needs and wishes. Dr. Wahlstedt is able to offer continued drug treatment and can also provide other treatment recommendations. All subjects, regardless of treatment group, will also be offered an established Internet-administered cognitive behavioral therapy (CBT) program for a maximum of 9 weeks after the initial SSRI treatment. Participants can start, on their own initiative, any treatment during the CBT period and until the trial is complete after 12 months follow-up. The clinical evaluation will include questions about other treatments.

The possible early termination of the study

The sponsor may terminate the study at any time if any of the following occur:

- The safety of any of the preparations can be questioned
- Difficulties in recruiting participants
- Lack of adherence to the protocol
- Incorrect or incomplete data
- Unsafe or unethical practices
- Administrative decisions

If an ongoing trial would end prematurely, the sponsor will inform, within 15 days, to the MPA and the Ethics Review Board about the reasons for this and the necessary (for safety reasons) actions taken.

Trial end

The trial is regarded as ended when the last follow-up, 12 months after the final treatment with CBT, has been completed.

Insurance and financial benefits

The subjects will receive SEK 2500 in compensation for participation. The 24 subjects who only undergo data collection (A), where the PET is not included, the compensation is SEK 1500. In addition economic compensation is paid for putative loss of income and travel (the cheapest means of transport) for persons living outside Uppsala. No fee is paid for the study drug or CBT treatment.

Information to other relevant staff

Before the start of the study, we will have an initial day meeting for the staff, in Uppsala. At this meeting, staff from the hospital pharmacy will also be invited. Special emphasis will be placed on information on randomization procedure and management of side effects and other safety aspects. Information that may threaten the integrity of the study will not be disclosed. Those who are unable to attend on this occasion will be contacted personally and given study-related information.

Allocation of responsibility

The sponsor of the study is professor Tomas Furmark.
Coordinating investigator of the study is professor Tomas Furmark.
Principal investigator (and psychiatrists) is Dr. Kurt Wahlstedt. Responsible psychiatrist in charge, provides and collects returned study medicine.
PET and MRI assessments take place at the respective departments at Uppsala University Hospital, Uppsala. Blood or saliva samples are collected in connection with PET/MRI assessments.
Genetic analyses are conducted by professor Elias Eriksson at the Dept. of Pharmacology, University of Gothenburg, Sweden.
Analysis of drug concentration after treatment is performed by Dr. Margareta Reis, Dept. of Medicine and Health Sciences, Linköping University.
Documents for delegation of responsibility during the course of the study will be at hand.

Data analysis

Handling of data

The source data will be saved under the Archives Act. Data will be recorded in the statistical programme for further analysis. Data will be decoded, and will be treated as confidential and de-identified.

Statistical analysis

Because this will be a research study that examines the relationship between altered brain function and behavior (social anxiety), where several response domains are relevant, a single primary endpoint cannot be specified. The primary outcome in terms of brain functions is the BOLD signal measured with fMRI (though under multiple conditions), as well as binding potentials for the serotonin and dopamine transporter as measured by PET. With regard to symptoms change, the LSAS will be a primary measure in accordance with international studies. Also, STAI-S is important because it is more clearly linked to the perceived state anxiety during brain imaging operations. Other outcomes are considered to be secondary but nevertheless important, e.g., in order to relate the results to previous studies that we and other research groups have done.

Statistical analyses will be carried out with sex taken into account (covariate). Brain data is analyzed with the software Statistical Parametric Mapping (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8) and voxel based statistics, taking multiple comparisons into account, i.e. corrected significance levels are reported. Correlations between change values (behavior data and brain data) will also be carried out.

Analyses of behavioral data are carried out mainly with SPSS (IBM Corporation, Somers, NY) where the treatment effects are evaluated using ANOVA, or ANCOVA models in the event of significant group differences before treatment has been started. Loss of data will not be replaced but the effect according to the "intention-to-treat" and "completer" analyses will be compared. Attrition is in our previous PET studies on social anxiety disorder has been very small. In addition, non-parametric tests,

like the Chi-square test, are to be used for category variables. In all cases, we will be using a Bonferroni procedure to correct for multiple comparisons and thus reduce the risk of false positives.

The threshold for significant difference is $p < .05$. This applies to the primary outcome measure LSAS. For secondary outcomes we perform analyses family-wise e.g. for symptom specific social anxiety scales and other scales like level of depression, general anxiety and quality of life, and we intend to use Bonferroni correction for multiple comparisons. For brain data (PET and fMRI) the $p< .05$ level also applies with FWE (family wise error rate) correction for multiple comparisons.

Selection of subjects for statistical analysis

All subjects who participated in at least one PET/fMRI study will be included in the statistical analysis.

Policy for reporting

Results of the study will be published in a peer-reviewed journal. Within 90 days after the end of the trial, the sponsor will notify the MPA and Ethics Review Board in Uppsala that the trial has been ended in sites. After closing of the trial, a final report will be submitted to the MPA no later than 12 months after the trial was ended. In addition, adverse events are presented annually in a compilation/safety report (as above). Reporting to the MPA will be written on EU common forms submitted electronically.

Report of deviation from the original study protocol

Deviation from the original study protocol will be reported on the form designed for this purpose.

Archiving of materials

All the source data will be archived in our research lab for 15 years.

Significance

Anxiety is a common feature in mental illnesses and about a quarter of the population suffers from an anxiety disorder at some point during the life course. Social anxiety disorder is among the most common anxiety disorders and constitutes a serious public health problem. There are still many sufferers who do not seek help for their problems, and among those undergoing pharmacological or psychological treatment, it is an unsatisfactory high percentage who do not achieve a sufficient therapeutic improvement. Consequently, it is necessary to develop more effective treatments. A putatively fruitful research strategy is to examine the clinical and neurobiological processes behind successful treatment with anti-anxiety drugs. Selective serotonin reuptake inhibitors (SSRIs) are considered to be the treatment of choice for anxiety disorders, including social anxiety disorder, but it has recently been the subject of lively debate within the scientific community. The real effectiveness of these drugs has been questioned, as a considerable portion of the SSRI-efficacy may actually be attributed to placebo. Expectancy effects, i.e., the patient's positive beliefs and desires to be improved by treatment, are at the core of the placebo phenomenon. Studies have shown that manipulation of expectations can lead to clinically meaningful effects, e.g., a blocked or even reversed effect of active medications such as benzodiazepines and opioids. This project will examine the mechanisms of successful treatment with SSRIs and evaluate the role that expectations play both for the clinical and the neural treatment outcome. This is still an unanswered but extremely relevant matter in treatment research.

Signatures

Sponsor:

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Professor Tomas Furmark

Coordinating investigator:

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Professor Tomas Furmark

Principal investigator:

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Dr. Kurt Wahlstedt

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