BJPsych | The British Journal of Psychiatry (2016)
209, 229–235. doi: 10.1192/bjp.bp.115.175794

Combining escitalopram and cognitive–behavioural therapy for social anxiety disorder: randomised controlled fMRI trial

Malin Gingnell,* Andreas Frick,* Jonas Engman, Iman Alaie, Johannes Björkstrand, Vanda Faria, Per Carlbring, Gerhard Andersson, Margareta Reis, Elna-Marie Larsson, Kurt Wahlstedt, Mats Fredrikson and Tomas Furmark

Background
Selective serotonin reuptake inhibitors (SSRIs) and cognitive–behavioural therapy (CBT) are often used concomitantly to treat social anxiety disorder (SAD), but few studies have examined the effect of this combination.

Aims
To evaluate whether adding escitalopram to internet-delivered CBT (ICBT) improves clinical outcome and alters brain reactivity and connectivity in SAD.

Method
Double-blind, randomised, placebo-controlled neuroimaging trial of ICBT combined either with escitalopram ($n = 24$) or placebo ($n = 24$), including a 15-month clinical follow-up (trial registration: ISRCTN24929928).

Results
Escitalopram+ICBT, relative to placebo+ICBT, resulted in significantly more clinical responders, larger reductions in anticipatory speech state anxiety at post-treatment and larger reductions in social anxiety symptom severity at 15-month follow-up and at a trend-level ($P = 0.09$) at post-treatment. Right amygdala reactivity to emotional faces also decreased more in the escitalopram+ICBT combination relative to placebo+ICBT, and in treatment responders relative to non-responders.

Conclusions
Adding escitalopram improves the outcome of ICBT for SAD and decreased amygdala reactivity is important for anxiolytic treatment response.

Declaration of interest
None.

Social anxiety disorder (SAD), characterised by excessive fear of being negatively evaluated or scrutinised in social situations, is among the most common anxiety disorders with a lifetime prevalence exceeding 10%.[1,2] Without treatment, the condition is considered chronic, imposing great individual suffering and costs for society.[3] Standard treatment options for SAD include selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and cognitive–behavioural therapy (CBT).[4,5] Several randomised controlled trials have shown that CBT for SAD can successfully be delivered via the internet (ICBT),[6–9] with effects comparable to face-to-face CBT.[10] Even though SSRIs and CBT/ICBT are effective treatments for SAD,[11] a substantial proportion of patients relapse or do not respond to monotherapy and combining the treatments is therefore common in the clinic.[5,12] Studies assessing the added benefit of adjuvant therapy for SAD, however, are scarce and findings are mixed,[12–14] although recent meta-analytic work suggests added value of combined treatment in affective disorders.[15] Also, experimental research in animals[16] and humans[17] has suggested beneficial effects of SSRIs on extinction learning, i.e. the laboratory analogue to exposure-based therapy.

Neuroimaging activation studies of patients with SAD during emotional challenges, such as public speaking and emotional face-processing tasks, have revealed amygdala hyperactivity[18,19] and a relationship between amygdala reactivity and clinical symptoms.[19,20] Decreased neural reactivity after treatment of SAD either with SSRIs or CBT have been reported for several brain regions, although most consistently for the amygdala,[21–25] and recent work from our lab suggest that SSRI, CBT/ICBT and placebo monotherapies all exert anxiolytic effects through a common pathway including reduction of amygdala reactivity.[21–23,25] It is thus likely that reduced amygdala reactivity accompanies successful treatment outcome. However, to the best of our knowledge, no study has assessed brain correlates of combined treatment with SSRI and CBT. Studies of this kind could be of therapeutic importance, enabling better understanding of the mediating neural mechanisms in pharmacological and psychosocial treatments.

In this double-blind, randomised, placebo-controlled neuroimaging trial, we evaluated the effect of SSRI-augmented ICBT for SAD on clinical symptoms, anticipatory anxiety before public speaking and brain reactivity during an emotional face-processing task.[26] Assessments were performed before and after 9 weeks of treatment with ICBT combined with escitalopram 20 mg or pill placebo. We hypothesised that escitalopram would enhance the anxiolytic effect of ICBT and that successful treatment would be associated with greater reduction in amygdala reactivity.[21–25] In addition, we performed exploratory comparisons of treatment-induced changes in amygdala connectivity and whole brain reactivity after the initial 9-week period. A follow-up assessment of clinical symptoms was also administered 15 months after termination of treatment.

Method

Participants

Forty-eight participants (mean age 33.2. years, s.d. = 8.8; 24 women) meeting the DSM-IV[1] criteria for SAD as primary diagnosis were randomised to escitalopram+ICBT or placebo+ICBT. One participant per group was left-handed.

*These authors contributed equally to the work.

Recruitment procedure

Participants were recruited through newspaper advertisements. Initial screening included the Social Phobia Screening Questionnaire (SPSQ)[27] and the Montgomery–Åsberg Depression Rating Scale – self-rated version (MADRS-S)[28] administered online. Patients passing initial screening were interviewed using the Mini International Neuropsychiatric Interview (MINI),[29] the SAD section of the Structured Clinical Interview for DSM-IV (SCID-I),[30] and they underwent a medical check-up (see online Fig. DS1 for a CONSORT diagram).

Exclusion criteria were: contraindications for magnetic resonance imaging, presence of severe somatic disease or serious psychiatric disorder such as psychosis or severe major depression, treatment for any psychiatric disorder (ongoing or terminated within 3 months), menopause, and drug or alcohol dependency/misuse.

Study design

This was an investigator-initiated, double-blind, randomised, parallel-group clinical trial with ICBT combined either with escitalopram or pill placebo, conducted between September 2011 and September 2013 (trial registration: ISRCTN24929928). ICBT and pharmacological treatments were started simultaneously. Randomisation, stratified by gender and age, was performed by an independent third party (Apoteket Production and Laboratories (APL), Stockholm, Sweden) and determined by a computerised random-number generator in blocks of two. Allocation was implemented by use of numbered containers, and randomisation codes were kept secret at the Uppsala University Hospital Pharmacy until completion of the study.

Study procedure

Participants underwent two functional magnetic resonance imaging (fMRI) scanning sessions with an emotional face-matching task, one before and one in the last week of treatment, each followed by a behavioural test. After the first session, an experienced psychiatrist (K.W.) assessed baseline symptom severity using the clinician-administered Liebowitz Social Anxiety Scale (LSAS)[31] and the allocated treatment was distributed. After the second scanning session, the same psychiatrist again administered LSAS and rated clinical response status using the Clinical Global Impression – Improvement scale (CGI-I).[32] Patients receiving CGI-I scores of 1 or 2 (very much or much improved) were defined as treatment responders and patients scoring $\geqslant 3$ were non-responders.[32] Fifteen months post-treatment, participants completed the self-report version of LSAS (LSAS-SR) online.[31] During the follow-up period, participants were free to initiate any treatment at their own cost.

Treatments

ICBT

The clinician-guided treatment, based on Clark & Wells' model of SAD,[33] was delivered via the internet and included nine weekly modules.[6,10,22,34,35] Each module contained a reading section: CBT and SAD (module 1), the cognitive model of SAD and cognitive restructuring (modules 2–4), exposure exercises (modules 5–7), and social skills training and relapse prevention (modules 8 and 9). In addition, the patients were given weekly homework assignments. A therapist provided written feedback on each assignment to reinforce and modify the patients' work and thereafter introduced the next week's module. Adherence to ICBT was assessed through registration of each completed module and homework assignment.

Escitalopram

APL, Stockholm, Sweden, prepared identical capsules containing either escitalopram 20 mg (10 mg during the first week) (H. Lundbeck AB, Helsingborg, Sweden) or pill placebo administered once daily during 9 weeks. Adherence to escitalopram was assessed by analyses of blood metabolites at the final visit.

Treatment credibility and masking

Treatment credibility was assessed 1 week after treatment onset by five questions, each yielding scores between 1 (minimum) and 10 (maximum).[6,36] Following treatment, before unmasking, participants were asked to guess which of the two treatment combinations they had received.

Treatment outcome

Clinical outcome measures

The main clinical outcome measures were treatment response according to CGI-I[32] and symptom severity as measured with LSAS.[31] Secondary outcomes were the Social Interaction Anxiety Scale (SIAS),[37] Social Phobia Scale (SPS),[37] MADRS-S,[28] Beck Anxiety Inventory (BAI),[38] and the Quality of Life Inventory (QOLI).[39]

Behavioural test, public speaking

After each fMRI session, participants were instructed to give a 2 min speech on a freely chosen topic in front of five to eight silent participants. Anticipatory anxiety was assessed with the Spielberger State-Trait Anxiety Inventory – State version (STAI-S)[40] immediately after 3 min of speech preparation.

fMRI

Emotional challenge paradigm. An established amygdala-activating paradigm including matching of fearful or angry facial expressions and geometrical shapes[26] was used. A target face or shape was displayed at the top of the screen and, by pressing a button with their left or right index finger, participants indicated which one of two lower images displayed the same emotion or shape as the target (online Fig. DS2). Face and shape trials were presented in blocks of six, in which images were presented for 4 s, interspaced with a fixation cross (2 s for shape trials and random duration of 2, 4 or 6 s for face trials). The expressed emotion or shape of the target varied from trial to trial, and each face block had an equal mix of emotions as well as gender of the actors. Accuracy and reaction times were registered for each trial.

Image acquisition. MRI was performed using a Philips Achieva 3.0T whole body MR scanner (Philips Medical Systems, Best, The Netherlands) equipped with an 8-channel head-coil. An anatomical T_1-weighted image (echo time (TE) = 15 ms; repetition time (TR) = 5700 ms; inversion time = 400 ms; field of view = $230 \times 230\ mm^2$; voxel size = $0.8 \times 1.0 \times 2.0\ mm^3$; 60 contiguous slices) and a blood oxygenation level-dependent (BOLD) echo planar imaging (EPI) sequence were acquired (TE = 35 ms; TR = 3000 ms; flip angle = 90°, acquisition matrix = 76×77, voxel size = $3.0 \times 3.0 \times 3.0\ mm^3$, gap = 1 mm, 30 axial slices). Participants were positioned supine in the scanner. Visual stimuli were presented through goggles (Visual System, NordicNeuroLab, Bergen, Norway) using E-prime (Psychology Software Tools, Sharpsburg, Pennsylvania, USA).

Image pre-processing. Data were analysed in MATLAB (MathWorks, Natick, Massachusetts, USA) using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8). Each participant's BOLD EPI images were realigned to the mean image of each session, slice timing corrected to the middle slice of each volume, co-registered with the anatomical scan and normalised to Montreal Neurological Institute (MNI) standard space using parameters obtained from unified segmentation of the anatomical image. Finally, smoothing was performed using an 8 mm Gaussian kernel (full width, half maximum). BOLD signal in each voxel was high-pass filtered with 128 s, regressed on the stimulus function (boxcar, onsets and durations of face and shape stimuli), six movement parameters obtained from the realignment step and convolved with the canonical haemodynamic response function provided by SPM. For each participant and session, emotional faces were contrasted against geometrical shapes. Psychophysiological interaction (PPI) analyses of amygdala connectivity were conducted with time-series fMRI data extracted from the amygdala, and entered as a regressor together with task and the interaction between the two. For each individual, difference images representing changes in reactivity/connectivity, calculated by subtracting the pre-treatment from the post-treatment contrast map, were used in second level group comparisons.

Statistical analyses

Demographic and pre-treatment clinical data were compared between groups by *t*-tests, Mann–Whitney *U*-tests or chi-squared tests using IBM SPSS Statistics 20. Treatment effects were evaluated using repeated measurement ANOVAs with group (escitalopram+ICBT/placebo+ICBT or responders/non-responders) and time (pre- and post-treatment) as factors, with *t*-test for follow-up analyses. Two participants (one per group) were not available for all post-treatment measurements, and eight (four per group) were unavailable for 15-month follow-up (Fig. DS1), and we therefore performed intention-to-treat analyses on clinical and behavioural measures.

Neural reactivity and connectivity changes in treatment (escitalopram+ICBT *v.* placebo+ICBT) and response (responders *v.* non-responders) groups were analysed within SPM8 using between-group *t*-tests. Follow-up reactivity analyses in responder/non-responder subgroups were conducted to evaluate whether change in amygdala reactivity could be explained by clinical improvement or SSRI administration. The region of interest for the reactivity analyses and extraction of PPI time-series consisted of the bilateral amygdala from the Automated Anatomical Labelling atlas within the Wake Forest University Pick atlas.[41] Associations between change in amygdala reactivity and symptom improvement were assessed in the whole sample by including LSAS change scores in regression analyses within SPM8. Spatial localisations are reported in MNI coordinates. The statistical threshold for main fMRI analyses was set at $P<0.05$ family-wise error corrected (FWE), but as we had a strong *a priori* hypothesis of attenuated amygdala response following treatment, we balanced the risk for type I and type II errors by also reporting all amygdala voxel values significant at uncorrected $P<0.05$. Exploratory whole brain reactivity and whole brain PPI analyses applied a statistical threshold of $P<0.001$ with $\geqslant 10$ voxels cluster extent.

Power calculations based on previous SSRI trials[21,42] assumed a difference between escitalopram and placebo in mean (s.d.) LSAS scores of 11.4 (11.7). Given $\alpha=0.05$ and $n=24$ per group, the study had 80% power to detect a difference between treatments.

Ethical statement

The study was approved by the Regional Ethical Review Board, Uppsala, and the Medical Products Agency in Sweden. All participants were fully informed about the study aims and procedures and gave written informed consent prior to inclusion.

Results

Pre-treatment

There were no significant differences between groups on any of the demographic variables (Table 1) or outcome measures (online Table DS1) at pre-treatment.

Treatment outcome

Clinical measures

Escitalopram+ICBT yielded a significantly ($\chi^2(1)=4.08$, $P=0.04$) higher number of responders (16/24, 67%), according to the

Table 1 Patient characteristics prior to treatment

	Escitalopram+ICBT ($n=24$)	Placebo+ICBT ($n=24$)	Statistic	*P*
Age, years: mean (s.d.)	35.4 (9.8)	32.2 (8.7)	$t=1.20$	0.24
Men, *n* (%)	24 (50)	24 (50)	$\chi^2=0$	1
Education ⩾12 years, *n* (%)	13 (54)	12 (50)	$\chi^2=0.08$	0.77
Duration of SAD, mean years (s.d.)	24.9 (12.2)	21.0 (11.1)	$t=1.15$	0.26
Generalised SAD, *n* (%)	13 (54)	17 (71)	$\chi^2=1.42$	0.23
Comorbidity,[a] *n* (%)	11 (46)	7 (29)	$\chi^2=1.42$	0.23
GAD	6 (25)	4 (17)		
Specific phobia	4 (17)	3 (13)		
Depressive episode, current	3 (13)	0 (0)		
Panic disorder	1 (4)	1 (4)		
OCD	1 (4)	0 (0)		
Earlier psychological treatment, *n* (%)	1 (4)	3 (13)		0.61[b]
Earlier psychotropic medication, *n* (%)	5 (21)	2 (8)	$\chi^2=3.82$	0.23
SSRI	3 (3)	1 (4)		
Unknown antidepressants	1 (4)	1 (4)		
Perphenazine	1 (4)	0 (0)		

GAD, generalised anxiety disorder; ICBT, internet-delivered cognitive–behavioural therapy; OCD, obsessive–compulsive disorder; SAD, social anxiety disorder; SSRI, selective serotonin reuptake inhibitor.
a. Seven participants in the escitalopram+ICBT group and five in the placebo+ICBT group reported multiple comorbidities.
b. Fisher's exact test.

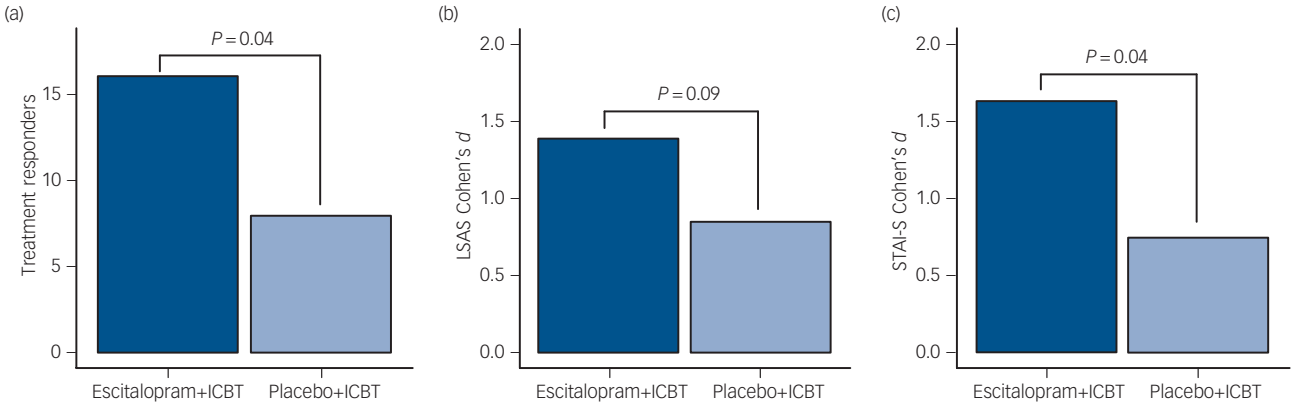

Fig. 1 Comparisons between participants treated with combined escitalopram and internet-delivered cognitive–behavioral therapy (ICBT) (dark blue; $n = 24$) or combined placebo and ICBT (light blue; $n = 24$).

(a) Number of treatment responders in each group. (b) Effect sizes of improvement (pre–post) on the Liebowitz Social Anxiety Scale (LSAS). (c) Effect sizes of improvement in anticipatory speech anxiety (pre–post) as measured by the Spielberger State-Trait Anxiety Inventory – State version (STAI-S).

CGI-I, compared with placebo+ICBT (8/24, 33%) (Fig. 1). For LSAS, there was a significant main effect of time ($F(1,46) = 85.2$, $P < 0.0001$) and a trend for a group time interaction ($F(1,46) = 2.97$, $P = 0.09$) favouring escitalopram+ICBT at post-treatment (Fig. 1 and Table DS1). Long-term follow-up analysis at 15 months showed a significant interaction group × time ($F(2,46) = 3.8$, $P = 0.03$) favouring escitalopram+ICBT (online Table DS2). There was no difference (group × time) on LSAS change scores (pre-treatment to follow-up) between the patients that were on SSRIs during the follow-up period (escitalopram+ICBT: $n = 5$; placebo+ICBT: $n = 6$) and those who were not ($F(2,38) = 0.07$, $P = 0.94$).

Behavioural test

For speech anticipatory anxiety (STAI-S), there was a significant main effect of time ($F(1,46) = 46.23$, $P < 0.0001$) and a group × time interaction ($F(1,46) = 4.62$, $P = 0.04$) favouring escitalopram+ICBT (Fig. 1 and Table DS1).

fMRI

Significantly greater reduction (pre- to post-treatment) in amygdala reactivity to the emotional face-matching task was observed in treatment responders compared with non-responders (MNI *x*, *y*, *z*: 33, −1, −17; $Z = 3.38$, $P_{FWE} = 0.019$, 27 mm^3). In the whole sample, improvement in LSAS scores correlated with reduced right amygdala reactivity (MNI *x*, *y*, *z*: 33, −1, −17; $Z = 3.44$, $P_{FWE} = 0.016$, 27 mm^3) (online Fig. DS3).

At a more lenient ($P_{uncorrected} < 0.05$) statistical threshold, patients treated with escitalopram+ICBT relative to placebo+ICBT, and responders within each group, showed larger reduction in amygdala reactivity (Table 2 and Fig. 2).

Neither treatment nor responder groups differed on treatment-induced changes in accuracy or reaction times during the fMRI task (data not shown).

Exploratory fMRI analyses

Whole brain PPI analyses revealed a greater increase in amygdala–insula (Brodmann area (BA) 13) coupling in responders than non-responders (MNI *x*, *y*, *z*: −36, 26, 10; $Z = 3.35$, $P_{uncorrected} < 0.001$, 270 mm^3), and in the whole brain analyses of reactivity, greater attenuation in the escitalopram+ICBT group relative to placebo+ICBT and in responders compared with non-responders was observed in several cortical areas (online Table DS3). Treatment-induced reduction in LSAS score was positively correlated with decreased neural reactivity in the precentral gyrus (BA 6).

Additional analyses

Secondary outcome measures

Both treatment groups improved on all secondary outcome measures with the largest effect sizes found with escitalopram+ICBT. A significant between-group difference (escitalopram+ICBT > placebo+ ICBT) was noted on quality of life (Table DS1).

Table 2 Treatment-related reductions in amygdala BOLD signal during an emotional face-matching task after treatment with ICBT combined with escitalopram or pill placebo

	Hemisphere	MNI *x*, *y*, *z*			*Z*	Height $P_{uncorrected}$	Cluster volume, mm^3
Main analyses							
Escitalopram+ICBT > placebo+ICBT	Right	33	−1	−17	2.38	0.009	243
Responders > non-responders	Right	33	−1	−17	3.38	<0.001[b]	513
	Left	−18	−4	−17	2.04	0.02	324
Follow-up analyses[a]							
Escitalopram+ICBT responders > escitalopram+ICBT	Right	33	−1	−17	2.60	0.005	81
non-responders	Left	−18	−7	−17	2.44	0.007	567
Placebo+ICBT responders > placebo+ICBT non-responders	Right	30	−4	−17	2.04	0.02	108

BOLD, blood oxygenation level-dependent; ICBT, internet-delivered cognitive–behavioural therapy; MNI, Montreal Neurological Institute.
a. Escitalopram+ICBT responders *v.* placebo+ICBT responders: no significant clusters. Escitalopram+ICBT non-responders *v.* placebo+ICBT non-responders: no significant clusters.
b. $P_{FWE} = 0.019$.

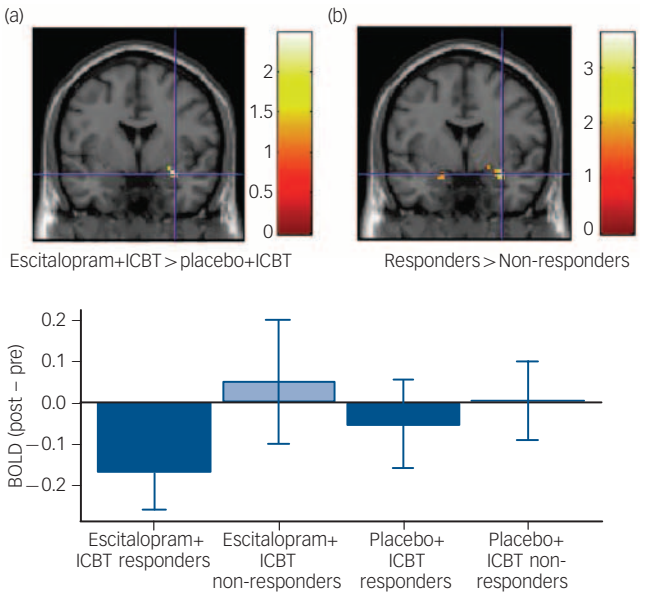

Fig. 2 Treatment-related reductions in amygdala reactivity during an emotional face-matching task.

(a) Escitalopram and internet-delivered cognitive–behavioral therapy (ICBT) decreased more than placebo+ICBT in the right amygdala. (b) Treatment responders decreased more than non-responders bilaterally in the amygdala. Crosshair in all images at Montreal Neurological Institute coordinates *x*, *y*, *z*: 33, −1, −17. All images are displayed at $P_{uncorrected} < 0.05$, but the difference between responders and non-responders is also significant at $P_{FWE} < 0.05$. Bar plot depicts mean reduced blood oxygenation level-dependent (BOLD) signal, parameter estimates (arbitrary units) from pre- to post-treatment. Error bars represent standard error of the mean.

Adverse events

Significantly ($\chi^2(1) = 11.73$, $P < 0.001$) more participants in the escitalopram+ICBT group (22/24, 92%) than in the placebo+ICBT group (11/24, 46%) reported drug-related adverse events, and the escitalopram+ICBT group reported significantly ($t(46) = 3.40$, $P < 0.001$) more adverse events (mean 2.3, s.d. = 1.3) than the placebo+ICBT group (mean 1.0, s.d. = 1.3). There was no difference in number of adverse events in the responder compared with the non-responder group ($t(46) = 0.30$, $P = 0.77$). A total of 41 adverse events were reported in the trial, the most common being nausea ($n = 10$), headache ($n = 7$), insomnia ($n = 3$), increased anxiety ($n = 3$) and tiredness ($n = 2$). Events were generally mild or moderate, usually transient and all were resolved at post-treatment.

Adherence to ICBT

There was no significant difference in number of completed modules between treatment groups (Mann–Whitney $U = 229.0$, $P = 0.15$). The majority of participants completed all nine modules (escitalopram+ICBT: 18/24, 75%; placebo+ICBT: 14/24, 58%) and all but one participant in each group completed at least five modules. Across both groups, significantly more responders to treatment (20/24, 83%) than non-responders (12/24, 50%) completed all nine modules ($\chi^2(1) = 6.00$, $P = 0.01$), whereas this was not observed within each treatment group (P's > 0.12).

Adherence to escitalopram

Blood serum analyses of escitalopram concentrations[43] indicated that all participants in the escitalopram+ICBT group (median (25th–75th percentile) 65.0 (39.5–103.0) nmol/L), but none in the placebo+ICBT group (0 (0–0) nmol/L), had taken the medication. One person in the placebo+ICBT group discontinued treatment owing to side-effects (feeling emotionally unaware), but participated in post-assessments.

Relapse

Following Montgomery *et al*,[44] relapse was defined as an increase > 10 in LSAS score from post-assessment to 15-month follow-up. Four participants (4/40; 10%) relapsed, two in each treatment group, three of which being responders (escitalopram+ICBT: $n = 2$; placebo+ICBT: $n = 1$). The responder who relapsed in the placebo+ICBT group had also started SSRI treatment during the follow-up period.

Expectancy and credibility

There were no significant differences between treatment groups regarding total credibility score ($t(45) = 1.26$, $P = 0.22$) or expectancy of improvement ($t(45) = 1.24$, $P = 0.22$). Participants were not able to guess their treatment at better than chance level ($\chi^2(1) = 1.73$, $P = 0.19$).

Discussion

Summary of findings

This randomised, double-blind, pharmaco-fMRI trial indicates that adding escitalopram to ICBT for SAD increases the number of responders, reduces anticipatory speech anxiety, and attenuates amygdala reactivity to an emotional face-matching task. Fifteen-month follow-up data corroborated the beneficial clinical effect. These findings are in line with clinical observations that SSRIs may enhance the effect of CBT and are in agreement with observations from neuroimaging trials that attenuation of amygdala reactivity may underlie symptom improvement in patients with anxiety disorder.[21–23,25]

Behavioural treatment effects

Only two prior studies have reported on clinical effects of concurrent SSRI and CBT treatment for SAD, with mixed findings.[12,13] Davidson et *al*[13] found no benefit of adding fluoxetine to CBT, whereas Blomhoff *et al*[12] suggested a possible advantage of combined sertraline and behaviour therapy relative to behaviour treatment alone. In addition, combining the monoamine oxidase inhibitor phenelzine with group CBT was superior to either treatment alone in one trial.[45] In line with the present findings, the combination of SSRI and CBT has shown positive effects in other anxiety and mood disorders in adults[15] and in adolescents.[14] There were no indications that the add-on effect of escitalopram was due to reduction of depressive symptoms. Concomitant SSRI treatment could, however, help build resilience with CBT by enhancing extinction learning[16,17] or by reducing anxiety[42,44] or cognitive biases.[46] Interestingly, at 15-month follow-up, the escitalopram+ICBT group had lower LSAS scores than the placebo+ICBT group, indicating stable long-term improvement of adding escitalopram to CBT for SAD.

Neural treatment effects

The fMRI data suggested that amygdala reactivity to emotional faces was more attenuated in responders as well as in the escitalopram+ICBT group, consistent with the notion that dampened amygdala activation constitutes a common anxiolytic pathway for various SAD treatments.[21–23,25] We have previously shown that the clinical response following treatment with SSRI,[21,23,25] CBT[23] and placebo[21] is associated with reduced amygdala reactivity to symptom provocation (i.e. public speaking). Here, we extend these findings to include combined treatment and

a different end-point of neural response, an emotional face-matching task. Similar to the results by Faria *et al*,[21] attenuation of especially the right amygdala was associated with clinical response, both in between-group comparisons and as reflected in the positive correlation between symptom improvement and reduced amygdala reactivity. We argue that our amygdala results reflect anxiolytic rather than general pharmacodynamic effects,[21] as escitalopram+ICBT non-responders did not show diminished amygdala reactivity, whereas placebo+ICBT responders did. This notion is also supported by the lack of evidence for differential amygdala reduction between escitalopram+ICBT responders *v.* placebo+ICBT responders.

Amygdala connectivity to the right insula increased in responders, indicating that the successful treatment alters inter-connectivity between central nodes of the fear processing network. We could, however, not demonstrate evidence for treatment-related changes in amygdala-frontal connectivity, putatively involved in symptom improvement through enhanced emotion regulation.[20] Aside from the amygdala, reduced symptom (LSAS) severity also had a positive correlation with diminished reactivity in the precentral motor cortex (BA 6), again with escitalopram+ICBT exhibiting the greatest reduction, possibly reflecting improvement in the motor component of anxiety[47] or changes in the salience network.[48]

Limitations

Among the study limitations it should be noted that we could not directly compare combined treatment with monotherapies, although we note relatively higher effect sizes on comparable social anxiety scales for escitalopram+ICBT in comparison with ICBT alone as reported in our previous large-scale randomised controlled trials using the same ICBT treatment programme.[6,34,35] Also, our findings of stable long-term improvement for escitalopram+ICBT even after termination of the drug treatment period, with low relapse rate in comparison to previous data on long-term administration of escitalopram *v.* placebo,[44] suggest SSRI potentiation of CBT learning rather than a mere drug effect. The present design did not include a control for placebo+ICBT but this treatment yielded considerably higher effects sizes than waiting-list[6,34,35] and placebo[21] comparison groups in our previous reports, and similar effect sizes as for ICBT monotherapy.[6,34,35] Further limitations include the relatively modest sample size especially when comparing responders with non-responders within treatments. Also, the failure to show a significant effect on the LSAS at post-treatment may have been due to the low sample size, given the fact that the patients also had an additional treatment, ICBT, which may further reduce the difference between active drug and placebo. Although our main fMRI results of a larger reduction in amygdala reactivity connected to symptom improvement rely on corrected *P*-levels, we also chose to report results at a more liberal level with uncorrected *P*-values. We are aware that this approach may increase the risk of false positives; however, an overly strict approach may also lead to type II errors which we think might otherwise have been present as the pattern of results observed was highly consistent with our previous imaging treatment studies.[21–23,25]

Implications

To our knowledge, this is the first randomised neuroimaging trial of combined first-line pharmacological and psychosocial treatments. We demonstrate that the SSRI escitalopram adds to the clinical effect of CBT for SAD and that decreased amygdala reactivity may serve as a biomarker for successful anxiolytic treatment.

Malin Gingnell, MD, PhD, **Andreas Frick**, PhD, **Jonas Engman**, MSc, **Iman Alaie**, MSc, **Johannes Björkstrand**, MSc, Department of Psychology, Uppsala University, Uppsala, Sweden; **Vanda Faria**, PhD, Department of Psychology, Uppsala University, Uppsala, Sweden, and Center for Pain and the Brain, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; **Per Carlbring**, PhD, Department of Psychology, Stockholm University, Stockholm, Sweden; **Gerhard Andersson**, PhD, Department of Behavioural Sciences and Learning, Psychology, Linköping University, Linköping, and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; **Margareta Reis**, PhD, Division of Drug Research/Clinical Pharmacology, Department of Health Sciences, Linköping University, Linköping, Sweden; **Elna-Marie Larsson**, MD, PhD, Department of Surgical Sciences/Radiology, Uppsala University, Uppsala, Sweden; **Kurt Wahlstedt**, MD, PhD, Department of Psychology, Uppsala University, Uppsala, Sweden; **Mats Fredrikson**, DMSc, PhD, Department of Psychology, Uppsala University, Uppsala, and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; **Tomas Furmark**, PhD, Department of Psychology, Uppsala University, Uppsala, Sweden

Correspondence: Malin Gingnell, Department of Psychology, Uppsala University, Box 1225, SE-751 42 Uppsala, Sweden. Email: malin.gingnell@psyk.uu.se

First received 17 Sep 2015, final revision 9 Feb 2016, accepted 15 Feb 2016

References

1 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. (Fourth Edition, Text Revision) (DSM-IV-TR)*. APA, 2000.

2 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005; **62**: 593–602.

3 Fehm L, Pelissolo A, Furmark T, Wittchen H-U. Size and burden of social phobia in Europe. *Eur Neuropsychopharmacol* 2005; **15**: 453–62.

4 Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol* 2014; **28**: 403–39.

5 National Institute for Health and Care Excellence. *Social Anxiety Disorder: Recognition, Assessment and Treatment* (Clinical Guideline CG159). NICE, 2013.

6 Furmark T, Carlbring P, Hedman E, Sonnenstein A, Clevberger P, Bohman B, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. *Br J Psychiatry* 2009; **195**: 440–7.

7 Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2014; **1**: 368–76.

8 Titov N, Andrews G, Schwencke G, Robinson E, Peters L, Spence J. Randomized controlled trial of Internet cognitive behavioural treatment for social phobia with and without motivational enhancement strategies. *Aust NZ J Psychiatry* 2010; **44**: 938–45.

9 Berger T, Hohl E, Caspar F. Internet-based treatment for social phobia: a randomized controlled trial. *J Clin Psychol* 2009; **65**: 1021–35.

10 Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry* 2014; **13**: 288–95.

11 Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. *Int Clin Psychopharmacol* 2015; **30**: 183–92.

12 Blomhoff S, Haug TT, Hellström K, Holme I, Humble M, Madsbu HP, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry* 2001; **179**: 23–30.

13 Davidson JRT, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, et al. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; **61**: 1005–13.

14 Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 2008; **359**: 2753–66.

15 Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014; **13**: 56–67.

16 Karpova NN, Pickenhagen A, Lindholm J, Tiraboschi E, Kulesskaya N, Ágústsdóttir A, et al. Fear erasure in mice requires synergy between antidepressant drugs and extinction training. *Science* 2011; **334**: 1731–4.

17 Bui E, Orr SP, Jacoby RJ, Keshaviah A, LeBlanc NJ, Milad MR, et al. Two weeks of pre-treatment with escitalopram facilitates extinction learning in healthy individuals. *Hum Psychopharmacol Clin Exp* 2013; **28**: 447–56.

18 Brühl AB, Delsignore A, Komossa K, Weidt S. Neuroimaging in social anxiety disorder – a meta-analytic review resulting in a new neurofunctional model. *Neurosci Biobehav Rev* 2014; **47**: 260–80.

19 Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry* 2006; **59**: 424–9.

20 Goldin PR, Manber T, Hakimi S, Canli T, Gross JJ. Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. *Arch Gen Psychiatry* 2009; **66**: 170–80.

21 Faria V, Appel L, Åhs F, Linnman C, Pissiota A, Frans Ö, et al. Amygdala subregions tied to SSRI and placebo response in patients with social anxiety disorder. *Neuropsychopharmacology* 2012; **37**: 2222–32.

22 Månsson KNT, Carlbring P, Frick A, Engman J, Olsson C-J, Bodlund O, et al. Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder. *Psychiatry Res Neuroimaging* 2013; **214**: 229–37.

23 Furmark T, Tillfors M, Marteinsdottir I, Fischer H, Pissiota A, Långström B, et al. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry* 2002; **59**: 425–33.

24 Phan KL, Coccaro EF, Angstadt M, Kreger KJ, Mayberg HS, Liberzon I, et al. Corticolimbic brain reactivity to social signals of threat before and after sertraline treatment in generalized social phobia. *Biol Psychiatry* 2013; **73**: 329–36.

25 Furmark T, Appel L, Michelgård Å, Wahlstedt K, Åhs F, Zancan S, et al. Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biol Psychiatry* 2005; **58**: 132–42.

26 Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 2002; **297**: 400–3.

27 Furmark T, Tillfors M, Everz P, Marteinsdottir I, Gefvert O, Fredrikson M. Social phobia in the general population: prevalence and sociodemographic profile. *Soc Psychiatry Psychiatr Epidemiol* 1999; **34**: 416–24.

28 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–9.

29 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (suppl 20): 22–33.

30 First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders – Non-Patient Edition*. Biometrics Research, New York State Psychiatric Institute, 1997.

31 Fresco DM, Coles ME, Heimberg RG, Liebowitz MR, Hami S, Stein MB, et al. The Liebowitz social anxiety scale: a comparison of the psychometric properties of self-report and clinician-administered formats. *Psychol Med* 2001; **31**: 1025–35.

32 Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. *Psychol Med* 2003; **33**: 611–22.

33 Clark DM, Wells A. A cognitive model of social phobia. In *Social Phobia: Diagnosis, Assessment, and Treatment* (eds RG Heimberg, MR Liebowitz, DA Hope, FR Schneier): 69–93. Guilford Press, 1995.

34 Andersson G, Carlbring P, Holmström A, Sparthan E, Furmark T, Nilsson-Ihrfelt E, et al. Internet-based self-help with therapist feedback and in vivo group exposure for social phobia: a randomized controlled trial. *J Consult Clin Psychol* 2006; **74**: 677–86.

35 Carlbring P, Gunnarsdóttir M, Hedensjö L, Andersson G, Ekselius L, Furmark T. Treatment of social phobia: randomised trial of internet-delivered cognitive–behavioural therapy with telephone support. *Br J Psychiatry* 2007; **190**: 123–8.

36 Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972; **3**: 257–60.

37 Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther* 1998; **36**: 455–70.

38 Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; **56**: 893–7.

39 Frisch MB, Cornell J, Villanueva M, Retzlaff PJ. Clinical validation of the Quality of Life Inventory. A measure of life satisfaction for use in treatment planning and outcome assessment. *Psychol Assess* 1992; **4**: 92–101.

40 Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. 1970. Available at http://ubir.buffalo.edu/xmlui/handle/10477/2895 (accessed 18 Feb 2016).

41 Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; **19**: 1233–9.

42 Lader M, Stender K, Bürger V, Nil R. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19**: 241–8.

43 Reis M, Cherma MD, Carlsson B, Bengtsson F. Therapeutic drug monitoring of escitalopram in an outpatient setting. *Ther Drug Monit* 2007; **29**: 758–66.

44 Montgomery SA, Nil R, Dürr-Pal N, Loft H, Boulenger J-P. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. *J Clin Psychiatry* 2005; **66**: 1270–8.

45 Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, et al. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy and their combination for social anxiety disorder. *Arch Gen Psychiatry* 2010; **67**: 286–95.

46 Harmer CJ, Cowen PJ. 'It's the way that you look at it' – a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120407.

47 Åhs F, Pissiota A, Michelgård Å, Frans Ö, Furmark T, Appel L, et al. Disentangling the web of fear: amygdala reactivity and functional connectivity in spider and snake phobia. *Psychiatry Res Neuroimaging* 2009; **172**: 103–8.

48 Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci Off J Soc Neurosci* 2007; **27**: 2349–56.

EXTRA CONTENT ONLINE