Attachment 6

Meta-Analysis Strategy and Results for GAD

Table of Contents

Background

To examine the efficacy and safety of escitalopram in treating patients with generalised anxiety disorder (GAD). It is anticipated that there could be 2 meta-analyses:

1. Patients with GAD and no-co morbidities using placebo as the comparator.
2. An indirect comparison of escitalopram and benzodiazepines, for patients with GAD and no-co morbidities using placebo as a common comparator.

Greater details are provided below:

Types of Analyses	Analysis 1	Analysis 2
GAD Esc vs Placebo	Patients with GAD and no-co morbidities. This includes a relapse study.	
GAD Benz DSM-IV		Diazepam, oxazepam and placebo only. Escitalopram and placebo. Using placebo as common comparator.

Objectives

- To assess the effects of escitalopram versus placebo in the treatment of patients with GAD (DSM-IV).
- To assess the effects of escitalopram versus benzodiazepines in the treatment of patients with GAD (DSM-IV) via an indirect comparison to placebo.

s38 [redacted]

Types of studies

All randomised controlled trials of escitalopram for GAD were considered for inclusion. The meta-analysis included published and unpublished studies written in English.

Types of participants

Studies of participants with GAD defined as DSM-. No restriction on trial inclusion was applied with respect to subject age, inpatient/outpatient status, or secondary psychiatric co-morbidity.

Studies concerning anxiety symptoms that were part of the clinical presentation of another primary diagnosis (eg anxiety symptoms in depression) were, however, excluded.

Current but not prior treatment with psychotherapy was used as an additional exclusion criterion.

Literature Search

This is presented in detail in Attachment 2. The studies included in the meta-analysis are:

Trial	Reports
Comparative randomised trials	
Escitalopram vs placebo	
SCT-MD-05	Flexible dose comparison of the safety and efficacy of Lu 26-054 (i.e. escitalopram) and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002.
SCT-MD-06	Flexible dose comparison of the safety and efficacy of escitalopram and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002.
SCT-MD-07	Flexible dose comparison of the safety and efficacy of Lu 26-054 (i.e. escitalopram) and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002. Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study. *Depression and Anxiety* 2004;19(4):234-240.[1]
SCT-MD-31	A double-blind flexible dose comparison of escitalopram, venlafaxine XR and placebo in the treatment of Generalised Anxiety Disorder. 24 June, 2005
99815	A double-blind, randomised, placebo-controlled trial comparing the efficacy and safety of fixed dosages of escitalopram with that of placebo in patients with Generalised Anxiety Disorder. 27 May 2004. Baldwin DS, Trap Huusom AK, Mæhlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder. British Journal of Psychiatry, 2006, 189: 264-272[2].

The following study was not included as it was a relapse prevention study.

99769	A double-blind, randomised, placebo-controlled, multicentre, relapse-prevention trial with 20mg escitalopram in patients with Generalised Anxiety Disorder. 9 December 2004. Allgulander C, Florea I, Huusom AKT. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *International Journal of Neuropsychopharmacology* 2006;9(5):495-505[3]

It was also not possible to meta-analyse Hackett with the escitalopram studies, however statistical testing was conducted and is presented in the results section.

Indirect comparison of escitalopram versus benzodiazepines	
Diazepam vs placebo (DSM-IV diagnosed patients)	
Hackett et al[4].	Hackett, D., V. Haudiquet, and E. Salinas, A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. European Psychiatry, 2003. 18(4): 182-187.

Outcomes

Primary and secondary outcome analyses were stratified by pre-defined primary and secondary outcomes of each study.

Primary outcomes

Both dichotomous outcome measures of treatment response and continuous symptom severity scales were included.

Dichotomous outcome measures
Proportion of patients with CGI-I score ≤ 2

Continuous symptom severity scales
Symptom severity was assessed by the Hamilton Anxiety Scale (HAM-A) for generalised anxiety disorder (Hamilton 1959).

Secondary outcomes

Dichotomous outcome measures

(a) Treatment response (number of responders) was determined from the improvement item of the Clinical Global Impressions scale (CGI-I), a widely used categorical

measure of treatment response in which responders are defined as having a change item score of 1 = "very much" or 2 = "much" improved (patients with CGI-I score ≤ 2) (Guy 1976)

(b) Proportion of responders (patients with a ≥ 50% reduction in HAM-A total score) from baseline to each visit
(c) Proportion of remitters (patients with a HAM-A total score ≤ 7) per visit

Continuous symptom severity scales

Scores on symptom rating scales for disorders, other than the primary anxiety disorder, included:

(a) The HAM-A subscales for psychic and somatic anxiety (Hamilton 1959).
(b) Anxiety symptom severity scales, such as the HAM-A subscales for psychic and somatic anxiety (Hamilton 1959).
(c) HAM-A score for item 1 (anxious mood)
(d) HAM-A score for item 2 (tension)
(e) HAD anxiety subscale
(f) CGI-S score final visit
(g) CGI-S score
(h) CGI-I score
(i) Change from baseline to end point in HAD anxiety score

Other Assessments

The effectiveness of medication was also assessed through measurement of:

(a) Functional disability, such as the Sheehan Disability Scale (SDS), which included subscales to assess work, social and family related impairment (Sheehan 1996).

Finally, the acceptability of medication was determined by:

(a) Calculating the proportion of participants who:
    a. Withdrew from the interventions due to adverse events.
    b. Withdrew due to lack of efficacy
    c. Withdrew due to treatment emergent adverse events
    d. Withdrawals

Time points utilised in the meta-analysis

The time points in the meta-analysis will be baseline and 8 weeks. A time point of 12 weeks was utilised for one particular study (Study 99815) with respect to one efficacy endpoint only and all the safety endpoints, since the information presented at 12 weeks was all that was available. The distribution of the studies are as follows:

Weeks	Baseline	8	12
Number of studies	5	5	1

Data extraction and management

Spreadsheet forms were designed for the purpose of recording descriptive information, as well as the summary statistics of the outcome measures, the quality scale ratings and associated commentary. Investigators of the original trials were contacted by reviewers via e-mail in an attempt to obtain any missing information. The data regarding outcomes were subsequently exported to the Review Manager (RevMan) 4.2.9 and RevMan Analyses 1.0.5 software, which was used to conduct the meta-analysis.

Dichotomous variables were analysed using the Der Simonian and Laird random effects model of meta-analysis which calculates a point estimate and 95% confidence interval for each study included in the analysis. This random effects methodology also intuitively calculates a combined overall point estimate and 95% confidence interval by assigning weighting to the analysed studies according to the size of each study, the number of observed events occurring within each study, the accuracy of each study (represented by the preciseness of each confidence interval), and the variability between the studies.

Continuous variables were pooled utilising the inverse variance method in accordance with the data presented. Amongst the studies analysed, data were provided as change from baseline for all time-points and end-points of interest, with the exception of the end-point concerning CGI-Improvement which is implicitly a change from baseline indicator already.

Sensitivity and sub-group analyses were not performed in an effort to investigate the effect of individual trials upon the overall effect estimates obtained from each section of the meta-analyses. This was due to the fact that sensitivity and sub-group analyses are pointless when combining only two studies that have been pooled in the meta-analysis process.

Measures of treatment effect

Dichotomous data

Relative risk (RR) was used as the summary statistic for the dichotomous outcomes of interest (CGI-I or HAMA-A), given the common occurrence of the adverse outcome of interest (more than 20%), and the greater ease of interpreting this statistic compared to the odds ratio. Where data were available, RR was also used for other dichotomous outcomes of interest.

Continuous data

Weighted mean differences (WMD) were utilised for continuous summary data obtained from studies employing identical scales.

Assessment of heterogeneity

Heterogeneity of treatment response, that is whether the differences between the results of trials were greater than would be expected by chance alone, was assessed visually from the forest plot of relative risk. It was also determined by means of the chi-squared test of heterogeneity, with a significance level of less than 0.10 interpreted as evidence of heterogeneity, given the low power of the chi-squared statistic when the number of trials is small (Deeks 2005).

In addition, the I-square heterogeneity statistic reported by RevMan was used to test the robustness of the chi-squared statistic to differences in the number of trials included in the groups being compared within each subgroup analysis (Higgins 2003). Differences on continuous measures in medication efficacy between these groups were assessed by means of Deeks' stratified test of heterogeneity (Deeks 2001). This method subtracts the sum of the chi-squared statistics for each of the groups from the total chi squared for the subgroup analysis, to provide a measure (Qb) of heterogeneity between groups.

Data synthesis (meta-analysis)

A random-effects model was employed for the analysis of dichotomous outcome measures whilst an inverse-variance method was utilised for the analysis of continuous outcome measures. As these models included both within-study sampling error and between-studies variation, there was less risk of committing a Type I error (falsely concluding that there is a treatment effect when there is none) through overestimating the precision of effect size estimates, than would be the case were the fixed-effect model employed for dichotomous outcome measures (Hunter 2000).

Results of Meta-Analysis

Four trials were combined through the methods of meta-analysis for this condition in the primary analysis. Study results of a fifth trial were also combined for sake of completeness, yet limitations which have been discussed elsewhere apply to an analysis of this nature. Dichotomous outcomes with respect to this fifth trial involved a combination of two arms of escitalopram treatment (10mg and 20mg), whilst continuous variable outcomes were separately analysed by combining one arm individually with the remaining four trials.

All end-points of interest with respect to efficacy achieved statistical significance when comparing escitalopram treated patients against placebo treated patients. Consideration must always be made as to whether a statistically significant difference can be extrapolated and interpreted as a clinically significant difference in the general population, based upon results obtained from carefully constructed randomised controlled trials involving specifically selected participants.

The change in HAM-A Total Score was statistically significant in favour of escitalopram compared to placebo at all analysed time-points of 4 weeks, 8 weeks and 12 weeks. At 4 weeks, patients treated with escitalopram achieved a 1.60 unit higher decrease in HAM-A Total Score (95% CI: 0.89 to 2.3, p<0.001). At 8 weeks, patients treated with escitalopram achieved a 2.29 unit higher decrease in HAM-A Total Score (95% CI: 1.48 to 3.1, p<0.001). When involving the 10mg escitalopram arm of the fifth trial at 8 weeks, patients treated with escitalopram achieved a 2.19 unit higher decrease in HAM-A Total Score (95% CI: 1.45 to 2.93, p<0.001). When involving the 20mg escitalopram arm of the fifth trial at 8 weeks, patients treated with escitalopram achieved a 2.24 unit higher decrease in HAM-A Total Score (95% CI: 1.49 to 2.98, p<0.001).

Changes in continuous variables with respect to CGI Severity and CGI Improvement were also statistically significant in favour of escitalopram compared to placebo at the time-point of 8 weeks – a 0.4 unit higher decrease (95% CI: 0.27 to 0.53, p<0.001) and a 0.29 unit lesser increase (95% CI: 0.16 to 0.42, p<0.001), respectively. Negligible differences were observed upon including either arm of the escitalopram treatment arm of the fifth trial, as observed with respect to HAM-A Total Score above.

There was a 36% statistically significant increase in relative risk of a patient achieving a CGI Improvement score of less than or equal to 2 at 8 weeks in escitalopram treated patients compared to placebo treated patients (95% CI: 20% to 55%, p<0.001). The inclusion of the fifth trial in the analysis reduced the relative risk to a 31% statistically significant increase (95% CI: 18% to 45%, p<0.001).

Escitalopram treatment was more effective at improving Quality of Life measures when compared to placebo treatment (a 3.19 unit higher increase, 95% CI: 2.04 to 4.34, p<0.001).

The change in HAM-D was statistically significant in favour of escitalopram compared to placebo at the time-point of 8 weeks for the four initial studies – a 1.02 unit higher decrease (95% CI: 0.55 to 1.49, p<0.001).

The analysis of the dichotomous outcomes concerning the proportion of patients with a fifty percent or greater reduction in HAM-A Total Score and the proportion of patients with a HAM-A score of less than or equal to 7 combined only the SCT-MD-31 trial with both arms of the fifth trial, Study 99815. There was a 20% statistically significant increase in relative risk of a patient achieving a fifty percent or greater reduction in HAM-A Total Score at 8 weeks in escitalopram treated patients compared to placebo treated patients (95% CI: 3% to 40%, p=0.018). There was a 44% statistically significant increase in relative risk of a patient achieving a HAM-A score of less than or equal to 7 at 8 weeks in escitalopram treated patients compared to placebo treated patients (95% CI: 10% to 87%, p=0.008).

Escitalopram treatment was more effective at reducing HAD Anxiety Scores when compared to placebo treatment (a 1.64 unit higher increase, 95% CI: 1.13 to 2.15, p<0.001). Negligible differences were observed upon including either arm of the escitalopram treatment arm of the fifth trial, as observed with respect to HAM-A Total Score above.

Changes in continuous variables with respect to HAM-A Psychic Anxiety Subscale, HAM-A Anxiety Item and HAM-A Tension Item were also statistically significant in favour of escitalopram compared to placebo at the time-point of 8 weeks – a 1.76 unit higher decrease (95% CI: 1.28 to 2.25, p<0.001), a 0.36 unit higher decrease (95% CI: 0.25 to 0.47, p<0.001) and a 0.34 unit higher decrease (95% CI: 0.21 to 0.47, p<0.001), respectively. Negligible differences were observed upon including either arm of the escitalopram treatment arm of the fifth trial, as observed with respect to HAM-A Total Score above.

There was a 45% non-statistically significant reduced risk of an escitalopram treated patient withdrawing from the study at any time due to lack of efficacy when compared to placebo treated patients (95% CI: 62% increased risk to 81% reduced risk, p=0.278). No statistically significant difference was also observed between escitalopram treated patients and placebo treated patients withdrawing from the study overall (4% lower risk in escitalopram treated patients, 95% CI: 23% lower risk to 19% higher risk, p=0.703). Negligible differences were observed upon including all patients of the escitalopram treatment arms of the fifth trial (12 week results).

All end-points in relation to adverse events favoured placebo treated patients with respect to a statistically significant difference at the final time-point of 8 weeks. There was a 102% increased risk of an adverse event leading to withdrawal amongst escitalopram treated patients (95% CI: 22% to 234%, p=0.006) and an 84% increased risk of a treatment-emergent adverse event amongst escitalopram treated patients (95% CI: 18% to 188%, p=0.008). Negligible differences were observed upon including the 12 week results of all patients of the escitalopram treatment arms from the fifth trial.

Sensitivity analyses with respect to GAD analyses

Individual removal of studies from the pooled analyses with respect to the condition of GAD resulted in only three changes of statistical significance.

(1) The change in HAM-D became statistically insignificant upon removal of the SCT-MD-07 trial: 0.74 unit higher decrease (95% CI: 0.0 to 1.49, p=0.051).

(2) Removal of the SCT-MD-06 trial resulted in the introduction of statistical significance with respect to reduced risk of escitalopram treated patients withdrawing from the study at any time due to lack of efficacy: RR 0.39 (95% CI: 0.16 to 0.92, p=0.032).

(3) The end-point in relation to an increased risk of an adverse event leading to withdrawal amongst escitalopram treated patients lost statistical significance upon the removal of the SCT-MD-05 trial: RR 1.73 (95% CI: 0.98 to 3.05, p=0.059).

Statistical Analysis Comparing Indirect Comparison of escitalopram and diazepam

Given that there was only one relevant DSM-IV benzodiazepine trial (Hackett, '03) that trial's outcome has been compared to that of the Escitalopram meta-analysis for the one common outcome measure available namely, *the proportion of patients with at least a 50% reduction in HAM-A from baseline* ***at 8 weeks*** *of treatment*. This indirect comparison (using placebo as the common comparator) showed no statistically significant difference between the two medications, at 8 weeks (*p=0.8628*). The calculations for which are presented below.

This is not an unexpected finding given the relative speed with which diazepam acts compared to the much slower acting (yet long term tolerable) Escitalopram.

Calculation of significance between 2 groups by comparing the z-statistic
(Deeks et al, cited in Egger et al 2001, p.300).
JAVASTAT web-site: http://members.aol.com/johnp71/pdfs.html

META-ANALYSIS #1: Number and Percentage of Patients with ≥50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint – 8 weeks - escitalopram vs placebo

R					
R	1.20362	lnRR	0.185333682	SE(lnRR) using LL	0.078482309
LL	1.03201	lnLL	0.031508357	SE(lnRR) using UL	0.078479933
UL	1.40376	lnUL	0.339154351	mean SE(lnRR)	0.078481121

META-ANALYSIS #2: Number and Percentage of Patients with ≥50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint – 8 weeks - diazepam vs placebo **(Hackett trial only)**					
RR	1.23851	lnRR	0.213909044	SE(lnRR) using LL	0.145538103
LL	0.93114	lnLL	-0.071345637	SE(lnRR) using UL	0.145537154
UL	1.64734	lnUL	0.499161866	mean SE(lnRR)	0.145537628
z	-0.17282	p-value via use of JAVASTAT:			**0.8628**
	-0.17282				

Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint - 4 weeks – without Study 99815

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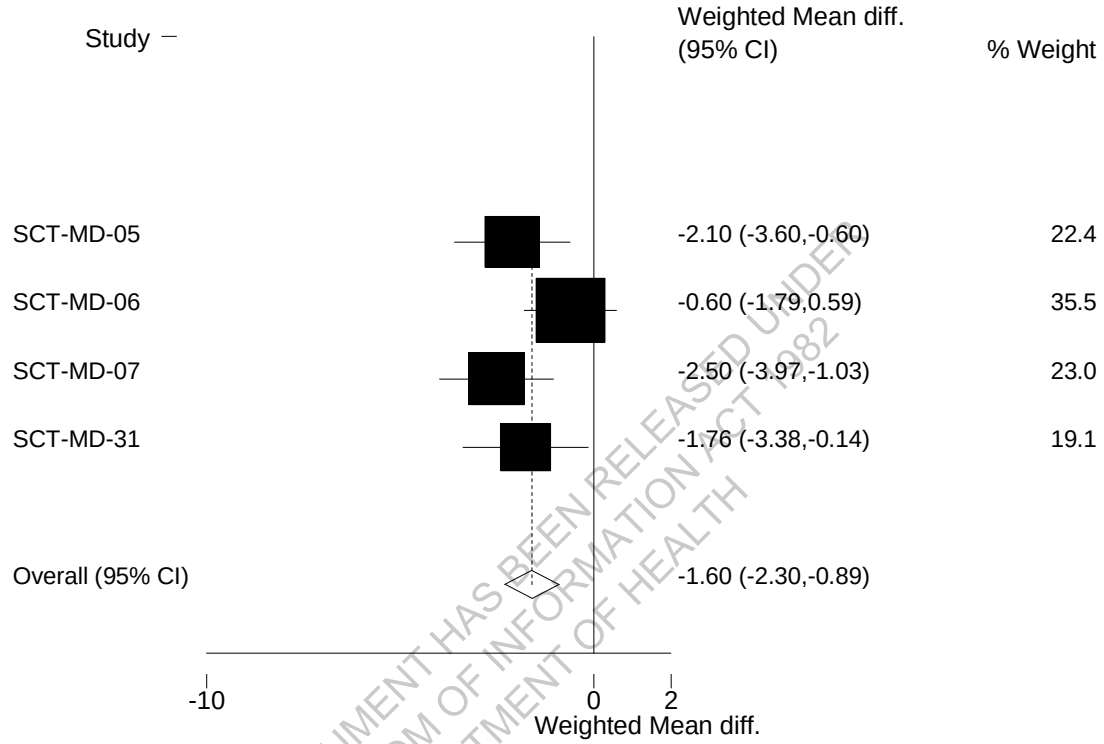
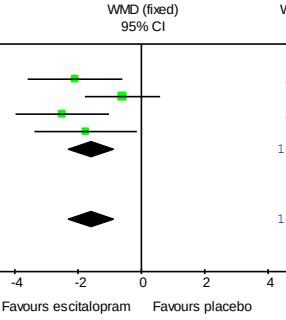


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-2.1	-3.59508	-.604921	22.3917
SCT-MD-06	-.6	-1.78807	.588073	35.4591
SCT-MD-07	-2.5	-3.97444	-1.02556	23.0229
SCT-MD-31	-1.76	-3.37767	-.142326	19.1264
I-V pooled WMD	-1.59517	-2.30264	-.887706	

Heterogeneity chi-squared = 4.62 (d.f. = 3) p = 0.202
Test of WMD=0 : z= 4.42 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 01 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - 4 weeks - without Study 99815

Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-8.40 (6.29)	128	-6.30 (5.80)		22.39	-2.10 [-3.60, -0.60]
SCT-MD-06	143	-7.10 (5.09)	138	-6.50 (5.07)		35.46	-0.60 [-1.79, 0.59]
SCT-MD-07	154	-8.80 (6.53)	153	-6.30 (6.65)		23.02	-2.50 [-3.97, -1.03]
SCT-MD-31	125	-8.74 (6.74)	135	-6.98 (6.55)		19.13	-1.76 [-3.38, -0.14]
Subtotal (95% CI)	546		554			100.00	-1.60 [-2.30, -0.89]
Test for heterogeneity: Chi² = 4.62, df = 3 (P = 0.20), I² = 35.1%							
Test for overall effect: Z = 4.42 (P < 0.00001)							
Total (95% CI)	546		554			100.00	-1.60 [-2.30, -0.89]
Test for heterogeneity: Chi² = 4.62, df = 3 (P = 0.20), I² = 35.1%							
Test for overall effect: Z = 4.42 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint - 8 weeks – without Study 99815

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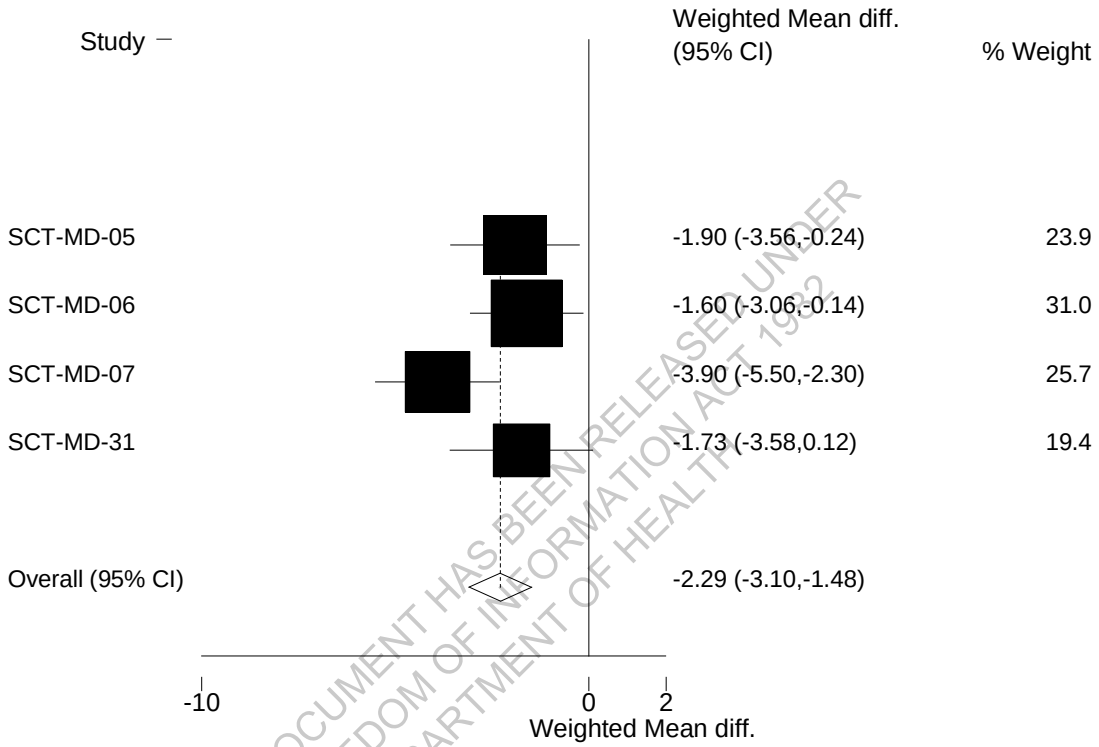
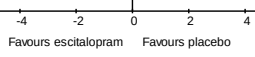


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.9	-3.56334	-.236662	23.8808
SCT-MD-06	-1.6	-3.06052	-.139483	30.974
SCT-MD-07	-3.9	-5.50197	-2.29803	25.7456
SCT-MD-31	-1.73	-3.57548	.11548	19.3996
I-V pooled WMD	-2.28901	-3.10185	-1.47617	

Heterogeneity chi-squared = 5.30 (d.f. = 3) p = 0.151
Test of WMD=0 : z= 5.52 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 02 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-9.60 (7.14)	128	-7.70 (6.29)		23.88	-1.90 [-3.56, -0.24]
SCT-MD-06	143	-9.20 (6.45)	138	-7.60 (6.04)		30.97	-1.60 [-3.06, -0.14]
SCT-MD-07	154	-11.30 (7.27)	153	-7.40 (7.05)		25.75	-3.90 [-5.50, -2.30]
SCT-MD-31	125	-10.94 (7.44)	135	-9.21 (7.74)		19.40	-1.73 [-3.58, 0.12]
Subtotal (95% CI)	546		554			100.00	-2.29 [-3.10, -1.48]
Test for heterogeneity: Chi² = 5.30, df = 3 (P = 0.15), I² = 43.4%							
Test for overall effect: Z = 5.52 (P < 0.00001)							
Total (95% CI)	546		554			100.00	-2.29 [-3.10, -1.48]
Test for heterogeneity: Chi² = 5.30, df = 3 (P = 0.15), I² = 43.4%							
Test for overall effect: Z = 5.52 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint – 8 weeks (with Study 99815 – one arm)

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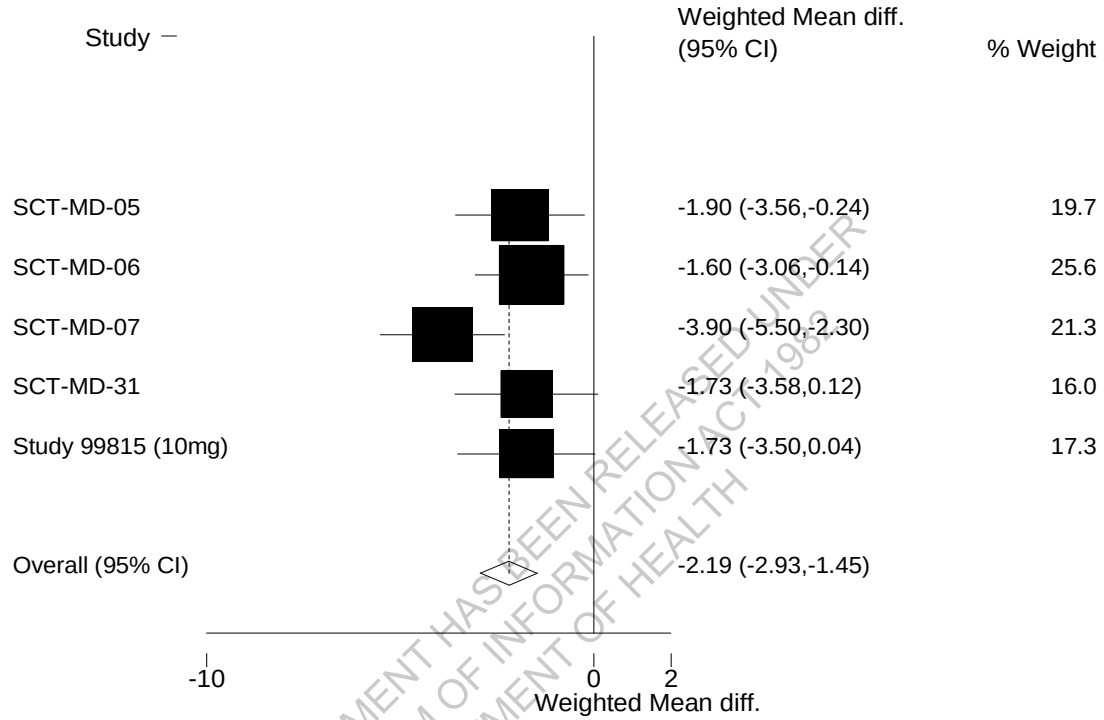

Study	WMD	[95% Conf.	Interval]	% Weight
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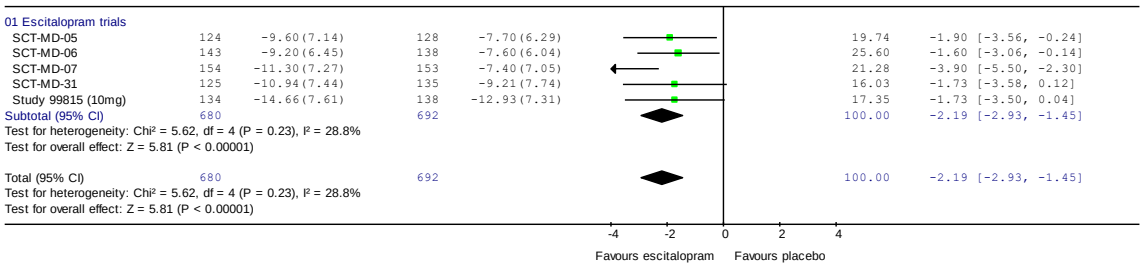
SCT-MD-07	-3.9	-5.50197	-2.29803	25.7456
SCT-MD-31	-1.73	-3.57548	.11548	19.3996
I-V pooled WMD	-2.28901	-3.10185	-1.47617	

Heterogeneity chi-squared = 5.30 (d.f. = 3) p = 0.151
Test of WMD=0 : z= 5.52 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 03 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

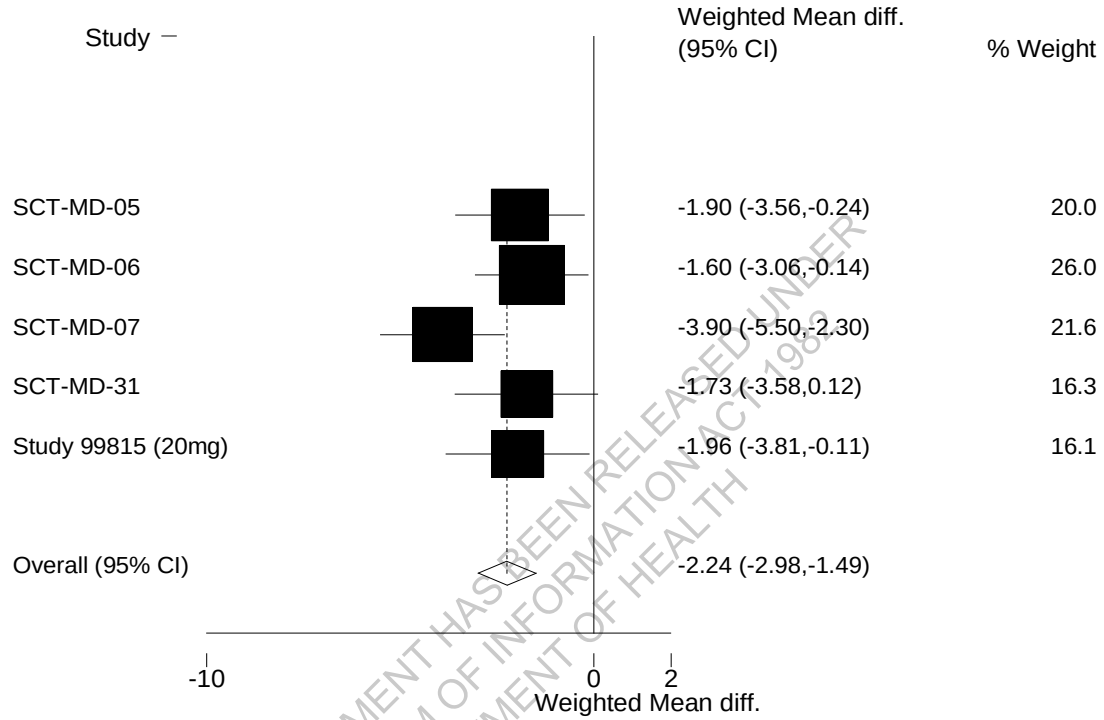
Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-9.60(7.14)	128	-7.70(6.29)		19.74	-1.90 [-3.56, -0.24]
SCT-MD-06	143	-9.20(6.45)	138	-7.60(6.04)		25.60	-1.60 [-3.06, -0.14]
SCT-MD-07	154	-11.30(7.27)	153	-7.40(7.05)		21.28	-3.90 [-5.50, -2.30]
SCT-MD-31	125	-10.94(7.44)	135	-9.21(7.74)		16.03	-1.73 [-3.58, 0.12]
Study 99815 (10mg)	134	-14.66(7.61)	138	-12.93(7.31)		17.35	-1.73 [-3.50, 0.04]
Subtotal (95% CI)	680		692			100.00	-2.19 [-2.93, -1.45]
Test for heterogeneity: Chi² = 5.62, df = 4 (P = 0.23), I² = 28.8%							
Test for overall effect: Z = 5.81 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-2.19 [-2.93, -1.45]
Test for heterogeneity: Chi² = 5.62, df = 4 (P = 0.23), I² = 28.8%							
Test for overall effect: Z = 5.81 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2) label(namevar=trialname)

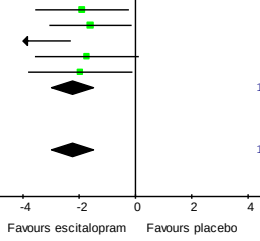


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.9	-3.56334	-.236662	20.0282
SCT-MD-06	-1.6	-3.06052	-.139483	25.9771
SCT-MD-07	-3.9	-5.50197	-2.29803	21.5921
SCT-MD-31	-1.73	-3.57548	.11548	16.2699
Study 99815 (20m	-1.96	-3.81331	-.106688	16.1327
I-V pooled WMD	-2.23593	-2.98032	-1.49154	

Heterogeneity chi-squared = 5.40 (d.f. = 4) p = 0.248
Test of WMD=0 : z= 5.89 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 04 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

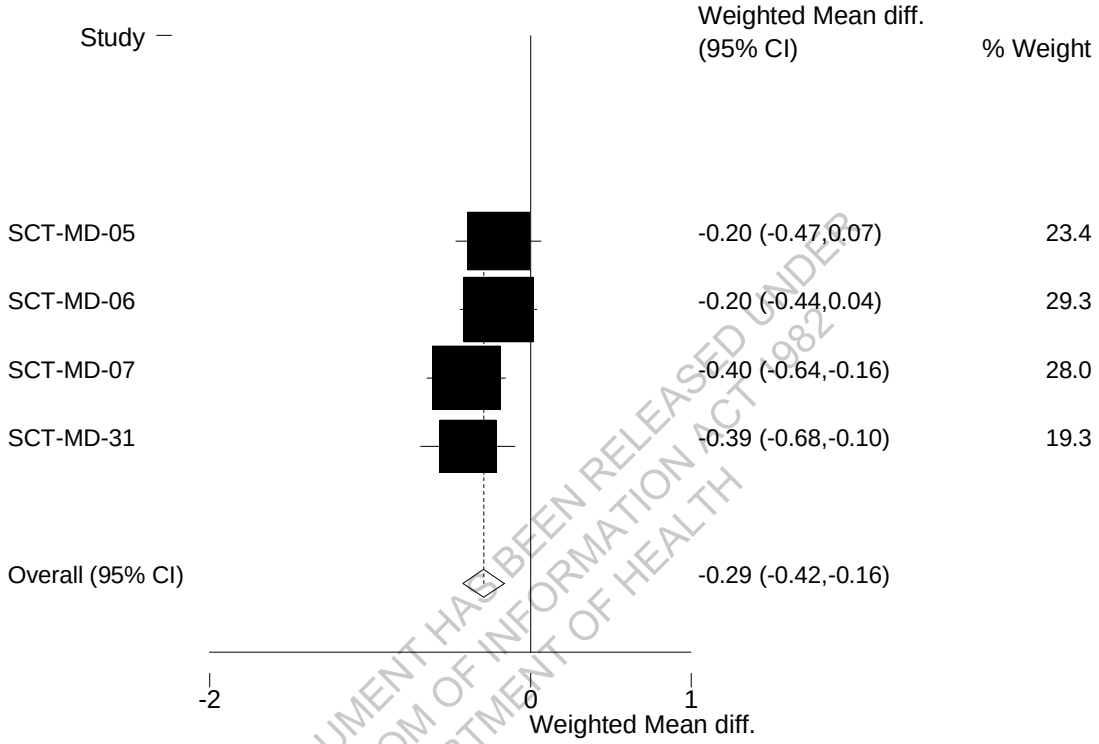
Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-9.60(7.14)	128	-7.70(6.29)		20.03	-1.90 [-3.56, -0.24]
SCT-MD-06	143	-9.20(6.45)	138	-7.60(6.04)		25.98	-1.60 [-3.06, -0.14]
SCT-MD-07	154	-11.30(7.27)	153	-7.40(7.05)		21.59	-3.90 [-5.50, -2.30]
SCT-MD-31	125	-10.94(7.44)	135	-9.21(7.74)		16.27	-1.73 [-3.58, 0.12]
Study 99815 (20mg)	132	-14.89(8.18)	138	-12.93(7.31)		16.13	-1.96 [-3.81, -0.11]
Subtotal (95% CI)	678		692			100.00	-2.24 [-2.98, -1.49]
Test for heterogeneity: Chi² = 5.40, df = 4 (P = 0.25), I² = 26.0%							
Test for overall effect: Z = 5.89 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-2.24 [-2.98, -1.49]
Test for heterogeneity: Chi² = 5.40, df = 4 (P = 0.25), I² = 26.0%							
Test for overall effect: Z = 5.89 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: CGI Improvement (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

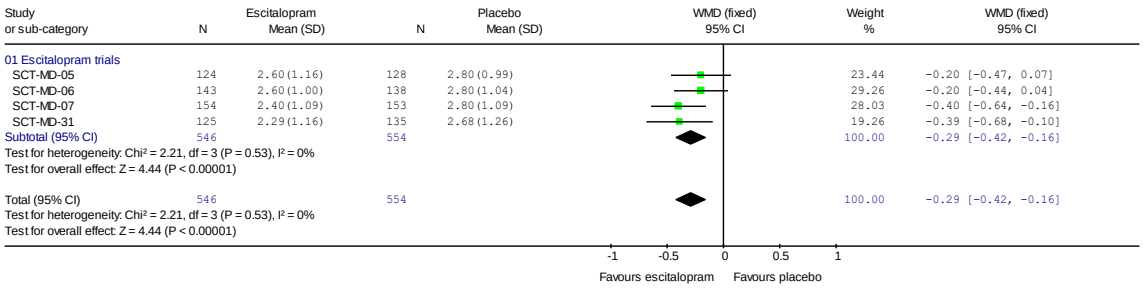
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)



Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.466646	.066646	23.4449
SCT-MD-06	-.2	-.438687	.038687	29.2591
SCT-MD-07	-.4	-.643858	-.156141	28.0313
SCT-MD-31	-.39	-.684157	-.095844	19.2647
I-V pooled WMD	-.292666	-.421775	-.163556	

Heterogeneity chi-squared = 2.21 (d.f. = 3) p = 0.530
Test of WMD=0 : z= 4.44 p = 0.000 **(p<0.001)**

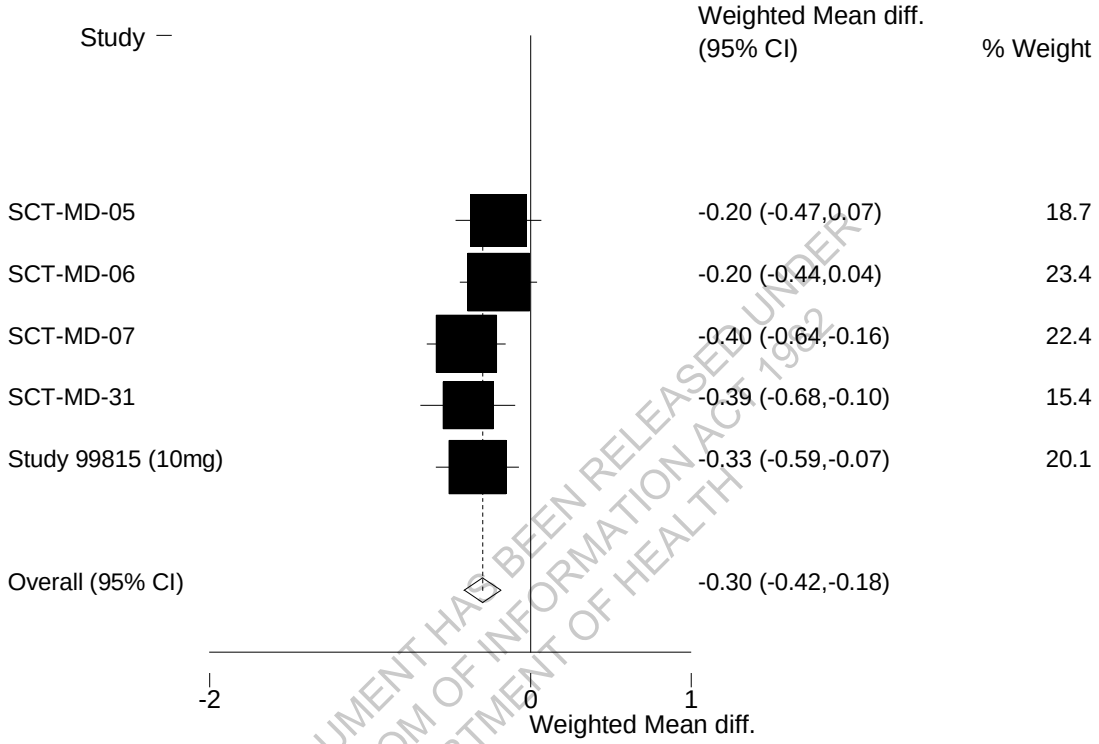
Review: Escitalopram (Lexapro) - GAD
Comparison: 02 CGI Improvement (ITT LOCF) - a change characteristic - secondary endpoint
Outcome: 01 CGI Improvement (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: CGI Improvement (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)

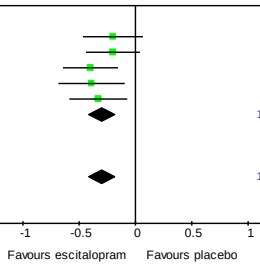


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.466646	.066646	18.7409
SCT-MD-06	-.2	-.438687	.038687	23.3886
SCT-MD-07	-.4	-.643858	-.156141	22.4071
SCT-MD-31	-.39	-.684157	-.095844	15.3994
Study 99815 (10m	-.33	-.587705	-.072295	20.0639
I-V pooled WMD	-.300156	-.41559	-.184723	

Heterogeneity chi-squared = 2.27 (d.f. = 4) p = 0.686
Test of WMD=0 : z= 5.10 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 02 CGI Improvement (ITT LOCF) - a change characteristic - secondary endpoint
Outcome: 02 CGI Improvement (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

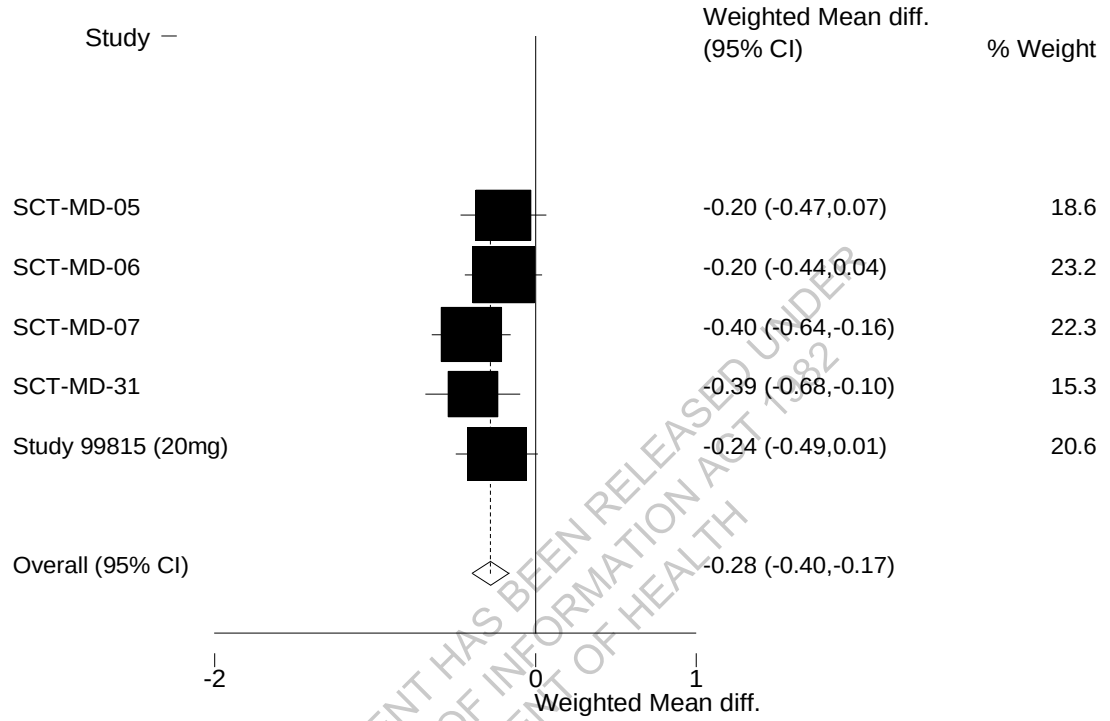
Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	2.60(1.16)	128	2.80(0.99)		18.74	-0.20 [-0.47, 0.07]
SCT-MD-06	143	2.60(1.00)	138	2.80(1.04)		23.39	-0.20 [-0.44, 0.04]
SCT-MD-07	154	2.40(1.09)	153	2.80(1.09)		22.41	-0.40 [-0.64, -0.16]
SCT-MD-31	125	2.29(1.16)	135	2.68(1.26)		15.40	-0.39 [-0.68, -0.10]
Study 99815 (10mg)	134	2.08(1.16)	138	2.41(1.00)		20.06	-0.33 [-0.59, -0.07]
Subtotal (95% CI)	680		692			100.00	-0.30 [-0.42, -0.18]
Test for heterogeneity: Chi² = 2.27, df = 4 (P = 0.69), I² = 0%							
Test for overall effect: Z = 5.10 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.30 [-0.42, -0.18]
Test for heterogeneity: Chi² = 2.27, df = 4 (P = 0.69), I² = 0%							
Test for overall effect: Z = 5.10 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: CGI Improvement (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)

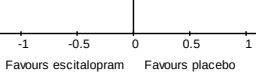


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.466646	.066646	18.6207
SCT-MD-06	-.2	-.438687	.038687	23.2386
SCT-MD-07	-.4	-.643858	-.156141	22.2634
SCT-MD-31	-.39	-.684157	-.095844	15.3007
Study 99815 (20m	-.24	-.493658	.013658	20.5765
I-V pooled WMD	-.281829	-.396891	-.166766	

Heterogeneity chi-squared = 2.34 (d.f. = 4) p = 0.674
Test of WMD=0 : z= 4.80 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 02 CGI Improvement (ITT LOCF) - a change characteristic - secondary endpoint
Outcome: 03 CGI Improvement (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

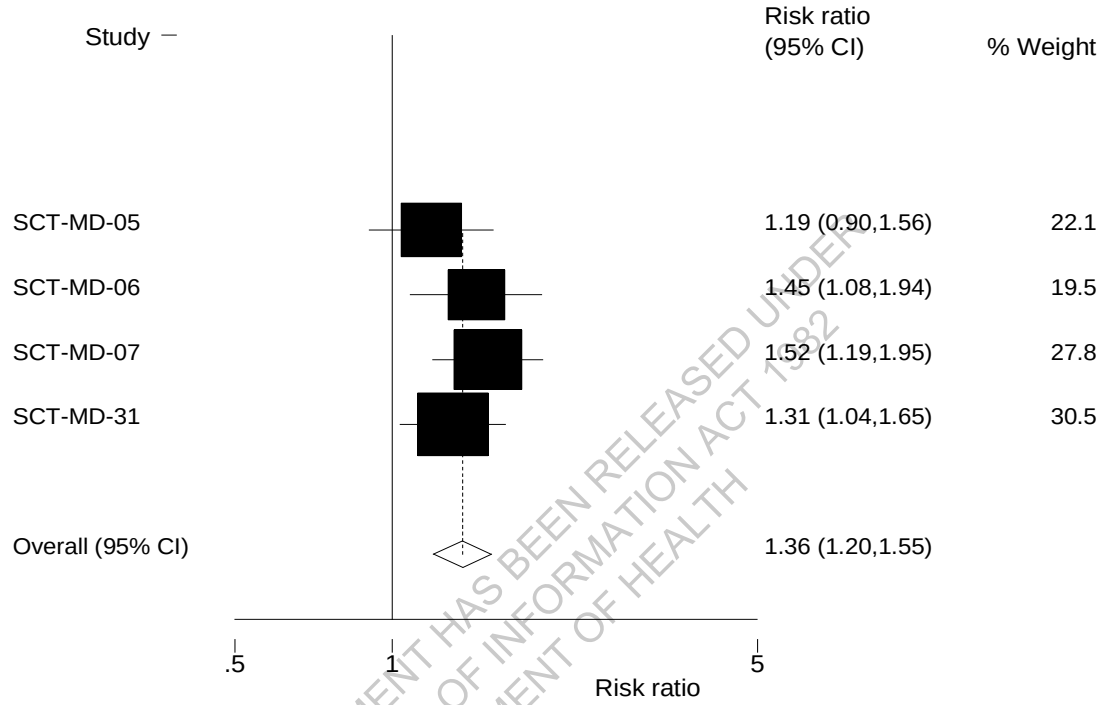
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	2.60(1.16)	128	2.80(0.99)		18.62	-0.20 [-0.47, 0.07]
SCT-MD-06	143	2.60(1.00)	138	2.80(1.04)		23.24	-0.20 [-0.44, 0.04]
SCT-MD-07	154	2.40(1.09)	153	2.80(1.09)		22.26	-0.40 [-0.64, -0.16]
SCT-MD-31	125	2.29(1.16)	135	2.68(1.26)		15.30	-0.39 [-0.68, -0.10]
Study 99815 (20mg)	132	2.17(1.12)	138	2.41(1.00)		20.58	-0.24 [-0.49, 0.01]
Subtotal (95% CI)	678		692			100.00	-0.28 [-0.40, -0.17]
Test for heterogeneity: Chi² = 2.34, df = 4 (P = 0.67), I² = 0%							
Test for overall effect: Z = 4.80 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-0.28 [-0.40, -0.17]
Test for heterogeneity: Chi² = 2.34, df = 4 (P = 0.67), I² = 0%							
Test for overall effect: Z = 4.80 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Number and Percentage of Patients with CGI-I ≤2 (ITT LOCF) - secondary endpoint - 8 weeks – without Study 99815

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	1.18807	.904339	1.56082	22.1464
SCT-MD-06	1.44755	1.08244	1.93583	19.52
SCT-MD-07	1.52452	1.19492	1.94504	27.7898
SCT-MD-31	1.30645	1.03557	1.64819	30.5439
D+L pooled RR	1.36233	1.19815	1.54901	

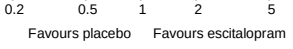
Heterogeneity chi-squared = 2.08 (d.f. = 3) p = 0.556
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.72 p = 0.000 **(p<0.001)**

Fixed-effects analysis: 1.37 (1.20,1.55), z=4.76, p<0.001

Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients with CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients with CGI-I <=2 (ITT LOCF) - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	61/124	53/128		22.15	1.19 [0.90, 1.56]
SCT-MD-06	69/143	46/138		19.52	1.45 [1.08, 1.94]
SCT-MD-07	89/154	58/153		27.79	1.52 [1.19, 1.95]
SCT-MD-31	75/125	62/135		30.54	1.31 [1.04, 1.65]
Total (95% CI)	546	554		100.00	1.36 [1.20, 1.55]

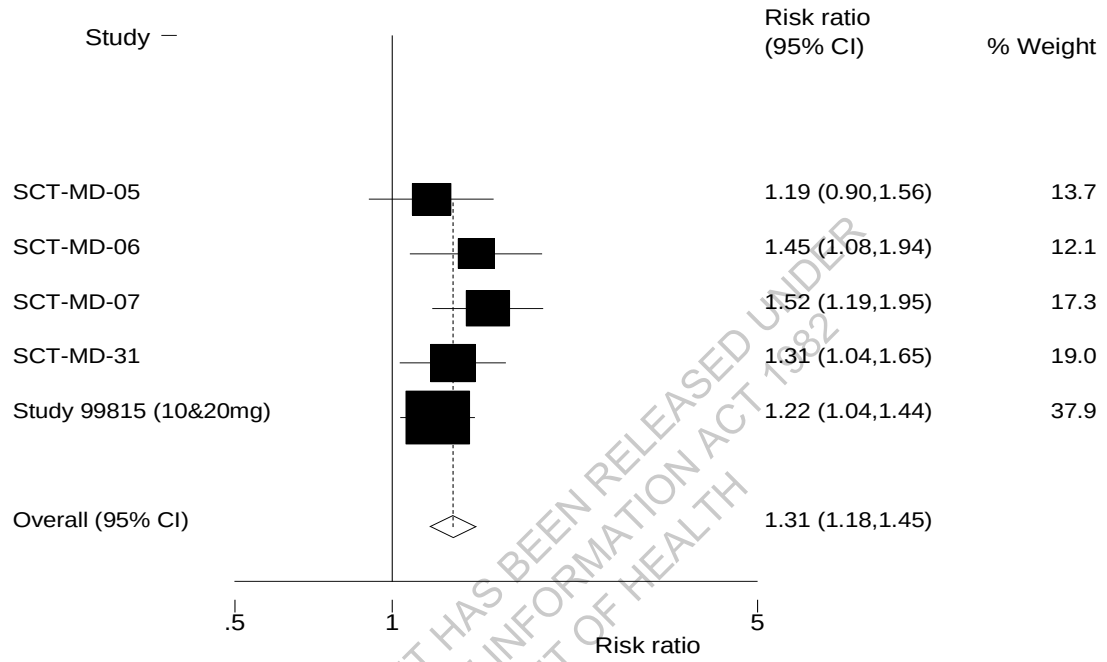
Total events: 294 (Escitalopram), 219 (Placebo)
Test for heterogeneity: Chi² = 2.08, df = 3 (P = 0.56), I² = 0%
Test for overall effect: Z = 4.72 (P < 0.00001)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Number and Percentage of Patients with CGI-I ≤2 (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5) label(namevar=trialname)

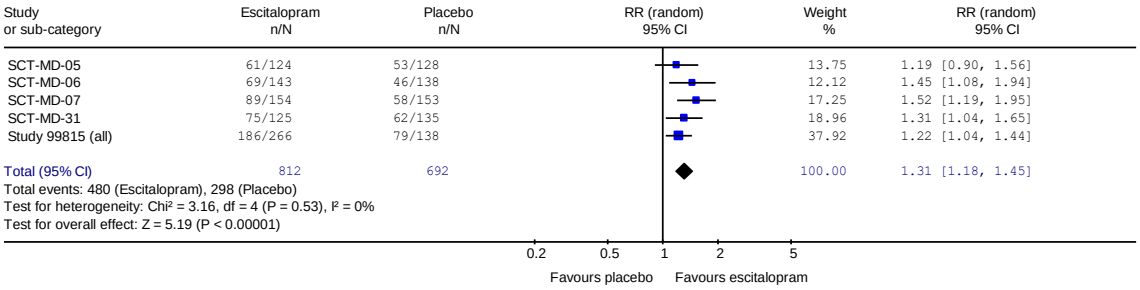


Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	1.18807	.904339	1.56082	13.749
SCT-MD-06	1.44755	1.08244	1.93583	12.1185
SCT-MD-07	1.52452	1.19492	1.94504	17.2525
SCT-MD-31	1.30645	1.03557	1.64819	18.9624
Study 99815 (10&	1.22147	1.03638	1.43961	37.9176
D+L pooled RR	1.3071	1.18132	1.44628	

Heterogeneity chi-squared = 3.16 (d.f. = 4) p = 0.531
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 5.19 p = 0.000 **(p<0.001)**

Fixed-effects analysis: 1.32 (1.19,1.46), z=5.31, p<0.001

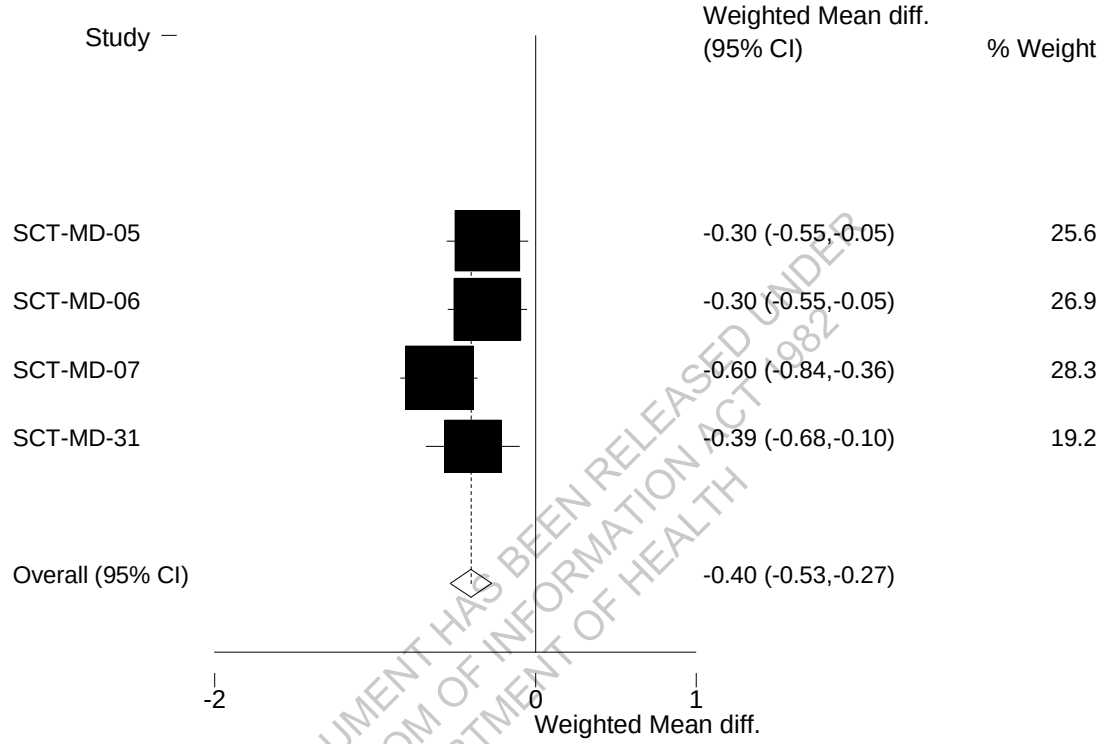
Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients with CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients with CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in CGI Severity (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)

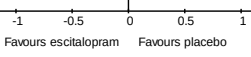


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.3	-.552415	-.047585	25.5608
SCT-MD-06	-.3	-.546271	-.053729	26.852
SCT-MD-07	-.6	-.839716	-.360284	28.3405
SCT-MD-31	-.39	-.680887	-.099113	19.2466
I-V pooled WMD	-.402344	-.529959	-.274729	

Heterogeneity chi-squared = 3.91 (d.f. = 3) p = 0.271
Test of WMD=0 : z= 6.18 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 04 Change in CGI Severity (ITT LOCF) - secondary endpoint
Outcome: 01 Change in CGI Severity (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

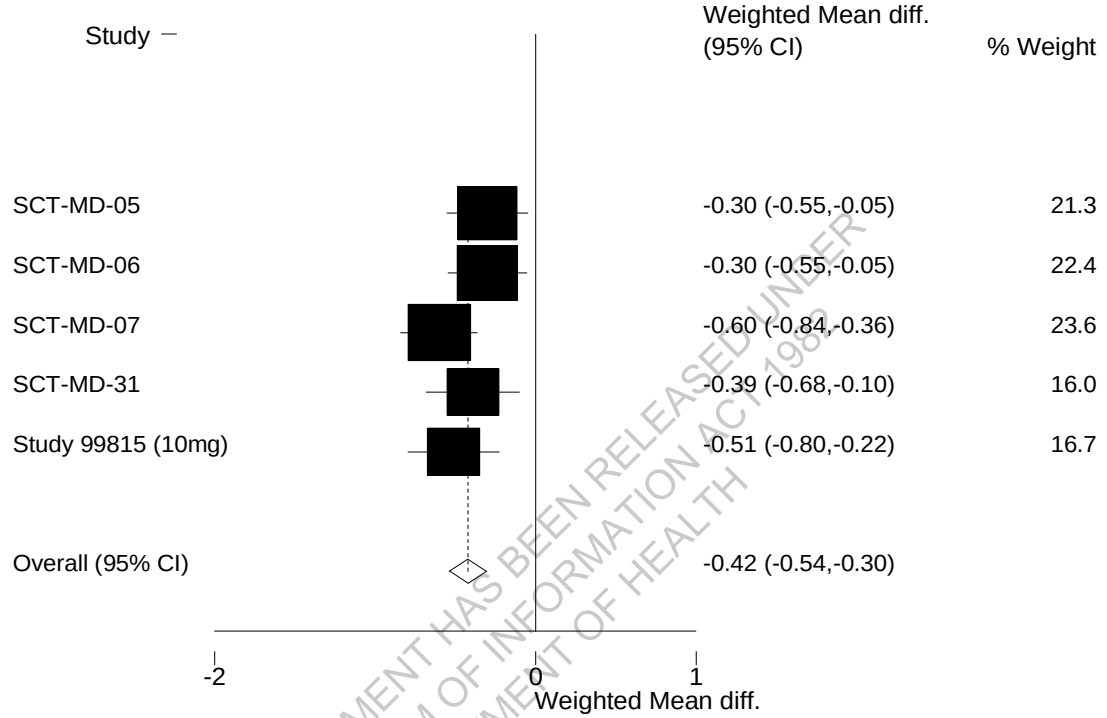
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.20 (1.12)	128	-0.90 (0.91)		25.56	-0.30 [-0.55, -0.05]
SCT-MD-06	143	-1.20 (1.15)	138	-0.90 (0.95)		26.85	-0.30 [-0.55, -0.05]
SCT-MD-07	154	-1.40 (1.13)	153	-0.80 (1.01)		28.34	-0.60 [-0.84, -0.36]
SCT-MD-31	125	-1.50 (1.21)	135	-1.11 (1.18)		19.25	-0.39 [-0.68, -0.10]
Subtotal (95% CI)	546		554			100.00	-0.40 [-0.53, -0.27]
Test for heterogeneity: Chi² = 3.91, df = 3 (P = 0.27), I² = 23.3%							
Test for overall effect: Z = 6.18 (P < 0.00001)							
Total (95% CI)	546		554			100.00	-0.40 [-0.53, -0.27]
Test for heterogeneity: Chi² = 3.91, df = 3 (P = 0.27), I² = 23.3%							
Test for overall effect: Z = 6.18 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in CGI Severity (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)

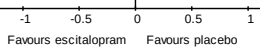


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.3	-.552415	-.047585	21.298
SCT-MD-06	-.3	-.546271	-.053729	22.3739
SCT-MD-07	-.6	-.839716	-.360284	23.6141
SCT-MD-31	-.39	-.680887	-.099113	16.0368
Study 99815 (10m	-.51	-.795247	-.224752	16.6772
I-V pooled WMD	-.420298	-.536786	-.303809	

Heterogeneity chi-squared = 4.37 (d.f. = 4) p = 0.358
Test of WMD=0 : z= 7.07 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 04 Change in CGI Severity (ITT LOCF) - secondary endpoint
Outcome: 02 Change in CGI Severity (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

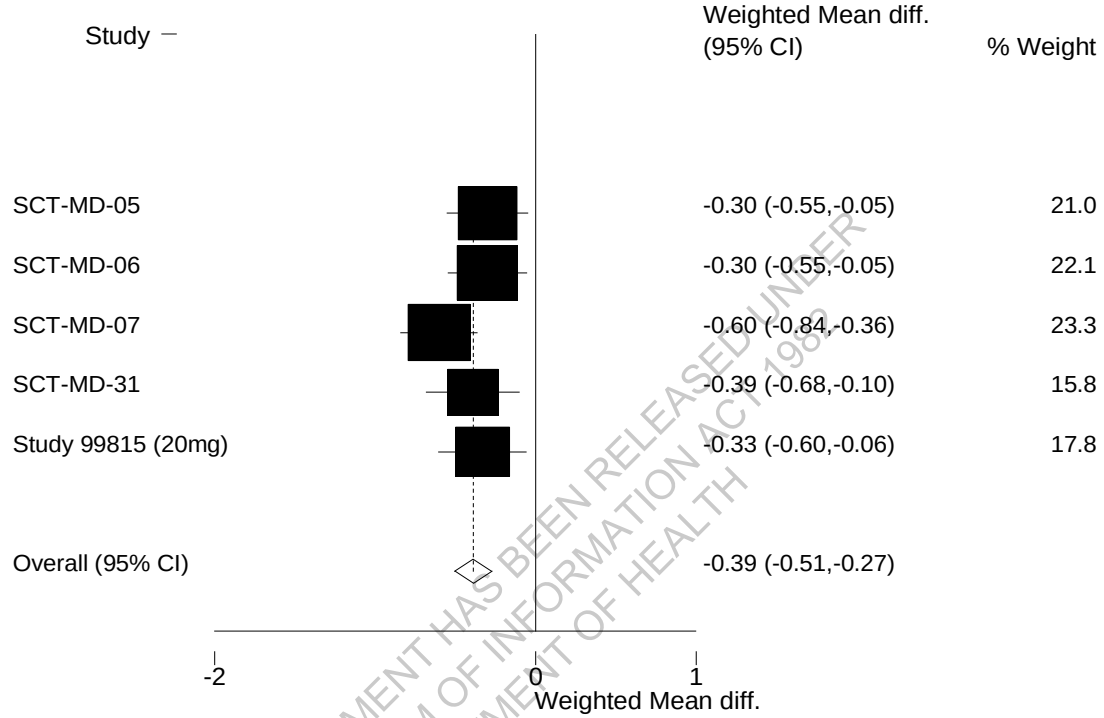
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.20(1.12)	128	-0.90(0.91)		21.30	-0.30 [-0.55, -0.05]
SCT-MD-06	143	-1.20(1.15)	138	-0.90(0.95)		22.37	-0.30 [-0.55, -0.05]
SCT-MD-07	154	-1.40(1.13)	153	-0.80(1.01)		23.61	-0.60 [-0.84, -0.36]
SCT-MD-31	125	-1.50(1.21)	135	-1.11(1.18)		16.04	-0.39 [-0.68, -0.10]
Study 99815 (10mg)	134	-1.96(1.20)	138	-1.45(1.20)		16.68	-0.51 [-0.80, -0.22]
Subtotal (95% CI)	680		692			100.00	-0.42 [-0.54, -0.30]
Test for heterogeneity: Chi² = 4.37, df = 4 (P = 0.36), I² = 8.5%							
Test for overall effect: Z = 7.07 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.42 [-0.54, -0.30]
Test for heterogeneity: Chi² = 4.37, df = 4 (P = 0.36), I² = 8.5%							
Test for overall effect: Z = 7.07 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in CGI Severity (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

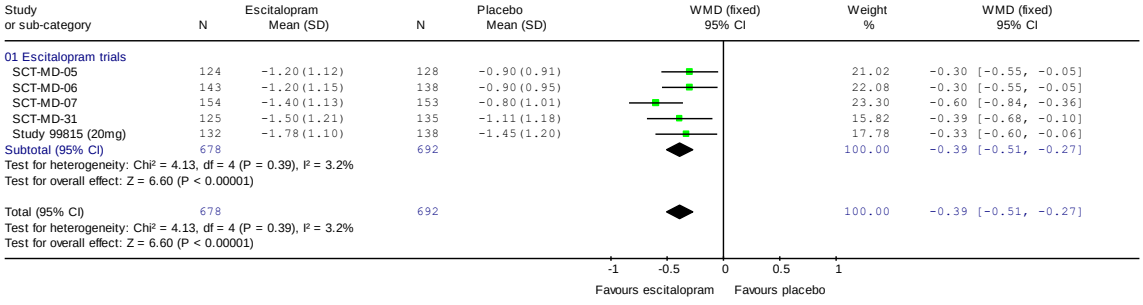
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)



Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.3	-.552415	-.047585	21.0155
SCT-MD-06	-.3	-.546271	-.053729	22.0772
SCT-MD-07	-.6	-.839716	-.360284	23.301
SCT-MD-31	-.39	-.680887	-.099113	15.8241
Study 99815 (20m	-.33	-.604405	-.055595	17.7822
I-V pooled WMD	-.389479	-.505193	-.273766	

Heterogeneity chi-squared = 4.13 (d.f. = 4) p = 0.388
Test of WMD=0 : z= 6.60 p = 0.000 **(p<0.001)**

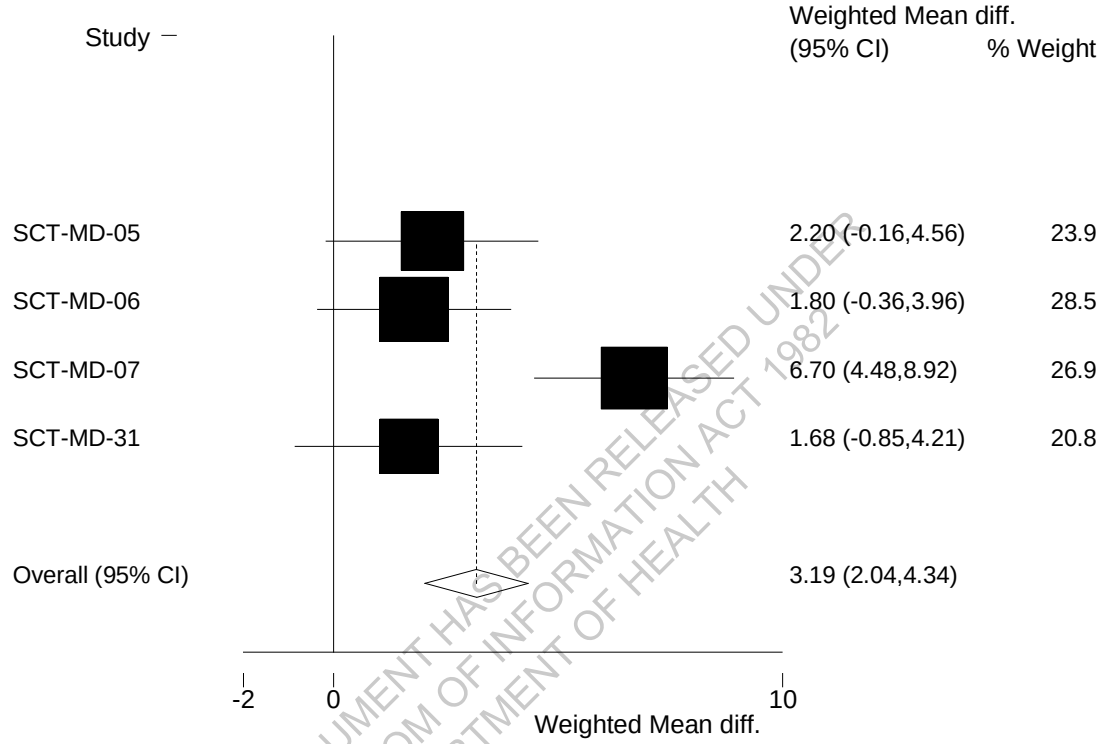
Review: Escitalopram (Lexapro) - GAD
Comparison: 04 Change in CGI Severity (ITT LOCF) - secondary endpoint
Outcome: 03 Change in CGI Severity (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in Quality of Life (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,10) label(namevar=trialname)

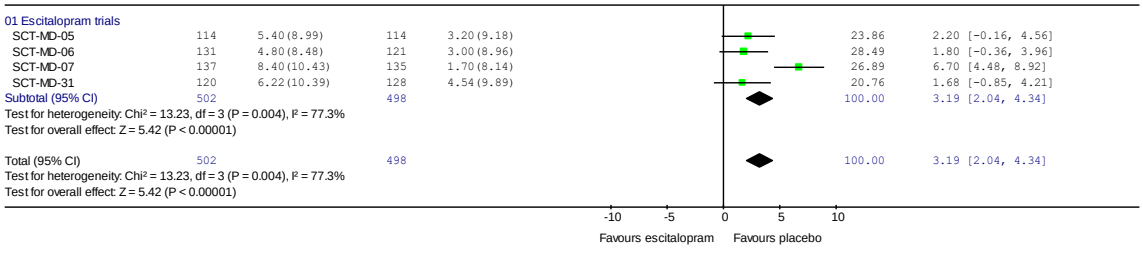


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	2.2	-.158627	4.55863	23.855
SCT-MD-06	1.8	-.358114	3.95811	28.4937
SCT-MD-07	6.7	4.47835	8.92165	26.8872
SCT-MD-31	1.68	-.848094	4.20809	20.764
I-V pooled WMD	3.18798	2.03598	4.33997	

Heterogeneity chi-squared = 13.23 (d.f. = 3) *p = 0.004*
Test of WMD=0 : z= 5.42 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 05 Change in Quality of Life (ITT LOCF) - secondary endpoint
Outcome: 01 Change in Quality of Life (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

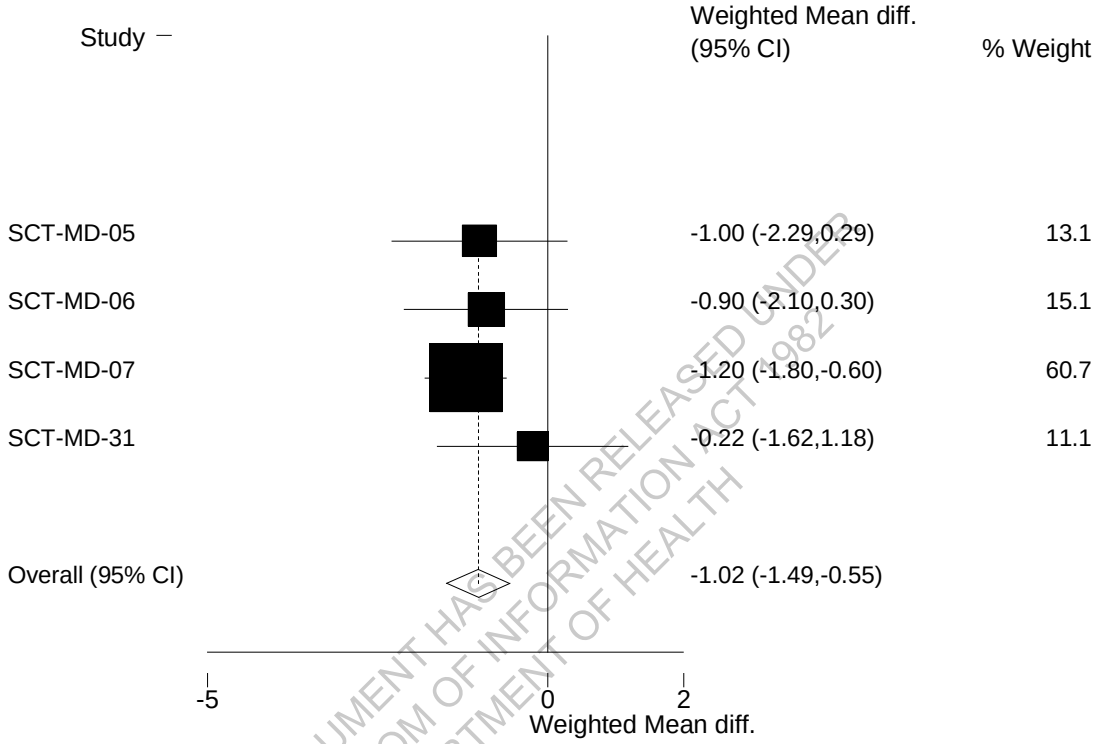
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	114	5.40 (8.99)	114	3.20 (9.18)		23.86	2.20 [-0.16, 4.56]
SCT-MD-06	131	4.80 (8.48)	121	3.00 (8.96)		28.49	1.80 [-0.36, 3.96]
SCT-MD-07	137	8.40 (10.43)	135	1.70 (8.14)		26.89	6.70 [4.48, 8.92]
SCT-MD-31	120	6.22 (10.39)	128	4.54 (9.89)		20.76	1.68 [-0.85, 4.21]
Subtotal (95% CI)	502		498			100.00	3.19 [2.04, 4.34]
Test for heterogeneity: Chi² = 13.23, df = 3 (P = 0.004), I² = 77.3%							
Test for overall effect: Z = 5.42 (P < 0.00001)							
Total (95% CI)	502		498			100.00	3.19 [2.04, 4.34]
Test for heterogeneity: Chi² = 13.23, df = 3 (P = 0.004), I² = 77.3%							
Test for overall effect: Z = 5.42 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-D (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)

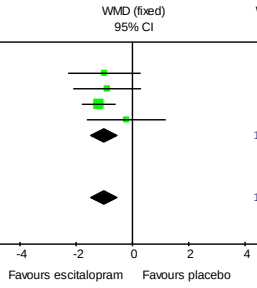


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1	-2.28898	.288978	13.1386
SCT-MD-06	-.9	-2.10292	.302925	15.0856
SCT-MD-07	-1.2	-1.79986	-.600137	60.6647
SCT-MD-31	-.22	-1.62166	1.18166	11.111
I-V pooled WMD	-1.01958	-1.4868	-.552359	

Heterogeneity chi-squared = 1.64 (d.f. = 3) p = 0.651
Test of WMD=0 : z= 4.28 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 06 Change in HAM-D (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAM-D (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

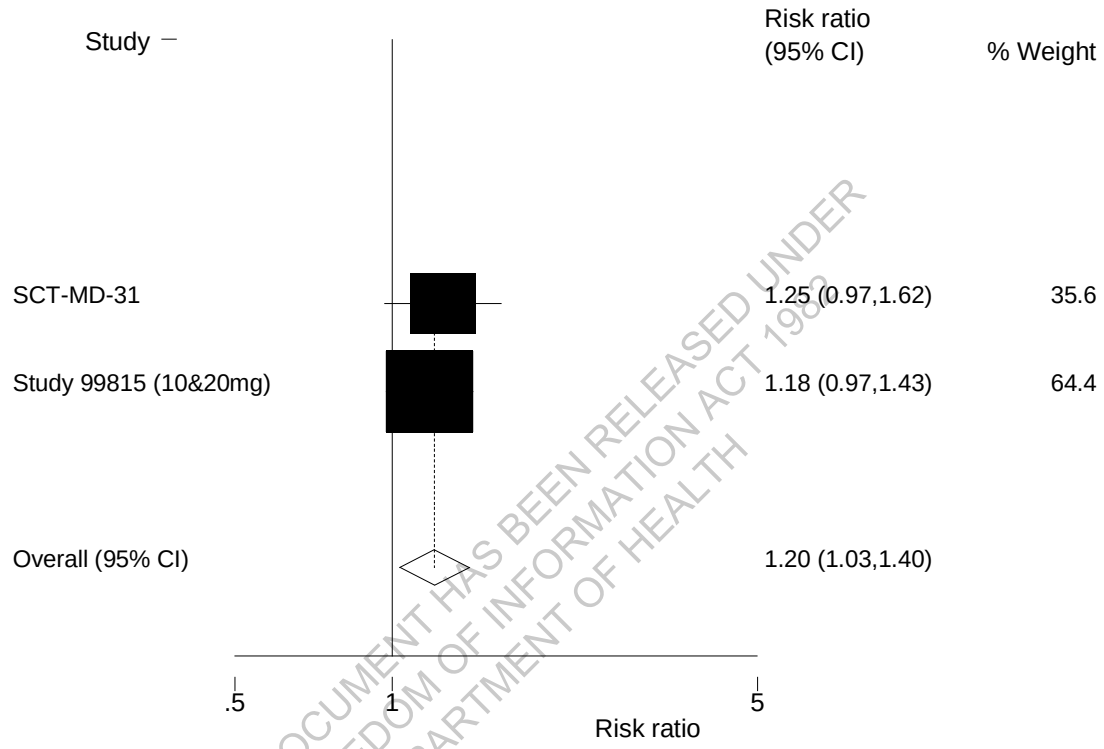
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	116	-2.50 (4.65)	115	-1.50 (5.32)		13.14	-1.00 [-2.29, 0.29]
SCT-MD-06	132	-3.60 (4.84)	122	-2.70 (4.93)		15.09	-0.90 [-2.10, 0.30]
SCT-MD-07	140	-1.90 (2.38)	137	-0.70 (2.70)		60.66	-1.20 [-1.80, -0.60]
SCT-MD-31	118	-2.92 (5.59)	124	-2.70 (5.53)		11.11	-0.22 [-1.62, 1.18]
Subtotal (95% CI)	506		498			100.00	-1.02 [-1.49, -0.55]
Test for heterogeneity: Chi² = 1.64, df = 3 (P = 0.65), I² = 0%							
Test for overall effect: Z = 4.28 (P < 0.0001)							
Total (95% CI)	506		498			100.00	-1.02 [-1.49, -0.55]
Test for heterogeneity: Chi² = 1.64, df = 3 (P = 0.65), I² = 0%							
Test for overall effect: Z = 4.28 (P < 0.0001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Number and Percentage of Patients with ≥50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-31	1.25053	.966437	1.61812	35.6301
Study 99815 (10&	1.17841	.972814	1.42746	64.3699
D+L pooled RR	1.20362	1.03201	1.40376	

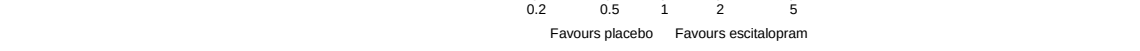
Heterogeneity chi-squared = 0.13 (d.f. = 1) p = 0.717
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.36 **p = 0.018**

Fixed-effects analysis: 1.21 (1.03,1.41), z=2.38, p=0.017

Review: Escitalopram (Lexapro) - GAD
Comparison: 07 Number of Patients with =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients with =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	66/125	57/135		35.63	1.25 [0.97, 1.62]
Study 99815 (all)	159/266	70/138		64.37	1.18 [0.97, 1.43]
Total (95% CI)	391	273		100.00	1.20 [1.03, 1.40]

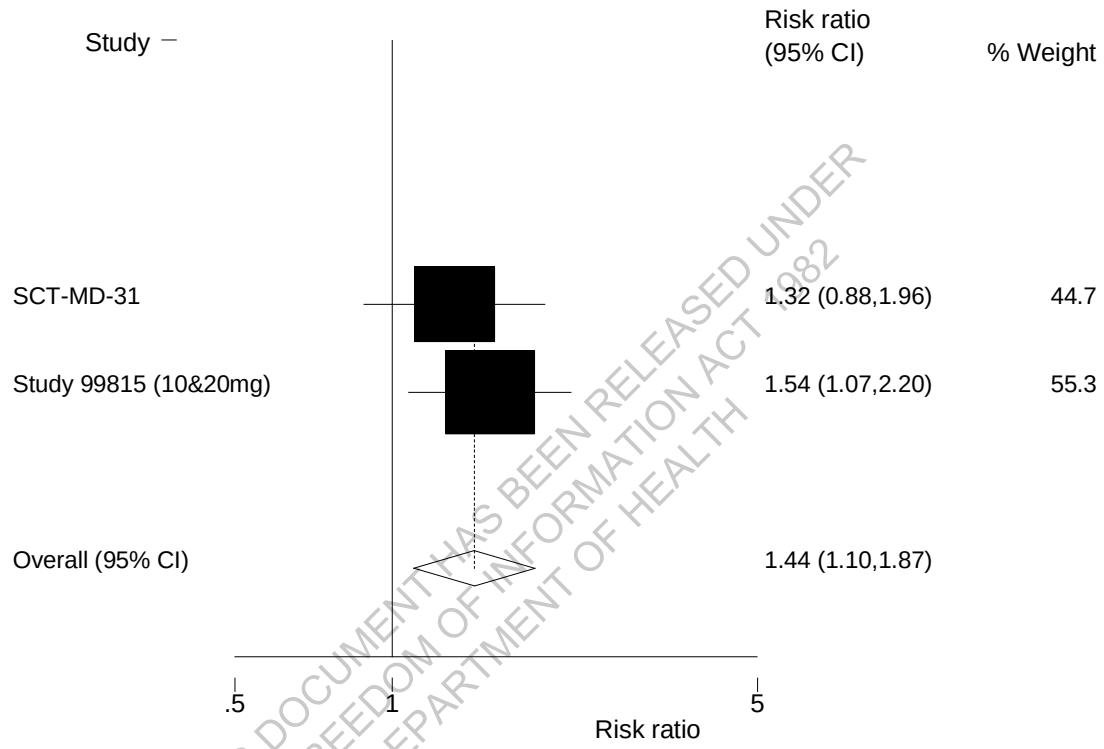
Total events: 225 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Number and Percentage of Patients with HAM-A ≤7 (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5) label(namevar=trialname)



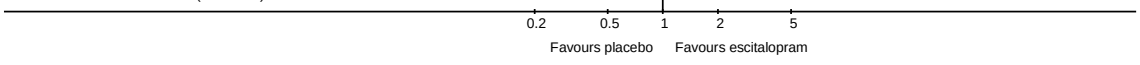
Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-31	1.31625	.883018	1.96204	44.7232
Study 99815 (10&	1.5391	1.07479	2.20399	55.2768
D+L pooled RR	1.43511	1.09887	1.87425	

Heterogeneity chi-squared = 0.33 (d.f. = 1) p = 0.567
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.65 **p = 0.008**

Review: Escitalopram (Lexapro) - GAD
Comparison: 08 Number of Patients with HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients with HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	39/125	32/135		44.72	1.32 [0.88, 1.96]
Study 99815 (all)	89/266	30/138		55.28	1.54 [1.07, 2.20]
Total (95% CI)	391	273		100.00	1.44 [1.10, 1.87]

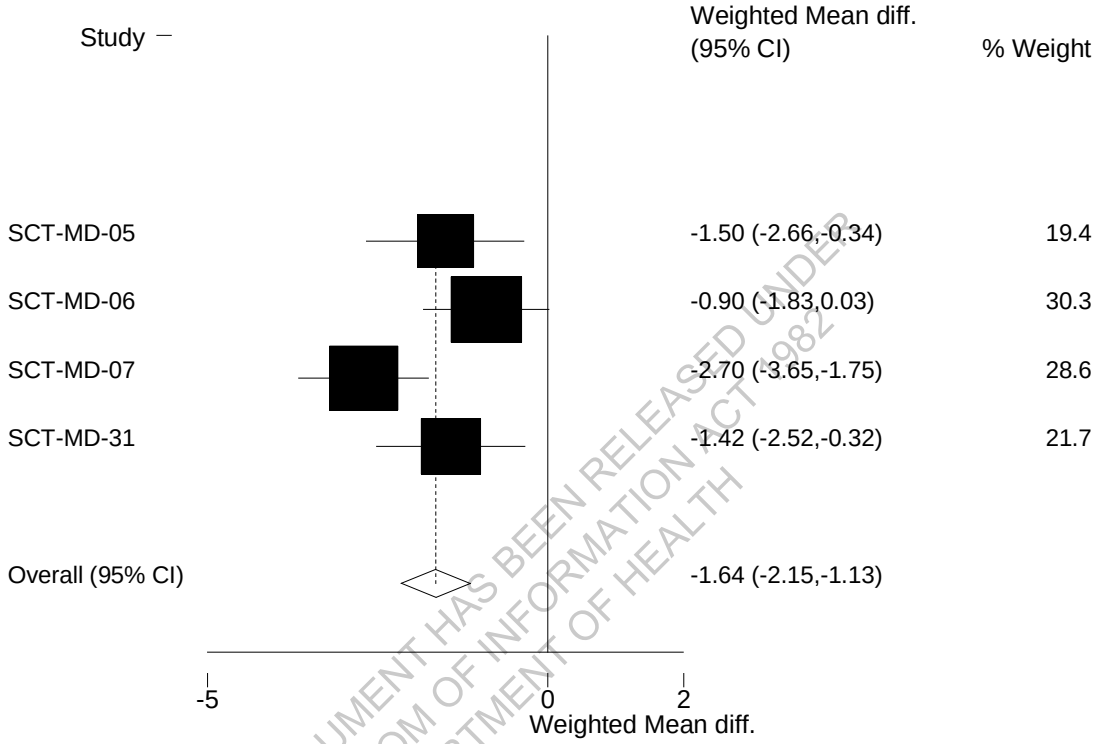
Total events: 128 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)

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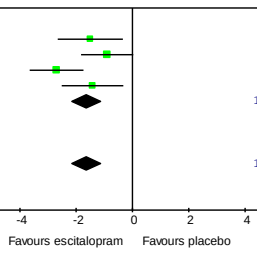
-----------------+-------------------------------------------------------
SCT-MD-05        |   -1.5    -2.66005  -.339951      19.3631
SCT-MD-06        |   -.9     -1.82669   .026693      30.3427
SCT-MD-07        |   -2.7    -3.65478  -1.74522      28.5836
SCT-MD-31        |  -1.42    -2.51554  -.324463      21.7106
-----------------+-------------------------------------------------------
  I-V pooled WMD | -1.64358    -2.15404  -1.13312
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   7.39 (d.f. = 3) p = 0.060
  Test of WMD=0 : z= 6.31 p = 0.000 (p<0.001)
```

Review: Escitalopram (Lexapro) - GAD
Comparison: 09 Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAD Anxiety Score (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

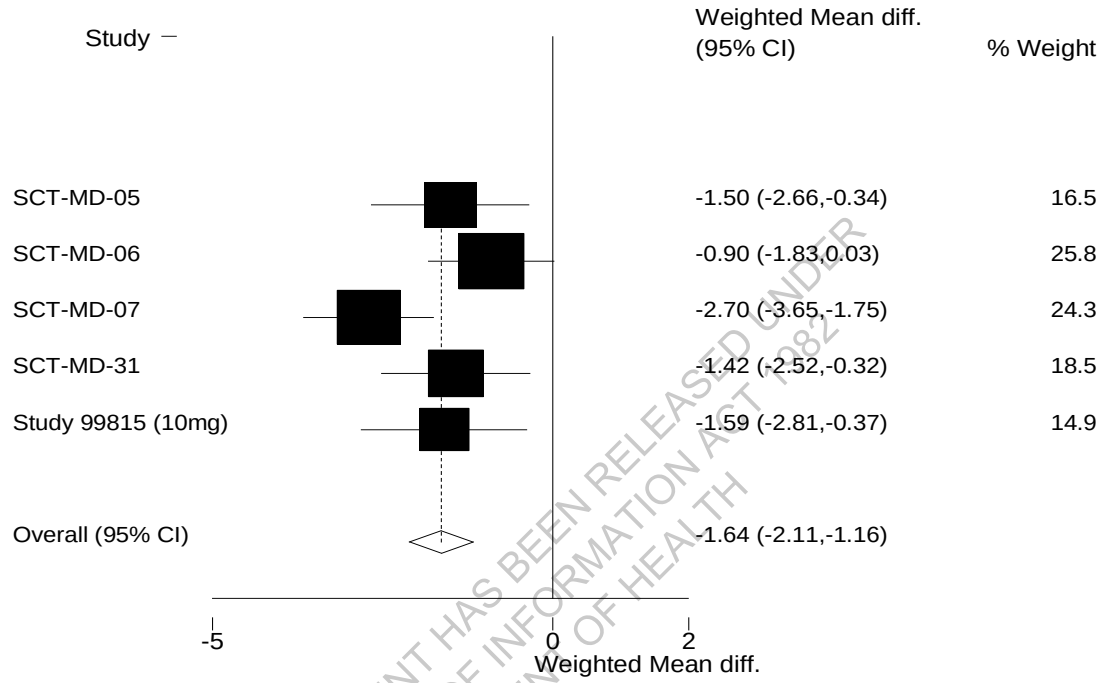
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	119	-3.80 (4.58)	120	-2.30 (4.57)		19.36	-1.50 [-2.66, -0.34]
SCT-MD-06	139	-3.20 (3.87)	130	-2.30 (3.88)		30.34	-0.90 [-1.83, 0.03]
SCT-MD-07	145	-4.40 (4.59)	144	-1.70 (3.64)		28.58	-2.70 [-3.65, -1.75]
SCT-MD-31	122	-4.12 (4.65)	128	-2.70 (4.16)		21.71	-1.42 [-2.52, -0.32]
Subtotal (95% CI)	525		522			100.00	-1.64 [-2.15, -1.13]
Test for heterogeneity: Chi² = 7.40, df = 3 (P = 0.06), I² = 59.4%							
Test for overall effect: Z = 6.31 (P < 0.00001)							
Total (95% CI)	525		522			100.00	-1.64 [-2.15, -1.13]
Test for heterogeneity: Chi² = 7.40, df = 3 (P = 0.06), I² = 59.4%							
Test for overall effect: Z = 6.31 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

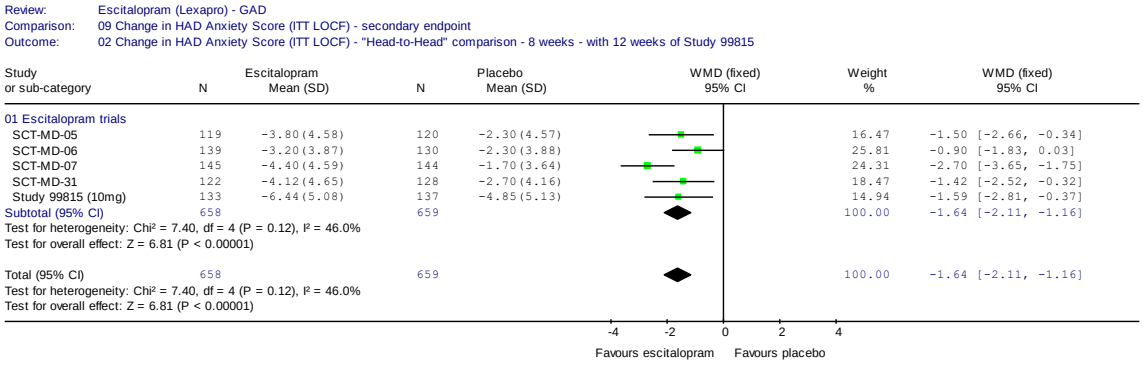
End-point: Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint – 8 weeks (with 12 week study of Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)



Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.5	-2.66005	-.339951	16.4698
SCT-MD-06	-.9	-1.82669	.026693	25.8088
SCT-MD-07	-2.7	-3.65478	-1.74522	24.3126
SCT-MD-31	-1.42	-2.51554	-.324463	18.4666
Study 99815 (10m	-1.59	-2.8079	-.372095	14.9422
I-V pooled WMD	-1.63557	-2.10636	-1.16479	

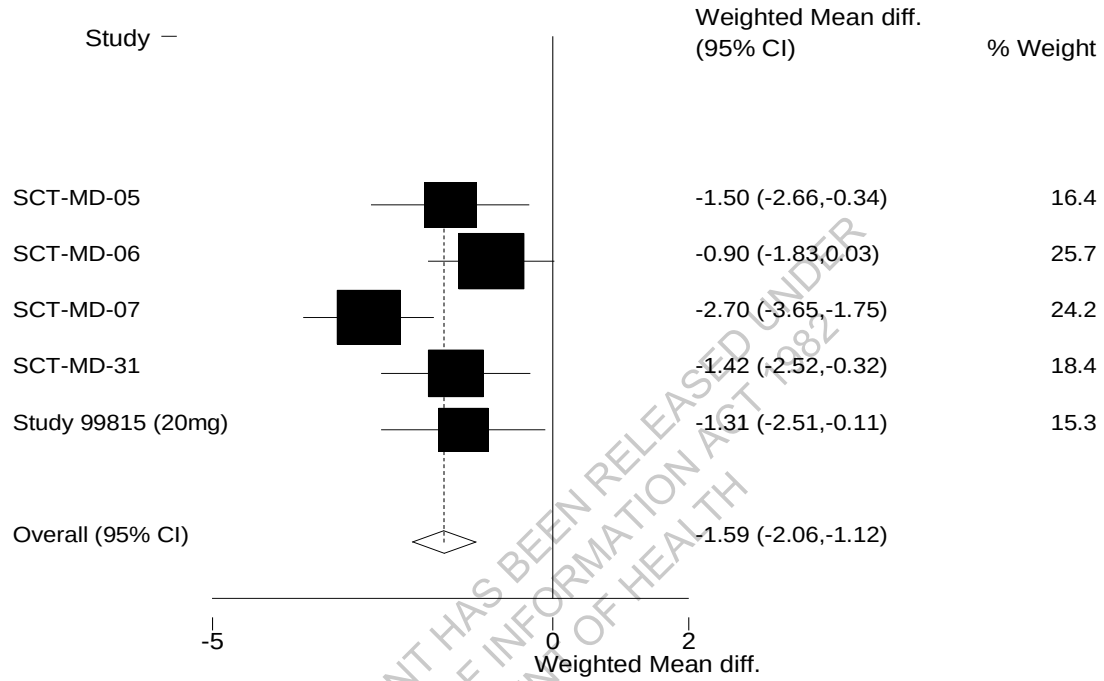
Heterogeneity chi-squared = 7.40 (d.f. = 4) p = 0.116
Test of WMD=0 : z= 6.81 p = 0.000 **(p<0.001)**



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint – 8 weeks (with 12 week study of Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)

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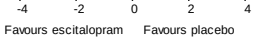
-----------------+-------------------------------------------------------
SCT-MD-05        |      -1.5    -2.66005  -.339951      16.4003
SCT-MD-06        |       -.9    -1.82669   .026693      25.6999
SCT-MD-07        |      -2.7    -3.65478  -1.74522        24.21
SCT-MD-31        |     -1.42    -2.51554  -.324463      18.3886
Study 99815 (20m |     -1.31    -2.51099  -.109011      15.3012
-----------------+-------------------------------------------------------
  I-V pooled WMD | -1.59254    -2.06232  -1.12275
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   7.65 (d.f. = 4) p = 0.105
  Test of WMD=0 : z= 6.64 p = 0.000 (p<0.001)
```

Review: Escitalopram (Lexapro) - GAD
Comparison: 09 Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAD Anxiety Score (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with 12 weeks of Study 99815

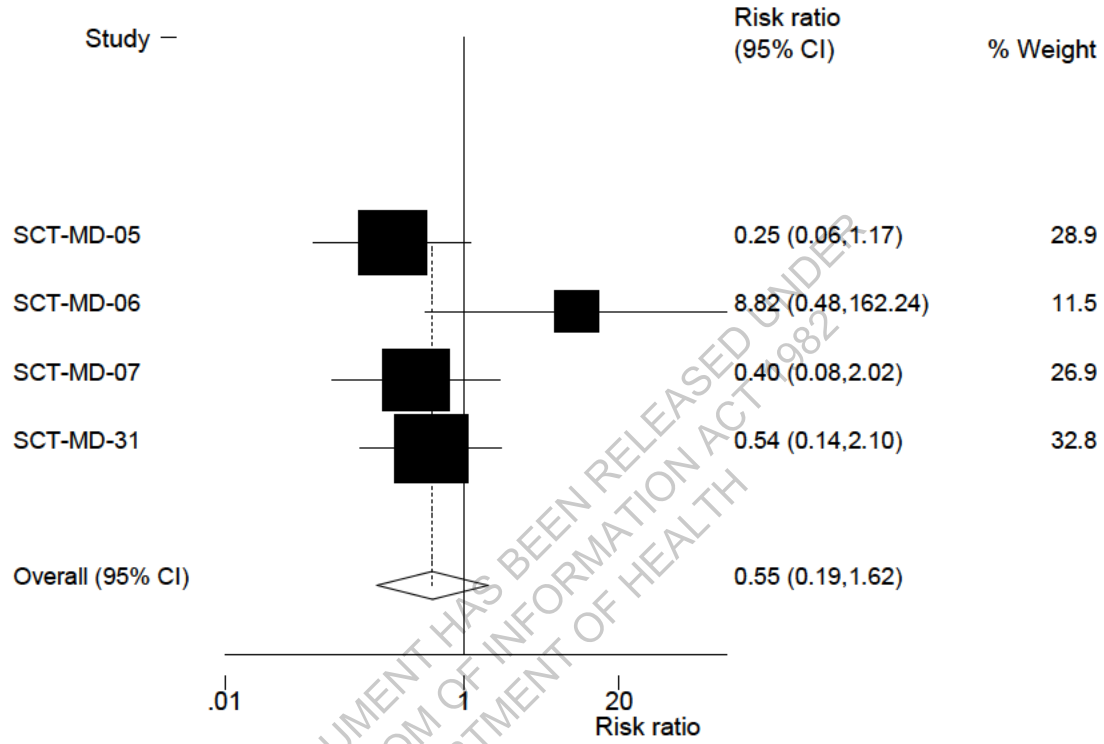
Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	119	-3.80(4.58)	120	-2.30(4.57)		16.40	-1.50 [-2.66, -0.34]
SCT-MD-06	139	-3.20(3.87)	130	-2.30(3.88)		25.70	-0.90 [-1.83, 0.03]
SCT-MD-07	145	-4.40(4.59)	144	-1.70(3.64)		24.21	-2.70 [-3.65, -1.75]
SCT-MD-31	122	-4.12(4.65)	128	-2.70(4.16)		18.39	-1.42 [-2.52, -0.32]
Study 99815 (20mg)	132	-6.16(4.92)	137	-4.85(5.13)		15.30	-1.31 [-2.51, -0.11]
Subtotal (95% CI)	657		659			100.00	-1.59 [-2.06, -1.12]
Test for heterogeneity: Chi² = 7.65, df = 4 (P = 0.11), I² = 47.7%							
Test for overall effect: Z = 6.64 (P < 0.00001)							
Total (95% CI)	657		659			100.00	-1.59 [-2.06, -1.12]
Test for heterogeneity: Chi² = 7.65, df = 4 (P = 0.11), I² = 47.7%							
Test for overall effect: Z = 6.64 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Withdrawals from study due to lack of efficacy - secondary endpoint – 8 weeks – without Study 99815

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.01,1,20) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	.253968	.055002	1.17268	28.8837
SCT-MD-06	8.81507	.478947	162.242	11.4712
SCT-MD-07	.397468	.078275	2.01827	26.8914
SCT-MD-31	.535433	.136789	2.09585	32.7538
D+L pooled RR	.549408	.18636	1.6197	

Heterogeneity chi-squared = 4.76 (d.f. = 3) p = 0.190
Estimate of between-study variance Tau-squared = 0.4442
Test of RR=1 : z= 1.09 **p = 0.278**

Fixed-effects analysis: 0.60 (0.29,1.24), z=1.38, p=0.167

Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 01 Withdrawals from study due to lack of efficacy - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		28.88	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		11.47	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		26.89	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		32.75	0.54 [0.14, 2.10]
Total (95% CI)	556	563		100.00	0.55 [0.19, 1.62]

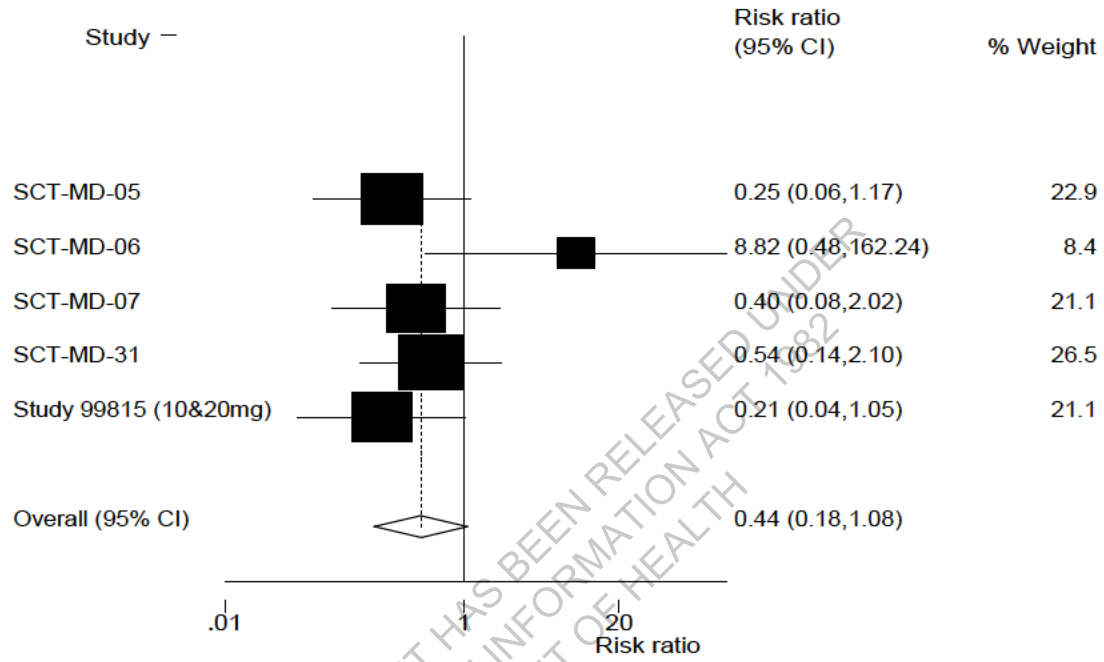
Total events: 11 (Escitalopram), 19 (Placebo)
Test for heterogeneity: Chi² = 4.76, df = 3 (P = 0.19), I² = 37.0%
Test for overall effect: Z = 1.09 (P = 0.28)

0.1 0.2 0.5 1 2 5 10
Favours escitalopram Favours placebo

Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Withdrawals from study due to lack of efficacy - secondary endpoint – 8 weeks (with 12 week study of Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.1,1,10) label(namevar=trialname)



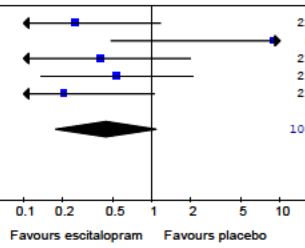
Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	.253968	.055002	1.17268	22.9152
SCT-MD-06	8.81507	.478947	162.242	8.37665
SCT-MD-07	.397468	.078275	2.01827	21.1256
SCT-MD-31	.535433	.136789	2.09585	26.4947
Study 99815 (10&	.206691	.040619	1.05176	21.0879
D+L pooled RR	.438399	.178135	1.07892	

Heterogeneity chi-squared = 5.70 (d.f. = 4) p = 0.223
Estimate of between-study variance Tau-squared = 0.3121
Test of RR=1 : z= 1.79 **p = 0.073**
Fixed-effects analysis: 0.50 (0.26,0.96), z=1.38, p=0.036

Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 02 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		22.92	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		8.38	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		21.13	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		26.49	0.54 [0.14, 2.10]
Study 99815 (all)	2/269	5/139		21.09	0.21 [0.04, 1.05]
Total (95% CI)	825	702		100.00	0.44 [0.18, 1.08]

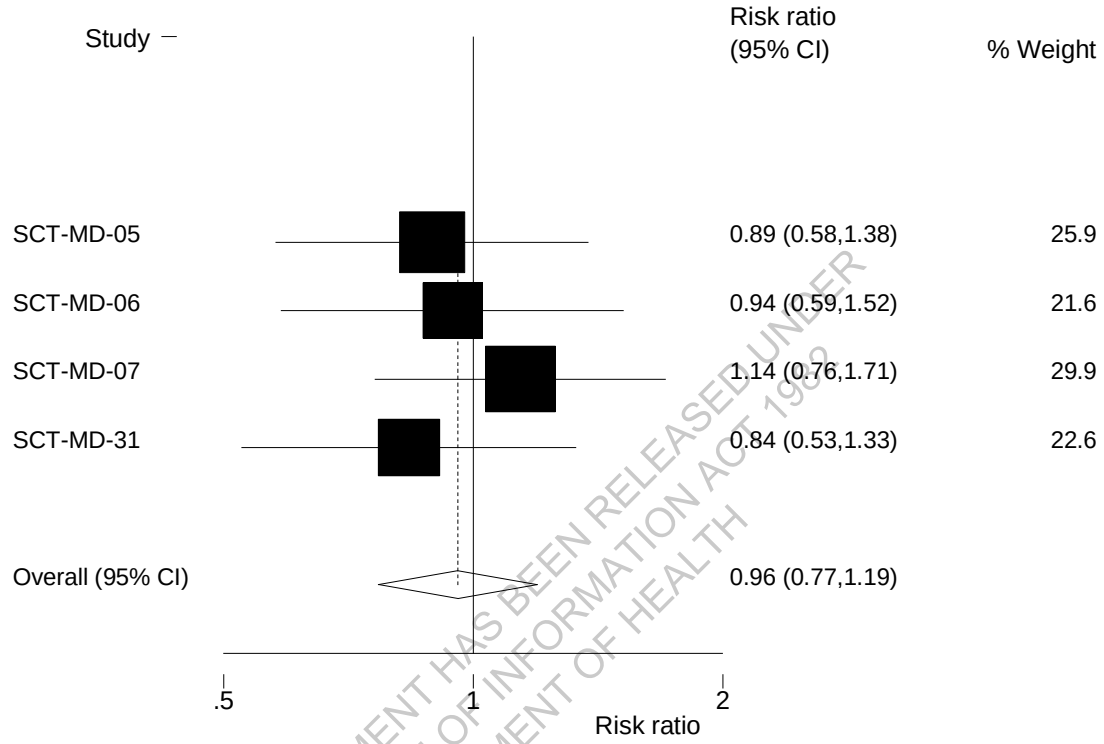
Total events: 13 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 5.70, df = 4 (P = 0.22), I² = 29.8%
Test for overall effect: Z = 1.79 (P = 0.07)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patient withdrawals - secondary endpoint – 8 weeks – without Study 99815

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,2) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	.892737	.578404	1.37789	25.8608
SCT-MD-06	.944335	.587082	1.51898	21.5623
SCT-MD-07	1.1398	.761465	1.70611	29.9411
SCT-MD-31	.836614	.526081	1.33045	22.6359
D+L pooled RR	.958013	.768274	1.19461	

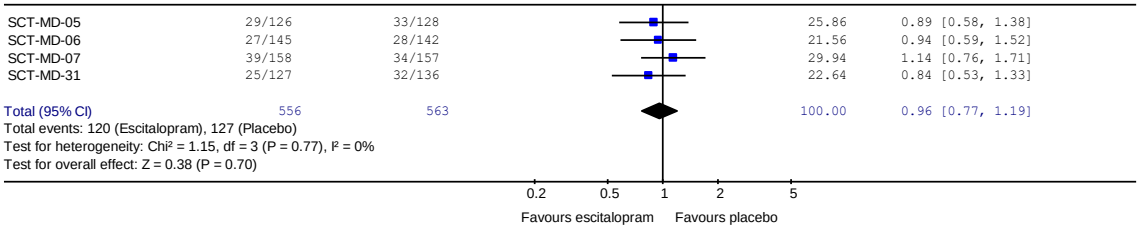
Heterogeneity chi-squared = 1.15 (d.f. = 3) p = 0.766
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.38 **p = 0.703**

Fixed-effects analysis: 0.96 (0.77,1.19), z=0.39, p=0.699

Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 01 Patient withdrawals - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		25.86	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		21.56	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		29.94	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		22.64	0.84 [0.53, 1.33]
Total (95% CI)	556	563		100.00	0.96 [0.77, 1.19]

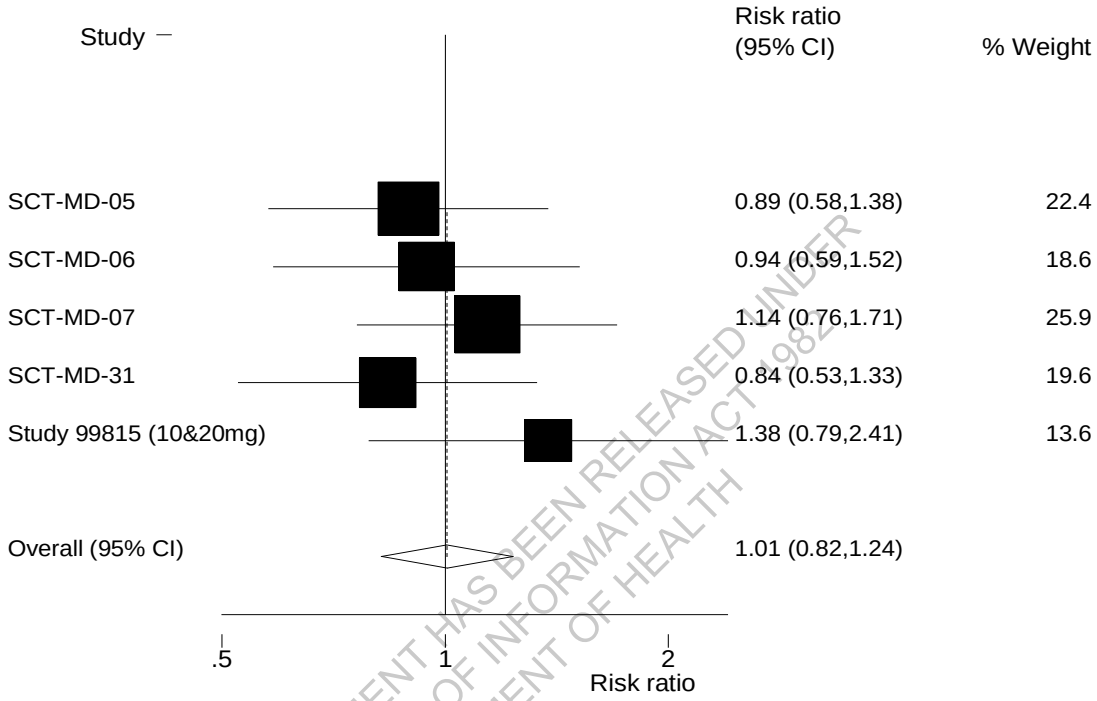
Total events: 120 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 1.15, df = 3 (P = 0.77), I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patient withdrawals - secondary endpoint – 8 weeks (with 12 week study of Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,2) label(namevar=trialname)

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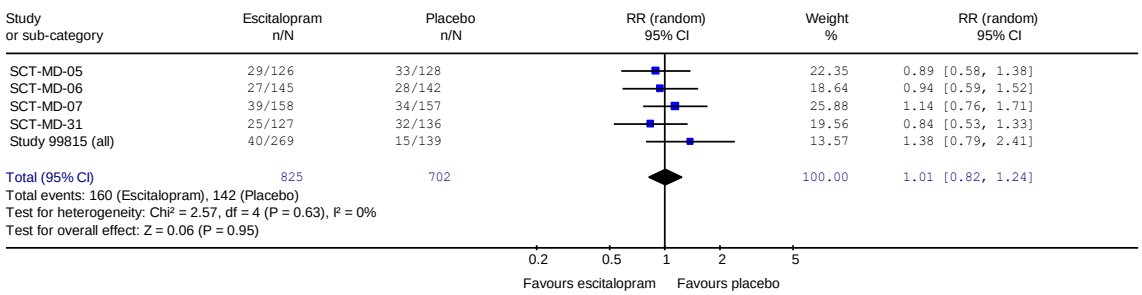
-----------------+-------------------------------------------------------
SCT-MD-05        |  .892737     .578404    1.37789      22.3509
SCT-MD-06        |  .944335     .587082    1.51898      18.6358
SCT-MD-07        |   1.1398     .761465    1.70611      25.8774
SCT-MD-31        |  .836614     .526081    1.33045      19.5637
Study 99815 (10& |  1.37794     .789481    2.40503      13.5721
-----------------+-------------------------------------------------------
  D+L pooled RR  |  1.00646     .819753    1.23569
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   2.57 (d.f. = 4) p = 0.633
  Estimate of between-study variance Tau-squared =  0.0000
  Test of RR=1 : z= 0.06 p = 0.951
Fixed-effects analysis:  1.01 (0.83,1.25), z=0.14, p=0.891
```

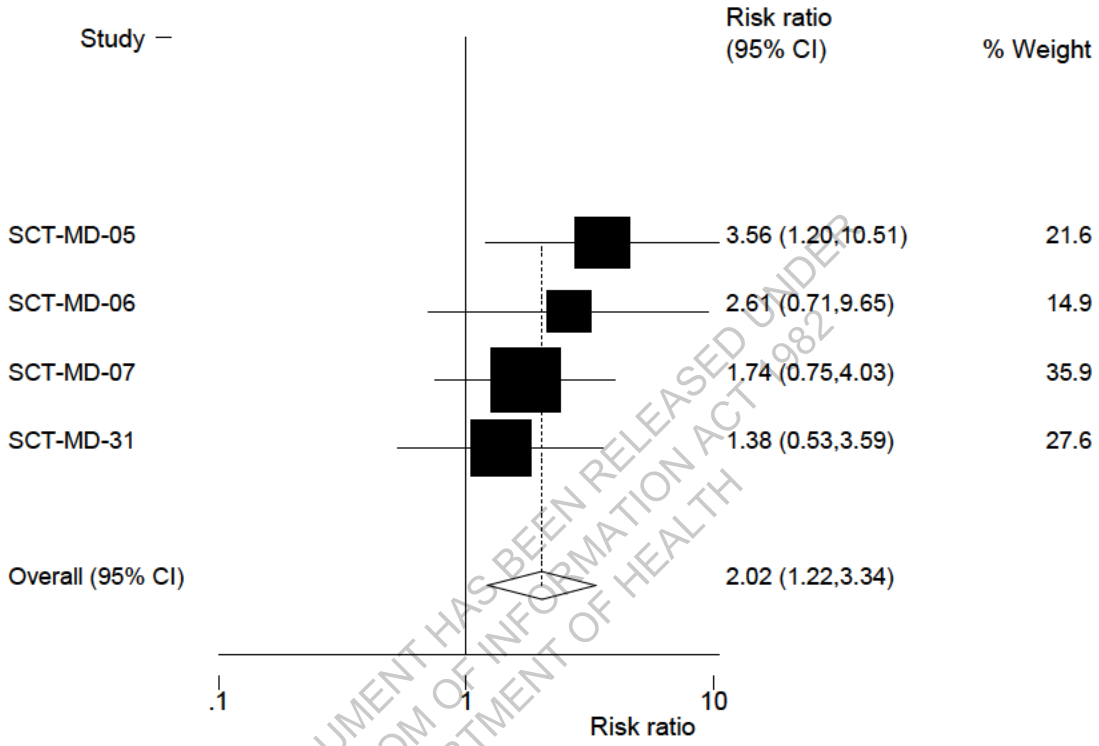
Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 02 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patients with adverse events leading to withdrawal - secondary endpoint – 8 weeks – without Study 99815

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.1,1,10) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	3.55556	1.20307	10.5081	21.589
SCT-MD-06	2.61149	.707055	9.6455	14.8502
SCT-MD-07	1.73892	.750626	4.02845	35.9186
SCT-MD-31	1.37683	.528412	3.58746	27.6422
D+L pooled RR	2.02087	1.22144	3.34353	

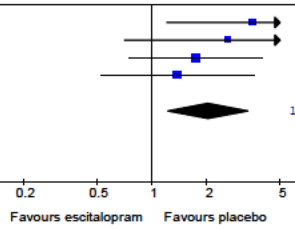
Heterogeneity chi-squared = 1.94 (d.f. = 3) p = 0.584
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.74 **p = 0.006**

Fixed-effects analysis: 2.08 (1.27,3.42), z=2.89, p=0.004

Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 03 Patients with adverse events leading to withdrawal - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		21.59	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		14.85	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		35.92	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		27.64	1.38 [0.53, 3.59]
Total (95% CI)	556	563		100.00	2.02 [1.22, 3.34]

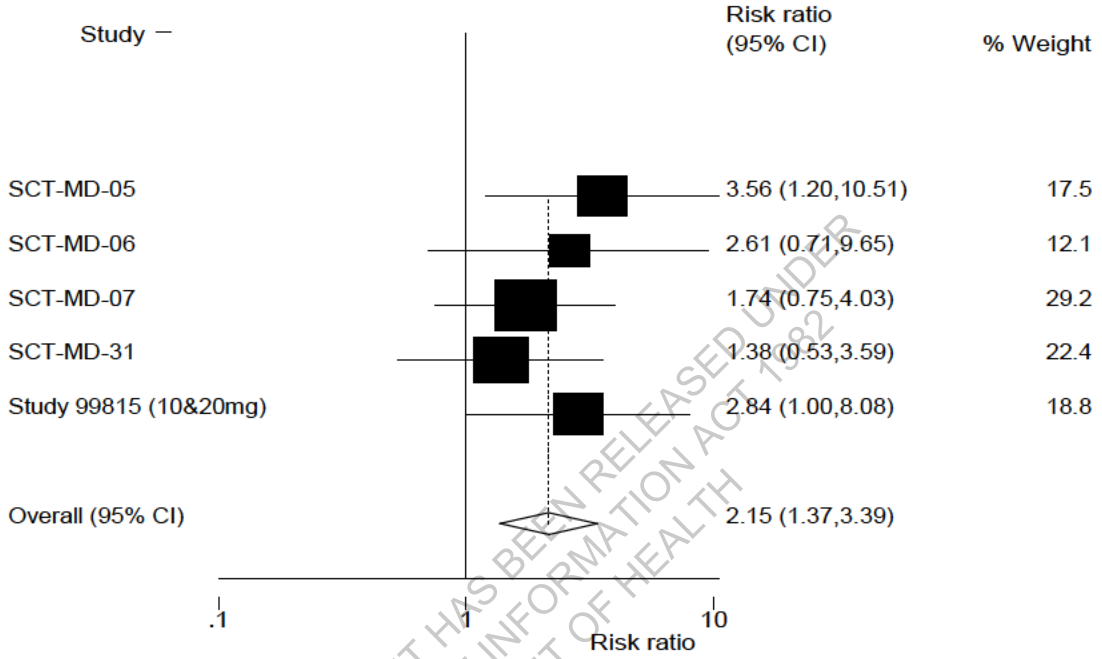
Total events: 45 (Escitalopram), 22 (Placebo)
Test for heterogeneity: Chi² = 1.94, df = 3 (P = 0.58), I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patients with adverse events leading to withdrawal - secondary endpoint – 8 weeks (with 12 week study of Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.1,1,10) label(namevar=trialname)

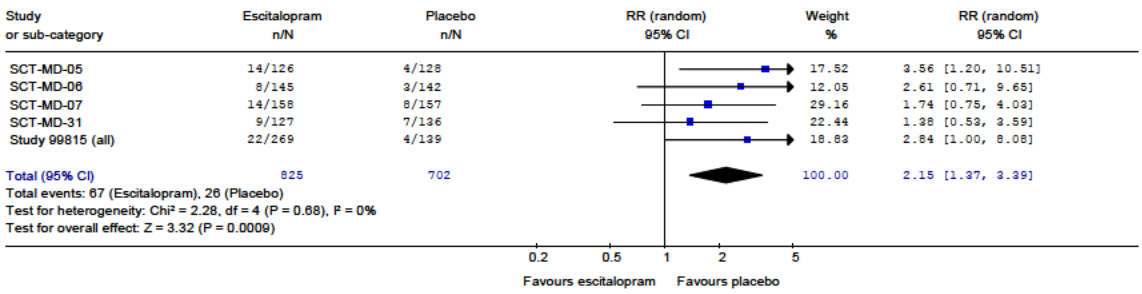


Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	3.55556	1.20307	10.5081	17.5246
SCT-MD-06	2.61149	.707055	9.6455	12.0544
SCT-MD-07	1.73892	.750626	4.02845	29.1564
SCT-MD-31	1.37683	.528412	3.58746	22.4382
Study 99815 (10&	2.84201	.999016	8.08496	18.8264
D+L pooled RR	2.15486	1.36901	3.39179	

Heterogeneity chi-squared = 2.28 (d.f. = 4) p = 0.684
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 3.32 **p = 0.001**

Fixed-effects analysis: 2.23 (1.42,3.49), z=3.49, p<0.001

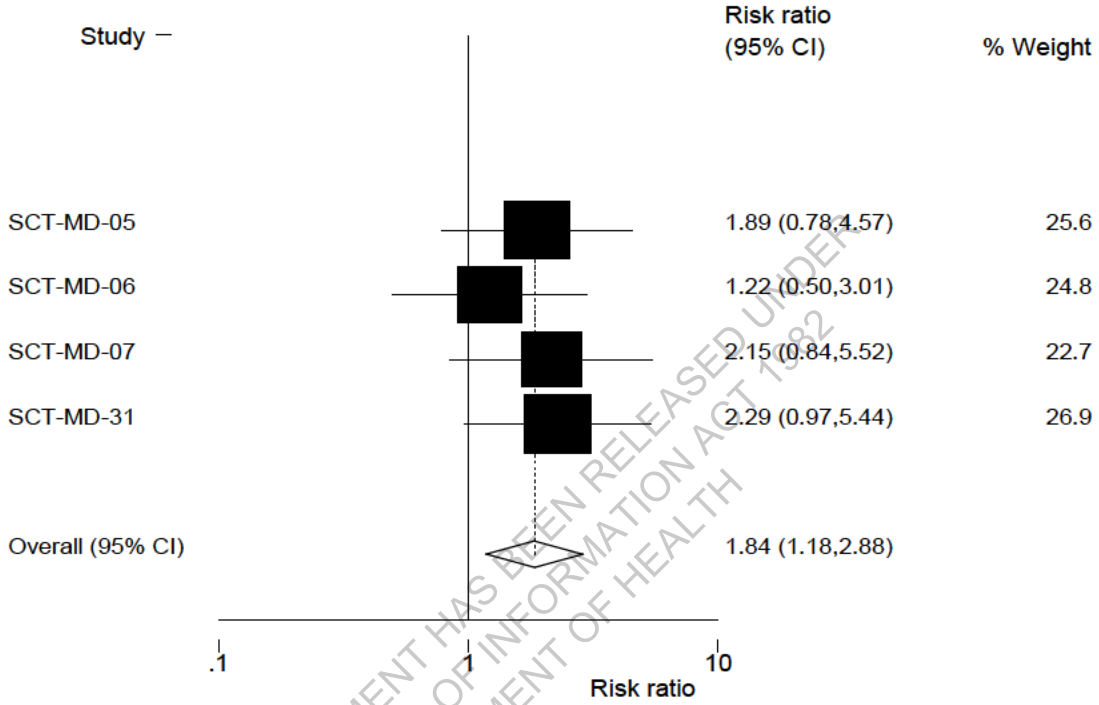
Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 04 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patients with Treatment-Emergent Adverse Events occurring in ≥5% of patients - secondary endpoint – 8 weeks – without Study 99815

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.1,1,10) label(namevar=trialname)

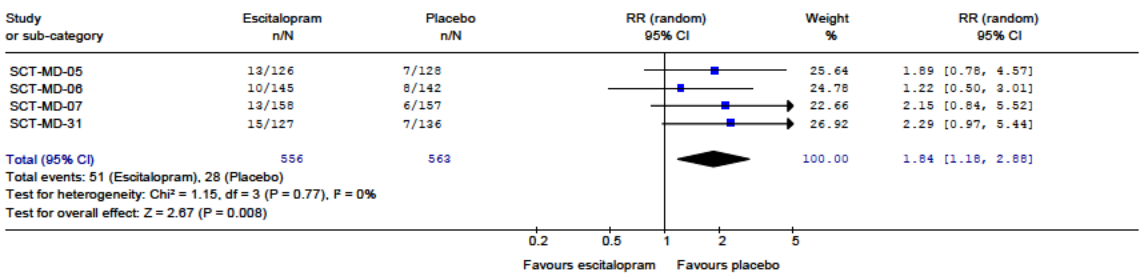


Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	1.88662	.778392	4.57268	25.638
SCT-MD-06	1.22414	.497481	3.0122	24.7841
SCT-MD-07	2.15295	.839504	5.52137	22.6555
SCT-MD-31	2.29471	.967222	5.44416	26.9225
D+L pooled RR	1.84084	1.1758	2.88201	

Heterogeneity chi-squared = 1.15 (d.f. = 3) p = 0.765
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.67 **p = 0.008**

Fixed-effects analysis: 1.85 (1.19,2.89), z=2.71, p=0.007

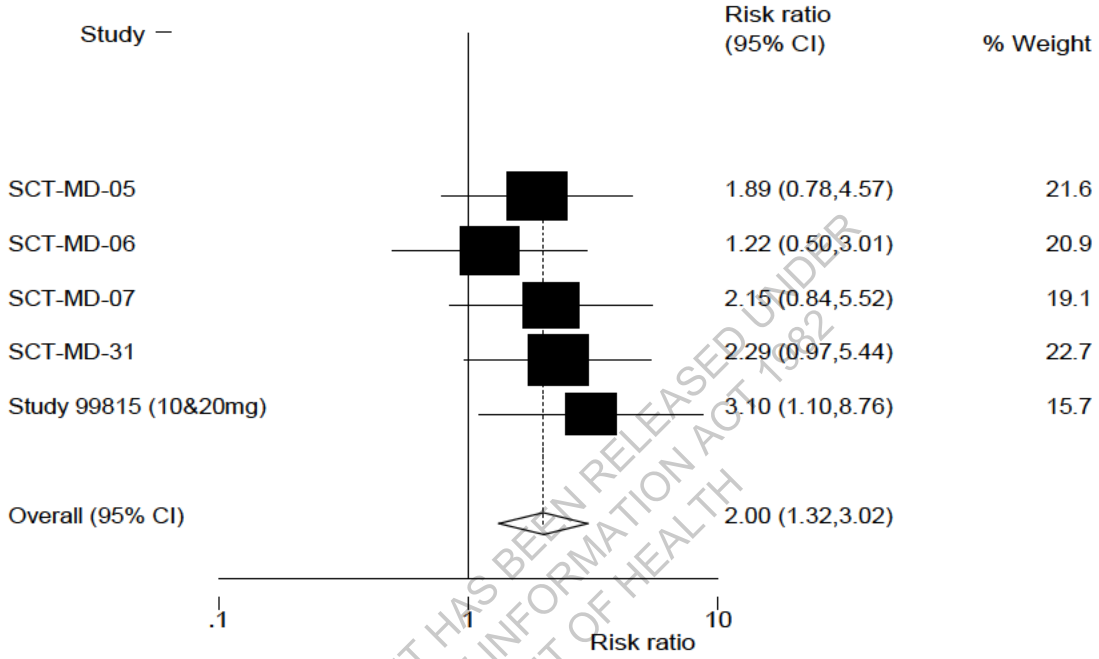
Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 05 Patients with TEAE's occurring in =>5% of patients - 8 weeks - without Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Patients with Treatment-Emergent Adverse Events occurring in ≥5% of patients - secondary endpoint – 8 weeks (with 12 week study of Study 99815)

metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.1,1,10) label(namevar=trialname)



Study	RR	[95% Conf.	Interval]	% Weight
SCT-MD-05	1.88662	.778392	4.57268	21.6114
SCT-MD-06	1.22414	.497481	3.0122	20.8916
SCT-MD-07	2.15295	.839504	5.52137	19.0973
SCT-MD-31	2.29471	.967222	5.44416	22.6942
Study 99815 (10&	3.10037	1.09747	8.75859	15.7055
D+L pooled RR	1.99789	1.32383	3.01518	

Heterogeneity chi-squared = 1.98 (d.f. = 4) p = 0.740
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 3.30 **p = 0.001**

Fixed-effects analysis: 2.05 (1.36,3.09), z=3.43, p=0.001

Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 06 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815

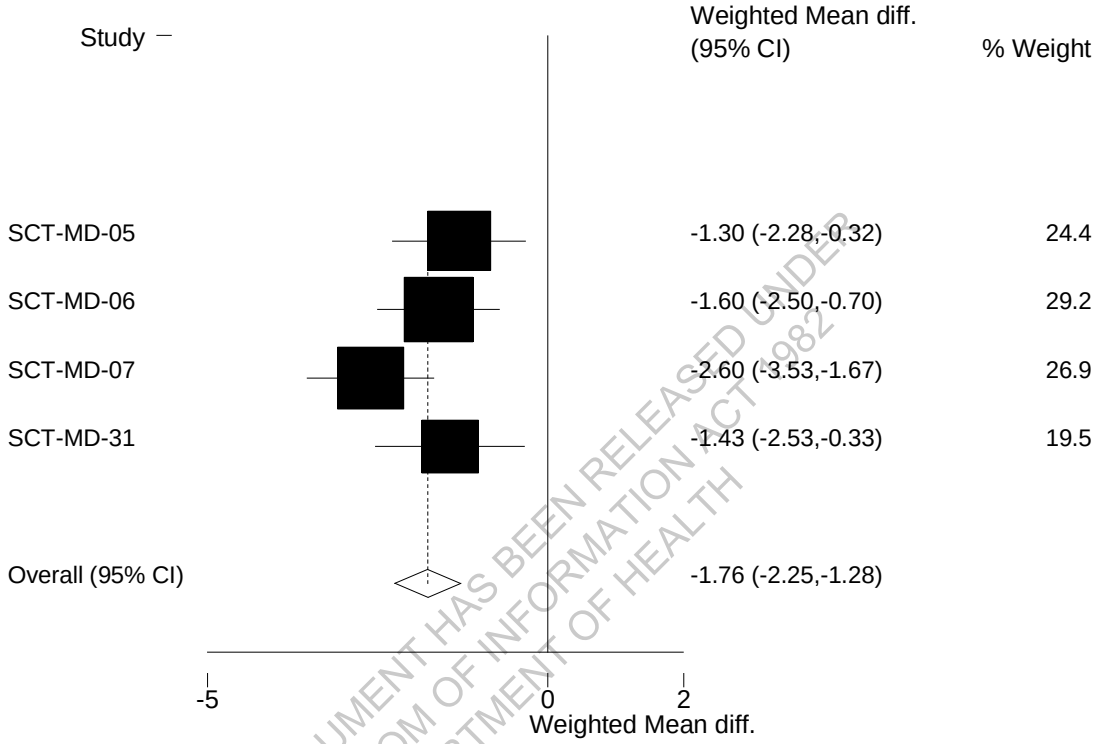
Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	13/126	7/128		21.61	1.89 [0.78, 4.57]
SCT-MD-06	10/145	8/142		20.89	1.22 [0.50, 3.01]
SCT-MD-07	13/158	6/157		19.10	2.15 [0.84, 5.52]
SCT-MD-31	15/127	7/136		22.69	2.29 [0.97, 5.44]
Study 99815 (all)	24/269	4/139		15.71	3.10 [1.10, 8.76]
Total (95% CI)	825	702		100.00	2.00 [1.32, 3.02]

Total events: 75 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 1.98, df = 4 (P = 0.74), I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)

Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)

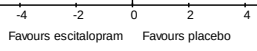


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.3	-2.28	-.319996	24.4184
SCT-MD-06	-1.6	-2.49566	-.704336	29.2336
SCT-MD-07	-2.6	-3.53455	-1.66545	26.8512
SCT-MD-31	-1.43	-2.52674	-.333255	19.4967
I-V pooled WMD	-1.76211	-2.24638	-1.27784	

Heterogeneity chi-squared = 4.42 (d.f. = 3) p = 0.220
Test of WMD=0 : z= 7.13 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 12 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - "Head-to-Head" comparison - 8 weeks -without Study 99

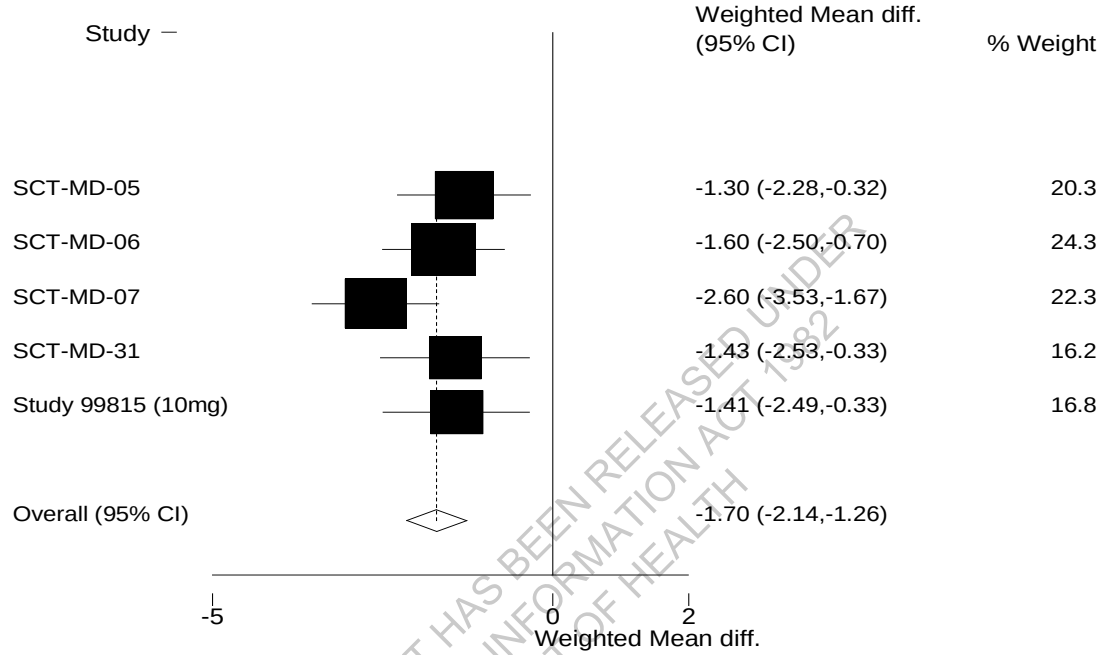
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-5.30 (4.16)	128	-4.00 (3.76)		24.42	-1.30 [-2.28, -0.32]
SCT-MD-06	143	-5.50 (3.86)	138	-3.90 (3.80)		29.23	-1.60 [-2.50, -0.70]
SCT-MD-07	154	-6.40 (4.05)	153	-3.80 (4.30)		26.85	-2.60 [-3.53, -1.67]
SCT-MD-31	125	-6.27 (4.45)	135	-4.84 (4.57)		19.50	-1.43 [-2.53, -0.33]
Subtotal (95% CI)	546		554			100.00	-1.76 [-2.25, -1.28]
Test for heterogeneity: Chi² = 4.42, df = 3 (P = 0.22), I² = 32.1%							
Test for overall effect: Z = 7.13 (P < 0.00001)							
Total (95% CI)	546		554			100.00	-1.76 [-2.25, -1.28]
Test for heterogeneity: Chi² = 4.42, df = 3 (P = 0.22), I² = 32.1%							
Test for overall effect: Z = 7.13 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)



Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.3	-2.28	-.319996	20.314
SCT-MD-06	-1.6	-2.49566	-.704336	24.3199
SCT-MD-07	-2.6	-3.53455	-1.66545	22.3379
SCT-MD-31	-1.43	-2.52674	-.333255	16.2196
Study 99815 (10m	-1.41	-2.48736	-.332639	16.8085
I-V pooled WMD	-1.70293	-2.14463	-1.26123	

Heterogeneity chi-squared = 4.76 (d.f. = 4) p = 0.313
Test of WMD=0 : z= 7.56 p = 0.000 **(p<0.001)**

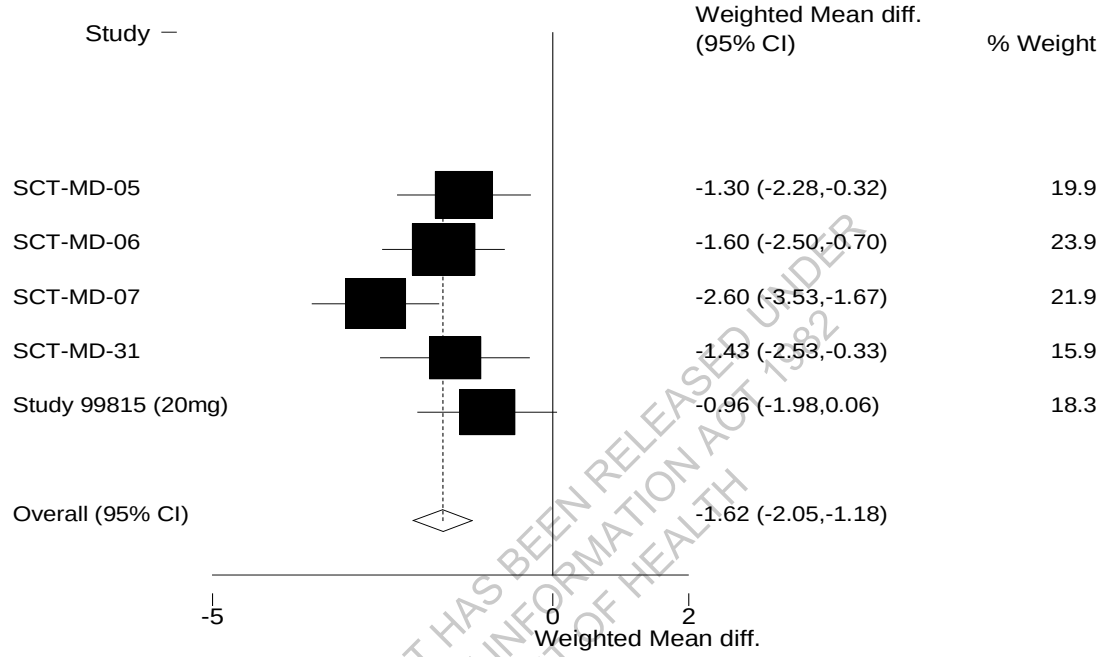
Review: Escitalopram (Lexapro) - GAD
Comparison: 12 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 9981

Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-5.30(4.16)	128	-4.00(3.76)		20.31	-1.30 [-2.28, -0.32]
SCT-MD-06	143	-5.50(3.86)	138	-3.90(3.80)		24.32	-1.60 [-2.50, -0.70]
SCT-MD-07	154	-6.40(4.05)	153	-3.80(4.30)		22.34	-2.60 [-3.53, -1.67]
SCT-MD-31	125	-6.27(4.45)	135	-4.84(4.57)		16.22	-1.43 [-2.53, -0.33]
Study 99815 (10mg)	134	-7.81(4.85)	138	-6.40(4.18)		16.81	-1.41 [-2.49, -0.33]
Subtotal (95% CI)	680		692			100.00	-1.70 [-2.14, -1.26]
Test for heterogeneity: Chi² = 4.76, df = 4 (P = 0.31), I² = 16.0%							
Test for overall effect: Z = 7.56 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-1.70 [-2.14, -1.26]
Test for heterogeneity: Chi² = 4.76, df = 4 (P = 0.31), I² = 16.0%							
Test for overall effect: Z = 7.56 (P < 0.00001)							

Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-5,0,2) label(namevar=trialname)

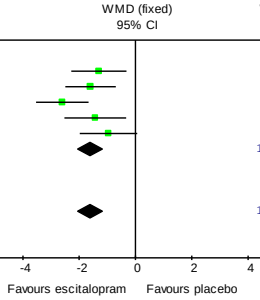


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-1.3	-2.28	-.319996	19.9417
SCT-MD-06	-1.6	-2.49566	-.704336	23.8742
SCT-MD-07	-2.6	-3.53455	-1.66545	21.9285
SCT-MD-31	-1.43	-2.52674	-.333255	15.9224
Study 99815 (20m	-.96	-1.98209	.062094	18.3331
I-V pooled WMD	-1.61506	-2.05269	-1.17743	

Heterogeneity chi-squared = 6.35 (d.f. = 4) p = 0.174
Test of WMD=0 : z= 7.23 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 12 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 9981

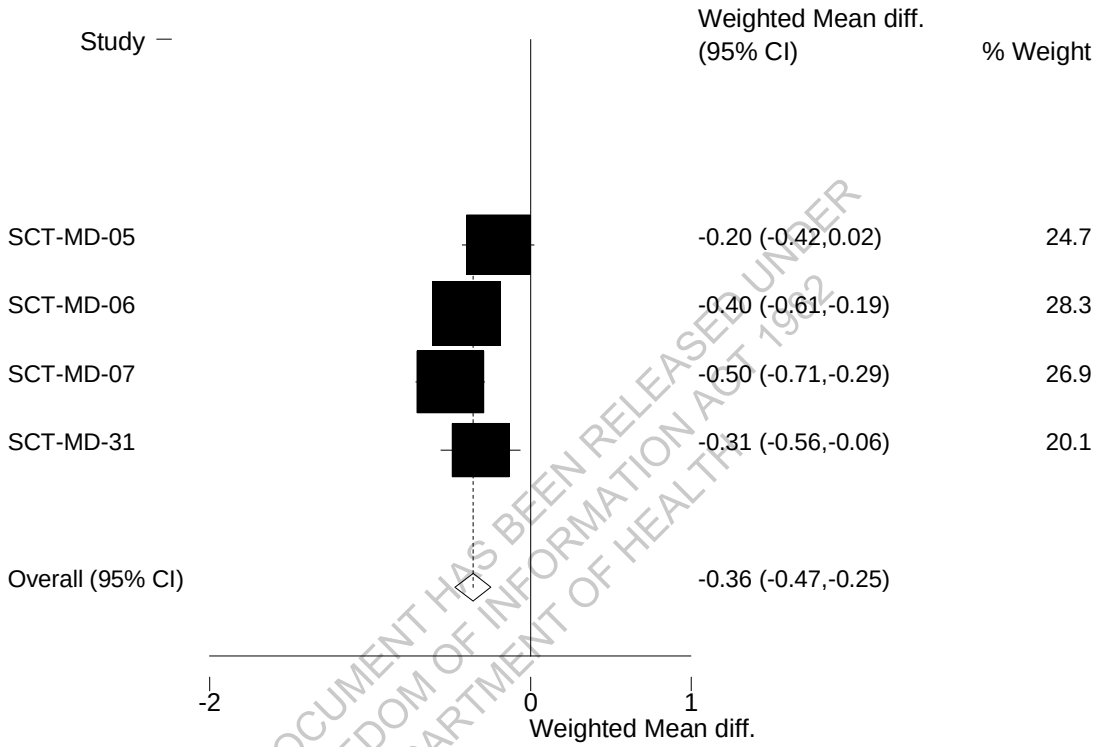
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-5.30(4.16)	128	-4.00(3.76)		19.94	-1.30 [-2.28, -0.32]
SCT-MD-06	143	-5.50(3.86)	138	-3.90(3.80)		23.87	-1.60 [-2.50, -0.70]
SCT-MD-07	154	-6.40(4.05)	153	-3.80(4.30)		21.93	-2.60 [-3.53, -1.67]
SCT-MD-31	125	-6.27(4.45)	135	-4.84(4.57)		15.92	-1.43 [-2.53, -0.33]
Study 99815 (20mg)	132	-7.36(4.38)	138	-6.40(4.18)		18.33	-0.96 [-1.98, 0.06]
Subtotal (95% CI)	678		692			100.00	-1.62 [-2.05, -1.18]
Test for heterogeneity: Chi² = 6.35, df = 4 (P = 0.17), I² = 37.0%							
Test for overall effect: Z = 7.23 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-1.62 [-2.05, -1.18]
Test for heterogeneity: Chi² = 6.35, df = 4 (P = 0.17), I² = 37.0%							
Test for overall effect: Z = 7.23 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

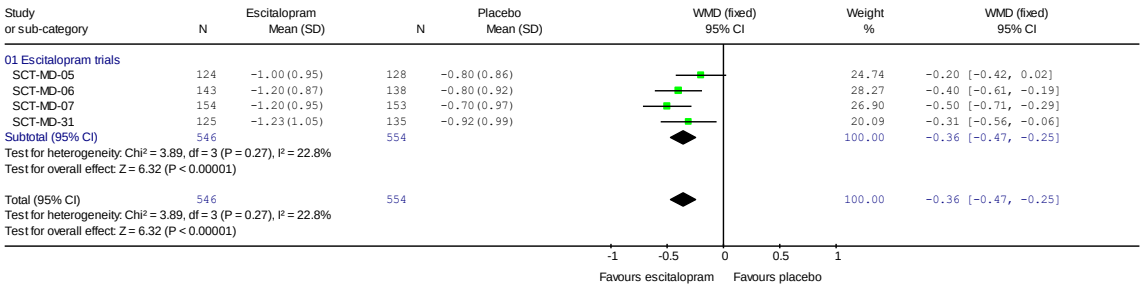
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)



Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.423954	.023954	24.7419
SCT-MD-06	-.4	-.609509	-.190492	28.2714
SCT-MD-07	-.5	-.714793	-.285207	26.8973
SCT-MD-31	-.31	-.558537	-.061463	20.0895
I-V pooled WMD	-.359333	-.470731	-.247936	

Heterogeneity chi-squared = 3.89 (d.f. = 3) p = 0.274
Test of WMD=0 : z= 6.32 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 13 Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAM-A Anxiety Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

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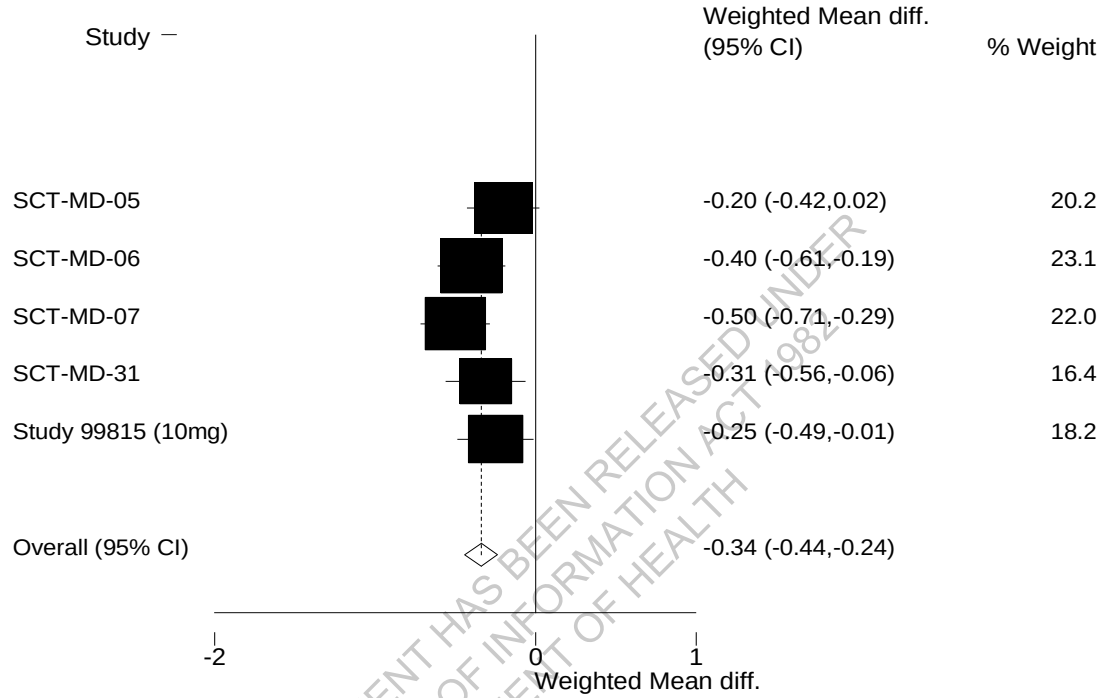
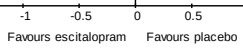


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.423954	.023954	20.2454
SCT-MD-06	-.4	-.609509	-.190492	23.1334
SCT-MD-07	-.5	-.714793	-.285207	22.0091
SCT-MD-31	-.31	-.558537	-.061463	16.4385
Study 99815 (10m	-.25	-.486375	-.013625	18.1736
I-V pooled WMD	-.339463	-.440231	-.238696	

Heterogeneity chi-squared = 4.56 (d.f. = 4) p = 0.335
Test of WMD=0 : z= 6.60 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 13 Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Anxiety Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.00(0.95)	128	-0.80(0.86)		20.25	-0.20 [-0.42, 0.02]
SCT-MD-06	143	-1.20(0.87)	138	-0.80(0.92)		23.13	-0.40 [-0.61, -0.19]
SCT-MD-07	154	-1.20(0.95)	153	-0.70(0.97)		22.01	-0.50 [-0.71, -0.29]
SCT-MD-31	125	-1.23(1.05)	135	-0.92(0.99)		16.44	-0.31 [-0.56, -0.06]
Study 99815 (10mg)	134	-1.51(1.07)	138	-1.26(0.91)		18.17	-0.25 [-0.49, -0.01]
Subtotal (95% CI)	680		692			100.00	-0.34 [-0.44, -0.24]
Test for heterogeneity: Chi² = 4.56, df = 4 (P = 0.34), I² = 12.3%							
Test for overall effect: Z = 6.60 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.34 [-0.44, -0.24]
Test for heterogeneity: Chi² = 4.56, df = 4 (P = 0.34), I² = 12.3%							
Test for overall effect: Z = 6.60 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

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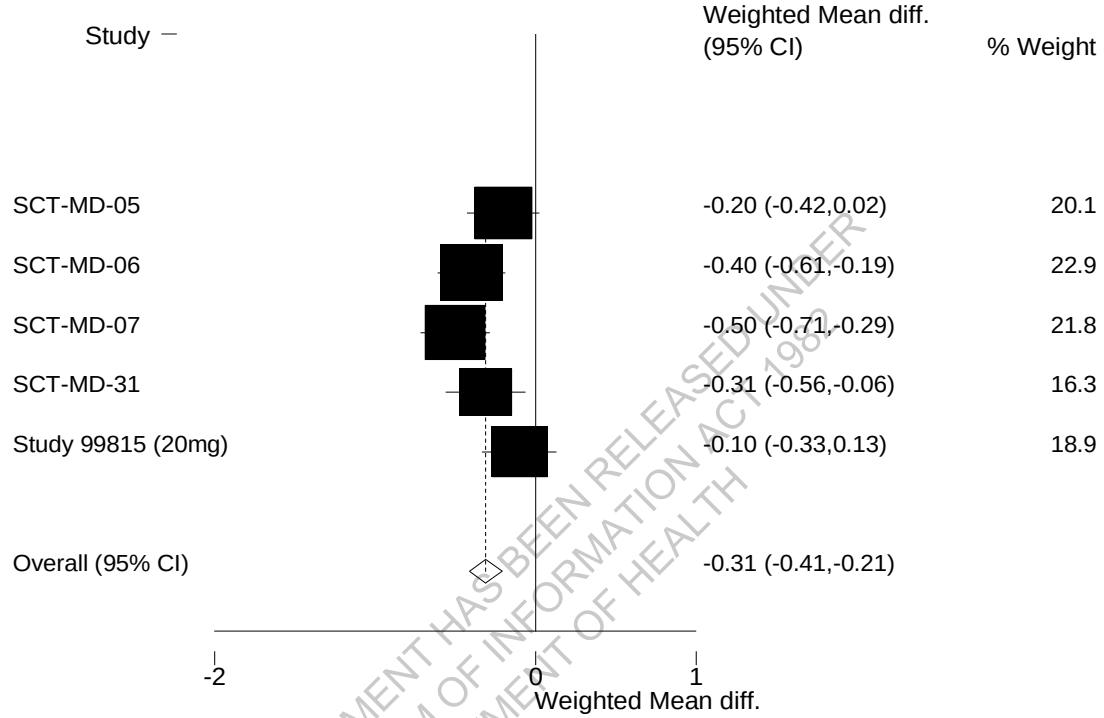
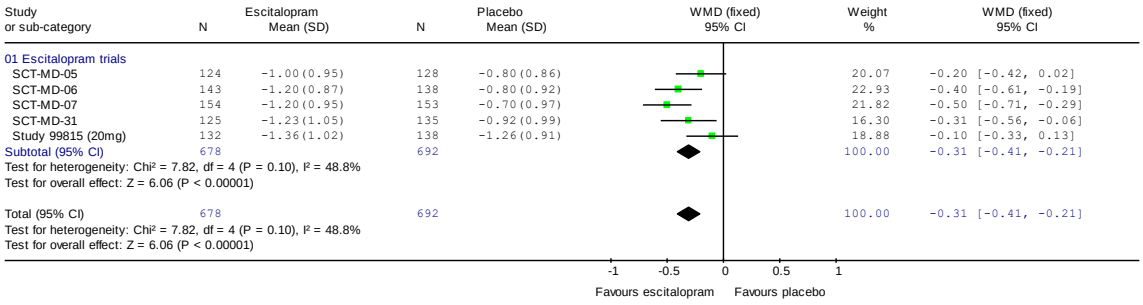


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.423954	.023954	20.0714
SCT-MD-06	-.4	-.609509	-.190492	22.9346
SCT-MD-07	-.5	-.714793	-.285207	21.8199
SCT-MD-31	-.31	-.558537	-.061463	16.2972
Study 99815 (20m	-.1	-.330931	.130931	18.8769
I-V pooled WMD	-.310379	-.410713	-.210045	

Heterogeneity chi-squared = 7.82 (d.f. = 4) p = 0.098
Test of WMD=0 : z= 6.06 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 13 Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Anxiety Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint – 8 weeks – without Study 99815

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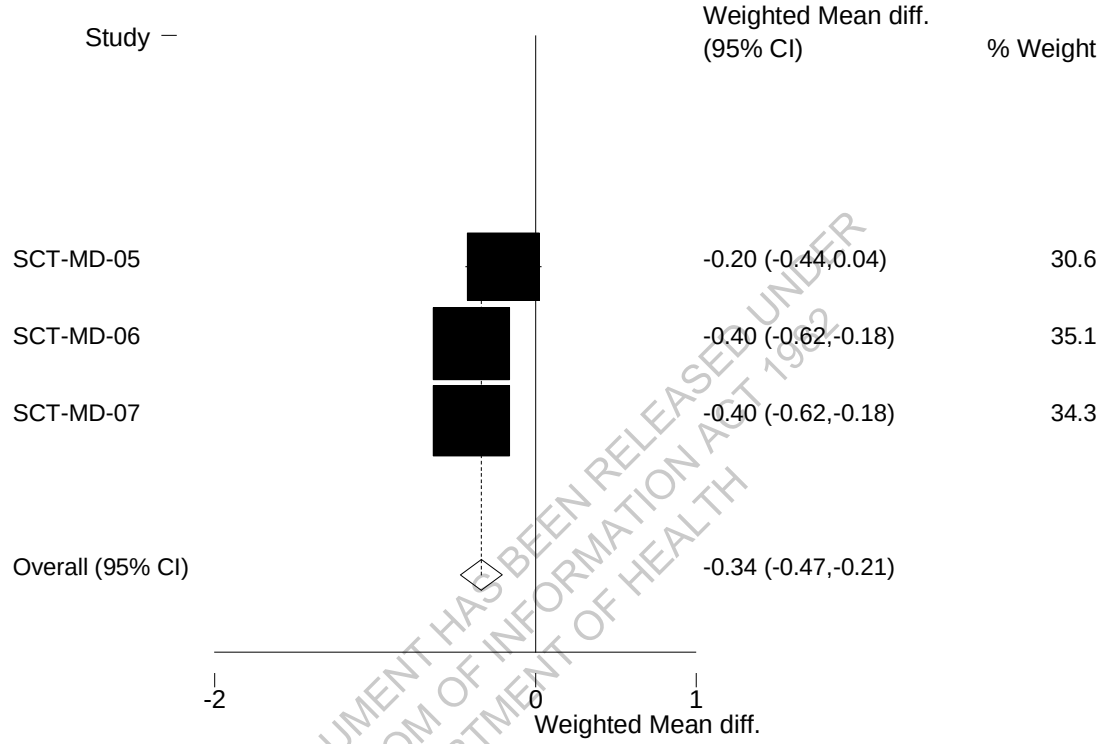
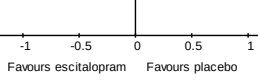


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.43665	.03665	30.6421
SCT-MD-06	-.4	-.621198	-.178802	35.0726
SCT-MD-07	-.4	-.623723	-.176277	34.2853
I-V pooled WMD	-.338716	-.469714	-.207718	

Heterogeneity chi-squared = 1.90 (d.f. = 2) p = 0.386
Test of WMD=0 : z= 5.07 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 14 Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAM-A Tension Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - without Study 99815

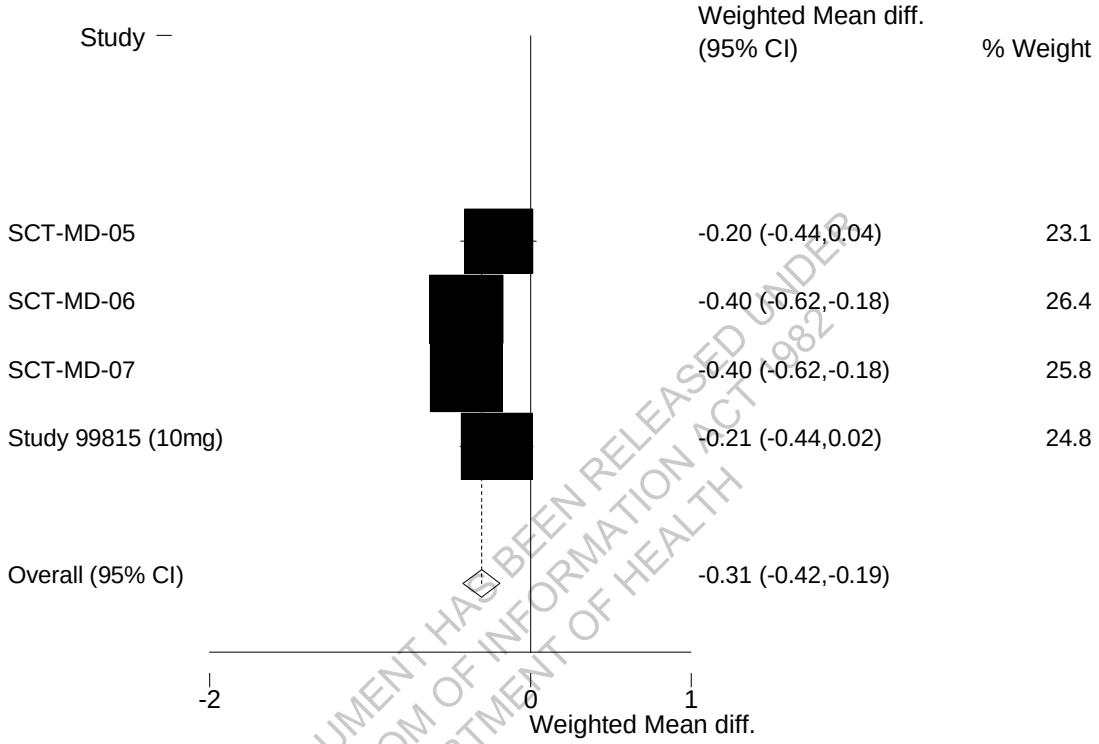
Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-0.90(1.02)	128	-0.70(0.89)		30.64	-0.20 [-0.44, 0.04]
SCT-MD-06	143	-1.10(0.92)	138	-0.70(0.97)		35.07	-0.40 [-0.62, -0.18]
SCT-MD-07	154	-1.20(1.00)	153	-0.80(1.00)		34.29	-0.40 [-0.62, -0.18]
Subtotal (95% CI)	421		419			100.00	-0.34 [-0.47, -0.21]
Test for heterogeneity: Chi² = 1.90, df = 2 (P = 0.39), I² = 0%							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Total (95% CI)	421		419			100.00	-0.34 [-0.47, -0.21]
Test for heterogeneity: Chi² = 1.90, df = 2 (P = 0.39), I² = 0%							
Test for overall effect: Z = 5.07 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2 gp2changeinscore gp2sdchangeinscore, nostandard xla(-2,0,1) label(namevar=trialname)

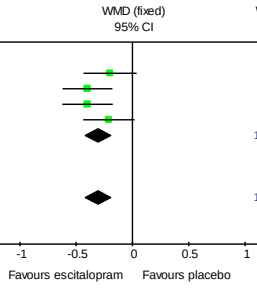


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.43665	.03665	23.058
SCT-MD-06	-.4	-.621198	-.178802	26.3919
SCT-MD-07	-.4	-.623723	-.176277	25.7995
Study 99815 (10m	-.21	-.438414	.018414	24.7507
I-V pooled WMD	-.306858	-.420494	-.193222	

Heterogeneity chi-squared = 2.82 (d.f. = 3) p = 0.420
Test of WMD=0 : z= 5.29 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 14 Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Tension Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-0.90 (1.02)	128	-0.70 (0.89)		23.06	-0.20 [-0.44, 0.04]
SCT-MD-06	143	-1.10 (0.92)	138	-0.70 (0.97)		26.39	-0.40 [-0.62, -0.18]
SCT-MD-07	154	-1.20 (1.00)	153	-0.80 (1.00)		25.80	-0.40 [-0.62, -0.18]
Study 99815 (10mg)	134	-1.63 (0.99)	138	-1.42 (0.93)		24.75	-0.21 [-0.44, 0.02]
Subtotal (95% CI)	555		557			100.00	-0.31 [-0.42, -0.19]
Test for heterogeneity: Chi² = 2.82, df = 3 (P = 0.42), I² = 0%							
Test for overall effect: Z = 5.29 (P < 0.00001)							
Total (95% CI)	555		557			100.00	-0.31 [-0.42, -0.19]
Test for heterogeneity: Chi² = 2.82, df = 3 (P = 0.42), I² = 0%							
Test for overall effect: Z = 5.29 (P < 0.00001)							



Escitalopram vs placebo "head-to-head" (GAD trials)

End-point: Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint – 8 weeks (with Study 99815 – one arm)

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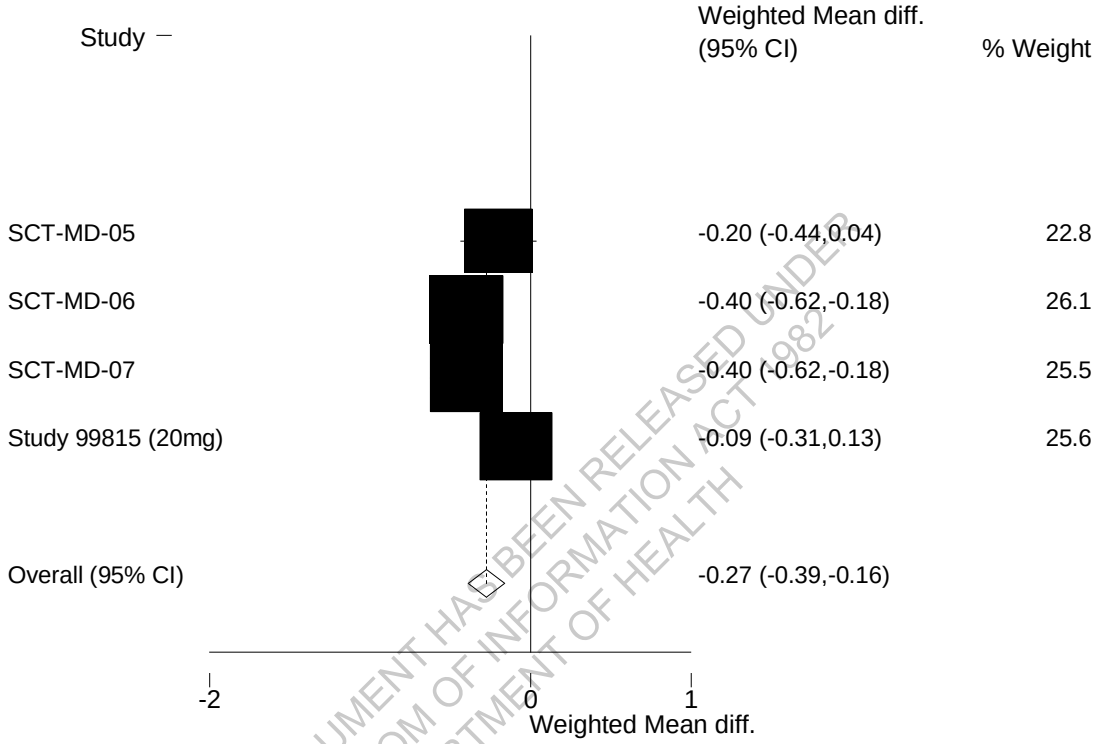
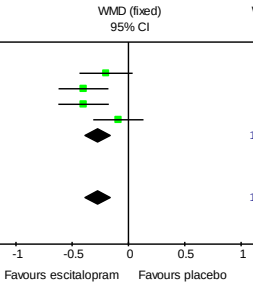


Study	WMD	[95% Conf.	Interval]	% Weight
SCT-MD-05	-.2	-.43665	.03665	22.7881
SCT-MD-06	-.4	-.621198	-.178802	26.0829
SCT-MD-07	-.4	-.623723	-.176277	25.4975
Study 99815 (20m	-.09	-.313138	.133138	25.6315
I-V pooled WMD	-.274966	-.387935	-.161997	

Heterogeneity chi-squared = 5.45 (d.f. = 3) p = 0.142
Test of WMD=0 : z= 4.77 p = 0.000 **(p<0.001)**

Review: Escitalopram (Lexapro) - GAD
Comparison: 14 Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Tension Item (ITT LOCF) - "Head-to-Head" comparison - 8 weeks - with Study 99815 (one arm)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-0.90 (1.02)	128	-0.70 (0.89)		22.79	-0.20 [-0.44, 0.04]
SCT-MD-06	143	-1.10 (0.92)	138	-0.70 (0.97)		26.08	-0.40 [-0.62, -0.18]
SCT-MD-07	154	-1.20 (1.00)	153	-0.80 (1.00)		25.50	-0.40 [-0.62, -0.18]
Study 99815 (20mg)	132	-1.51 (0.94)	138	-1.42 (0.93)		25.63	-0.09 [-0.31, 0.13]
Subtotal (95% CI)	553		557			100.00	-0.27 [-0.39, -0.16]
Test for heterogeneity: Chi² = 5.45, df = 3 (P = 0.14), I² = 45.0%							
Test for overall effect: Z = 4.77 (P < 0.00001)							
Total (95% CI)	553		557			100.00	-0.27 [-0.39, -0.16]
Test for heterogeneity: Chi² = 5.45, df = 3 (P = 0.14), I² = 45.0%							
Test for overall effect: Z = 4.77 (P < 0.00001)							



Attachment 7

Secondary outcome results for the individual studies (Section B.6.3 of the submission)

Table of Contents

List of Tables

The key secondary outcome results are presented for the 6 treatment studies (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31 and 99815) followed by the relapse prevention study (Study 99769) in the tables below. Relevant available data for Hackett et al.[1], the study comparing placebo and benzodiazepines (diazepam) is also presented.

All efficacy data is reported for the "Intention to Treat (ITT), LOCF" population, i.e. all patients randomised to active treatment with at least one valid post baseline assessment, using last observation carried forward methodology. In Study 99769 the ITT population is called the "Full Analysis Set" (i.e. all patients randomised who received at least one dose of double-blind study medication in the double-blind period).

All safety data is reported for the "All Patients Treated Set (APTS)" (i.e. all patients randomised who received at least one dose of double-blind study medication). In Study 99769 this population is called the "APTS II" population and includes all randomised patients who took at least one dose of study medication in the double-blind period.

Some of the mean change endpoints are analysed using ANCOVA, as pre-specified in the study analysis plan. Where these analyses have been conducted they are reported in the results tables.

Some relative risk and risk difference calculations and all number-needed-to-treat calculations were not performed as part of the pre-specified analyses for the dichotomous outcome data in the Clinical Study Reports. These calculations have been done for this submission (marked with an asterisk next to the outcome) or were calculated in the meta-analysis.

The efficacy results are presented first for each of the studies followed by the safety results. This is followed by a listing of all serious adverse events, including hospitalizations and deaths in each of the studies.

Efficacy results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

The results presented in Table 1 are available for Study SCT-MD-31, but not for SCT-MD-05, SCT-MD-06 or SCT-MD-07 as the outcomes weren't reported in these studies.

Table 1 Results of key secondary outcomes (% patients with HAMA≤7, % patients with ≥50% reduction in HAMA) – Study SCT-MD-31

Outcome	Escitalopram	Placebo	Source of information (Study Report)
Patients with HAMA total score ≤7			
n reporting data / N (%)	125 / 131 (95)	135 / 140 (96)	
n (%) patients with HAMA≤7 at: Week 8	39 (31.2)	32 (23.7)	Table 4.20A
Difference in proportion of patients with HAMA≤7 vs placebo (95% CI)# at: Week 8	0.07 (-0.03, 0.18)	-	Meta-analysis Report
Relative Risk# (95% CI) vs placebo: Week 8	1.32 (0.88, 1.96)	-	Meta-analysis Report
NNT* (95% CI) vs placebo Week 8	14 (6, 33)	-	
Patients with ≥50% reduction in HAMA total score			
n reporting data / N (%)	125 / 131 (95)	135 / 140 (96)	
n (%) patients with ≥50% reduction in HAMA at: Week 8	66 (52.8)	57 (42.2)	Table 4.18A
Difference in proportion of patients with ≥50% reduction in HAMA vs placebo (95% CI) # at: Week 8	0.11 (-0.02, 0.23)	-	Meta-analysis Report
Relative Risk# (95% CI) vs placebo: Week 8	1.25 (0.97, 1.62)	-	Meta-analysis Report
NNT* (95% CI) vs placebo Week 8	9 (4, 50)	-	

HAMA = Hamilton Anxiety Scale, NNT = number needed to treat
# Calculated value, from meta-analysis
* Calculated value

Table 2 Results of key secondary outcomes (HAMA Psychic Anxiety Subscale, HAMA Anxiety Item)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	124 / 128 (96)	128 / 128 (100)	143 / 149 (96)	138 / 145 (95)	154 / 161 (96)	153 / 159 (96)	125 / 131 (95)	135 / 140 (96)
HAMA Psychic Anxiety Subscale:								
Mean (SD) at:								
Baseline	13.1 (2.24)	13.1 (2.17)	13.5 (2.10)	13.0 (2.05)	13.6 (2.57)	13.3 (2.36)	13.92 (2.13)	13.57 (2.24)
Week 8	7.8 (4.53)	9.1 (3.97)	8.1 (4.10)	9.2 (3.73)	7.2 (4.25)	9.4 (4.20)	7.65 (4.83)	8.73 (4.85)
Mean change from baseline (SD) at:								
Week 8	-5.3 (4.16)	-4.0 (3.76)	-5.5 (3.86)	-3.9 (3.80)	-6.4 (4.05)	-3.8 (4.30)	-6.27 (4.45)	-4.84 (4.57)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.3 (-2.3, -0.3)		-1.43 (-2.30, -0.57)		-2.35 (-3.23, -1.47)		-1.22 (-2.25, -0.18)	
HAMA Anxiety Item:								
Mean (SD) at:								
Baseline	2.6 (0.50)	2.7 (0.52)	2.7 (0.44)	2.7 (0.46)	2.6 (0.51)	2.6 (0.55)	2.78 (0.49)	2.75 (0.47)
Week 8	1.7 (0.99)	1.9 (0.83)	1.6 (0.88)	1.9 (0.83)	1.4 (0.91)	1.9 (0.85)	1.54 (0.94)	1.83 (0.98)
Mean change from baseline (SD) at:								
Week 8	-1.0 (0.95)	-0.8 (0.86)	-1.2 (0.87)	-0.8 (0.92)	-1.2 (0.95)	-0.7 (0.97)	-1.23 (1.05)	-0.92 (0.99)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.4, 0.0)		-0.36 (-0.56, -0.17)		-0.52 (-0.71, -0.33)		-0.29 (-0.51, -0.06)	

HAMA = Hamilton Anxiety Scale

Source – Clinical Study Reports: Table 3.2 (all studies); 3.13 (SCT-MD-05, SCT-MD-06, SCT-MD-07); 4.15A, 5.15A (SCT-MD-31)

Table 3 Results of key secondary outcomes (HAMA Tension Item, CGI-I)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	124 / 128 (96)	128 / 128 (100)	143 / 149 (96)	138 / 145 (95)	154 / 161 (96)	153 / 159 (96)	125 / 131 (95)	135 / 140 (96)
HAMA Tension Item:								
Mean (SD) at:								
Baseline	2.6 (0.51)	2.6 (0.53)	2.7 (0.48)	2.7 (0.47)	2.7 (0.56)	2.6 (0.52)	NR	NR
Week 8	1.7 (0.95)	1.9 (0.83)	1.7 (0.89)	2.0 (0.84)	1.4 (0.95)	1.8 (0.92)	NR	NR
Mean change from baseline (SD) at:								
Week 8	-0.9 (1.02)	-0.7 (0.89)	-1.1 (0.92)	-0.7 (0.97)	-1.2 (1.00)	-0.8 (1.00)	NR	NR
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.5, -0.0)		-0.31 (-0.51, -0.10)		-0.38 (-0.58, -0.18)		NR	
Clinical Global Impression – Improvement*:								
Mean (SD) at:								
Week 8	2.6 (1.16)	2.8 (0.99)	2.6 (1.00)	2.8 (1.04)	2.4 (1.09)	2.8 (1.09)	2.29 (1.16)	2.68 (1.26)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.5, 0.1)		-0.25 (-0.49, -0.02)		-0.46 (-0.69, -0.23)		-0.43 (-0.71, -0.15)	

* Measured as improvement from baseline by definition

CGI-I = Clinical Global Impression - Improvement, HAMA = Hamilton Anxiety Scale, NR = not reported

Source – Clinical Study Reports: Table 3.14, 4.3A (SCT-MD-05, SCT-MD-06, SCT-MD-07); Table 4.4A (SCT-MD-31)

Table 4 Results of key secondary outcomes (% patients with CGI-I≤2, CGI-S Score)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	124 / 128 (96)	128 / 128 (100)	143 / 149 (96)	138 / 145 (95)	154 / 161 (96)	153 / 159 (96)	125 / 131 (95)	135 / 140 (96)
Patients with CGI≤2:								
n (%) patients with CGI-I≤2 at:								
Week 8	61 (49)	53 (41)	69 (48)	46 (33)	89 (58)	58 (38)	75 (60)	62 (46)
Difference# (using proportions) in mean change (95% CI) - escitalopram versus placebo:								
Week 8	0.08 (-0.04, 0.20)		0.15 (0.04, 0.26)		0.20 (0.09, 0.31)		0.14 (0.02, 0.26)	
Relative Risk# (95% CI) - escitalopram versus placebo at:								
Week 8	1.19 (0.90, 1.56)		1.45 (1.08, 1.94)		1.52 (1.19, 1.95)		1.31 (1.04, 1.65)	
NNT* (95% CI) - escitalopram versus placebo at:								
Week 8	13 (5, 25)		7 (4, 25)		5 (3, 11)		7 (4, 50)	
Clinical Global Impression – Severity:								
Mean (SD) at:								
Baseline	4.3 (0.50)	4.2 (0.53)	4.3 (0.50)	4.3 (0.52)	4.3 (0.49)	4.2 (0.46)	4.35 (0.54)	4.21 (0.48)
Week 8	3.1 (1.10)	3.3 (1.02)	3.1 (1.06)	3.4 (1.01)	2.9 (1.10)	3.4 (0.96)	2.86 (1.21)	3.10 (1.22)
Mean change from baseline (SD) at:								
Week 8	-1.2 (1.12)	-0.9 (0.91)	-1.2 (1.15)	-0.9 (0.95)	-1.4 (1.13)	-0.8 (1.01)	-1.50 (1.21)	-1.11 (1.18)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.3 (-0.5, -0.0)		-0.31 (-0.53, -0.08)		-0.47 (-0.70, -0.25)		-0.33 (-0.60, -0.05)	

CGI-I = Clinical Global Impression - Improvement, CGI-S = Clinical Global Impression – Severity, HAMA = Hamilton Anxiety Scale, NR = not reported

Source – Clinical Study Reports: 5.3A. 3.4 (SCT-MD-05, SCT-MD-06, SCT-MD-07); Table 4.19A, 3.3 (SCT-MD-31)

Calculated value, from Meta-analysis report

* Calculated value

Table 5 Results of key secondary outcomes (HAD Anxiety Subscale Score, QOL Score)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
HAD Anxiety Subscale Score:								
n reporting data / N (%)	119 / 128 (93)	120 / 128 (94)	139 / 149 (93)	130 / 145 (90)	145 / 161 (90)	144 / 159 (91)	122 / 131 (93)	128 / 140 (91)
Mean (SD) at:								
Baseline	12.7 (3.82)	12.9 (3.58)	12.2 (3.30)	12.6 (3.51)	12.7 (3.84)	12.2 (3.87)	12.80 (3.57)	12.25 (3.37)
Week 8	8.9 (4.43)	10.5 (4.26)	9.0 (4.10)	10.2 (3.89)	8.3 (4.36)	10.5 (4.24)	8.70 (4.45)	9.69 (4.27)
Mean change from baseline (SD) at:								
Week 8	-3.8 (4.58)	-2.3 (4.57)	-3.2 (3.87)	-2.3 (3.88)	-4.4 (4.59)	-1.7 (3.64)	-4.12 (4.65)	-2.70 (4.16)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.5 (-2.6, -0.4)		-1.15 (-2.00, -0.30)		-2.50 (-3.37, -1.63)		-1.10 (-2.11, -0.10)	
QOL Score:								
n reporting data / N (%)	114 / 128 (89)	114 / 128 (89)	131 / 149 (88)	121 / 145 (83)	137 / 161 (85)	135 / 159 (85)	120 / 131 (92)	128 / 140 (91)
Mean (SD) at:								
Baseline	49.7 (9.03)	49.6 (9.47)	51.8 (8.26)	51.3 (8.45)	49.5 (8.98)	51.7 (8.41)	48.51 (9.10)	49.37 (9.06)
Week 8	55.2 (10.00)	52.8 (10.68)	57.1 (9.99)	54.2 (9.78)	57.6 (10.14)	53.2 (10.38)	55.18 (11.15)	53.68 (11.33)
Mean change from baseline (SD) at:								
Week 8	5.4 (8.99)	3.2 (9.18)	4.8 (8.48)	3.0 (8.96)	8.4 (10.43)	1.7 (8.14)	6.22 (10.39)	4.54 (9.89)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	2.5 (0.3, 4.8)		2.18 (0.12, 4.24)		5.90 (3.79, 8.00)		1.52 (-0.91, 3.94)	

HAD = Hospital Anxiety and Depression Scale, QOL = Quality of Life Questionnaire
Source – Clinical Study Reports: Table 3.5, 3.9 (SCT-MD-05, SCT-MD-06, SCT-MD-07); Table 4.6A, 5.6A, 4.8A, 5.8A (SCT-MD-31)

Table 6 Results of key secondary outcomes (HAMD total score)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
HAMD Total Score:								
n reporting data / N (%)	116 / 128 (91)	115 / 128 (90)	132 / 149 (89)	122 / 145 (84)	140 / 161 (87)	137 / 159 (86)	118 / 131 (90)	124 / 140 (89)
Mean (SD) at:								
Baseline	11.8 (3.47)	12.0 (3.23)	12.9 (2.63)	12.8 (2.43)	12.4 (3.55)	11.9 (3.71)	11.45 (2.88)	11.81 (2.61)
Week 8	9.2 (5.34)	10.8 (5.93)	9.2 (4.91)	10.1 (4.93)	8.4 (5.47)	10.4 (4.92)	8.62 (6.04)	9.15 (5.83)
Mean change from baseline (SD) at:								
Week 8	-2.5 (4.65)	-1.5 (5.32)	-3.6 (4.84)	-2.7 (4.93)	-4.4 (5.50)	-1.4 (4.86)	-2.92 (5.59)	-2.70 (5.53)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.2 (-2.5, 0.1)		-0.98 (-2.13, 0.16)		-2.49 (-3.64, -1.35)		-0.19 (-1.52, 1.14)	

HAMD = Hamilton Depression Scale

Source – Clinical Study Reports: Table 3.10 (SCT-MD-05, SCT-MD-06, SCT-MD-07); Table 4.13A, 5.13A (SCT-MD-31)

Efficacy results for Study 99815

Table 7 Results of key secondary outcomes (% patients with HAMA≤7, % patients with HAMA≤9, % patients with ≥50% reduction in HAMA – Study 99815

Outcome	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
Patients with HAMA total score ≤7				
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
n (%) patients with HAMA≤7 at:				Table 49
Week 8	46 (34.3)	43 (32.6)	30 (21.7)	
Week 12	64 (47.8)	57 (43.2)	41 (29.7)	
Difference in % patients with HAMA≤7 vs placebo (95% CI) at:				Table 49
Week 8	12.6 (2.0, 23.2)	10.8 (0.3, 21.4)	-	
Week 12	18.1 (6.7, 29.4)	13.5 (2.1, 24.9)	-	
Relative Risk# (95% CI) vs placebo:				
Week 8	1.58 (1.07, 2.34)	1.50 (1.00, 2.24)		
Week 12	1.61 (1.18, 2.20)	1.45 (1.05, 2.01)		
NNT* (95% CI) vs placebo				
Week 8	8 (4, 50)	9 (5, 333)		
Week 12	6 (3, 15)	7 (4, 48)		
Patients with HAMA total score <9				
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
n (%) patients with HAMA≤9 at:				Table 47
Week 8	64 (47.8)	50 (37.9)	43 (31.2)	
Week 12	75 (56.0)	74 (56.1)	60 (43.5)	
Difference in % patients with HAMA≤9 vs placebo (95% CI) at:				Table 47
Week 8	16.6 (5.1, 28.1)	6.7 (-4.6, 18.0)	-	
Week 12	12.5 (0.7, 24.3)	12.6 (0.7, 24.4)	-	
Relative Risk* (95% CI) vs placebo:				
Week 8	1.53 (1.13, 2.08)	1.22 (0.87, 1.69)	-	
Week 12	1.29 (1.01, 1.64)	1.29 (1.01, 1.64)	-	
NNT* (95% CI) vs placebo				
Week 8	6 (4, 20)	15 (6, 22)	-	
Week 12	8 (4, 143)	8 (4, 99)	-	
Patients with ≥50% reduction in HAMA Total Score				
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
n (%) patients with ≥50% reduction in HAMA at:				Table 45
Week 8	82 (61.2)	77 (58.3)	70 (50.7)	
Week 12	96 (71.6)	93 (70.5)	85 (61.6)	
Difference in % patients with ≥50% reduction in HAMA vs placebo (95% CI) at:				Table 45
Week 8	10.5 (-1.3, 22.2)	7.6 (-4.2, 19.5)	-	
Week 12	10.0 (-1.1, 21.2)	8.9 (-2.4, 20.1)	-	
Relative Risk* (95% CI) vs placebo:				
Week 8	1.21 (0.98, 1.49)	1.15 (0.92, 1.43)		
Week 12	1.16 (0.98, 1.38)	1.14 (0.96, 1.36)		
NNT* (95% CI) vs placebo				
Week 8	9.5 (4.5, 91)	13 (5.1, 24)	-	
Week 12	10 (4.7, 91)	11 (5, 42)	-	

HAMA = Hamilton Anxiety Scale, NNT = number needed to treat
# From meta-analysis
* Calculated value

Table 8 Results of key secondary outcomes (HAMA Psychic Anxiety Subscale, HAMA Anxiety Item) – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
HAMA Psychic Anxiety Subscale Score: Mean (SD) at:				
Baseline	13.88 (2.56)	14.52 (2.59)	14.27 (2.51)	Table 22
Week 8	6.07 (4.55)	7.16 (4.82)	7.87 (4.27)	
Week 12	5.21 (4.62)	6.12 (4.94)	6.92 (4.64)	
Mean change from baseline* (SE) at:				
Week 8	-7.97 (0.38)	-7.17 (0.38)	-6.22 (0.37)	Table 26
Week 12	-8.77 (0.39)	-8.18 (0.39)	-7.14 (0.38)	
Difference in mean change* (95% CI) – escitalopram versus placebo:				
Week 8	-1.76 (-2.79, -0.73)	-0.95 (-1.98, 0.08)	-	Table 26
Week 12	-1.63 (-2.69, -0.57)	-1.04 (-2.11, 0.03)	-	
HAMA Anxiety# Item Score: Mean (SD) at:				
Baseline	2.77 (0.53)	2.78 (0.57)		Table 34
Week 8	1.25 (1.00)	1.42 (1.05)		
Week 12	1.04 (0.99)	1.23 (1.06)		
Mean change from baseline* (SE) at:				
Week 8	-1.54 (0.08)	-1.36 (0.08)	-1.22 (0.08)	Table 38
Week 12	-1.74 (0.08)	-1.55 (0.08)	-1.38 (0.08)	
Difference in mean change* (95% CI) – escitalopram versus placebo:				
Week 8	-0.32 (-0.54, -0.10)	-0.14 (-0.36, 0.08)	-	Table 38
Week 12	-0.37 (-0.59, -0.14)	-0.18 (-0.40, 0.05)	-	

HAMA = Hamilton Anxiety Scale, SE = Standard error

* Analysed using ANCOVA

Called "Anxious Mood" in this study

Table 9 Results of key secondary outcomes (HAMA Tension Item, CGI-I Total Score) – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
HAMA Tension Item Score: Mean (SD) at:				
Baseline	2.67 (0.56)	2.73 (0.55)	2.81 (0.49)	Table 40
Week 8	1.12 (0.93)	1.34 (1.00)	1.46 (0.95)	
Week 12	1.00 (1.00)	1.14 (0.97)	1.30 (0.92)	
Mean change from baseline* (SE) at:				
Week 8	-1.62 (0.08)	-1.40 (0.08)	-1.28 (0.08)	Table 44
Week 12	-1.70 (0.08)	-1.58 (0.08)	-1.43 (0.08)	
Difference in mean change* (95% CI) - escitalopram versus placebo:				
Week 8	-0.33 (-0.55, -0.12)	-0.11 (-0.33, 0.10)	-	Table 44
Week 12	-0.27 (-0.50, -0.04)	-0.15 (-0.38, 0.07)	-	
Clinical Global Impression – Improvement (CGI-I) Total Score#: Mean (SE)* at:				
Week 8	2.11 (0.09)	2.22 (0.09)	2.49 (0.09)	Table 66
Week 12	1.93 (0.10)	2.07 (0.10)	2.34 (0.10)	
Difference in mean change* (95% CI) - escitalopram versus placebo:				
Week 8	-0.38 (-0.63, -0.13)	-0.26 (-0.51, -0.01)	-	Table 66
Week 12	-0.40 (-0.67, -0.14)	-0.27 (-0.53, -0.00)	-	

HAMA = Hamilton Anxiety Scale, SE = Standard error
* Analysed using ANCOVA
# Measured as improvement from baseline by definition

Table 10 Results of key secondary outcomes (Patients with CGI-I≤2, CGI-S) – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
Patients with CGI-I≤2:				
n (%) patients with CGI-I≤2:				
Week 8	97 (72.4)	89 (67.4)	79 (57.2)	Table 67
Week 12	105 (78.4)	98 (74.2)	87 (63.0)	
Difference in % patients (95% CI) with CGI-I≤2 versus placebo at:				
Week 8	15.1 (3.9, 26.3)	10.2 (-1.3, 21.7)	-	Table 67
Week 12	15.3 (4.7, 26.0)	11.2 (0.2, 22.2)	-	
Relative Risk (95% CI) versus placebo:				
Week 8	1.26 (1.06, 1.51)	1.18 (0.98, 1.42)		
Week 12	1.24 (1.06, 1.45)	1.18 (1.00, 1.39)		
NNT (95% CI) versus placebo:				
Week 8	7 (4, 26)	10 (5, 77)		
Week 12	7 (4, 21)	9 (5, 500)		
Clinical Global Impression – Severity (CGI-S) Score:				
Mean (SD) at:				
Baseline	4.51 (0.70)	4.57 (0.70)	4.62 (0.72)	Table 58
Week 8	2.60 (1.23)	2.76 (1.30)	3.09 (1.21)	
Week 12	2.25 (1.20)	2.40 (1.26)	2.75 (1.36)	
Mean change from baseline* (SE) at:				
Week 8	-1.96 (0.10)	-1.78 (0.10)	-1.45 (0.10)	Table 62
Week 12	-2.31 (0.10)	-2.15 (0.11)	-1.81 (0.10)	
Difference in mean change* (95% CI) - escitalopram versus placebo:				
Week 8	-0.51 (-0.78, -0.25)	-0.33 (-0.60, -0.06)	-	Table 62
Week 12	-0.50 (-0.78, -0.21)	-0.34 (-0.62, -0.05)	-	

CGI-I = Clinical Global Impression - Improvement, CGI-S = Clinical Global Impression – Severity, SE = Standard error

* Analysed using ANCOVA

Table 11 Results of key secondary outcomes (HAD Anxiety Subscale Score) – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
HAD Anxiety Subscale Score:				
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
Mean (SD) at:				
Baseline	13.14 (3.65)	13.64 (3.26)	13.47 (3.57)	Table 52
Week 12	6.76 (4.73)	7.48 (4.64)	8.62 (5.02)	
Mean change from baseline* (SE) at:				
Week 12	-6.65 (0.37)	-6.55 (0.38)	-4.96 (0.36)	Table 55
Difference in mean change* (95% CI) - escitalopram versus placebo:				
Week 12	-1.69 (-2.69, -0.69)	-1.59 (-2.61, -0.57)	-	Table 55

HAD = Hospital Anxiety and Depression Scale, QOL = Quality of Life Questionnaire
* Analysed using ANCOVA

Efficacy results for Study 99769

Table 12 Results of key secondary outcomes (HAMA Psychic Anxiety Subscale, HAMA Anxiety Item) – Study 99769

Outcome Timepoint	Escitalopram	Placebo	Source of information (Study Report)
n reporting data / N (%)	186 / 187 (99)	187 / 188 (99)	
HAMA Psychic Anxiety Subscale Score:			
Mean (SD) at:			
Baseline	3.08 (1.98)	2.77 (2.03)	Table 107
Week 12	4.43 (3.89)	7.81 (5.01)	
Week 24	4.53 (4.37)	8.13 (5.21)	
Mean change from baseline (SD) at:			
Week 12	1.35 (3.97)	5.04 (5.30)	Table 108
Week 24	1.45 (4.43)	5.36 (5.39)	
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 12	-3.69 (-4.64 to -2.74, p<0.001)		-
Week 24	-3.91 (-4.91 to -2.91, p<0.001)		-
HAMA Anxiety# Item Score:			
Mean (SD) at:			
Baseline	0.75 (0.65)	0.63 (0.58)	Table 111
Week 12	0.98 (0.88)	1.66 (0.99)	
Week 24	1.00 (0.91)	1.69 (1.05)	
Mean change from baseline (SD) at:			
Week 12	0.23 (0.98)	1.03 (1.10)	Table 112
Week 24	0.25 (1.04)	1.06 (1.15)	
Difference in mean change (95% CI) - escitalopram versus placebo:			
Week 12	-0.8 (-1.01 to -0.59, p<0.001)		
Week 24	-0.81 (-1.03 to -0.59, p<0.001)		

Called "Anxious mood" rather than anxiety in Study Report

Table 13 Results of key secondary outcomes (HAMA Tension Item, CGI-S) – Study 99769

Outcome Timepoint	Escitalopram	Placebo	Source of information (Study Report)
n reporting data / N (%)	186 / 187 (99)	187 / 188 (99)	
HAMA Tension Item Score:			
Mean (SD) at:			
Baseline	0.68 (0.59)	0.55 (0.57)	Table 113
Week 12	0.85 (0.88)	1.53 (1.02)	
Week 24	0.94 (0.97)	1.62 (1.05)	
Mean change from baseline (SD) at:			
Week 12	0.18 (0.99)	0.98 (1.17)	Table 114
Week 24	0.26 (1.07)	1.07 (1.17)	
Difference in mean change (95% CI) - escitalopram versus placebo:			
Week 12	-0.8 (-1.02 to -0.58, p<0.001)		-
Week 24	-0.81 (-1.04 to -0.58, p<0.001)		-
Clinical Global Impression – Severity (CGI-S) Score:			
Mean (SD) at:			
Baseline	0.88 (0.72)	1.72 (0.69)	Table 121
Week 12	2.05 (0.99)	2.92 (1.39)	
Week 24	2.02 (1.11)	3.05 (1.41)	
Mean change from baseline (SD) at:			
Week 12	0.17 (1.09)	1.20 (1.44)	Table 122
Week 24	0.14 (1.21)	1.33 (1.47)	
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 12	-1.03 (-1.29 to -0.77, p<0.001)		
Week 24	-1.19 (-1.46 to -0.92, p<0.001)		

Table 14 Results of key secondary outcomes (HAD Anxiety Score) – Study 99769

Outcome Timepoint	Escitalopram	Placebo	Source of information (Study Report)
n reporting data / N (%)	186 / 187 (99)	187 / 188 (99)	
HAD Anxiety Score: Mean (SD) at:			
Baseline	5.45 (3.44)	5.26 (3.54)	Table 117
Week 12	5.85 (4.38)	8.48 (4.94)	
Week 24	5.77 (4.50)	8.65 (5.09)	
Mean change from baseline (SD) at:			
Week 12	0.40 (3.57)	3.22 (4.83)	Table 118
Week 24	0.32 (3.95)	3.39 (5.13)	
Difference in mean change (95% CI) - escitalopram versus placebo:			
Week 12	-2.82 (-3.68 to -1.96, p<0.001)		-
Week 24	-3.07 (-4.00 to -2.14, p<0.001)		-

HAD = Hospital Anxiety and Depression Scale

Efficacy results for Hackett et al.

The results for Hackett et al.[1] are from the published paper. Very little data is presented on the overall study results that compare placebo with benzodiazepines (diazepam), as most of the results discuss sub-group analyses based on placebo response rates.

Table 15 Secondary efficacy results for Hackett et al.

Outcome Timepoint	Benzodiazepine (diazepam 15mg/day)	Placebo	Source of information (publication)
n reporting data / N (%)	89 / NR	97 / NR	
Patients with ≥50% reduction in HAMA Total Score: **n (%) patients:** **Week 8**	50 (56)	44 (45)	Calculated from Figure 1, p. 185, see Table 16
Difference in % patients (95% CI)* versus placebo at: **Week 8**	11 (-3.5, 25.1)	-	
Relative Risk (95% CI)* versus placebo: **Week 8**	1.24 (0.93, 1.65)	-	
NNT (95% CI)* versus placebo: **Week 8**	9 (4, 28)	-	
Patients with Clinical Global Impression – Improvement (CGI-I) ≤2: **n (%) patients:** **Week 8**	70 (78)	64 (66)	Calculated from Figure 2, p. 185, see Table 16
Difference in % patients (95% CI)* versus placebo at: **Week 8**	12.7 (-0.3, 25.4)	-	
Relative Risk (95% CI)* versus placebo: **Week 8**	1.19 (0.996, 1.426)	-	
NNT (95% CI)* versus placebo: **Week 8**	8 (4, 33)	-	

* calculated values
HAMA - Hamilton Anxiety Scale

Table 16 below calculates the total number and percentage of HAMA responders (i.e. patients with a ≥50% reduction in HAMA from baseline) and CGI-I responders (i.e. patients with CGI≤2) from the information provided in Figures 1 and 2 of Hackett and the total patient numbers reported in Table 1.

Table 16 Calculation of total HAMA responders and CGI responders from Hackett et al.

	HAMA responders					
	Diazepam			Placebo		
	n	N	%	n	N	%
Verum sensitive	24	36	67%	11	34	32%
Verum insensitive	26	53	49%	33	63	52%
Total	50	89	56%	44	97	45%
	CGI-responders					
	Diazepam			Placebo		
	n	N	%	n	N	%
Verum sensitive	30	36	82%	15	34	43%
Verum insensitive	40	53	76%	49	63	78%
Total	70	89	78%	64	97	66%

Safety results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

Table 17 Patient withdrawals (total, due to lack of efficacy)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	126 / 128 (98)	128 / 128 (100)	145 / 149 (97)	142 / 145 (98)	158 / 161 (98)	157 / 159 (99)	127 / 131 (97)	136 / 140 (97)
Patient withdrawals: Number (%) of patients at:								
Week 8	29 (23.0)	33 (25.8)	27 (18.6)	28 (19.7)	39 (24.7)	34 (21.7)	25 (19.7)	32 (23.5)
Risk difference (95% CI) versus placebo*:								
Week 8	-0.03 (-0.13, 0.08)		-0.01 (-0.10, 0.08)		0.03 (-0.06, 0.12)		-0.04 (-0.14, 0.06)	
Relative risk (95% CI) versus placebo*:								
Week 8	0.89 (0.58, 1.38)		0.94 (0.59, 1.52)		1.14 (0.76, 1.71)		0.84 (0.53, 1.33)	
Patient withdrawals due to lack of efficacy: Number (%) of patients at:								
Week 8	2 (1.6)	8 (6.3)	4 (2.8)	0	2 (1.3)	5 (3.2)	3 (2.4)	6 (4.4)
Risk difference (95% CI) versus placebo:								
Week 8	-0.05 (-0.09, 0.00)		0.03 (0.00, 0.06)		-0.02 (-0.05, 0.01)		-0.02 (-0.06, 0.02)	
Relative risk (95% CI) versus placebo:								
Week 8	0.25 (0.06, 1.17)		8.82 (0.48, 162.24)		0.40 (0.08, 2.02)		0.54 (0.14, 2.10)	

Source: Clinical Study Report, Table 1.2 (all studies)
* From Meta-analysis Report

Table 18 Patient withdrawals due to lack of adverse events, Treatment-emergent adverse events occurring in ≥5% of patients

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	126 / 128 (98)	128 / 128 (100)	145 / 149 (97)	142 / 145 (98)	158 / 161 (98)	157 / 159 (99)	127 / 131 (97)	136 / 140 (97)
Patient withdrawals due to adverse events: Number (%) of patients at:								
Week 8	14 (11.1)	4 (3.1)	8 (5.5)	3 (2.1)	14 (8.9)	8 (5.1)	9 (7.1)	7 (5.1)
Risk difference (95% CI) versus placebo*:								
Week 8	0.08 (0.02, 0.14)		0.03 (-0.01, 0.08)		0.04 (-0.02, 0.09)		0.02 (-0.04, 0.08)	
Relative risk (95% CI) versus placebo*:								
Week 8	3.56 (1.20, 10.51)		2.61 (0.71, 9.65)		1.74 (0.75, 4.03)		1.38 (0.53, 3.59)	
Treatment-emergent adverse events occurring in ≥5% of patients#: Number (%) of patients at:								
Week 8	13 (10)	7 (5.5)	10 (6.9)	8 (5.6)	13 (8.2)	6 (3.8)	15 (11.8)	7 (5.1)
Risk difference (95% CI) versus placebo:								
Week 8	0.05 (-0.02, 0.11)		0.01 (-0.04, 0.07)		0.04 (-0.01, 0.10)		0.07 (0.00, 0.13)	
Relative risk (95% CI) versus placebo:								
Week 8	1.89 (0.78, 4.57)		1.22 (0.50, 3.01)		2.15 (0.84, 5.52)		2.29 (0.97, 5.44)	

Source: Clinical Study Report, Table 1.2 (all studies), Table 7.4

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Safety results for Study 99815

Table 19 Patient withdrawals and withdrawals due to lack of efficacy – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
n reporting data / N (%)	136 / 136 (100)	133 / 133 (100)	139 / 139 (100)	
Patient withdrawals: Number (%) of patients at:				
Week 12	18 (13.2)	22 (16.5)	15 (10.8)	Table 3
Risk difference (95% CI) versus placebo*:				
Week 12	0.02 (-0.05, 0.10)	0.06 (-0.02, 0.14)		
Relative risk (95% CI) versus placebo*:				
Week 12	1.23 (0.64, 2.33)	1.53 (0.83, 2.83)		
Patient withdrawals due to lack of efficacy: Number (%) of patients at:				
Week 12	0	2 (1.5)	5 (3.6)	Table 3
Risk difference (95% CI) versus placebo:				
Week 12	-0.04 (-0.07, 0.00)	-0.02 (-0.06, 0.02)		
Relative risk (95% CI) versus placebo:				
Week 12	0.09 (0.01, 1.66)	0.42 (0.08, 2.12)		

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Table 20 Patient withdrawals due to adverse events, Treatment-emergent adverse events occurring in ≥5% of patients – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source of information (Study Report)
n reporting data / N (%)	136 / 136 (100)	133 / 133 (100)	139 / 139 (100)	
Patient withdrawals due to adverse events: Number (%) of patients at:				
Week 12	8 (5.9)	14 (10.5)	4 (2.9)	Table 3
Risk difference (95% CI) versus placebo*:				
Week 12	0.03 (-0.02, 0.08)	0.08 (0.02, 0.14)		
Relative risk (95% CI) versus placebo*:				
Week 12	2.04 (0.63, 6.63)	3.66 (1.24, 10.83)		
Treatment-emergent adverse events occurring in ≥5% of patients#: Number (%) of patients at:				
Week 12	11	13	4	Panel 37, p. 81
Risk difference (95% CI) versus placebo:				
Week 12	0.05 (0.00, 0.11)	0.07 (0.01, 0.13)		
Relative risk (95% CI) versus placebo:				
Week 12	2.81 (0.92, 8.61)	3.40 (1.14, 10.15)		

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Safety results for Study 99769

Safety data is reported for all patients in the double-blind period. This was a minimum of 24 weeks, but could be longer for some patients, as the study was designed so that all patients completed treatment at the same time regardless of when they started.

Table 21 Patient withdrawals and withdrawals due to lack of efficacy – Study 99769

Outcome Timepoint	Escitalopram	Placebo	Source of information (Study Report)
n reporting data / N (%)	187 / 187 (100)	188 / 188 (100)	
Patient withdrawals: Number (%) of patients at: Study endpoint	71 (38.0)	136 (72.3)	Table 9
Risk difference (95% CI) versus placebo*: Study endpoint	-34.4% (-43.8% to -24.9%, p<0.001)		
Relative risk (95% CI) versus placebo*: Study endpoint	0.52 (0.43 to 0.64, p<0.001)		
Patient withdrawals due to lack of efficacy: Number (%) of patients at: Study endpoint	40 (21.4)	103 (54.8)	Table 9
Risk difference (95% CI) versus placebo: Study endpoint	-33.4% (-42.6% to -24.2%, p<0.001)		
Relative risk (95% CI) versus placebo: Study endpoint	0.39 (0.29 to 0.53, p<0.001)		

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Table 22 Patient withdrawals due to adverse events, Treatment-emergent adverse events occurring in ≥5% of patients – Study 99769

Outcome Timepoint	Escitalopram	Placebo	Source of information (Study Report)
n reporting data / N (%)	187 / 187 (100)	188 / 188 (100)	
Patient withdrawals due to adverse events: Number (%) of patients at: Study endpoint	13 (7.0)	16 (8.5)	Table 9
Risk difference (95% CI) versus placebo*: Study endpoint	-1.6% (-7.0% to 3.8%, p=0.572)		
Relative risk (95% CI) versus placebo*: Study endpoint	0.82 (0.40 to 1.65, p=0.573)		
Treatment-emergent adverse events occurring in ≥5% of patients#: Number (%) of patients at: Study endpoint	10 (5.3)	5 (2.7)	Panel 39, p. 77
Risk difference (95% CI) versus placebo: Study endpoint	2.7% (-1.3% to 6.6%, p=0.183)		
Relative risk (95% CI) versus placebo: Study endpoint	2.01 (0.70 to 5.77, p=0.194)		

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Safety results for Hackett et al.

Table 23 Patient withdrawals, withdrawals due to lack of efficacy and adverse events – Hackett et al.

Outcome Timepoint	Diazepam	Placebo	Source of information (Study Report)
n reporting data / N (%)	89 / NR	97 / NR	
Patient withdrawals: Number (%) of patients at:			
Week 8	14 (16)	16 (17)	Table 2, p. 184
Risk difference (95% CI) versus placebo*:			
Week 8	-0.008 (-0.113, 0.098)		
Relative risk (95% CI) versus placebo*:			
Week 8	0.95 (0.49, 1.84)		
Patient withdrawals due to lack of efficacy: Number (%) of patients at:			
Week 8	3 (3)	6 (6)	Table 2, p. 184
Risk difference (95% CI) versus placebo:			
Study endpoint	-0.028 (-0.089, 0.033)		
Relative risk (95% CI) versus placebo:			
Week 8	0.55 (0.14, 2.11)		
Patient withdrawals due to adverse events: Number (%) of patients at:			
Week 8	2 (2)	4 (4)	Table 2, p. 184
Risk difference (95% CI) versus placebo*:			
Week 8	-0.019 (-0.069, 0.031)		
Relative risk (95% CI) versus placebo*:			
Week 8	0.55 (0.10, 2.90)		

* Calculated value

Additional safety data - escitalopram versus placebo studies

The treatment-emergent adverse events (TEAEs) occurring in any arm of the escitalopram versus placebo studies are reported below in Table 24 to. For Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31 TEAEs occurring in ≥10 of patients were reported, while in Study 99815 and 99769 those occurring in ≥5% of patients were summarised in the Study Reports. Serious adverse events, including hospitalisations and deaths are also reported.

Treatment-emergent adverse events occurring in ≥10% of patients

Table 24 Treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in Study SCT-MD-05

Treatment-emergent adverse event	Escitalopram (N=126) n (%)	Placebo (N= 126) n (%)
Patients with at least 1 TEAE	110 (87.3)	94 (73.4)
Headache	35 (27.8)	18 (14.1)
Ejaculation disorder	12 (23.5)	1 (2.1)
Nausea	23 (18.3)	9 (7.0)
Insomnia	16 (12.7)	7 (5.5)
Somnolence	16 (12.7)	7 (5.5)
Diarrhoea	15 (11.9)	9 (7.0)
Mouth dry	14 (11.1)	5 (3.9)

Source: Study Report Panel 14, p. 44

Table 25 Treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in Study SCT-MD-06

Treatment-emergent adverse event	Escitalopram (N=145) n (%)	Placebo (N= 142) n (%)
Patients with at least 1 TEAE	122 (84.1)	99 (69.7)
Headache	29 (20.0)	25 (17.6)
Nausea	25 (17.2)	9 (6.3)
Somnolence	21 (14.5)	12 (8.5)
Insomnia	20 (13.8)	10 (7.0)
Fatigue	19 (13.1)	1 (0.7)
Ejaculation disorder	9 (16.1)	0

Source: Study Report Panel 14, p. 42

Table 26 Treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in Study SCT-MD-07

Treatment-emergent adverse event	Escitalopram (N=158) n (%)	Placebo (N= 157) n (%)
Patients with at least 1 TEAE	126 (79.7)	109 (69.4)
Headache	37 (23.4)	28 (17.8)
Nausea	30 (19.0)	14 (8.9)
Somnolence	19 (12.0)	9 (5.7)
Ejaculation disorder	18 (11.4)	12 (17.6)

Source: Study Report Panel 14, p. 43

Table 27 Treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in Study SCT-MD-31

Treatment-emergent adverse event	Escitalopram (N=127 n (%)	Placebo (N= 136) n (%)
Patients with at least 1 TEAE	107 (84.3)	98 (72.1)
Ejaculation disorder (males only)*	11 (24.4)	0
Nausea	26 (20.5)	11 (8.1)
Headache	20 (15.7)	21 (15.4)
Insomnia	17 (13.4)	18 (13.2)
Impotence (males only)*	5 (11.1)	0
Somnolence	13 (10.2)	10 (7.4)
Mouth dry	11 (8.7)	8 (5.9)
Fatigue	8 (6.3)	5 (3.7)
Sweating increased	5 (3.9)	6 (4.4)

* escitalopram N=45, placebo N=51
Source: Study Report Panel 13, p. 40

Table 28 Treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients in Study 99815

Treatment-emergent adverse event	Escitalopram 10mg (N=136) n (%)	Escitalopram 20mg (N=133) n (%)	Placebo (N= 139) n (%)
Patients with at least 1 TEAE	94 (69.1)	94 (70.7)	88 (63.3)
Nausea	28 (20.6)	28 (21.1)	17 (12.2)
Fatigue	14 (10.3)	22 (16.5)	4 (2.9)
Headache	34 (25.0)	21 (15.8)	23 (16.5)
Insomnia	17 (12.5)	14 (10.5)	3 (2.2)
Diarrhoea	13 (9.6)	13 (9.8)	4 (2.9)
Dizziness	14 (10.3)	12 (9.0)	8 (5.8)
Rhinitis	9 (6.6)	12 (9.0)	8 (5.8)
Sweating increased	11 (8.1)	12 (9.0)	4 (2.9)
Somnolence	5 (3.7)	10 (7.5)	3 (2.2)
Ejaculation failure*	3 (6.7)	3 (7.3)	0
Mouth dry	9 (6.6)	9 (6.8)	3 (2.2)
Libido decreased	3 (2.2)	8 (6.0)	3 (2.2)
Yawning	1 (0.7)	7 (5.3)	0
Abdominal pain	4 (2.9)	4 (3.0)	5 (3.6)
Anxiety	3 (2.2)	4 (3.0)	4 (2.9)
Back pain	7 (5.1)	4 (3.0)	4 (2.9)
Anorgasmia	6 (4.4)	2 (1.5)	0

Source: Study Report Panel 37, p. 81
* gender specific

Table 29 Treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients in Study 99769

Treatment-emergent adverse event	Escitalopram (N=187) n (%)	Placebo (N= 188) n (%)
Patients with at least 1 TEAE	132 (70.6)	107 (56.9)
Rhinitis	32 (17.1)	11 (5.9)
Headache	28 (15.0)	17 (9.0)
Dizziness	20 (10.7)	29 (15.4)
Upper respiratory tract infection	14 (7.5)	6 (3.2)
Back pain	13 (7.0)	10 (5.3)
Insomnia	13 (7.0)	18 (9.6)
Fatigue	12 (6.4)	8 (4.3)
Weight increase	12 (6.4)	2 (1.1)
Anxiety	10 (5.3)	5 (2.7)
Nausea	10 (5.3)	7 (3.7)

Source: Study Report Panel 39, p. 77

Serious adverse events, including hospitalisations and death

SCT-MD-05

No deaths occurred during this study.

No serious adverse events were reported.

(Study Report p. 41)

SCT-MD-06

No deaths occurred during this study.

No serious adverse events were reported during treatment.

(Study Report p. 40)

SCT-MD-07

No deaths occurred during this study.

One of 158 (0.6%) of escitalopram-treated patients experienced a serious adverse event, which was considered not related to treatment by the investigator. The patient, who was receiving multiple medications for hypertension, was hospitalized due to hypertension (200/110 mm Hg) on day 12 and was discontinued from the study due to hypertension, disorientation, dizziness and headache. She was treated with increased metoprolol, amlodipine and an ACE inhibitor and was discharged after 3 days when the hypertension, disorientation and dizziness had resolved.

(Study Report p. 40)

99815

No deaths occurred during this study.

There were no serious adverse events reported in the escitalopram group during the study.

In the placebo group one patient had a serious adverse event. A woman was hospitalized due to increased anxiety after 66 days of treatment. The patient was discharged from hospital

(Study Report p. 83)

99769

No deaths occurred during this study.

During the double-blind phase of the study 3 patients in the escitalopram group had serious adverse events (SAEs) (2 *not related* and 1 *possibly related*) and 4 patients in the placebo group had 9 SAEs (3 *not related* and 6 *possibly related*, the latter all in 1 patient)

SAEs considered **possibly related** to study treatment

Placebo:

- One woman had 6 SAEs, all of which occurred on the same day: worsening of insomnia, worsening of dysponoea, worsening of anxiety, mouth dry, fatigue and concentration impaired. She was hospitalized and withdrew her consent 2 days later. Study treatment was discontinued and treatment with citalopram and alprazolam was initiated. She was discharged from hospital one week later.

SAEs considered **not related** to study treatment

Escitalopram:

- One man had a joint dislocation, was hospitalized and recovered. He completed the study.
- One woman had a lumbar disc lesion, was hospitalized and recovered. She completed the study.
- One man had an aneurysm of the aorta (patient had a history of essential primary hypertension), was hospitalized and underwent surgery. He completed the study.

Placebo:

- One woman was hospitalized with haemmorhoids and was withdrawn due to this and non-compliance with study therapy (due to hospitalization and subsequent surgery).
- One woman had family stress after conflict with her partner and was hospitalized. She withdrew from the study due to this.
- One woman had colitis ulcerative and was withdrawn due to this. She had previously had diarrhoea and anaemia (both not related), for which she was hospitalized.

(Study Report p. 82-84)

Additional safety data - benzodiazepine versus placebo study (Hackett et al.)

Hackett et al. reports that "*The most frequently reported treatment-emergent adverse events were nausea, headache, asthenia, somnolence, dry mouth, dizziness. Nausea, reported most commonly in the venlafaxine XR groups, was mild to moderate in severity and tended to occur early in the course of treatment, subsiding with continued therapy. Conversely, asthenia, the most common adverse event in the diazepam group, persisted throughout the course of the study*." (p. 184)

No other details are reported.

Reference

1. Hackett D, Haudiquet V, Salinas E. A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. *European Psychiatry* 2003;18(4):182-187.

Attachment 9

Additional Statistical Analyses

Study 99769

End-point: Patient withdrawals - secondary endpoint

```
metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |  .524851     .428249   .643243          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |  .524851     .428249   .643243
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of RR=1 : z= 6.21 p = 0.000 (p<0.001)
```

```
metan gp1event gp1noevent gp2event gp2noevent, rd random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      | -.343725    -.438207  -.249244          100
-----------------+-------------------------------------------------------
  M-H pooled RD  | -.343725    -.438207  -.249244
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of RD=0 : z= 7.13 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -5.96    -7.54447  -4.37553          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -5.96    -7.54447  -4.37553
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.37 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in HAM-A Total Score (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -6.61    -8.28179  -4.93821          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -6.61    -8.28179  -4.93821
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.75 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in HAM-A Psychic Anxiety Subscale Score (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -3.69    -4.64003  -2.73997          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -3.69    -4.64003  -2.73997
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.61 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in HAM-A Psychic Anxiety Subscale Score (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -3.91    -4.91106  -2.90894          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -3.91    -4.91106  -2.90894
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.66 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in HAM-A Anxiety Item (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |      -.8     -1.0114  -.588596          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |      -.8     -1.0114  -.588596
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.42 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in HAM-A Anxiety Item (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |     -.81     -1.0325  -.587501          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |     -.81     -1.0325  -.587501
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.14 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in HAM-A Tension Item Score (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |      -.8    -1.01992  -.580085          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |      -.8    -1.01992  -.580085
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.13 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in HAM-A Tension Item Score (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |     -.81    -1.03752  -.582478          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |     -.81    -1.03752  -.582478
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 6.98 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in CGI-Severity Score (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -1.03     -1.2891  -.770896          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -1.03     -1.2891  -.770896
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 7.79 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in CGI-Severity Score (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -1.19    -1.46318  -.916818          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -1.19    -1.46318  -.916818
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 8.54 p = 0.000 (p<0.001)
```

Study 99769

End-point: Change in HAD Anxiety Score (ITT LOCF) - primary endpoint – 12 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -2.82    -3.68166  -1.95834          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -2.82    -3.68166  -1.95834
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 6.41 p = 0.000 (p<0.001)
```


Study 99769

End-point: Change in HAD Anxiety Score (ITT LOCF) - primary endpoint – 24 weeks

```
metan patientsgp1 gp1changeinscore gp1sdchangeinscore patientsgp2
gp2changeinscore gp2sdchangeinscore, nostandard xla(-10,0,2)
label(namevar=trialname)
```

```
           Study |       WMD  [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |    -3.07     -3.9989   -2.1411          100
-----------------+-------------------------------------------------------
  I-V pooled WMD |    -3.07     -3.9989   -2.1411
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of WMD=0 : z= 6.48 p = 0.000 (p<0.001)
```

Study 99769

End-point: Patient withdrawals due to lack of efficacy - secondary endpoint

```
metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |  .390426     .288109   .529081          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |  .390426     .288109   .529081
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =     .
  Test of RR=1 : z= 6.07 p = 0.000 (p<0.001)
```

```
metan gp1event gp1noevent gp2event gp2noevent, rd random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      | -.333969    -.426249  -.241688          100
-----------------+-------------------------------------------------------
  M-H pooled RD  | -.333969    -.426249  -.241688
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =     .
  Test of RD=0 : z= 7.09 p = 0.000 (p<0.001)
```

Study 99769

End-point: Patient with adverse events leading to withdrawal - secondary endpoint

```
metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |  .816845     .404302   1.65034          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |  .816845     .404302   1.65034
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of RR=1 : z= 0.56 p = 0.573
```

```
metan gp1event gp1noevent gp2event gp2noevent, rd random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      | -.015588    -.069623    .038448          100
-----------------+-------------------------------------------------------
  M-H pooled RD  | -.015588    -.069623    .038448
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of RD=0 : z= 0.57 p = 0.572
```

Study 99769

End-point: Patient with treatment-emergent adverse events occurring in ≥5% of patients - secondary endpoint

```
metan gp1event gp1noevent gp2event gp2noevent, rr random xlab(0.5,1,5)
label(namevar=trialname)


           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |   2.0107     .700628   5.77039          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |   2.0107     .700628   5.77039
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =     .
  Test of RR=1 : z= 1.30 p = 0.194



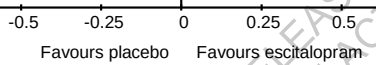
metan gp1event gp1noevent gp2event gp2noevent, rd random xlab(0.5,1,5)
label(namevar=trialname)

           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Study 99769      |   .02688    -.012728   .066488          100
-----------------+-------------------------------------------------------
  M-H pooled RD  |   .02688    -.012728   .066488
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =     .
  Test of RD=0 : z= 1.33 p = 0.183
```

Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	61/124	53/128		22.43	0.08 [-0.04, 0.20]
SCT-MD-06	69/143	46/138		26.14	0.15 [0.04, 0.26]
SCT-MD-07	89/154	58/153		28.10	0.20 [0.09, 0.31]
SCT-MD-31	75/125	62/135		23.33	0.14 [0.02, 0.26]
Total (95% CI)	546	554		100.00	0.15 [0.09, 0.20]

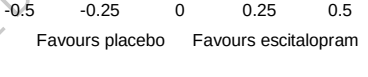
Total events: 294 (Escitalopram), 219 (Placebo)
Test for heterogeneity: Chi² = 2.09, df = 3 (P = 0.55), I² = 0%
Test for overall effect: Z = 4.90 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	61/124	53/128		16.71	0.08 [-0.04, 0.20]
SCT-MD-06	69/143	46/138		19.47	0.15 [0.04, 0.26]
SCT-MD-07	89/154	58/153		20.93	0.20 [0.09, 0.31]
SCT-MD-31	75/125	62/135		17.39	0.14 [0.02, 0.26]
Study 99815 (all)	186/266	79/138		25.49	0.13 [0.03, 0.23]
Total (95% CI)	812	692		100.00	0.14 [0.09, 0.19]

Total events: 480 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 2.19, df = 4 (P = 0.70), I² = 0%
Test for overall effect: Z = 5.49 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815 - 10mg arm only

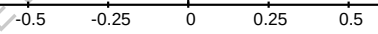
Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	61/124	53/128		17.68	0.08 [-0.04, 0.20]
SCT-MD-06	69/143	46/138		20.60	0.15 [0.04, 0.26]
SCT-MD-07	89/154	58/153		22.15	0.20 [0.09, 0.31]
SCT-MD-31	75/125	62/135		18.39	0.14 [0.02, 0.26]
Study 99815 (10mg)	97/134	79/138		21.18	0.15 [0.04, 0.26]
Total (95% CI)	680	692		100.00	0.15 [0.09, 0.20]

Total events: 391 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 2.10, df = 4 (P = 0.72), I² = 0%
Test for overall effect: Z = 5.57 (P < 0.00001)

Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 04 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	61/124	53/128		17.87	0.08 [-0.04, 0.20]
SCT-MD-06	69/143	46/138		20.82	0.15 [0.04, 0.26]
SCT-MD-07	89/154	58/153		22.38	0.20 [0.09, 0.31]
SCT-MD-31	75/125	62/135		18.59	0.14 [0.02, 0.26]
Study 99815 (20mg)	89/132	79/138		20.33	0.10 [-0.01, 0.22]
Total (95% CI)	678	692		100.00	0.14 [0.08, 0.19]

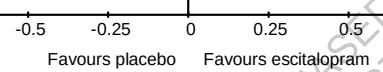
Total events: 383 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 2.53, df = 4 (P = 0.64), I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	66/125	57/135		41.67	0.11 [-0.02, 0.23]
Study 99815 (all)	159/266	70/138		58.33	0.09 [-0.01, 0.19]
Total (95% CI)	391	273		100.00	0.10 [0.02, 0.17]

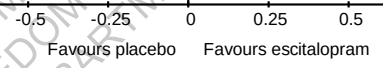
Total events: 225 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%
Test for overall effect: Z = 2.43 (P = 0.01)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815 - 10mg

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	66/125	57/135		48.53	0.11 [-0.02, 0.23]
Study 99815 (10mg)	82/134	70/138		51.47	0.10 [-0.01, 0.22]
Total (95% CI)	259	273		100.00	0.11 [0.02, 0.19]

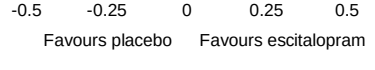
Total events: 148 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815 - 20mg

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	66/125	57/135		49.01	0.11 [-0.02, 0.23]
Study 99815 (20mg)	77/132	70/138		50.99	0.08 [-0.04, 0.19]
Total (95% CI)	257	273		100.00	0.09 [0.01, 0.18]

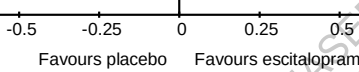
Total events: 143 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	39/125	32/135		40.37	0.07 [-0.03, 0.18]
Study 99815 (all)	89/266	30/138		59.63	0.12 [0.03, 0.21]
Total (95% CI)	391	273		100.00	0.10 [0.03, 0.17]

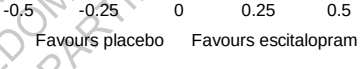
Total events: 128 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%
Test for overall effect: Z = 2.85 (P = 0.004)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	39/125	32/135		48.81	0.07 [-0.03, 0.18]
Study 99815 (10mg)	46/134	30/138		51.19	0.13 [0.02, 0.23]
Total (95% CI)	259	273		100.00	0.10 [0.03, 0.18]

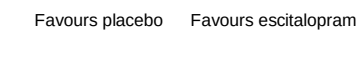
Total events: 85 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-31	39/125	32/135		48.66	0.07 [-0.03, 0.18]
Study 99815 (20mg)	43/132	30/138		51.34	0.11 [0.00, 0.21]
Total (95% CI)	257	273		100.00	0.09 [0.02, 0.17]

Total events: 82 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 01 Withdrawals from study due to lack of efficacy - 8 weeks - without Study 99815

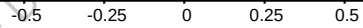
Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	2/126	8/128		21.22	-0.05 [-0.09, 0.00]
SCT-MD-06	4/145	0/142		28.67	0.03 [0.00, 0.06]
SCT-MD-07	2/158	5/157		27.40	-0.02 [-0.05, 0.01]
SCT-MD-31	3/127	6/136		22.72	-0.02 [-0.06, 0.02]
Total (95% CI)	556	563		100.00	-0.01 [-0.05, 0.02]

Total events: 11 (Escitalopram), 19 (Placebo)
Test for heterogeneity: Chi² = 9.52, df = 3 (P = 0.02), I² = 68.5%
Test for overall effect: Z = 0.70 (P = 0.48)

Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 02 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	2/126	8/128		15.99	-0.05 [-0.09, 0.00]
SCT-MD-06	4/145	0/142		23.08	0.03 [0.00, 0.06]
SCT-MD-07	2/158	5/157		21.80	-0.02 [-0.05, 0.01]
SCT-MD-31	3/127	6/136		17.35	-0.02 [-0.06, 0.02]
Study 99815 (all)	2/269	5/139		21.77	-0.03 [-0.06, 0.00]
Total (95% CI)	825	702		100.00	-0.02 [-0.04, 0.01]

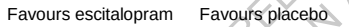
Total events: 13 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 10.78, df = 4 (P = 0.03), I² = 62.9%
Test for overall effect: Z = 1.11 (P = 0.27)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 03 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	2/126	8/128		16.35	-0.05 [-0.09, 0.00]
SCT-MD-06	4/145	0/142		22.93	0.03 [0.00, 0.06]
SCT-MD-07	2/158	5/157		21.78	-0.02 [-0.05, 0.01]
SCT-MD-31	3/127	6/136		17.64	-0.02 [-0.06, 0.02]
Study 99815 (10mg)	0/136	5/139		21.30	-0.04 [-0.07, 0.00]
Total (95% CI)	692	702		100.00	-0.02 [-0.04, 0.01]

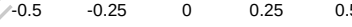
Total events: 11 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 11.61, df = 4 (P = 0.02), I² = 65.6%
Test for overall effect: Z = 1.18 (P = 0.24)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 04 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	2/126	8/128		16.15	-0.05 [-0.09, 0.00]
SCT-MD-06	4/145	0/142		23.73	0.03 [0.00, 0.06]
SCT-MD-07	2/158	5/157		22.35	-0.02 [-0.05, 0.01]
SCT-MD-31	3/127	6/136		17.58	-0.02 [-0.06, 0.02]
Study 99815 (20mg)	2/133	5/139		20.19	-0.02 [-0.06, 0.02]
Total (95% CI)	689	702		100.00	-0.01 [-0.04, 0.01]

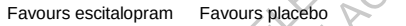
Total events: 13 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 9.89, df = 4 (P = 0.04), I² = 59.5%
Test for overall effect: Z = 0.98 (P = 0.33)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 01 Patient withdrawals - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	29/126	33/128		21.02	-0.03 [-0.13, 0.08]
SCT-MD-06	27/145	28/142		28.23	-0.01 [-0.10, 0.08]
SCT-MD-07	39/158	34/157		27.01	0.03 [-0.06, 0.12]
SCT-MD-31	25/127	32/136		23.74	-0.04 [-0.14, 0.06]
Total (95% CI)	556	563		100.00	-0.01 [-0.06, 0.04]

Total events: 120 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 1.14, df = 3 (P = 0.77), I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 02 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815

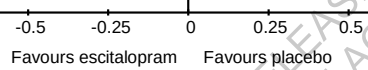
Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	29/126	33/128		13.79	-0.03 [-0.13, 0.08]
SCT-MD-06	27/145	28/142		18.52	-0.01 [-0.10, 0.08]
SCT-MD-07	39/158	34/157		17.72	0.03 [-0.06, 0.12]
SCT-MD-31	25/127	32/136		15.58	-0.04 [-0.14, 0.06]
Study 99815 (all)	40/269	15/139		34.39	0.04 [-0.03, 0.11]
Total (95% CI)	825	702		100.00	0.01 [-0.03, 0.05]

Total events: 160 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 2.64, df = 4 (P = 0.62), I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)

Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 03 Patients with adverse events leading to withdrawal - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	14/126	4/128		18.42	0.08 [0.02, 0.14]
SCT-MD-06	8/145	3/142		37.21	0.03 [-0.01, 0.08]
SCT-MD-07	14/158	8/157		22.95	0.04 [-0.02, 0.09]
SCT-MD-31	9/127	7/136		21.42	0.02 [-0.04, 0.08]
Total (95% CI)	556	563		100.00	0.04 [0.01, 0.07]

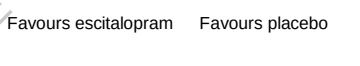
Total events: 45 (Escitalopram), 22 (Placebo)
Test for heterogeneity: Chi² = 2.14, df = 3 (P = 0.54), I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 04 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	14/126	4/128		13.24	0.08 [0.02, 0.14]
SCT-MD-06	8/145	3/142		26.74	0.03 [-0.01, 0.08]
SCT-MD-07	14/158	8/157		16.49	0.04 [-0.02, 0.09]
SCT-MD-31	9/127	7/136		15.40	0.02 [-0.04, 0.08]
Study 99815 (all)	22/269	4/139		28.13	0.05 [0.01, 0.10]
Total (95% CI)	825	702		100.00	0.04 [0.02, 0.07]

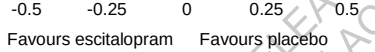
Total events: 67 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 2.37, df = 4 (P = 0.67), I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 05 Patients with TEAE's occurring in =>5% of patients - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	13/126	7/128		20.17	0.05 [-0.02, 0.11]
SCT-MD-06	10/145	8/142		28.10	0.01 [-0.04, 0.07]
SCT-MD-07	13/158	6/157		32.25	0.04 [-0.01, 0.10]
SCT-MD-31	15/127	7/136		19.47	0.07 [0.00, 0.13]
Total (95% CI)	556	563		100.00	0.04 [0.01, 0.07]

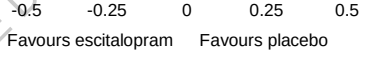
Total events: 51 (Escitalopram), 28 (Placebo)
Test for heterogeneity: Chi² = 1.62, df = 3 (P = 0.66), I² = 0%
Test for overall effect: Z = 2.67 (P = 0.007)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 06 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	13/126	7/128		13.85	0.05 [-0.02, 0.11]
SCT-MD-06	10/145	8/142		19.29	0.01 [-0.04, 0.07]
SCT-MD-07	13/158	6/157		22.14	0.04 [-0.01, 0.10]
SCT-MD-31	15/127	7/136		13.37	0.07 [0.00, 0.13]
Study 99815 (all)	24/269	4/139		31.34	0.06 [0.02, 0.10]
Total (95% CI)	825	702		100.00	0.05 [0.02, 0.07]

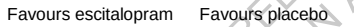
Total events: 75 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 2.15, df = 4 (P = 0.71), I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 07 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	29/126	33/128		15.05	-0.03 [-0.13, 0.08]
SCT-MD-06	27/145	28/142		20.21	-0.01 [-0.10, 0.08]
SCT-MD-07	39/158	34/157		19.34	0.03 [-0.06, 0.12]
SCT-MD-31	25/127	32/136		17.00	-0.04 [-0.14, 0.06]
Study 99815 (10mg)	18/136	15/139		28.40	0.02 [-0.05, 0.10]
Total (95% CI)	692	702		100.00	0.00 [-0.04, 0.04]

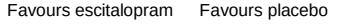
Total events: 138 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 1.71, df = 4 (P = 0.79), I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 08 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	29/126	33/128		15.54	-0.03 [-0.13, 0.08]
SCT-MD-06	27/145	28/142		20.87	-0.01 [-0.10, 0.08]
SCT-MD-07	39/158	34/157		19.97	0.03 [-0.06, 0.12]
SCT-MD-31	25/127	32/136		17.56	-0.04 [-0.14, 0.06]
Study 99815 (20mg)	22/133	15/139		26.05	0.06 [-0.02, 0.14]
Total (95% CI)	689	702		100.00	0.01 [-0.03, 0.05]

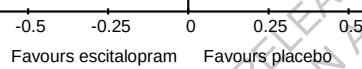
Total events: 142 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 3.12, df = 4 (P = 0.54), I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 09 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	14/126	4/128		14.07	0.08 [0.02, 0.14]
SCT-MD-06	8/145	3/142		28.42	0.03 [-0.01, 0.08]
SCT-MD-07	14/158	8/157		17.53	0.04 [-0.02, 0.09]
SCT-MD-31	9/127	7/136		16.36	0.02 [-0.04, 0.08]
Study 99815 (10mg)	8/136	4/139		23.61	0.03 [-0.02, 0.08]
Total (95% CI)	692	702		100.00	0.04 [0.01, 0.06]

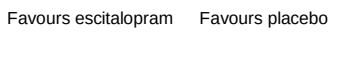
Total events: 53 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 2.27, df = 4 (P = 0.69), I² = 0%
Test for overall effect: Z = 3.15 (P = 0.002)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 10 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	14/126	4/128		15.27	0.08 [0.02, 0.14]
SCT-MD-06	8/145	3/142		30.84	0.03 [-0.01, 0.08]
SCT-MD-07	14/158	8/157		19.02	0.04 [-0.02, 0.09]
SCT-MD-31	9/127	7/136		17.75	0.02 [-0.04, 0.08]
Study 99815 (20mg)	14/133	4/139		17.13	0.08 [0.02, 0.14]
Total (95% CI)	689	702		100.00	0.05 [0.02, 0.07]

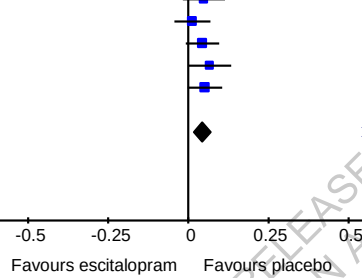
Total events: 59 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 3.36, df = 4 (P = 0.50), I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 11 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	13/126	7/128		15.43	0.05 [-0.02, 0.11]
SCT-MD-06	10/145	8/142		21.50	0.01 [-0.04, 0.07]
SCT-MD-07	13/158	6/157		24.67	0.04 [-0.01, 0.10]
SCT-MD-31	15/127	7/136		14.90	0.07 [0.00, 0.13]
Study 99815 (10mg)	11/136	4/139		23.50	0.05 [0.00, 0.11]
Total (95% CI)	692	702		100.00	0.04 [0.02, 0.07]

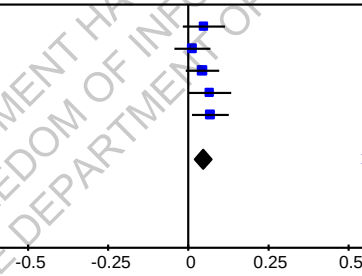
Total events: 62 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 1.75, df = 4 (P = 0.78), I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)



Review: Escitalopram (Lexapro) - GAD (Copy for RD calc'ns)
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 12 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI
SCT-MD-05	13/126	7/128		15.94	0.05 [-0.02, 0.11]
SCT-MD-06	10/145	8/142		22.20	0.01 [-0.04, 0.07]
SCT-MD-07	13/158	6/157		25.48	0.04 [-0.01, 0.10]
SCT-MD-31	15/127	7/136		15.39	0.07 [0.00, 0.13]
Study 99815 (20mg)	13/133	4/139		20.99	0.07 [0.01, 0.13]
Total (95% CI)	689	702		100.00	0.05 [0.02, 0.07]

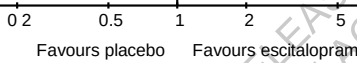
Total events: 64 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 2.35, df = 4 (P = 0.67), I² = 0%
Test for overall effect: Z = 3.45 (P = 0.0006)



Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	61/124	53/128		22.15	1.19 [0.90, 1.56]
SCT-MD-06	69/143	46/138		19.52	1.45 [1.08, 1.94]
SCT-MD-07	89/154	58/153		27.79	1.52 [1.19, 1.95]
SCT-MD-31	75/125	62/135		30.54	1.31 [1.04, 1.65]
Total (95% CI)	546	554		100.00	1.36 [1.20, 1.55]

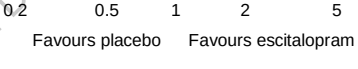
Total events: 294 (Escitalopram), 219 (Placebo)
Test for heterogeneity: Chi² = 2.08, df = 3 (P = 0.56), I² = 0%
Test for overall effect: Z = 4.72 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	61/124	53/128		13.75	1.19 [0.90, 1.56]
SCT-MD-06	69/143	46/138		12.12	1.45 [1.08, 1.94]
SCT-MD-07	89/154	58/153		17.25	1.52 [1.19, 1.95]
SCT-MD-31	75/125	62/135		18.96	1.31 [1.04, 1.65]
Study 99815 (all)	186/266	79/138		37.92	1.22 [1.04, 1.44]
Total (95% CI)	812	692		100.00	1.31 [1.18, 1.45]

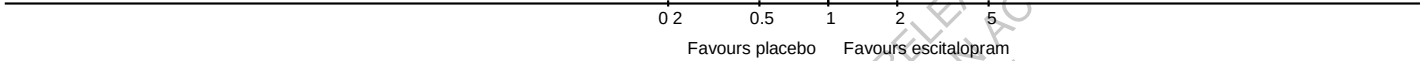
Total events: 480 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 3.16, df = 4 (P = 0.53), I² = 0%
Test for overall effect: Z = 5.19 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	61/124	53/128		14.57	1.19 [0.90, 1.56]
SCT-MD-06	69/143	46/138		12.84	1.45 [1.08, 1.94]
SCT-MD-07	89/154	58/153		18.28	1.52 [1.19, 1.95]
SCT-MD-31	75/125	62/135		20.10	1.31 [1.04, 1.65]
Study 99815 (10mg)	97/134	79/138		34.20	1.26 [1.06, 1.51]
Total (95% CI)	680	692		100.00	1.33 [1.20, 1.47]

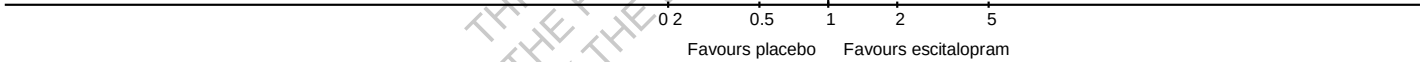
Total events: 391 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 2.55, df = 4 (P = 0.64), I² = 0%
Test for overall effect: Z = 5.34 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients wi h CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 04 Number of Patients wi h CGI-I <=2 (ITT LOCF) - 8 weeks - with Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	61/124	53/128		15.03	1.19 [0.90, 1.56]
SCT-MD-06	69/143	46/138		13.25	1.45 [1.08, 1.94]
SCT-MD-07	89/154	58/153		18.86	1.52 [1.19, 1.95]
SCT-MD-31	75/125	62/135		20.73	1.31 [1.04, 1.65]
Study 99815 (20mg)	89/132	79/138		32.12	1.18 [0.98, 1.42]
Total (95% CI)	678	692		100.00	1.30 [1.17, 1.45]

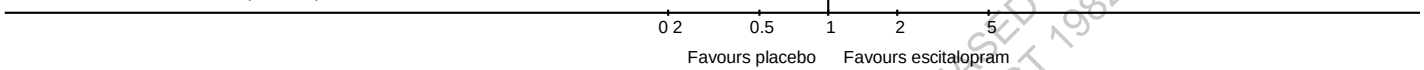
Total events: 383 (Escitalopram), 298 (Placebo)
Test for heterogeneity: Chi² = 3.72, df = 4 (P = 0.44), I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)



Review: Escitalopram (Lexapro) - GAD
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	66/125	57/135		35.63	1.25 [0.97, 1.62]
Study 99815 (all)	159/266	70/138		64.37	1.18 [0.97, 1.43]
Total (95% CI)	391	273		100.00	1.20 [1.03, 1.40]

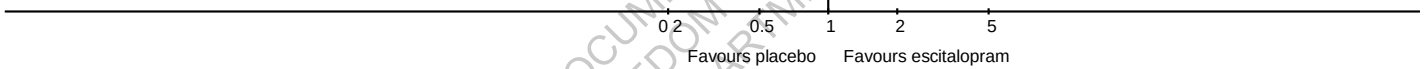
Total events: 225 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)



Review: Escitalopram (Lexapro) - GAD
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815 - 10mg

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	66/125	57/135		40.51	1.25 [0.97, 1.62]
Study 99815 (10mg)	82/134	70/138		59.49	1.21 [0.98, 1.49]
Total (95% CI)	259	273		100.00	1.22 [1.04, 1.44]

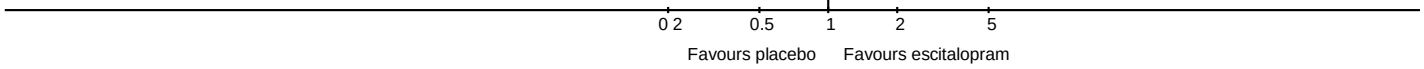
Total events: 148 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)



Review: Escitalopram (Lexapro) - GAD
Comparison: 07 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks - with Study 99815 - 20mg

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	66/125	57/135		41.87	1.25 [0.97, 1.62]
Study 99815 (20mg)	77/132	70/138		58.13	1.15 [0.92, 1.43]
Total (95% CI)	257	273		100.00	1.19 [1.01, 1.41]

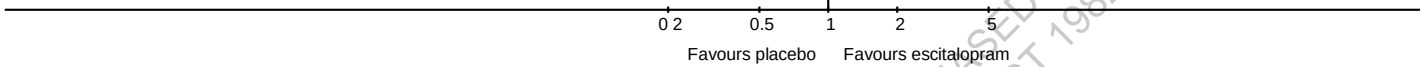
Total events: 143 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)



Review: Escitalopram (Lexapro) - GAD
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	39/125	32/135		44.72	1.32 [0.88, 1.96]
Study 99815 (all)	89/266	30/138		55.28	1.54 [1.07, 2.20]
Total (95% CI)	391	273		100.00	1.44 [1.10, 1.87]

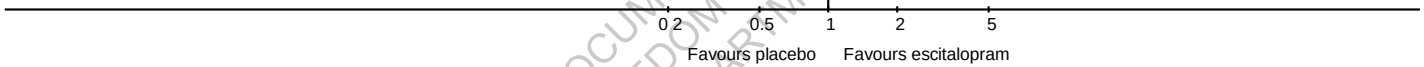
Total events: 128 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)



Review: Escitalopram (Lexapro) - GAD
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	39/125	32/135		49.32	1.32 [0.88, 1.96]
Study 99815 (10mg)	46/134	30/138		50.68	1.58 [1.07, 2.34]
Total (95% CI)	259	273		100.00	1.44 [1.09, 1.91]

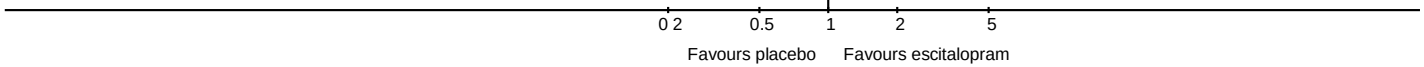
Total events: 85 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



Review: Escitalopram (Lexapro) - GAD
Comparison: 08 Number of Patients wi h HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 03 Number of Patients wi h HAM-A<=7 (ITT LOCF) - 8 weeks - with Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	39/125	32/135		50.17	1.32 [0.88, 1.96]
Study 99815 (20mg)	43/132	30/138		49.83	1.50 [1.00, 2.24]
Total (95% CI)	257	273		100.00	1.40 [1.06, 1.86]

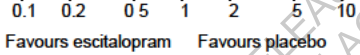
Total events: 82 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)



Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 01 Withdrawals from study due to lack of efficacy - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		28.88	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		11.47	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		26.89	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		32.75	0.54 [0.14, 2.10]
Total (95% CI)	556	563		100.00	0.55 [0.19, 1.62]

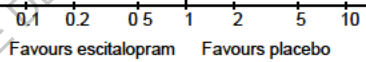
Total events: 11 (Escitalopram), 19 (Placebo)
Test for heterogeneity: Chi² = 4.76, df = 3 (P = 0.19), I² = 37.0%
Test for overall effect: Z = 1.09 (P = 0.28)



Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 02 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		22.92	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		8.38	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		21.13	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		26.49	0.54 [0.14, 2.10]
Study 99815 (all)	2/269	5/139		21.09	0.21 [0.04, 1.05]
Total (95% CI)	825	702		100.00	0.44 [0.18, 1.08]

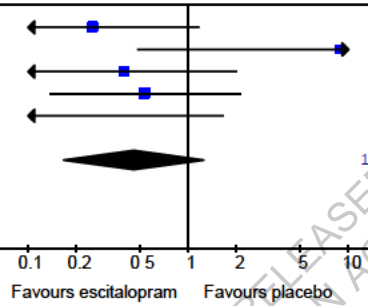
Total events: 13 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 5.70, df = 4 (P = 0.22), I² = 29.8%
Test for overall effect: Z = 1.79 (P = 0.07)



Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 03 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		25.96	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		10.10	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		24.11	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		29.58	0.54 [0.14, 2.10]
Study 99815 (10mg)	0/136	5/139		10.26	0.09 [0.01, 1.66]
Total (95% CI)	692	702		100.00	0.46 [0.17, 1.25]

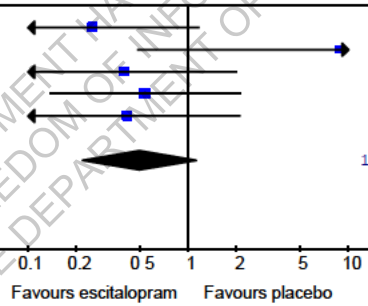
Total events: 11 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 5.84, df = 4 (P = 0.21), I² = 31.5%
Test for overall effect: Z = 1.53 (P = 0.13)



Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 04 Withdrawals from study due to lack of efficacy - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	2/126	8/128		23.08	0.25 [0.06, 1.17]
SCT-MD-06	4/145	0/142		7.38	8.82 [0.48, 162.24]
SCT-MD-07	2/158	5/157		20.91	0.40 [0.08, 2.02]
SCT-MD-31	3/127	6/136		27.66	0.54 [0.14, 2.10]
Study 99815 (20mg)	2/133	5/139		20.96	0.42 [0.08, 2.12]
Total (95% CI)	689	702		100.00	0.49 [0.22, 1.12]

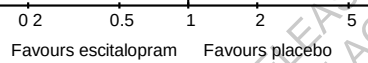
Total events: 13 (Escitalopram), 24 (Placebo)
Test for heterogeneity: Chi² = 4.78, df = 4 (P = 0.31), I² = 16.3%
Test for overall effect: Z = 1.69 (P = 0.09)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 01 Patient withdrawals - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		25.86	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		21.56	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		29.94	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		22.64	0.84 [0.53, 1.33]
Total (95% CI)	556	563		100.00	0.96 [0.77, 1.19]

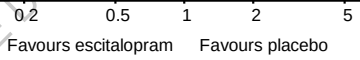
Total events: 120 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 1.15, df = 3 (P = 0.77), I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 02 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		22.35	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		18.64	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		25.88	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		19.56	0.84 [0.53, 1.33]
Study 99815 (all)	40/269	15/139		13.57	1.38 [0.79, 2.41]
Total (95% CI)	825	702		100.00	1.01 [0.82, 1.24]

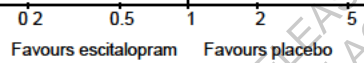
Total events: 160 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 2.57, df = 4 (P = 0.63), I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 03 Patients with adverse events leading to withdrawal - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		21.59	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		14.85	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		35.92	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		27.64	1.38 [0.53, 3.59]
Total (95% CI)	556	563		100.00	2.02 [1.22, 3.34]

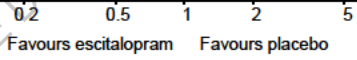
Total events: 45 (Escitalopram), 22 (Placebo)
Test for heterogeneity: Chi² = 1.94, df = 3 (P = 0.58), I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 04 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		17.52	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		12.05	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		29.16	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		22.44	1.38 [0.53, 3.59]
Study 99815 (all)	22/269	4/139		18.83	2.84 [1.00, 8.08]
Total (95% CI)	825	702		100.00	2.15 [1.37, 3.39]

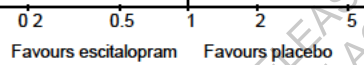
Total events: 67 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 2.28, df = 4 (P = 0.68), I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 05 Patients with TEAE's occurring in =>5% of patients - 8 weeks - without Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	13/126	7/128		25.64	1.89 [0.78, 4.57]
SCT-MD-06	10/145	8/142		24.78	1.22 [0.50, 3.01]
SCT-MD-07	13/158	6/157		22.66	2.15 [0.84, 5.52]
SCT-MD-31	15/127	7/136		26.92	2.29 [0.97, 5.44]
Total (95% CI)	556	563		100.00	1.84 [1.18, 2.88]

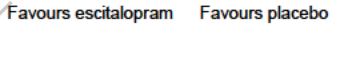
Total events: 51 (Escitalopram), 28 (Placebo)
Test for heterogeneity: Chi² = 1.15, df = 3 (P = 0.77), I² = 0%
Test for overall effect: Z = 2.67 (P = 0.008)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 06 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	13/126	7/128		21.61	1.89 [0.78, 4.57]
SCT-MD-06	10/145	8/142		20.89	1.22 [0.50, 3.01]
SCT-MD-07	13/158	6/157		19.10	2.15 [0.84, 5.52]
SCT-MD-31	15/127	7/136		22.69	2.29 [0.97, 5.44]
Study 99815 (all)	24/269	4/139		15.71	3.10 [1.10, 8.76]
Total (95% CI)	825	702		100.00	2.00 [1.32, 3.02]

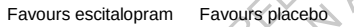
Total events: 75 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 1.98, df = 4 (P = 0.74), I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 07 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		23.14	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		19.29	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		26.79	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		20.25	0.84 [0.53, 1.33]
Study 99815 (10mg)	18/136	15/139		10.54	1.23 [0.64, 2.33]
Total (95% CI)	692	702		100.00	0.98 [0.80, 1.21]

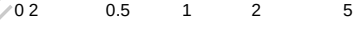
Total events: 138 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 1.65, df = 4 (P = 0.80), I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 08 Patient withdrawals - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		22.88	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		19.08	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		26.49	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		20.03	0.84 [0.53, 1.33]
Study 99815 (20mg)	22/133	15/139		11.52	1.53 [0.83, 2.83]
Total (95% CI)	689	702		100.00	1.01 [0.82, 1.24]

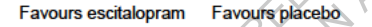
Total events: 142 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 3.16, df = 4 (P = 0.53), I² = 0%
Test for overall effect: Z = 0.11 (P = 0.92)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 09 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		18.25	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		12.55	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		30.36	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		23.36	1.38 [0.53, 3.59]
Study 99815 (10mg)	8/136	4/139		15.48	2.04 [0.63, 6.63]
Total (95% CI)	692	702		100.00	2.02 [1.27, 3.22]

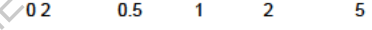
Total events: 53 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 1.94, df = 4 (P = 0.75), I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 10 Patients with adverse events leading to withdrawal - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		17.77	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		12.22	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		29.56	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		22.75	1.38 [0.53, 3.59]
Study 99815 (20mg)	14/133	4/139		17.71	3.66 [1.24, 10.83]
Total (95% CI)	689	702		100.00	2.24 [1.42, 3.54]

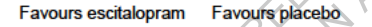
Total events: 59 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 2.90, df = 4 (P = 0.58), I² = 0%
Test for overall effect: Z = 3.47 (P = 0.0005)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 11 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815 - 10mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	13/126	7/128		22.10	1.89 [0.78, 4.57]
SCT-MD-06	10/145	8/142		21.36	1.22 [0.50, 3.01]
SCT-MD-07	13/158	6/157		19.53	2.15 [0.84, 5.52]
SCT-MD-31	15/127	7/136		23.20	2.29 [0.97, 5.44]
Study 99815 (10mg)	11/136	4/139		13.81	2.81 [0.92, 8.61]
Total (95% CI)	692	702		100.00	1.95 [1.29, 2.96]

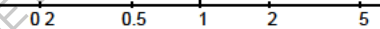
Total events: 62 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 1.62, df = 4 (P = 0.80), I² = 0%
Test for overall effect: Z = 3.15 (P = 0.002)



Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses - secondary endpoint
Outcome: 12 Patients with TEAE's occurring in =>5% of patients - 8 weeks - with 12 weeks of Study 99815 - 20mg arm only

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	13/126	7/128		21.96	1.89 [0.78, 4.57]
SCT-MD-06	10/145	8/142		21.23	1.22 [0.50, 3.01]
SCT-MD-07	13/158	6/157		19.40	2.15 [0.84, 5.52]
SCT-MD-31	15/127	7/136		23.06	2.29 [0.97, 5.44]
Study 99815 (20mg)	13/133	4/139		14.35	3.40 [1.14, 10.15]
Total (95% CI)	689	702		100.00	2.01 [1.33, 3.04]

Total events: 64 (Escitalopram), 32 (Placebo)
Test for heterogeneity: Chi² = 2.18, df = 4 (P = 0.70), I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)



ATTACHMENT 10

GAD AND CO-MORBIDITIES

CLINICAL EVIDENCE

1. Prevalence

The prevalence of co-morbidities has been discussed extensively in Attachment 2 (see Table 5 Attachment 2). A summary is presented in Table 1, with the prevalence based on DSM-IV criteria highlighted as it is the focus of our submission.

Table 1: Summary of prevalence of GAD and it's co-morbidities

Range for:	Any Co-morbidity		Major Depression		Agoraphobia		Alcoholism		SAD	
	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
DSM III-R	>60-66.3%	90.4%	27.7-38.6	62.4%	26.7%	25.7%	11.2-25%	37.6%	23.2%	34.4%
DSM IV	66.3-93.1%	88.3-90.4%	4.2-70.6%	60.9-88%	26.7%	20.7-25.7%	11.1-25%	37.6%		34%

Attachment 2 goes into greater detail regarding the epidemiology of co-morbidities and GAD. This Attachment aims to present clinical trial evidence regarding escitalopram in treating people with GAD and depression (being the largest co-morbidity).

As mentioned in Attachment 2, many of the symptoms of GAD overlap with those of depression and other anxiety disorders.[1] Major depression frequently co-exists with GAD, presenting clinicians with the diagnostic challenge of distinguishing social withdrawal due to depression from fearful social avoidance. A New Zealand study found that of those followed from 1972 till 2005, where patients with GAD had comorbid depression, 42% of these patients had GAD first.[2] They conclude that this comorbidity seemed to be associated with substantial health burden, as indicated by recurrent course, mental health service use and suicide attempt.

2. Impact on Impairment

Studies have shown that the status of GAD as an independent disorder is at least as strongly supported as it is for MDE.[3] It used to be thought that GAD, in the absence

of other disorders, was associated with a low level of disability.[4] However, the chronic nature of GAD means that the condition imposes a substantial individual burden. This may manifest in the quality and level of functioning in social and occupational interactions, resulting in significant though indirect costs to society. This burden is most notable in terms of substantial impairments resulting in days where a sufferer is restricted from or unable to carry out daily activities, causing a reduction in the patient's quality of life and well-being.[5]

A similar conclusion was arrived at in the analysis of the Australian NSMHWH. [6] In functional terms, persons with pure GAD had been unable to engage in their usual activities on an average of 6 days in the previous month, and their disability score on the SF-12 mental health scale fell more than one standard below the population average. **The authors conclude that the Australian data support that GAD, as a single disorder is significantly disabling.** Consequently, the data supported that patients with GAD have a use of health services.

3. Effects of Treatment with co-morbidities

Recent epidemiological data suggests that the impact of comorbidity in clinical outcomes is no greater in GAD than in other anxiety disorders.[7] Moreover, comorbidities such as major depression do not appear to change the course of GAD.[7] There are also data supporting the notion that psychotherapy may have an additional impact in the comorbid conditions associated to GAD.[8]

The National Comorbidity Survey (NCS) found that GAD preceded comorbities by the following proportion for each disorder[9 10] (approximate %; adapted) [10]:

Drug disorder	70%
Alcohol disorder	35%
Social Phobia	18%
Simple Phobia	10%
Agoraphobia	35%
Panic Disorder	18%

Dysthymia	35%
Major Depression	50%

4. Assessment of GAD with depression: Treatment with Escitalopram

As depression is the major co-morbidity found with GAD this section focuses on presenting evidence regarding such patients. The search terms for the literature review are presented in Appendix 1 (Table 7 and Table 8). The abstracts of the search results are presented in Appendix 2.

The ECNP consensus meeting in March 2000 confirms that where the aim of studies is to establish the efficacy of a medicine in GAD any co-morbidity, especially major depression the commonest comorbidity should be excluded.[11] Therefore no RCTs with GAD and depression as a comorbidity were identified. The two searches identified 21 separate articles, (1 duplicate was excluded). Reasons for exclusions were:

- Not a trial;
- Did not included comorbid population with GAD and MDD (if MDD was an exclusion criterion then the trial was not included), and
- Not an appropriate comparator.

The reasons for exclusion are presented below:

	Article Identified in Search	Reason for in clusion or exclusion
1	Chessick, C.A., MH; Thase, ME; Batista Miralha da Cunha, ABC; Kapczinski, FFK; de Lima, MSML; dos Santos Souza, JJSS Azapirones for generalized anxiety disorder. Cochrane Database of Systematic Reviews. , 2007. 3.	Not relevant outcomes
2	Christmas, D.C., I; Eljamel, MS; Fineberg, N; MacVicar, R; Matthews, K; Ruck, C; Stark, C. *Neurosurgery for obsessive-*	Protocol

	compulsive disorder, other anxiety disorders and depressive disorders. Cochrane Database of Systematic Reviews, 2007. **3**.	
3	Davidson JR et al. *Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder.* The Journal of Clinical Psychiatry, 1999. **60**(8): p. 528-35.	Not relevant patient population
4	Davidson, J.R.T., et al. *Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study.* Depression and Anxiety, 2004. **19**(4): p. 234-240.	Not relevant patient population
5	Haskins JT, A.L., Pallay A, Rudolph R. *Double-blind, placebo-controlled study of once daily venlafaxine XR in outpatients with generalized anxiety disorder CONFERENCE ABSTRACT*. in *11th European College of Neuropsychopharmacology Congress*. 1998. Paris, France.	Not relevant patient population
6	Haskins JT. Rudolph R. Aguiar L. Entsuah R. Double-blind, placebo-/comparator-controlled study of once daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD) in 11th European College of Neuropsychopharmacology Congress. 1998. Paris, France.	Not relevant patient population
7	Hunot, V.C., R; Teixeira, V; Silva de Lima, M. *Psychological therapies for generalised anxiety disorder.* Cochrane Database of Systematic Reviews. , 2007. **3**.	Not relevant patient population
8	Ipser JC, e.a., Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews., 2007. 3.	Not relevant patient population
9	Ipser, J.S., et al. *Newer anticonvulsants in the treatment of anxiety disorders.* Cochrane Database of Systematic Reviews., 2007. **3**.	Protocol
10	Kapczinski, F.L., MS. Souza, JS; Cunha, A; Schmitt, R, *Antidepressants for generalized anxiety disorder.* Cochrane Database of Systematic Reviews., 2007(3).	Not relevant patient population
11	Kimura M, T.A., Robinson RG. *Treatment of poststroke generalized anxiety disorder comorbid with poststroke depression:*	Not relevant patient population

	merged analysis of nortriptyline trials. The American journal of geriatric psychiatry 2003 May-Jun. **11**(3): p. 320-7.	
12	Kroenke, K., et al. *Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder.* Journal of Clinical Psychiatry, 2006. **67**(1): p. 72-80.	Not an appropriate comparator
13	Mayo-Wilson, E.M. P, *Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults.* Cochrane Database of Systematic Reviews., 2007. **3**.	Protocol
14	Miyasaka, L.A., AN. Soares, BGO, *Valerian for anxiety disorders.* Cochrane Database of Systematic Reviews, 2007. **3**.	Not relevant patient population
15	Miyasaka, L.A., AN. Soares, BGO, *Passiflora for anxiety disorder.* Cochrane Database of Systematic Reviews., 2007. **3**	Protocol
16	Mohamed, S., et al. *Escitalopram for comorbid depression and anxiety in elderly patients: A 12-week, open-label, flexible-dose, pilot trial.* American Journal Geriatric Pharmacotherapy, 2006. **4**(3): p. 201-209	Included
17	Rosenthal M. *Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control.* The Journal of Clinical Psychiatry, 2003. **64**(10): p. 1245-9.	Not an appropriate comparator
18	Silverstone PH. Salinas E. *Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder.* The Journal of Clinical Psychiatry, 2001. **62**(7): p. 523-9.	Not an appropriate comparator
19	Sramek JJ, T.M., Suri A, Hornig-Rohan M. Amsterdam JD, Stahl SM, Weisler RH, Cutler NR, *Efficacy of buspirone in generalized anxiety disorder with coexisting mild depressive symptoms.* The Journal of clinical psychiatry, 1996. **57**(7): p. 287-91.	Not an appropriate comparator
20	Stein, D.J. et al., *Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram.* Journal of Clinical Psychiatry, 2006. **67**(11): p. 1741-1746.	Not an trial
21	Stein, D.J. H.F. Andersen, and W.K.	Not relevant patient

Goodman, *Escitalopram for the treatment of GAD: Efficacy across different subgroups and outcomes.* Annals of Clinical Psychiatry, 2005. **17**(2): p. 71-75. population

Further hand searching identified the following trial:

1. Olie JP, Tonnoir B, Menard F, Galinowski A. A prospective study of escitalopram in the treatment of major depressive episodes in the presence or absence of anxiety. *Depression and Anxiety* 2007;24(5):318-324.

The trials included in this analysis are shown in Table 2:

Table 2: Clinical Trial: Anxiety with comorbid depression

	Study Characteristics	Patient Characteristics	Outcomes Measured	Aims of Study
Olie JP et al 2007[12]	Multicentre, open label, non-randomised, prospective, naturalistic setting 12 weeks	Age: 18-82 yrs Females: 64% Dose: 10-20mg MDD: DSM-IV-TR N=790 HAM-A≥20	Primary: MADRS Secondary HAM-A CGI-I CGI-S AEs	1. To assess any association between changes in the scores of depression rating scales over the study period and the scores of anxiety rating scales at baseline. 2. To evaluate the safety and tolerability of Escitalopram in this patient population. 3. To assess correlations between physician and patient measures of efficacy.
Mohamed S. et al, 2006[13]	Open label, flexible dose, pilot, Psychiatric Service, Veterans Affairs Medical Centre 12 weeks	Age: $\bar{x}$=73yrs Females: 30% Dose: 10-20mg MDD: DSM-IV-TR N=20 HAM-A≥18 MADRS≥22	Primary: MADRS HAM-A Secondary Medical Outcomes SF-36 AEs	To see if escitalopram helps treat elderly patients with comorbidity of major depression and GAD.

Details and outcomes of the trial are presented respectively in Table 3 and Table 5:

Table 3 Details of Trials

	% Co-morbidities	Population with Anxiety

Olie JP et al (2007)[12]	SAD: 11% GAD: 27% Panic disorder: 10% OCD: 6% Agoraphobia: 4% PTSD: 3%	No anxiety:390/790 1 anxiety:349/790 ≥2 anxieties: 129 Incomplete information: 4/790
Mohamed S. et al, 2006[13]	GAD: 100% Major Depression: 100%	100%

Table 4 Outcomes from Olie et al [12]

	Baseline	12 weeks
MADRS	31.5(5.8)	12.4
HAMA	25.6(7.8)	10.8
Responders ≥50% reduction MADRS %		72% (CI:68.8-75.2)%
Remitters MADRS ≤12		57.8% (CI:54.3-61.4%)
Responders ≥50% reduction HAM-A %		69%
Remitters HAMA<7		38.1% (CI:34.7-41.6%)

Table 5 Change in patients with or without anxiety Olie et al [12]

	MADRS	HAMA
Change in patients with no anxiety	20.5	13.8
Change in patients with ≥1 anxiety	18.3[i]	15.5[ii]
All patients	21.1	14.8

i: p<.0024 (LOCF) for patients with and without anxiety
ii: p<.0078 (LOCF) for patients with and without anxiety

Table 6 Outcomes from Mohamed et al[13]

MADRS	29.8(5.2)	14.6(7.9)	P<0.001	2.93
HAMA	23.8(5.6)	13.5(8.7)	P<0.001	1.83
Responders ≥50% reduction HAM-A %		65%		
Responders ≥50% reduction MADRS %		55%		

Conclusions:[12 13]

a) The use of anxiolytics had no impact on the outcome

b) Of the 61% of patients experiencing a co-morbidity, results showed that anxiety symptoms as measured with the HAM-A, improved in parallel to the improvement in depressive symptoms, with escitalopram treatment.

c) Patients with at least one anxiety disorder had a greater improvement in HAM-A scores than those without comorbid anxiety, but there was no statistically significant difference in the improvement in HAM-A scores as a function of baseline severity of depression, indicating that comorbid depression did not affect response to treatment of anxiety.

d) The remission rate for anxiety symptoms (38.1%) is very close to the 36% reported in a randomized, double-blind clinical trial of escitalopram in patients with pure GAD.[14] Patients with a comorbid anxiety disorder responded well to treatment, particularly those with GAD, SAD, or obsessive–compulsive disorder.

e) In a small study in elderly patients with comorbid GAD and MDD Escitalopram was associated with significant improvements in symptoms of anxiety and depression.

5. Summary

Epidemiologic studies have demonstrated the negative implications of comorbidity for course of illness.[15 16] Studies have found that the best predictors in cases of GAD and panic were severity and duration of symptoms, as well as comorbid depression. [15] The HARP study similarly found that the likelihood of remission of GAD and any other comorbid condition after 1 year was half the annual rate for GAD alone.[17] In a recent prospective study with nortriptyline or interpersonal psychotherapy, it was shown that while both treatments were effective, patients with comorbid GAD had a longer time to recovery.[18]

Evidence presented in this Attachment, regarding the impact of treatment in co-morbidities, is sparse and certainly does not meet Level 1 evidence. When pharmacotherapy is considered, upon examination of the two trials utilising escitalopram, it would seem that patients with at least one anxiety disorder and comorbid depression has a greater improvement in HAM-A scores than those without

comorbid anxiety. This would seem to indicated that at worst comorbid patients would respond similarly to those with pure depression and at best would show an improved outcome, when measured in terms of HAM-A. Response to both depression and anxiety has been shown in younger and elderly cohorts.

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Appendix 1: Search Strategy

An Embase and Medline search was conducted and the results are presented below:

The databases searched were Medline, Embase and all Evidence Based Medicine Databases. Table 7 presents the Embase and Medline search (highlighted in yellow) and Table 8 the EBM Databases search.:

Table 7 Embase and Medline Search 3 October

No.	Query	Results	Date
#1	**'major depression'**/exp/mj AND [english]/lim AND [humans]/lim	4,057	03 Oct 2007
#2	**'social anxiety disorder'**/exp/mj AND [english]/lim AND [humans]/lim	1,184	03 Oct 2007
#3	**'social phobia'**/exp AND [english]/lim AND [humans]/lim	2,575	03 Oct 2007
#4	**'sad'** AND [english]/lim AND [humans]/lim	2,388	03 Oct 2007
#5	**'escitalopram'**/exp OR **'lexapro'**/exp AND [english]/lim AND [humans]/lim	1,127	03 Oct 2007
#6	**'liebowitz social anxiety scale'** OR **'lsas'** AND [english]/lim AND [humans]/lim	132	03 Oct 2007
#7	**#2** OR **#3** OR **#4**	4,844	03 Oct 2007
#8	**#1** AND **#5** AND **#7**	12	03 Oct 2007
#9	**#6** AND **#8**	1	03 Oct 2007
#10	**'depression'**/exp AND [english]/lim AND [humans]/lim	132,009	03 Oct 2007
#11	**#5** AND **#6** AND **#7** AND **#10**	1	03 Oct 2007
#12	**#5** AND **#7** AND **#10**	60	03 Oct 2007
#13	**#5** AND **#7** AND **#10** AND ([article]/lim OR [conference paper]/lim OR [review]/lim) AND [english]/lim	48	03 Oct 2007
#14	**'generalised anxiety disorder'**/exp/mj OR **'gad'**/exp/mj AND [english]/lim AND [humans]/lim	1,026	03 Oct 2007
#15	**'hamilton anxiety scale'**/exp OR **'hamd'** OR **'ham-d'** AND [english]/lim AND [humans]/lim	1,522	03 Oct 2007
#16	**'hamilton anxiety scale'**/exp/mj AND [english]/lim AND [humans]/lim	0	03 Oct 2007
#17	**'ham-a'** AND [english]/lim AND [humans]/lim	320	03 Oct 2007
#18	**'ham-a'** AND [english]/lim AND [humans]/lim	320	03 Oct 2007
#19	(**'`hama`'**) AND [english]/lim AND [humans]/lim	1,541	03 Oct 2007
#20	**'hamilton anxiety scale'**/exp/mj AND [english]/lim AND [humans]/lim AND [english]/lim AND [humans]/lim	0	03 Oct 2007
#21	**#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20**	3,197	03 Oct 2007
#22	**'generalised anxiety disorder'**/exp/mj	456	03 Oct 2007
#23	**'gad'**/exp/mj AND [english]/lim AND [humans]/lim	627	03 Oct 2007
#24	**#14** OR **#22** OR **#23**	1,083	03 Oct 2007
#25	**#5** AND **#10** AND **#21** AND **#24**	4	03 Oct 2007

Table 8 EBM Databases Search 13 October

	Database: All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, and CCTR	Result
	Search Strategy:	
1	1 genral$ anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	0
2	2 gad.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (=	249
3	3 general$ anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	476
4	4 depression.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	19584
5	5 2 or 3	555
6	6 4 and 5	138
7	7 hamilton anxiety scale.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	211
8	8 ham-a.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	792
9	9 7 or 8	957
10	10 6 and 9	44
11	11 escitalopram.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	121
12	12 lexapro.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	1
13	13 11 or 12	121
14	14 10 and 13	2
15	15 from 14 keep 1-2	2
16	16 comorb$.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	2589
17	17 10 and 16	18
18	18 from 17 keep 1-18	18

Appendix : Abstracts of Searches

Chessick, C. A., MH; Thase, ME; Batista Miralha da Cunha, ABC; Kapczinski, FFK; de Lima, MSML; dos Santos Souza, JJSS (2007). "Azapirones for generalized anxiety disorder." Cochrane Database of Systematic Reviews. **3**.

Background

Azapirones are a group of drugs that work at the 5-HT1A receptor and are used to treat patients suffering from generalized anxiety disorder (GAD). However, several studies have shown conflicting results. Whether azapirones are useful as first line treatment in general anxiety disorders still needs to be answered.

Objectives

To assess the efficacy and the acceptability of azapirones for the treatment of GAD.

Search strategy

Initiallyt the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched, incorporating results of group searches of MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), CINAHL (1982 to June 2005), PsycLIT (1974 to June 2005), PSYNDEX (1977 to June 2005), and LILACS (1982 to June 2005). Subsequently the revised Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References) were searched on 21-10-2005. Reference lists of relevant papers and major text books of anxiety disorder were examined. Authors, other experts in the field and pharmaceutical companies were contacted for knowledge of suitable trials, published or unpublished. Specialist journals concerning azapirones were handsearched.

Selection criteria

Randomized controlled trials of azapirones, including buspirone versus placebo and/or other medication and/or psychological treatment, were included. Participants were males and females of all ages with a diagnosis of generalized anxiety disorder.

Data collection and analysis

Data were extracted from the original reports independently by CC, MA and MT. The main outcomes studied were related to the objectives stated above. Data were analysed for generalized anxiety disorder versus placebo, versus other medication and versus psychological treatment separately. Data were analysed using Review Manager Version 4.2.7.

Main results

Thirty six trials were included in the review, reporting on 5908 participants randomly allocated to azapirones and/or placebo, benzodiazepines, antidepressants, psychotherapy or kava kava. Azapirones, including buspirone, were superior to placebo in treating GAD. The calculated number needed to treat for azapirones using the Clinical Global Impression scale was 4.4 (95% confidence interval (CI) 2.16 to 15.4). Azapirones may be less effective than benzodiazepines and we were unable to conclude if azapirones were superior to antidepressants, kava kava or psychotherapy. Azapirones appeared to be well tolerated. Fewer participants stopped taking benzodiazepines compared to azapirones. The length of studies ranged from four to nine weeks, with one study lasting 14 weeks.

Authors' conclusions

Azapirones appeared to be useful in the treatment of GAD, particularly for those participants who had not been on a benzodiazepine. Azapirones may not be superior to benzodiazepines and do not appear as acceptable as benzodiazepines. Side effects appeared mild and non serious in the azapirone treated group. Longer term studies are needed to show that azapirones are effective in treating GAD, which is a chronic long-term illness.

Christmas, D. C., I; Eljamel, MS; Fineberg, N; MacVicar, R; Matthews, K; Ruck, C; Stark, C (2007). "Neurosurgery for obsessive-compulsive disorder, other anxiety disorders and depressive disorders." Cochrane Database of Systematic Reviews **3**.

his is the protocol for a review and there is no abstract. The objectives are as follows:

(1) Primary objectives:

1.1 To determine the efficacy and adverse outcomes of neurosurgical interventions for:

(a) Obsessive-compulsive disorder (OCD)

(b) Major Depressive Disorder

(c) Other Anxiety disorders (Generalised Anxiety Disorder, Panic Disorder and/ or Agoraphobia, Social Phobia/ Social Anxiety Disorder)

Each condition will be considered separately. Treatment comparisons will consist of each neurosurgical intervention versus control. The control group is expected to be either waiting list or treatment as usual for ablative neurosurgery, and 'no stimulation' for VNS and DBS.

(2) Secondary objectives:

2.1 To establish the relative efficacy of different neurosurgical procedures, attempting to compare directly where possible. Comparisons will not be performed if the data are not sufficient to permit this.

2.2 To determine whether different neurosurgical procedures confer differential risks of side effects and adverse outcomes.

Davidson JR et al (1999). "Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder." The Journal of Clinical Psychiatry **60**(8): 528-35.

BACKGROUND: The objective of this randomized, double-blind study was to compare the efficacy and safety of venlafaxine extended release (XR) and buspirone in outpatients with generalized anxiety disorder (GAD) but without concomitant major depressive disorder. METHOD: Male and female outpatients at least 18 years old who met the DSM-IV criteria for GAD and had scores of 18 or higher on the Hamilton Rating Scale for Anxiety (HAM-A) were randomly assigned to treatment with either venlafaxine XR (75 or 150 mg/day), buspirone (30 mg/day in 3 divided doses), or placebo for 8 weeks. The primary efficacy variables were changes in anxiety as determined by final on-therapy HAM-A total and psychic anxiety scores and Clinical Global Impressions scale (CGI) scores. Other key efficacy variables were HAM-A anxious mood and tension scores and the anxiety subscale scores of the patient-rated Hospital Anxiety and Depression scale (HAD). RESULTS: The efficacy analysis included 365 patients and the safety analysis, 405. At week 8, adjusted mean HAM-A psychic anxiety, anxious mood, and tension scores were significantly lower for venlafaxine XR-treated patients than for placebo-treated patients. On the HAD anxiety subscale, venlafaxine XR, 75 or 150 mg/day, was significantly more efficacious than placebo at all time points except weeks 1 (both dosages) and 2 (150-mg/day dosage only) and significantly more efficacious than buspirone at all time points except week 1. On the CGI-Improvement scale, scores for venlafaxine XR (both dosages) and buspirone were numerically superior to those for placebo at all time points, and statistical significance was observed at weeks 3, 4, 6, and 8 for venlafaxine XR and at weeks 6 and 8 for buspirone. The adverse events were not essentially different between treatment groups. CONCLUSION: Venlafaxine XR is an effective, safe, and well-tolerated once-daily anxiolytic agent in patients with GAD without comorbid major depressive disorder. This agent was significantly superior to buspirone on the HAD anxiety subscale. Buspirone demonstrated statistical significance versus placebo on a measure of anxiolytic response.

Davidson, J. R. T., A. Bose, et al. (2004). "Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study." Depression and Anxiety **19**(4): 234-240.

Escitalopram has been shown in clinical trials to improve anxiety symptoms associated with depression, panic disorder, and social anxiety disorder. This study was designed to evaluate the efficacy and

tolerability of escitalopram in the treatment of generalized anxiety disorder (GAD). Outpatients (18 years or older) who met DSM-IV criteria for GAD, with baseline Hamilton Rating Scale for Anxiety (HAMA) scores (greater-than or equal to)18, were randomly assigned to double blind treatment with escitalopram (10 mg/day for the first 4 weeks and then flexibly dosed from 10-20 mg/day) or placebo for 8 weeks, following a 1-week, single-blind, placebo lead-in period. The primary efficacy variable was the mean change from baseline in total HAMA score at Week 8. The escitalopram group (N = 158) showed a statistically significant, and clinically relevant, greater improvement at endpoint compared with placebo (N = 157) in all prospectively defined efficacy parameters. Significant improvement in HAMA total score and HAMA psychic anxiety subscale score for the escitalopram-treated group vs. the placebo-treated group was observed beginning at Week 1 and at each study visit thereafter. Mean changes from baseline to Week 8 on the HAMA total score using a last-observation-carried-forward (LOCF) approach were -11.3 for escitalopram and -7.4 for placebo (P < .001). Response rates at Week 8 were 68% for escitalopram and 41% for placebo (P < .01) for completers, and 58% for escitalopram and 38% for placebo LOCF values (P < 01). Treatment with escitalopram was well tolerated, with low rates of reported adverse events and an incidence of discontinuation due to adverse events not statistically different from placebo (8.9% vs. 5.1%; P = .27). Escitalopram 10-20 mg/day is effective, safe, and well tolerated in the treatment of patients with GAD. (copyright) 2004 Wiley-Liss, Inc.

Haskins JT, A. L., Pallay A, Rudolph R (1998). Double-blind, placebo-controlled study of once daily venlafaxine XR in outpatients with generalized anxiety disorder CONFERENCE ABSTRACT. 11th European College of Neuropsychopharmacology Congress., Paris, France.

This randomized, double-blind, placebo-controlled, 8-week study compared the safety and anxiolytic efficacy of once daily venlafaxine XR (V-XR) 75 mg, 150 mg, or 225 mg with placebo (Pbo) in outpatients with Generalized Anxiety Disorder (GAD). V-XR is a new formulation of the serotonin norepinephrine reuptake inhibitor antidepressant, venlafaxine (Effexor(r)). Design: Patients (n = 377) who met DSM-IV criteria for GAD, but not Major Depressive Disorder (MDD), and who did not improve significantly during a 4 to 10 day prestudy washout period could be enrolled into the study. Patients who had a current, or within 6 months of study day 1, diagnosis of MDD (using structured interview as a guide to complete diagnostic criteria), had a Raskin Depression Scale (RDS) score greater than the Covi Anxiety Scale (CAS) score, had a total RDS score greater than 9 or who had any single RDS item score greater than 3 were excluded from the study. Patients began treatment with Pbo or V- XR 75 mg/day. At week 2, the V-XR middle-dose and high-dose groups were increased to 150 mg/day; at week 3 the V-XR high-dose group was increased to 225 mg/day. Improvement was evaluated at 1, 2, 3, 4, 6, and 8 weeks using the HAM-A total score, the HAM-A psychic anxiety factor, the Clinical

Global Impressions (CGI) scale, the anxiety subscale of the Hospital Anxiety and Depression Scale (HAD), the HAM-A somatic anxiety factor, the CAS, and the anxious mood and tension items of the HAM-A. Final on-therapy was the primary time point. Efficacy parameters were compared using analysis of covariance for an intent-to-treat population (n = 349), and the last observation was carried forward for patients who discontinued prematurely. Safety: Discontinuations for adverse events occurred in 7 (7%), 14 (15%), 18 (20%), and 17 (19%) of the Pbo and V-XR 75 mg, 150 mg and 225 mg groups, respectively. The most common treatment-emergent adverse events reported in the V-XR groups were asthenia, dizziness, headache, insomnia, nausea, nervousness, and somnolence. Efficacy Results - At week 8 the following changes from baseline were observed on the HAM-A total score (significant differences from placebo indicated by *): Pbo ?9.5, V-XR 75 mg ?11.1, 150 mg ?11.7 and 225 mg ?12.1*. The corresponding changes on the HAM-A psychic anxiety factor score were Pbo ?5.6, V-XR 75 mg ?6.7, 150 mg ?7.1* and 225 mg ?7.3*. Effects were also observed on both CGI Severity (Pbo ?1.3, V-XR 75 mg ?1.6, 150 mg ?1.6, and 225 mg ?1.7*) and CGI Improvement (Pbo 2.6, V-XR 75 mg 2.3, 150 mg 2.3, and 225 mg 2.2*). Additional significant improvements were noted on the HAD (Pbo ?4.2, V-XR 75 mg ?5.8*, 150 mg ?6.0*, and 225 mg ?6.5*), the CAS (Pbo ?3.0, V-XR 75 mg ?3.5, 150 mg ?3.7 and 225 mg ?3.8*), and the anxious mood (Pbo ?1.2, V-XR 75 mg ?1.3, 150 mg ?1.4, and 225 mg ?1.6*) and tension (Pbo ?1.1, V-XR 75 mg ?1.3, 150 mg ?1.4*, and 225 mg ?1.5*) items of the HAM-A. Conclusion - This study is the first demonstration of the effectiveness of a psychotropic agent in treating outpatients meeting DSM-IV criteria for GAD who do not have comorbid major depressive disorder or other significant psychiatric illnesses. Significantly, these data suggest that V-XR is an effective, safe, once-daily agent for the treatment of GAD which may provide an important alternative to currently available anxiolytics. Abstract: P.3.010

Haskins JT. Rudolph R. Aguiar L. Entsuah R (1998). Double-blind, placebo-/comparator-controlled study of once daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD) 11th European College of Neuropsychopharmacology Congress., Paris, France.

This randomized, double-blind, placebo- and comparator-controlled, 8-week study compared the safety and anxiolytic efficacy of once daily V-XR 75 mg or 150 mg with placebo (Pbo) and Bsp 10 mg t.i.d. in outpatients with GAD. V-XR is a new formulation of the serotonin norepinephrine reuptake inhibitor antidepressant, venlafaxine (Effexor(r)). Design: Patients (n = 405) who met DSM-IV criteria for GAD, but not for Major Depressive Disorder (MDD), and who did not improve during a 7 +/- 3-day pre-study single-blind placebo lead-in period could be enrolled into the study. Patients who had a current, or within 6 months of study day 1, diagnosis of MDD (using structured interview as a guide to complete diagnostic criteria), had a Raskin Depression Scale (RDS) score greater than the Covi Anxiety Scale (CAS) score, had a total RDS score greater than 9 or who had any

single RDS item score greater than 3 were excluded from the study. Patients began treatment with V-XR 75 mg/day, Bsp 5 mg t.i.d., or Pbo. At day 8, one V-XR group increased to 150 mg/day. By day 8, the Bsp group had titrated to 10 mg t.i.d. Improvement was evaluated at 1, 2, 3, 4, 6, and 8 weeks using the HAM-A total score, the HAM-A psychic anxiety factor, the Clinical Global Impressions (CGI) scale, the anxiety subscale of the Hospital Anxiety and Depression Scale (HAD), the HAM-A somatic anxiety factor, the Covi Anxiety Scale, and the anxious mood and tension items of the HAM-A. Efficacy parameters were compared using analysis of covariance for an intent-to-treat population (n = 369), and the last observation was carried forward for patients who discontinued prematurely. Results - At week 8 the following changes from baseline were observed on the HAM-A total score (significant differences from placebo indicated by *): Pbo ? 8.0, V-XR 75 mg ? 10.6, 150 mg ? 9.8 and Bsp ? 9.5. The corresponding changes on the HAM-A psychic anxiety factor score were Pbo ? 4.3, V-XR 75 mg ? 6.2*, 150 mg ? 5.8* and Bsp ? 5.2. Effects were also observed on both CGI Severity (Pbo ? 0.9, V-XR 75 mg ? 1.4*, 150 mg ? 1.2, and Bsp ? 1.1) and CGI Improvement (Pbo 2.7, V-XR 75 mg 2.2, 150 mg 2.4, and Bsp 2.5). Additional significant improvements were noted on the HAD (Pbo ? 2.9, V-XR 75 mg ? 4.6, 150 mg ? 4.3, and Bsp ? 3.0), and the anxious mood (Pbo ? 0.8, V-XR 75 mg ? 1.2, 150 mg ? 1.2, and Bsp ? 1.0) and tension (Pbo ? 0.8, V-XR 75 mg ? 1.3, 150 mg ? 1.1, and Bsp ? 1.0) items of the HAM-A. Safety: The safety profile was consistent with that of Effexor(r) and V-XR use in depressed patients. Conclusion - This study showed that venlafaxine XR (75 or 150 mg/day) is an efficacious treatment for outpatients with GAD who do not have comorbid MDD, and suggested V-XR also has significant advantages vs Bsp. Abstract: P.3.045

Hunot, V. C., R; Teixeira, V; Silva de Lima, M (2007.). "Psychological therapies for generalised anxiety disorder." Cochrane Database of Systematic Reviews. **3**.

Background

Generalised anxiety disorder (GAD) is a highly prevalent condition, characterised by excessive worry or anxiety about everyday events and problems. The effectiveness and comparative effectiveness of psychological therapies as a group has not yet been evaluated in the treatment of GAD.

Objectives

To examine the efficacy and acceptability of psychological therapies, categorised as cognitive behavioural therapy (CBT), psychodynamic therapy and supportive therapy, compared with treatment as usual/waiting list (TAU/WL) and compared with one another, for patients with GAD.

Search strategy

We searched the Cochrane Depression, Anxiety & Neurosis Group (CCDAN) Controlled Trials Register and conducted supplementary searches of MEDLINE, PsycInfo, EMBASE, LILACS and in February 2006. We searched reference lists of retrieved articles, and contacted trial authors and experts in the field for information on ongoing/completed trials.

Selection criteria

Randomised and quasi-randomised controlled trials conducted in non-inpatient settings, involving adults aged 18-75 years with a primary diagnosis of GAD, assigned to a psychological therapy condition compared with TAU/WL or another psychological therapy.

Data collection and analysis

Data on patients, interventions and outcomes were extracted by two review authors independently, and the methodological quality of each study was assessed. The primary outcome was anxiety reduction, based on a dichotomous measure of clinical response, using relative risk (RR), and on a continuous measure of symptom reduction, using the standardised mean difference (SMD), with 95% confidence intervals.

Main results

Twenty five studies (1305 participants) were included in the review, of which 22 studies (1060 participants) contributed data to meta-analyses. Based on thirteen studies, psychological therapies, all using a CBT approach, were more effective than TAU/WL in achieving clinical response at post-treatment (RR 0.64, 95%CI 0.55 to 0.74), and also in reducing anxiety, worry and depression symptoms. No studies conducted longer-term assessments of CBT against TAU/WL. Six studies compared CBT against supportive therapy (non-directive therapy and attention-placebo conditions). No significant difference in clinical response was indicated between CBT and supportive therapy at post-treatment (RR 0.86, 95%CI 0.70 to 1.06), however, significant heterogeneity was indicated, which was partly explained by the number of therapy sessions.

Authors' conclusions

Psychological therapy based on CBT principles is effective in reducing anxiety symptoms for short-term treatment of GAD. The body of evidence comparing CBT with other psychological therapies is small and heterogeneous, which precludes drawing conclusions about which psychological therapy is more effective. Further studies examining non-CBT models are required to inform health care policy on the most appropriate forms of psychological therapy in treating GAD.

Ipser JC, e. a. (2007). "Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders." Cochrane Database of Systematic Reviews. **3**.

Background

A large proportion of patients with anxiety disorders fail to respond to first-line medication interventions, despite evidence of the effectiveness of these agents.

Objectives

To assess the effects of medication versus placebo augmentation in the treatment of patients with anxiety disorders who have failed to respond adequately to first-line drug therapies.

Search strategy

The Cochrane Depression, Anxiety & Neurosis Group (CCDAN) specialised registers (CCDANCTR-Studies and CCDANCTR-References) were searched on 3/8/2005, MEDLINE (January 1966 to July 2005) and PsycINFO (1966 to 2005, Part A). Unpublished trials were identified through the Controlled Trials database and the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972 to 2005). Additional studies in any language were sought in reference lists of retrieved articles.

Selection criteria

All randomised controlled trials (RCTs) of the medication augmentation of pharmacotherapy for treatment resistant anxiety disorders.

Data collection and analysis

Two raters independently assessed RCTs for inclusion in the review, collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by class of augmentation agent and anxiety disorder. Overall effect estimates were calculated using a random-effects model, heterogeneity was assessed and subgroup/sensitivity analyses were undertaken.

Main results

Twenty eight short-term (average of seven weeks) randomised controlled trials (740 participants) were included in the review, 20 of which investigated augmentation of medication for treatment-resistant obsessive compulsive disorder (OCD). Summary statistics for responder status from nine trials demonstrate overall superiority of a variety of medication agents to placebo (relative risk of non-response (RR) 3.16, 95% CI 1.08 to 9.23). Similarly, symptom severity was significantly reduced in the medication groups, relative to placebo

(number of trials (N) = 14, standardised mean difference (SMD) -0.87, 95% CI -1.37 to -0.36). There is no evidence of a difference between medication and placebo in total dropout rate, or in the number of dropouts due to adverse events.

Authors' conclusions

Medication augmentation can be an effective and well-tolerated short-term treatment strategy for non-responders to first-line pharmacotherapy of anxiety disorders. However, any conclusions must be tentative in view of methodological and clinical heterogeneity, and the fact that much of the relevant database is based on antipsychotic augmentation trials in OCD patients resistant to serotonin reuptake inhibitors (SRIs). Additional data are needed to address several areas, including the efficacy of augmentation over the longer-term, and the value of medication augmentation in comparison to other strategies (eg switching medication, adding psychotherapy).

Ipser, J. S., DJ (2007). "Newer anticonvulsants in the treatment of anxiety disorders." Cochrane Database of Systematic Reviews. **3**.

This is the protocol for a review and there is no abstract. The objectives are as follows:

1) To use evidence from RCTs in providing an estimate of the overall effects of the newer anticonvulsants in improving treatment response and reducing symptom severity in the treatment of anxiety disorders.

2) To determine whether particular anticonvulsants are more effective and tolerable than others in the treatment of anxiety disorders.

3) To determine whether the particular anxiety disorder treated predicts the effectiveness of anticonvulsants in terms of efficacy and tolerability.

4) To identify which factors (clinical, methodological) predict response to pharmacotherapy.

Kapczinski, F. L., MS; Souza, JS; Cunha, A; Schmitt, R (2007). "Antidepressants for generalized anxiety disorder." Cochrane Database of Systematic Reviews.(3).

Background

Pharmacological treatments have been successfully used to treat Generalized Anxiety Disorder (GAD). Benzodiazepine and non benzodiazepine anxiolytics used to be the mainstay for the pharmacological treatment of GAD. However, data emerging over the last two decades have shown that antidepressants may be as effective as anxiolytics in this condition. The use of antidepressants may also be beneficial, because GAD often coexists with major depressive disorder (62% comorbidity) and dysthymia (37%).

Objectives

To assess the efficacy and acceptability of antidepressants for treating generalized anxiety disorder.

Search strategy

Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register - CCDANCTR (up to May 2002), Anxiety Neurosis (up to May 2002) and Cochrane Controlled Trials Register (CENTRAL/CCTR) (up to May 2002), MEDLINE (1966 to May 2002), LILACS (1982 to May 2002); reference searching; personal communication; conference abstracts and book chapters on the treatment of generalized anxiety disorder.

Selection criteria

Randomized controlled trials were included. Non randomized studies and those that included patients with both GAD and another Axis I co-morbidity were excluded.

Data collection and analysis

The data from studies were extracted independently by two reviewers. Relative risks, weighted mean difference and number needed to treat were estimated. People who died or dropped out were regarded as having had no improvement.

Main results

Antidepressants (imipramine, venlafaxine and paroxetine) were found to be superior to placebo in treating GAD. The calculated NNT for antidepressants in GAD is 5.15. Dropout rates did not differ between antidepressants. Only one study presented data on imipramine and trazodone. Imipramine was chosen as the reference drug and, therefore, data on trazodone could not be included in the meta analysis. Only one study was conducted among children and adolescents (Rynn 2000). This showed very promising results of sertraline in children and adolescents with GAD, which warrants replication in larger samples.

Authors' conclusions

The available evidence suggests that antidepressants are superior to placebo in treating GAD. There is evidence from one trial suggesting that paroxetine and imipramine have a similar efficacy and tolerability. There is also evidence from placebo-controlled trials suggesting that these drugs are well tolerated by GAD patients. Further trials of antidepressants for GAD will help to demonstrate which antidepressants should be used for which patients.

Kimura M, T. A., Robinson RG (2003 May-Jun). "Treatment of poststroke generalized anxiety disorder comorbid with poststroke depression: merged analysis of nortriptyline trials." The American journal of geriatric psychiatry **11**(3): 320-7.

OBJECTIVE: The existence of anxiety disorders plays an important role in the prognosis and associated impairment among patients with poststroke depression. The authors examined the efficacy of nortriptyline treatment for patients with comorbid generalized anxiety disorder (GAD) and depression after stroke. METHODS: Data from three studies were merged to provide 27 patients with comorbid GAD and depression, who participated in double-blind treatment studies comparing nortriptyline (N=13) and placebo (N=14). Severity of anxiety was measured with the Hamilton Rating Scale for Anxiety (Ham-A), and severity of depression was measured with the Hamilton Rating Scale for Depression (Ham-D). Activities of daily living were assessed by use of the Johns Hopkins Functioning Inventory (JHFI). RESULTS: There were no significant differences between the nortriptyline and placebo groups in demographic characteristics, stroke type, and neurological findings. Patients receiving nortriptyline treatment showed significantly greater improvement on the Ham-A, Ham-D, and JHFI than patients receiving placebo. The anxiety symptoms showed earlier improvement than depressive symptoms in patients treated with nortriptyline. CONCLUSIONS: These findings suggest that poststroke GAD comorbid with poststroke depression may be effectively treated with nortriptyline, and data indicate the need for a trial specifically designed to examine treatment of anxiety disorder.

Kroenke, K., N. Messina Iii, et al. (2006). "Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder." Journal of Clinical Psychiatry **67**(1): 72-80.

Objective: This pilot study explored the efficacy and tolerability of extended-release venlafaxine (venlafaxine ER) in anxious and/or depressed patients with multisomatoform disorder (MSD). Method: This 12-week, multicenter, randomized, double-blind study evaluated adult primary care outpatients with MSD and comorbid major depressive disorder, generalized anxiety disorder, or social anxiety disorder (DSM-IV criteria). The intent-to-treat population included 112 patients (venlafaxine ER, N = 55; placebo, N = 57). The primary efficacy variable was the change in the 15-item Patient Health Questionnaire (PHQ-15) somatic symptom severity score. Secondary outcomes included the Hamilton Rating Scale for Depression (HAM-D-17) and for Anxiety (HAM-A), Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, McGi1l Quality of Life Questionnaire Physical Symptoms Scale (MQOL-PS), and Medical Outcomes Study Short-Form 36-Item questionnaire (MOS SF-36). Data were collected from April 2003 to December 2003. Results: The decline by week 12 in PHQ-15 scores was significant ($p < .0001$) in both groups; however, the difference between the venlafaxine ER and placebo groups (-8.3 vs. -6.6, respectively) was not ($p = .097$). Improvement was greater with venlafaxine ER than placebo on the PHQ-15 pain subscale ($p = .03$), SF-36 bodily pain scale (26.1 vs. 14.5, $p = .03$), MQOL-PS (-11.7 vs. -6.0, $p = .02$), HAM-A psychic anxiety subscale ($p = .02$), SF-36 mental component summary ($p = .03$), time to response (54 vs. 71 days, $p = .01$), and CGI-I scale ($p = .009$).

Venlafaxine ER was generally well tolerated. Conclusion: These results suggest that venlafaxine ER may be effective in relieving some types of somatic physical symptoms, particularly pain, in patients with depression and/or anxiety disorders.

Mayo-Wilson, E. M., P (2007). "Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults." Cochrane Database of Systematic Reviews. **3**.

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review will examine the efficacy and effectiveness of media-delivered CBT and BT for anxiety disorders alone and in conjunction with other therapies in non-psychotic adults.

Miyasaka, L. A., AN; Soares, BGO (2007). " Passiflora for anxiety disorder." Cochrane Database of Systematic Reviews. **3**.

Background

Anxiety is a very common mental health problem in the general population and in the primary care setting. Herbal medicines are popularly used worldwide and could be an option for treating anxiety if shown to be effective and safe. Passiflora (passionflower extract) is one of these compounds.

Objectives

To investigate the effectiveness and safety of passiflora for treating any anxiety disorder.

Search strategy

The following sources were used: electronic databases: Cochrane Collaboration Depression, Anxiety and Neurosis Cochrane Controlled Trials Register (CCDANCTR-Studies), Medline and Lilacs; Cross-checking references; contact with authors of included studies and manufacturers of passiflora.

Selection criteria

Relevant randomised and quasi-randomised controlled trials of passiflora using any dose, regime, or method of administration for people with any primary diagnosis of general anxiety disorder, anxiety neurosis, chronic anxiety status or any other mental health disorder in which anxiety is a core symptom (panic disorder, obsessive compulsive disorder, social phobia, agoraphobia, other types of phobia, postraumatic stress disorder). Effectiveness was measured using clinical outcome measures such as Hamilton Anxiety Scale (HAM-A) and other scales for anxiety symptoms.

Data collection and analysis

Two reviewers independently selected the trials found through the search strategy, extracted data, performed the trial quality analyses and entered data. Where any disagreements occured, the third reviewer was consulted. Methodological quality of the trials included in this review was assessed using the criteria described in the Cochrane Handbook. For dichotomous outcomes, relative risk with 95% confidence intervals (CI) were calculated, and for continuous outcomes, weighted mean difference with 95%CI was used.

Main results

Two studies, with a total of 198 participants, were eligible for inclusion in this review. Based on one study, a lack of difference in the efficacy of benzodiazepines and passiflora was indicated. Dropout rates were similar between the two interventions. Although the findings from one study suggested an improvement in job performance in favour of passiflora (post-hoc outcome) and one study showed a lower rate of drowsiness as a side effect with passiflora as compared with mexazolam, neither of these findings reached statistical significance.

Authors' conclusions

RCTs examining the effectiveness of passiflora for anxiety are too few in number to permit any conclusions to be drawn. RCTs with larger samples that compare the effectiveness of passiflora with placebo and other types of medication, including antidepressants, are needed.

Miyasaka, L. A., AN; Soares, BGO (2007). "Valerian for anxiety disorders." Cochrane Database of Systematic Reviews **3**.

nxiety disorders are very common mental health problems in the general population and in primary care settings. Herbal medicines are popular and used worldwide and mght be considered as a treatment option for anxiety if shown to be effective and safe.

Objectives

To investigate the effectiveness and safety of valerian for treating anxiety disorders.

Search strategy

Electronic searches: The Cochrane Collaboration Depression, Anxiety and Neurosis Cochrane Controlled Trials Register (CCDANCTR-Studies and CCDANCTR-References) searched on 04/08/2006, MEDLINE, Lilacs. References of all identified studies were inspected for additional studies. First authors of each included study, manufacturers of valerian products, and experts in the field were contacted for information regarding unpublished trials.

Selection criteria

Randomised controlled trials (RCTs) and quasi-randomised trials of valerian extract of any dose, regime, or method of administration, for people with any primary diagnosis of general anxiety disorder, anxiety neurosis, chronic anxiety status, or any other disorder in which anxiety is the primary symptom (panic disorder, obsessive compulsive disorder, social phobia, agoraphobia, other types of phobia, postraumatic stress disorder). Effectiveness was measured using clinical outcome measures and other scales for anxiety symptoms.

Data collection and analysis

Two review authors independently applied inclusion criteria, extracted and entered data, and performed the trial quality assessments. Where disagreements occured, the third review author was consulted. Methodological quality of included trials was assessed using Cochrane Handbook criteria. For dichotomous outcomes, relative risk (RR) was calculated, and for continuous outcomes, the weighted mean difference (WMD) was calculated, with their respective 95% confidence intervals.

Main results

One RCT involving 36 patients wih generalised anxiety disorder was eligible for inclusion. This was a 4 week pilot study of valerian, diazepam and placebo. There were no significant differences between the valerian and placebo groups in HAM-A total scores, or in somatic and psychic factor scores. Similarly, there were no significant differences in HAM-A scores between the valerian and diazepam groups, although based on STAI-Trait scores, significantly greater symptom improvement was indicated in the diazepam group. There were no significant differences between the three groups in the number of patients reporting side effects or in dropout rates.

Authors' conclusions

Since only one small study is currently available, there is insufficient evidence to draw any conclusions about the efficacy or safety of valerian compared with placebo or diazepam for anxiety disorders. RCTs involving larger samples and comparing valerian with placebo or other interventions used to treat of anxiety disorders, such as antidepressants, are needed.

Mohamed, S., K. Osatuke, et al. (2006). "Escitalopram for comorbid depression and anxiety in elderly patients: A 12-week, open-label, flexible-dose, pilot trial." American Journal Geriatric Pharmacotherapy **4**(3): 201-209.

Background: Comorbid depression and anxiety may result in greater symptom severity and poorer treatment response than either condition alone. Selective serotonin reuptake inhibitors have been found to be effective in treating both depression and anxiety; however, pharmacodynamic and pharmacokinetic changes associated with aging warrant special attention in medication trials in older patients. Objective: The objective of this study was to assess the efficacy and tolerability of short-term (12-week) administration of escitalopram oxalate 10 to 20 mg/d for moderate to marked comorbid depression

and anxiety in elderly patients. Methods: This open-label, flexible-dose (10-20 mg/d), pilot trial was conducted at the Psychiatry Service, Veterans Affairs Medical Center, Cincinnati, Ohio. Outpatients aged (greater-than or equal to)65 years were included if they met the criteria for comorbid major depressive disorder (MDD) and generalized anxiety disorder (GAD), as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, for (greater-than or equal to)4 weeks and had a baseline Montgomery-sberg Depression Rating Scale (MADRS) score of >22 and a Hamilton Rating Scale for Anxiety (HAM-A) score of (greater-than or equal to)18. All patients received escitalopram 10 to 20 mg/d. The primary efficacy variables were the mean changes from baseline in total MADRS and HAM-A scores at 12 weeks (last observation carried forward). The secondary efficacy end point was the change from baseline in Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) 8 subscale scores. Adverse events were assessed at each visit (treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12) with the use of open-ended questioning. Results: Twenty patients were enrolled (mean [SD] age, 73.0 [4.8] years; 6 [30%] women; race: 17 [85%] white, 2 [10%] black, and 1 [5%] "other"). Seventeen (85%) of 20 patients completed the study; 3 (15%) withdrew: 1 (5%) due to lack of efficacy and 2 (10%) due to adverse events (dizziness and somnolence [1 (5%) patient each]). Statistically significant improvements from baseline to end point were found with escitalopram treatment (MADRS: t19 = 7.38, P < 0.001, effect size = 2.93; HAM-A: t19 = 4.19, P < 0.001, effect size = 1.83). Significant changes from baseline in scores on 4 (Social Functioning, Role Functioning-Emotional, Mental Health, and Energy/Fatigue) of the 8 subscales of the SF-36 were als of ound (all, P < 0.01). Conclusion: In this small study in elderly patients with comorbid MDD and GAD, treatment with escitalopram 10 to 20 mg/d for 12 weeks was associated with significant improvements in symptoms of depression and anxiety. (copyright) 2006 Excerpta Medica, Inc.

Olie, J. P., B. Tonnoir, et al. (2007). "A prospective study of escitalopram in the treatment of major depressive episodes in the presence or absence of anxiety." Depression and Anxiety **24**(5): 318-324.

This open, multicenter, prospective study in France assessed the efficacy and tolerability of escitalopram inpatients with depression, with or without comorbid anxiety. Escitalopram was administered over a 12-week treatment period to 790 depressed patients, including 482 patients with at least one concomitant anxiety disorder. The study was completed by 649 patients. At baseline, the mean Montgomery-Asberg Depression Rating Scale (MADRS) total score was 31.5 and decreased to 12.4 at end point (last observation carried forward [LOCF]). The MADRS score decreased by 20.5 points in patients with no anxiety disorder and by 18.3 points in patients with at least one concomitant anxiety disorder. The mean Hamilton Anxiety Rating Scale (HAM-A) total score at baseline was 25.6, which decreased to 10.8 at end point (LOCF). The HAM-A score decreased by 13.8 points in patients with no anxiety disorder and by 15.5 points in patients with at least one anxiety

disorder. Adverse events were reported by 246 patients (31%). The most frequent adverse events were nausea in 65 patients (8%) and headache in 38 patients (5%); 61 patients (8%) discontinued treatment due to adverse events. Escitalopram was well tolerated and efficacious in reducing symptoms of depression in patients with or without comorbid anxiety over a 12-week treatment period. (copyright) 2006 Wiley-Liss, Inc.

Rosenthal M (2003). "Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control." The Journal of Clinical Psychiatry **64**(10): 1245-9.

BACKGROUND: Gamma-aminobutyric acid (GABA) plays a central role in the pathophysiology of anxiety. Tiagabine, a selective GABA reuptake inhibitor, enhances normal GABA tone. This 10-week, randomized, open-label trial evaluated tiagabine in patients with generalized anxiety disorder (GAD), with paroxetine serving as a positive control. METHOD: Adult patients with DSM-IV GAD were randomly assigned to receive either tiagabine or paroxetine. Tiagabine was initiated at 4 mg/day (2 mg morning and evening) during week 1. Between weeks 2 and 6, the dose was individually titrated in 2-mg increments (maximum increase of 4 mg/week) for optimal response to a maximum dose of 16 mg/day (8 mg morning and evening). During weeks 7 through 10, patients received the dosage determined during the titration period. Paroxetine was initiated at 20 mg nightly for the first week and similarly titrated in 10-mg increments to a maximum dose of 60 mg/day. Assessments included the Hamilton Rating Scale for Anxiety (HAM-A), Hospital Anxiety and Depression Scale (HADS), Hamilton Rating Scale for Depression (HAM-D), Pittsburgh Sleep Quality Index (PSQI), and Sheehan Disability Scale (SDS). RESULTS: Forty patients were enrolled (tiagabine, N = 20; paroxetine, N = 20). Mean final doses were tiagabine 10 mg/day (range, 4-16 mg/day) or paroxetine 27 mg/day (range, 20-40 mg/day). Tiagabine and paroxetine significantly reduced anxiety (HAM-A and HADS total and anxiety subscales). Although patients were not diagnosed with a mood disorder, both tiagabine and paroxetine reduced comorbid depressive symptoms (HAM-D total and HADS total and depressive subscale). Tiagabine and paroxetine significantly improved sleep quality (PSQI) and functioning (SDS). Both tiagabine and paroxetine were well tolerated. CONCLUSION: The selective GABA reuptake inhibitor tiagabine and the positive control paroxetine significantly reduced anxiety and comorbid depressive symptoms, improved sleep quality and functioning, and were well tolerated in patients with GAD. Tiagabine may be a therapeutic option for the treatment of anxiety disorders.

Silverstone PH. Salinas E (2001). "Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder." The Journal of Clinical Psychiatry **62**(7): 523-9.

BACKGROUND: A subset of patients with comorbid major depressive disorder and generalized anxiety disorder (GAD) was examined from a

double-blind. placebo-controlled study comparing the efficacy and safety of venlafaxine extended release (XR) and fluoxetine. METHOD: From a total of 368 patients, 92 patients meeting DSM-IV criteria for major depressive disorder who also had comorbid GAD were identified. The comparison group comprised 276 evaluable noncomorbid patients. Patients received venlafaxine XR (75-225 mg/day), fluoxetine (20-60 mg/day), or placebo for 12 weeks. Efficacy evaluations included Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions (CGI) scale. RESULTS: By the final assessment at week 12, comorbid patients in the venlafaxine XR group, but not in the fluoxetine group, showed a significantly greater decrease than those in the placebo group in the primary efficacy variables of mean HAM-D and HAM-A total scores ($p < .05$, pairwise comparison). In comorbid patients, significant pairwise differences were noted between venlafaxine XR and placebo at week 12 for the secondary variables of HAM-D anxiety-somatization and retardation factors, HAM-D depressed mood item. HAM-A psychic anxiety factor, the Hospital Anxiety and Depression scale (HAD) anxiety subscale score, and the Covi Anxiety Scale score. Fluoxetine was significantly different from placebo only on the HAD depression subscale score. Response, defined as > or = 50% decrease in symptoms score, was achieved in 66% and 59% of the comorbid patients for HAM-D and HAM-A, respectively, in the venlafaxine XR group at week 12. This response was higher than that seen with fluoxetine (52% and 45%) or placebo (36% and 24%). Onset of efficacy appeared to be slower in comorbid than in noncomorbid patients. CONCLUSION: This is the first evidence from a controlled study of the effectiveness of pharmacotherapy in patients with comorbid major depressive disorder and GAD. The delayed improvement in comorbid patients compared with noncomorbid patients suggests that a longer treatment period may be necessary in comorbid patients.

Sramek JJ, T. M., Suri A, Hornig-Rohan M, Amsterdam JD, Stahl SM, Weisler RH, Cutler NR (1996). "Efficacy of buspirone in generalized anxiety disorder with coexisting mild depressive symptoms." The Journal of clinical psychiatry **57**(7): 287-91.

ACKGROUND: This study was designed to evaluate the anxiolytic efficacy of buspirone in patients with a diagnosis of generalized anxiety disorder (GAD) with coexisting mild depressive symptoms. METHOD: Patients who participated in this multicenter study scored >/= 18 on the Hamilton Rating Scale for Anxiety (HAM-A) and between 12 and 17 on the Hamilton Rating Scale for Depression (HAM-D). Following a 7- to 10-day placebo lead-in phase, patients who continued to qualify were randomly assigned to receive either buspirone titrated from 15 to 45 mg/day (N = 80) or placebo (N = 82) for the next 6 weeks. 121 patients completed 6 weeks of treatment. The primary efficacy measure was the HAM-A, taken weekly during the study. RESULTS: Buspirone-treated patients averaged a 12.4-point reduction from their baseline total HAM-A score of 24.9, while their counterparts on placebo averaged a 9.5-point reduction from their mean baseline total HAM-A score of 25.6.

This 2.9-point difference in HAM-A reductions between treatment groups was significantly different ($p < .03$). Buspirone patients decreased their HAM-D scores by an average 5.7 points from their mean baseline total HAM-D score of 15.8, while placebo patients decreased their HAM-D scores by an average 3.5 points from their mean baseline score of 16.3 ($p < .05$). Overall, the incidence of adverse events was similar for both treatment groups, but buspirone-treated patients reported significantly more nausea, dizziness, somnolence, and sweating than placebo patients. CONCLUSION: Buspirone is superior to placebo in improving anxiety and depressive symptoms in GAD patients who have coexisting depressive symptoms.

Stein D. (2001). "Comorbidity in Generalized Anxiety Disorder: Impact and Implications." J. Clin. Psychiatry **62**(Suppl 1): 29-34.

Stein, D. J., H. F. Andersen, et al. (2005). "Escitalopram for the treatment of GAD: Efficacy across different subgroups and outcomes." Annals of Clinical Psychiatry **17**(2): 71-75.

Background. Generalized anxiety disorder (GAD) is characterized by anxiety, and also frequently associated with depressive symptoms. Benzodiazepines have commonly been used in the treatment of GAD, but are not effective antidepressant agents. In this study, we determined whether the selective serotonin reuptake inhibitor escitalopram, was effective across different subgroups and outcomes (anxious symptoms, depressive symptoms, and quality of life). Methods. Three randomized, placebo controlled studies of escitalopram in GAD have employed a similar design, allowing for pooling of the data. The primary efficacy measure was the Hamilton Anxiety Scale (HAMA). General linear models were used to determine the efficacy of escitalopram across different subgroups and outcomes. Results. Escitalopram was efficacious for GAD on a range of measures of both anxiety and depression, and improved the associated impairment in quality of life. There was no significant interaction of effects on the HAMA with demographic or clinical variables. Furthermore, escitalopram was efficacious on both primary and secondary scales in the subgroup of subjects with above-median severity of depressive symptoms at baseline (HAMD-17>12). Conclusions. Escitalopram reduces anxiety and depressive symptoms in GAD, and improves quality of life. It is equally effective in GAD patients, with an above-median level of depressive symptoms. Further research is needed to determine whether these results can be extrapolated to GAD patients with comorbid major depression. Copyright (copyright) Taylor & Francis Inc.

ATTACHMENT 2

EPIDEMIOLOGY OF SOCIAL ANXIETY DISORDER (SAD) OR SOCIAL PHOBIA

Table of Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	
ECA	Epidemiology Catchment Area
EDSP	Early Developmental Stages of Psychopathology
ESEMed	European Study of the Epidemiology of Mental Disorders
GHS	German Health Interview and Examination Survey
HARP	The Harvard/Brown Anxiety Research Program
ICPE	International Consortium in Psychiatric Epidemiology
MDD	Major Depressive Disorder
NCS	National Comorbidity Study
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NSMHW	National Survey of mental Health and Well-being
US	United States

Social Phobia Overview

Social phobia or social anxiety disorder (SAD) is an illness that effects peoples' quality of life.[1] Social phobia may cause children to drop out of school early and to become lonely and isolated. Social phobia makes it difficult or impossible for adolescents to go out with the opposite sex or to continue with further education.[2] It causes patients to turn down job promotions or to stay in dead-end, unrewarding positions because they fear having to interview for a new job. To cope, some turn to alcohol, which can help relieve social anxiety in the short term but long-term leads to alcoholism and its complications. When a patient has comorbid depression it also increases the chance of suicide.

Critics have questioned whether social phobia is a new disorder.[1] Social phobia has existed for centuries, but physicians have tended to ignore it; in part because good treatments have not been available, and in part because patients were unaware that physicians recognised their condition as a treatable disorder, and so they did not seek help. In 1980 the publication of DSM-III (Diagnostic and Statistical Manual of Mental Disorders) first attributed to social phobia a psychiatric taxonomy; phobic neurosis were subdivided into agoraphobia, social phobia, and simple phobia.[3] The subsequent revisions in DSM-III-R and DSM-IV deleted restrictive hierarchical rules, social phobia could be diagnosed in the presence of comorbid disorders.

There are two subtypes of SAD.[4] ***Non-generalized SAD*** is the less severe (but nonetheless disabling) subtype and includes those individuals who experience anxiety in only one or two types of social situations (primarily public speaking and/or performance anxiety experienced by entertainers). Individuals with non-generalized SAD usually have adequate social skills to function normally outside of these specific performance situations.

There is also ***generalised SAD*** (DSM-IV) in which individuals experience a broader array of fears that include both performance and interactional fears[5 6]. This is a more severe type of anxiety disorder. The majority (about 75%) of those who suffer from the

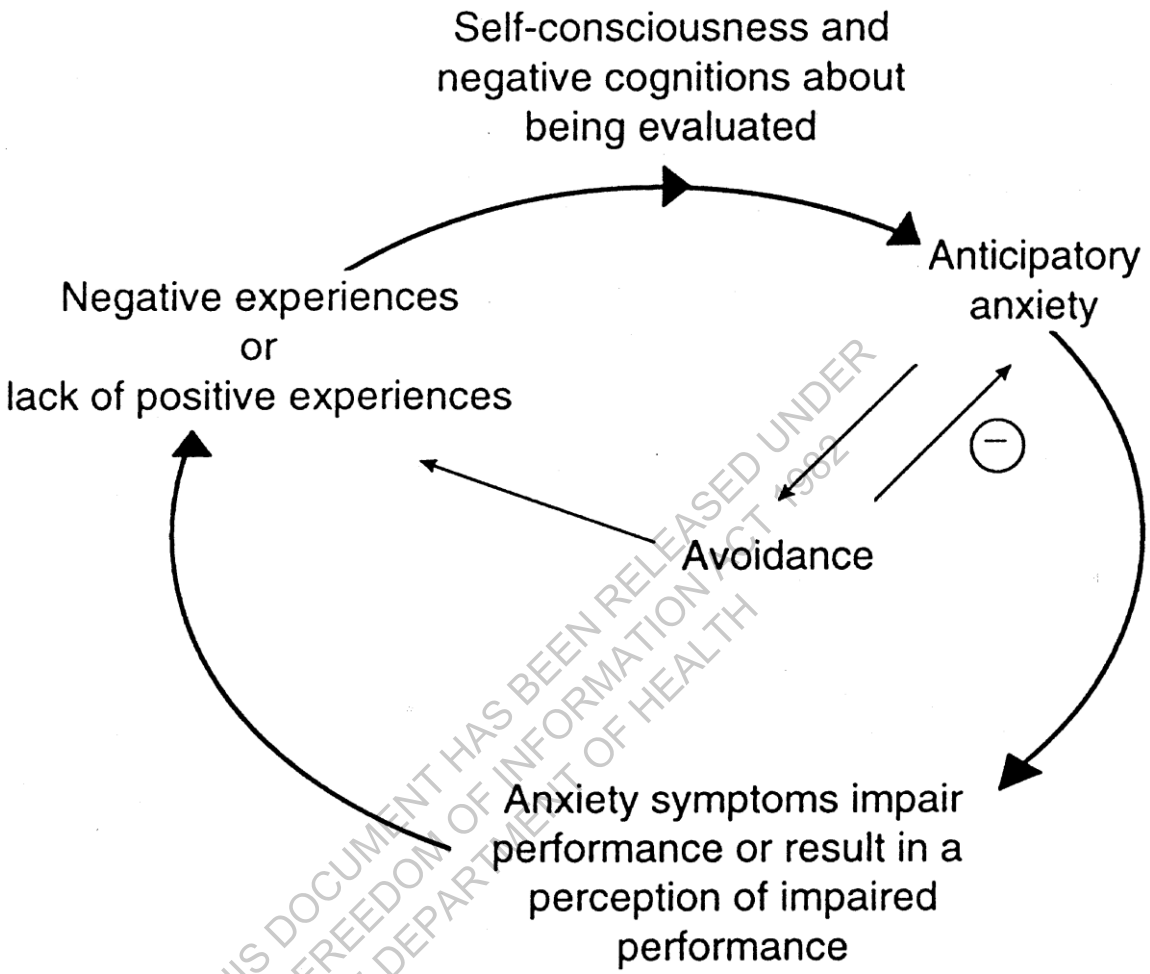
generalized subtype of SAD experience distress in nearly all interpersonal situations[4]. Typically it appears in the mid-teens, and rarely occurs after age 25.[7] When fears interfere with social, occupational, or family life, the affected individual is not suffering from normal shyness, but rather a treatable anxiety disorder. Social phobia is more prevalent among women, the female to male ratio ranging from 2:1 to 3:2.[8 9]

Generalized SAD confers functional impairment to roughly the same degree as major depression.[10]

'People with generalised social phobia are bothered by many or most social situations, especially those involving social interaction. In conversation with others, these people fear being embarrassed by what they say or not knowing what to say. In some their anxiety leads to panic attacks. Often it interferes with or even disrupts their behaviour. In feared situations patients, often find that their concentration is impaired and that they are unable to think. Their movements may become awkward or jerky, or they may temporarily find themselves frozen or unable to move. Typical somatic symptoms include palpitations, swearing, trembling and blushing…Commonly one or more of these symptoms become the focus of fearful preoccupation. For many social phobics, they are the dreaded outward signs of anxiety (e.g. blushing) that others might see. Consequently in phobic situations, the patient's attention becomes narrowly focused upon physiological activation; symptoms then become warning signals of impending danger, thus generating more anxiety. Patients describe a vicious cycle in which perceived threat leads to anxiety, and anxiety increases the perception of threat.……These patients, once treated, interact normally in the absence of interfering anxiety.' [11]

This is cycle is depicted in Figure 1.[12] Once social phobia has developed, it is maintained by a vicious circle of anxiety and perceived negative experiences. Anticipatory anxiety either impairs the sufferer's performance in the social situation or leads to a perception of impaired performance. The resulting negative experience fuels further anticipatory anxiety when faced with future social situations. The anxiety is relieved by avoidance of the feared situation, thereby reinforcing further avoidance behavior.[13]

Figure 1: The vicious circle of social phobia[12]



Recovery from generalised SAD without treatment is rare.[11] Generalised SAD, which often appears early in pre-pubertal children, can effectively cause a developmental psychosocial arrest by preventing normal peer interactions, assertiveness and optimal school performance due to extreme fear of negativity from peers or authority figures. It should be kept in mind that months, or even years, may be needed for the individual to achieve social competence even after treatment attenuates pathological social fear and avoidance to a manageable level. It is now widely observed that the onset of SAD occurs typically during adolescence.[14] SAD rarely develops after the age of 25 years.[5 7 15 16]

Long term studies of social phobia reveal it as being chronic in nature. During an 8 year study of 163 patients with social phobia[17], only 38 percent of women and 32 percent of men experienced full remission of the disorder. These findings highlight the chronicity of the disorder and indicate a similar course for men and women.

How does a person with social phobia feel?

Most people feel nervous in social situations, like having a job interview, going or giving a speech.[18] Most worry about what they're going to say, do or even wear during these events. These events often become easier with some experience. However, in people with social phobia , these events and other social situations can be frightening and disabling[19]. Social phobia is an anxiety disorder with varying degrees of severity. This condition is characterised by clinically significant anxiety reactions and extreme discomfort occurring in anticipation of or upon exposure to social settings, including performance and test situations. Social phobia can interfere with one's social or career development leaving the patient socially isolated and, in some cases, unable pursue intimate relationships and career fulfilment. Social phobics are more likely to be unemployed and dependant on the state for financial support than the general population.[7]

Social phobics have a strong fear of being humiliated or embarrassed in front of other people.[18] They feel as though everyone is watching them, until they blush, sweat or otherwise show their fear. They often believe that showing anxiety is a sign of weakness or inferiority. They also believe other people are more confident and competent than themselves. People with social phobia usually know their fears are not completely rational, but they still find themselves dreading social situations. They may go out of their way to avoid going to some events. If they do go to them, they usually feel very nervous before and very uncomfortable during the event. Afterward, the unpleasant feelings may linger as they worry about what other people thought of them.

Consequently, social phobics worry about symptoms that will draw attention or focus to them, such as blushing, heart racing, sweating and trembling when having panic attacks.[20] Below is an example from an individual with the diagnosis:

> *"Went to Centrelink, I usually avoid using the fax machine because of its proximity in relation to people waiting to be seen, I decided to use it for the first time. There were three people there and they were looking at the fax machine. I tried to operate it but I found it extremely hard to focus on the task at hand. I started to get nervous because I felt that they were watching me and starting to wonder why I couldn't use it. I became extremely anxious and started to blush and sweat…I began to have a panic attack."*[20]

Clinical Features

The Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)[21], describes social phobia as an intense, irrational and persistent fear of being scrutinized or negatively evaluated by others (Table 1).[22] Patients with this disorder fear social or performance situations and they typically provoke an immediate anxious reaction ranging from diffuse apprehension to situational panic. Social phobia is characterized by a persistent fear of negative evaluation or scrutiny by others in social situations, resulting in excessive fear of humiliation or embarrassment, decrease in adaptive functioning, and clinical distress. [21]

The types of fears and avoidance commonly associated with social phobia (Table 2) are, to some degree, experienced by most people. However, to meet the diagnostic criteria for this disorder, the symptoms must be severe enough to cause significant distress or disability.

Table 1: Diagnostic Criteria for Socia Anxiety Disorder or Social Phobia[21]

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.

B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.

C. The person recognizes that the fear is excessive or unreasonable. NOTE: In children, this feature may be absent.

D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under 18 years of age, the duration is at least six months.

G. The fear or avoidance is not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder or schizoid personality disorder).

H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it; (e.g., the fear is not of stuttering, trembling in Parkinson's disease or exhibiting abnormal eating behaviour in anorexia nervosa or bulimia nervosa.)

Specify if:

Generalized: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder).

Table 2: Common Fears in Social Phobia[14 21]

Public speaking or performing	Being watched doing something (e.g., eating, writing)
Making "small talk"	Attending social gatherings
Small group discussion	Using the telephone
Asking questions in groups	Using public restrooms
Being introduced	Interacting with "important" people
Meeting or talking with strangers	Indirect evaluation (e.g., test taking)
Being assertive	Writing while watched by others
Initiating social conversations	Entering crowded rooms

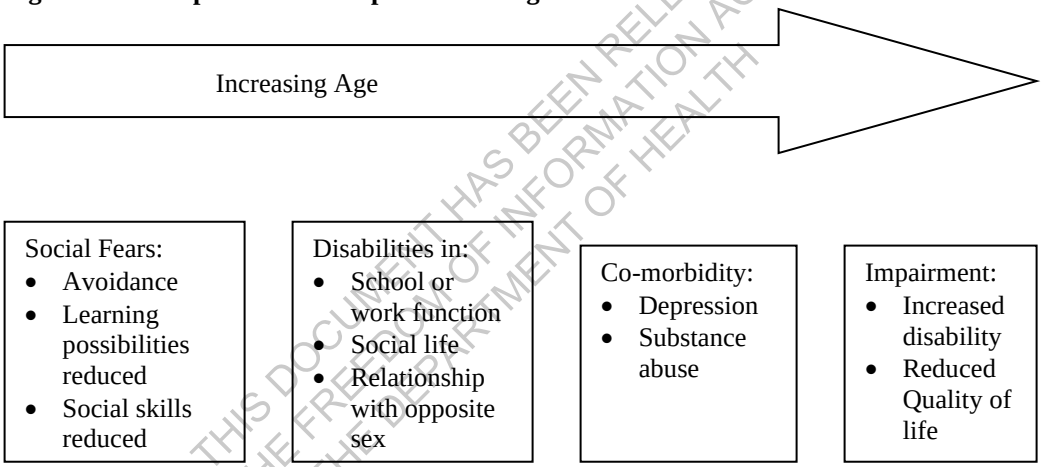
Social phobia is a valid clinical entity that differs from agoraphobia.[11] Although with both of these disorders are characterised by multiple phobia and, in many cases, panic attacks, there are differences, the most important being the social phobic's fear of embarrassment or humiliation. Agoraphobics, by contrast, fear an inability to get to safety in case of incapacitation.

In social phobia, fear and avoidance typically develop into a vicious cycle that can become severely distressing, debilitating and demoralizing over time. As discussed earlier although patients are usually aware that their fears are unreasonable, they still find themselves experiencing significant dread before facing a feared social encounter. The encounters themselves often evoke physical sensations of anxiety (e.g., blushing, sweating) and a preoccupation with possible embarrassment or humiliation. Encounters may be endured with distress or, more typically, avoided--either subtly (e.g., by modifying one's interactions within encounters) or overtly (e.g., by non-attendance). These various forms of avoidance preclude any change in the patient's core pathologic social fears and cause significant distress or functional impairment.

It should be noted that not everyone who suffers from social phobia appears shy, withdrawn or overtly nervous.[20] Presentation of symptoms varies widely. In some situations, the patient may not appear anxious, thus obscuring the underlying fear, avoidance, distress and disability. The clinical features may only be eliminated after a sensitive and detailed clinical examination.

In most cases the patient suffers not from shyness but rather from a more severe case of fear if embarrassment or humiliation that leads to disability and often, as will be seen below, to comorbid depression and/or alcohol abuse and dependence as it progresses, as shown in Figure 2 below:[20]

Figure 2: Development of social phobia with age[20]



As mentioned earlier, In later years impairment incurred by social phobia also extends to employment and economic status.[23] Social phobics are more often absent from work, had more often been terminated and are less often employed.[11] They are also more often financially dependent; in America 22% receiving welfare assistance or disability compensation.[24]

Further evidence for generalized social anxiety disorder is presented in a Managed Care study.[25] This study found that suffering from generalized SAD was associated with substantially decreased hourly wages and higher health service utilization. We computed the impact of generalized social anxiety disorder on educational and occupational attainment, controlling for age and gender (Figure 2). The average subject with pure generalized social anxiety disorder has a probability of graduating from college that is 10 percentage points lower and earns wages that are 10% lower than persons without generalized social anxiety disorder. In addition, the probability that a person with average-severity generalized social anxiety disorder holds a technical, professional, or managerial job is 14 percentage points lower than that of an otherwise healthy individual. Combined with our observation that generalized social anxiety disorder can begin in preadolescence, these findings underscore the profound effect on lifetime achievement.

Also social phobics have more chronic medication problems, more sick days, more medical and mental health visits and greater use of psychotropic drugs.[25] Comorbid disorders contribute to this morbidity, but the impairment seen in sub-threshold cases is comparable to that for social phobics meeting DSM-IV criteria.[11]

Some data regarding the impact social phobia has on lifetime comorbidity is shown in Table 3.[6] Table 3 highlights social phobias substantial impact on a patient's quality of life and ability to function without impairment. The more severe the condition (more fears the patient has) the more likely it is that they have an impairment. It also shows that the rate at which these patients sought help from a doctor or other health care professional is very low (10.7 - 23.1%) indicating a lack of diagnosis/treatment of this disease.[6] This data is supported by other studies which show that the majority of social phobics who obtain treatment have been ill more than 10 years, however most never seek treatment.[26] [27] In one epidemiological study, 19.6% sought treatment for emotional problems but only 5.4% consulted a mental health professional for social phobia.[28] This low rate may reflect fear[29] of treatment that involves social interaction.[11] This is also why Cognitive Behavioural Therapy and medication are often initiated simultaneously.

Table 3: Impairments Due to Lifetime Social Phobia Among Respondents in the National Comorbidity Survey (N=8,098) [6]

	Respondents With Social Phobia													
	Pure Speaking Fears[a]						Other Social Fears							
	Public Speaking Only		Others		Total		One Fear		Two Fears		Three or More Fears		Total	
Impairment Indicator	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Phobia ever interfered a lot with life or activities	11.5	3.0	17.5	3.5	13.8[b]	2.5	22.3[c]	5.4	20.7[c]	2.9	41.6[c]	3.3	33.9[b]	2.7
Ever sought treatment from a medical doctor	10.7	2.4	15.6	4.3	12.7[b]	2.4	18.1	5.5	27.2	4.3	22.6	2.6	23.1[b]	2.2
Ever sought treatment from any other professional	2.6	1.4	7.5	3.9	4.5[b]	2.2	14.3	4.5	16.5	3.1	15.6	2.4	15.7[b]	2.0
Ever took medication more than once	0.3	0.3	1.5	1.0	0.8[b]	0.5	5.4	2.8	6.3	2.4	11.6	1.7	9.5[b]	1.3
Any impairment	21.2	3.4	27.9	4.7	23.8[b]	2.7	34.2[c]	6.4	40.6[c]	4.4	53.4[c]	3.5	47.7[b]	3.0

[a]None of the impairment indicators differed significantly between the group with public speaking fear only and the group with other pure speaking fears.
[b]Significant difference between total group with pure speaking fears and total group with other social fears ($p \leq 0.05$, adjusted Wald chi-square test).
[c]Significant difference among groups with one, two, and three or more fears ($p \leq 0.05$, adjusted Wald chi-square test).

Pathophysiology

While definitive pathophysiological mechanisms have not yet been determined, anxiety symptoms and the resulting disorders are thought to be due to disrupted modulation within the central nervous system. Physical and emotional manifestations of this dysregulation are the result of heightened sympathetic arousal of varying degrees.[30] Several neurotransmitter systems have been implicated to have a role in one or several of the modulatory steps involved. The most commonly considered are the serotonergic and noradrenergic neurotransmitter systems. In general terms, it is thought that an under activation of the serotonergic system and an over activation of the noradrenergic system are involved. These systems regulate and are regulated by other pathways and neuronal circuits in various regions of the brain, resulting in dysregulation of physiological arousal and the emotional experience of this arousal.[31] Disruption of the gamma-butyric acid (GABA) system has also been implicated because of the response of many of the anxiety spectrum disorders to treatment with benzodiazepines.[32] More recently there has been

some interest in the role of corticosteroid regulation and its relationship to symptoms of fear and anxiety.[33] Corticosteroids may increase or decrease the activity of certain neural pathways, affecting not only behaviour under stress, but also the brain's processing of fear-inducing stimuli.

Many studies indicate that a genetic predisposition to developing an anxiety disorder is likely.[30] However, environmental stressors clearly play a role, in varying degrees. All of the disorders are affected in some way by external cues and how they are processed and reacted to.

Prevalence

Interpreting the epidemiological evidence:

Stage 1

Many of the earliest studies were based on DSM-III criteria and assessed with the Diagnostic Interview Schedule (DIS).[14] The prevalence ranged from 2.5% - 4.1%, however prevalence could be regarded as fairly conservative as the version of the DIS used in these surveys assessed social fears as part of the simple phobia section, covering only a very limited range of those social fears clinically relevant for the evaluation of social phobia. Examples of this are the Epidemiological Catchment Area ECA study [7 34].

Stage 2

This underestimation problem was corrected in the successor to the DIS, the World Health Organization's Composite International Diagnostic Interview, (CIDI) (World Health Organization, 1990) by developing a social phobia diagnostic module that comprehensively evaluates all the types specified in DSM-III-R and later DSM-IV. Community epidemiologic surveys using the CIDI have obtained considerably higher estimates of social phobia prevalence than earlier studies, including a 13.3% prevalence in the American National Comorbidity Survey [6 35] and 16.1% in Basel, Switzerland [36].

Although some part of the higher prevalence than in the earlier DIS surveys could be due to differences in sample composition or field procedures, the much more comprehensive screening questions for social fears has been held responsible for much of the increase.[10]

Stage 3

Currently prevalence estimates for DSM-IV social phobia are only available from one adolescent and young adults study of 2,548 subjects (3,021 interviews) aged 14 to 24 on the basis of the CIDI, indicating somewhat lower rates than DSM-III-R studies.[37 38] The study found a lifetime prevalence of DSM-IV SAD of 9.5% in females and 4.9% in males.[38] ***This difference in prevalence estimates is probably due to a higher threshold for severity demanded by the version of the CIDI used in this study rather than by differences between DSM-III-R and DSM-IV criteria***. The range in prevalence estimates that still remain can be accounted for by variations in sampling procedure and by slightly different diagnostic criteria employed.[39] Despite the prevalence differences, there is good agreement with regard to the psychosocial correlates and risk factors associated with social phobia in the earlier DIS studies and more recent CIDI studies. They all agree that rates of social phobia are slightly higher among women than men, are considerably more frequent in younger as compared to older age cohorts, and are significantly associated with lower socioeconomic status.

Australian Prevalence

In the late 1990's in Australia, 9.7% (1,299,900) people suffered an anxiety disorder, usually social phobia, generalised anxiety disorder or post-traumatic stress disorder.[40 41] The 12 month prevalence of social phobia, for males in Australia was 2.4% and females 3%; 2.7% for all Australians (age standardised rates). This is much lower than that reported in the literature for other countries. The Mental Health Survey however found that there was a much lower prevalence rate for anxiety disorders among females aged 55 years and over in comparison to those in the younger age groups, as is shown in Figure 3 and .[40] This may then provide some answer as to why the anxiety prevalence is lower in

Australia, as compared to the adolescent study. As noted earlier part of the difference in prevalence estimates may also be explained by the higher threshold for severity demanded by different versions of the CIDI that have been utilised.

Figure 3: Males, Prevalence of types of mental disorders[40]

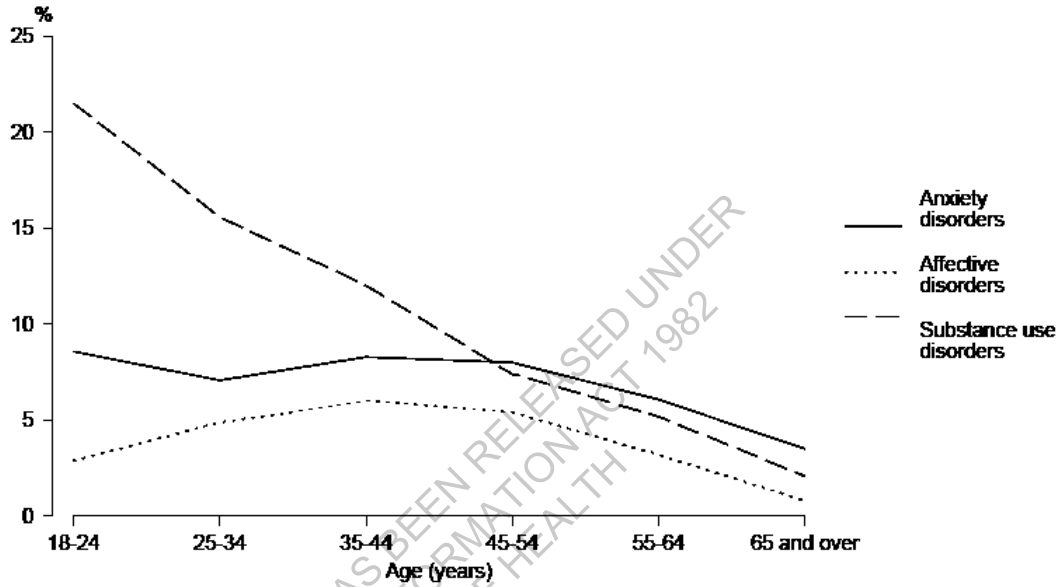
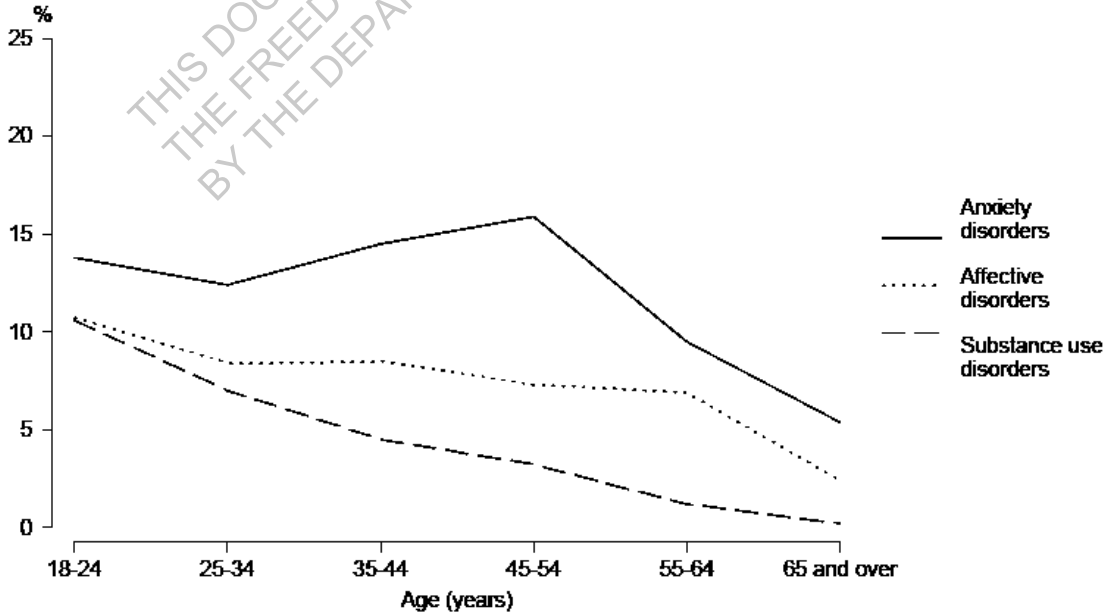


Figure 4: Females, Prevalence of types of mental disorders[40]



Summary of Prevalence

Table 4 summarised the prevalence results found from various studies.

One of the latest studies found that 27.3% of cases with lifetime social phobia were of the generalised subtype.[42]

Social phobics have onset by age 13 and 90% by age 23 [43]. This has led some leading researchers to recommend school based identification and intervention programmes be developed[44] such that the entire course of the disorder can be altered with a view to averting its significant health impacts.

Table 4: Lifetime Prevalence of Social Phobia

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
ECA (US)[7] N=13,000 (13-29 years)	1.8-3.2%			
Munich[45]	2.5			
NCS[46] N=8,098 (15-54 years)	All:7.9% Females: 9.1% Males" 6.6%			
NCS (US) [6 35] N=8,098 (15-54 years)		13.3%		
Basel, Switzerland[36]		16.1%		
France[15]		14.4%		
France[47]		5.1%		
NCS-Replication (US)[48]			12.1%	6.8%
EDSP (Germany) [37] N=3,021 (14-24 years) ***Baseline Results***			All: 3.5% Females: 4.8% Males: 3.5%	All: 2.6% Females:3.7% Males: 1.5%
EDSP (Germany)[42 49] N=3,021 (14-24 years) **Follow-up Results All SAD**			Females: 9.5% Males: 4.9%	Females: 7.2% Males: 3.2%
EDSP (Germany)[42 49] N=3,021 (14-24 years) **Follow-up Results Generalised SAD**			Females: 3.0% Males: 1.3%	Females: 2.7% Males: 1.0%
France General population[14 50]			Moderate:7.3% Severe: 1.9%	Moderate:2.3% Severe: 0.9%
Australia				All: 2.7%

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
>18 years[40]				Females: 3% Males: 2.4%
Australia[51] >18 years				1.3%
ESEMed[52] N=21,425 >18 years			All: 2.4% Female: 2.9% Male: 1.9%	All: 1.2% Female: 1.4% Male: 0.9%
Italyl[16]			3.09% F:M- 2:1	
Morocco[53]				3.4%
Range	**1.8-7.9%**	**5.1-16.1%**	**2.4-12.1%**	**1.2-6.8%**

Co-morbidity

Even clinicians familiar with SAD find it difficult to separate it from other co-existing conditions.[19] Many of the symptoms of SAD overlap with those of depression and other anxiety disorders. Individuals who present with anxiety, depression, alcohol- or substance-related disorders should be considered at high risk of undetected SAD. The fear and avoidance in SAD is invariably linked to feared social situations. Likewise, major depression frequently co-exists with SAD, presenting clinicians with the diagnostic challenge of distinguishing social withdrawal due to depression from fearful social avoidance.[22]

Table 5 shows the prevalence and incidence of co-morbidities with SAD. Approximately 50%-82.3% of patients with social phobia have comorbid mental, drug or alcohol problems.[54 55] Up to 23.6% of patients who present with social phobia have alcohol abuse problems; conversely, many patients presenting for treatment of substance abuse problems meet the criteria for social phobia.[56] Studies have shown that alcohol-related disorders occur twice as often in those affected by SAD than in those without.[7 57] Social phobia usually precedes alcohol abuse and about 20% of those treated for alcohol-related disorders have SAD.[58] If undetected, the risk of rapid relapse is high, since psychosocial treatments that are often a central aspect of treating alcohol abuse may be difficult or impossible to attend. Importantly, when SAD is treated in alcohol abusers, both social anxiety and alcohol use appear to improve.

Longitudinal data show that:

- Social phobia precedes approximately 70 percent of these comorbid conditions, suggesting that some comorbid conditions arise in response to the phobia[7 14]

- Social phobia may be a risk factor for other mental health issues[11 59] and is also associated with a more severe course and character of subsequent depressive illness[43]
- The presence of comorbidity in social phobia has been associated with an increased lifetime incidence of suicidal ideation and suicide attempts.[7]
- Comorbid disorders, particularly major depression, tend to be more prevalent in patients with an earlier onset of SAD and are associated with exacerbated disability and lower quality of life[47].

In an Australian study 21% of the people who met criteria for any mental disorder met criteria for three or more current disorders, and they accounted for 33% of the disability days and for 37% of the service use.[60] Comorbidity has serious consequences and, because of the linear nature of the relationships, is unlikely to be an artefact of the method of inquiry.

The co-occurrence of SAD and MDD is associated with greater impairment than SAD alone.[61] In a study that compared patients with SAD alone, patients with SAD and depression (MDD, dysthymia, or depressive disorder not otherwise specified (NOS)), and patients with SAD and comorbid anxiety disorders, those with SAD and depression had poorer overall functioning.[62] Furthermore, patients in the SAD and depression group reported an earlier age of onset of their SAD than did patients in the other two groups and had more severe social anxiety symptoms than patients in the SAD alone group.

Table 5: Lifetime Co-morbidities

	Population Studied	Any Co-morbidity		Major Depression		General Anxiety Disorder		Agoraphobia		Alcholism	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
DSM III											
Sanderson et al, 1990[55]	N=130 patients presenting at an anxiety disorders research clinic			33%							
Schneier et al, 92[7]	General N=13,000 Epidemiologic Catchment Area Study	76.3%			116.6%				44.9%		18.8%
Schneier, et al 89[63]	Social Phobics N-89									16%	
DSM III-R											
Katzelnick et al, 1998[25]	General	71.4%		50%							
Lecrubier and Weiller[47]	N=2,096			48.8%		15.5%		14.7%			
Weiller, 96 [15]	General			33%	44.2%	26.8%		18.5%	19.2%	23.6%[1]	
DSM IV											
Andrews et al. 01[60]	General N=10,641	40%									
De Menezes[64]	Trial	82.3%		41.9%		6.5%		3.2%		19.4%	

[1] This was similar whether or not social phobics had a comorbid major depressive episode

	Population Studied	Any Co-morbidity		Major Depression		General Anxiety Disorder		Agoraphobia		Alcholism	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
	N=62										
ESEMeD[52]	General N= 21,425										
ESEMeD/MHEDEA[65]	N=22,000	49.1%									
Faravelli et al[16]	General N=2,500		92%		40%		41.4%		15.7%		
Kadri, 2007[53]	N=800			20.7%				19.7%		3.4%	
Stein, et al 01[42]	Adol. and young adults N=2,548			23.7%							
Sobocki et al, 06[66]	Depressed patient in primary car clinics N=447	60%									
Wittchen et al, 98[37]	Adol. and young adults N=3,021			45%							
Katzelnick et al [67] Generalised SAD	N=7,165	43.6%		35.8%						11.3%	
Range DSM IV		**49.1-82.3%**	**92%**	**20.7-45%**	**40%**	**6.5%**	**41.4%**	**3.2-19.7%**	**15.7**	**3.4-19.4%**	

Impact on Impairment

Functioning and well-being are greatly diminished with comorbid MDD and anxiety. Health services research suggests that the impact of work loss has its greatest effect in patients with severe comorbid disease and that depression has the greatest economic impact.[44 48] Recent work suggests that for primary care outpatients with anxiety, MDD, panic, post traumatic stress disorder, and social phobia, each disorder causes equal decrements of function.[68] Thus, patients with clinically significant comorbidity suffer the greatest functional and economic burden.

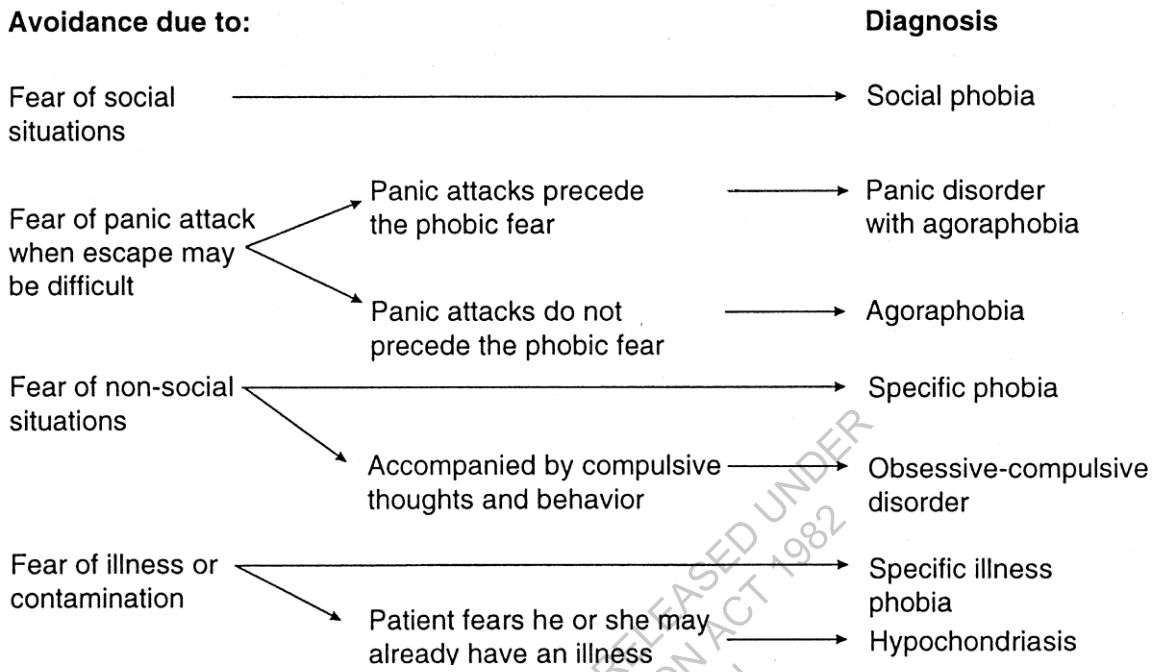
Suicide

About one in 10 depressed patients will attempt suicide, and although 70% of suicides revolve around depressive illness, anxiety disorders also pose a significant risk for suicide.[69] Comorbid anxiety and depression increases the chance of non-response to treatment, long-term poor outcome, and suicide. For example, with uncomplicated panic disorder, the risk of suicide is 7%, but if comorbid depression exists, the risk is increased to 23.6%. Likewise, major depression without anxiety was associated with a 7.9% risk of suicide, but when comorbid anxiety was present, this risk jumped to 19.8%.[70] In addition to the greater severity of SAD, higher rates of attempted suicide have been reported in this comorbid group.[47]

Detection

Social phobia is part of a spectrum of anxiety disorders, and an appropriate differential diagnosis is needed before a management strategy can be implemented. Figure 5[13]shows the differential diagnoses that can be made from a patient presenting with avoidance behaviour. If the patient specifically has a fear of social situations, then a diagnosis of social phobia should be considered.

Figure 5: Differential diagnosis of a patient presenting with avoidance behavior[13]



The first problem in establishing a diagnosis of social phobia is the issue of diagnostic thresholds.[14] Distinguishing social phobia from normal shyness is a quantitative issue related to the level of distress and impairment associated with social fears. Because shyness is usually self-defined, it probably represents a more heterogeneous group than social phobia, including cases that would not meet clinical criteria for the disorder. A recent telephone survey of a community sample, examined the effects of different thresholds for determining illness in persons with social anxiety. Different thresholds led to variations in prevalence from 1.9% to 18.7%, depending on the stringency of the definitions of distress and impairment.[6 37]

One study found that a diagnosis of anxiety disorder was made by GPs in only 24.2% of social phobics.[15] This may be due to the fact that patients with social phobia did not report their phobic symptoms; in fact, social phobics rarely consulted their GP for psychological problems, unless depressed. In fact, as is evident from findings consistently found in community and clinical studies, there is substantial comorbidity with major depression.[7 15 71] Although, depressive symptoms helped GPs to recognise the existence

of a psychological disorder, their presence obscured the identification of social phobia as an anxiety disorder. Social phobia was found to be particularly under diagnosed when it occurred with depression.

The avoidance of social interaction that is characteristic of SAD often prevents consultation with a physician, and only approximately 5%-30% of individuals with SAD seek help[6 47 72 51.73 2]. This may reflect their own possible perception that they suffer from shyness rather than a treatable psychiatric disorder. This is why, it is not until comorbid disorders develop that patients recognize they are ill, and consequently the proportion of those seeking medical help rises with comorbidity. However, in Scandinavia still only one-third of patients with SAD plus comorbid disorders seek help[72].

Similarly Australian data from, the 1997 Australian National Mental Health Survey has revealed the high rate of failing to seek medical consultations among those with comorbidity [51.73 3] Specific social phobia data from a recent analysis of the Australian National Survey of Mental Health and Well-being, show that only 21% of patients with social phobia had medical contact (and only 32% of these received interventions consistent with evidence-based care). [74] Interestingly, that study concludes that evidence base care for anxiety disorders would produce greater population health gains at a similar cost to that of current care, resulting in a substantial increase in the cost-effectiveness of treatment. The same Australian data set suggests that 58.4% of those with anxiety disorders do not seek help because "they prefer to manage themselves" with another 19.5% being "afraid to ask for help or because of what others might think of them"[74].

Based on the American National Comorbidity Survey, research suggests that only 9.5% of patients with "Social Fears" "ever took medication more than once"[6].

[2] This is in contrast to other research, particularly American studies which have concluded that there is no difference between treatment initiation between individuals with social anxiety alone and those who also had comorbid diagnoses (χ^2=2.31, p=0.13).

[3] This is in contrast to other research, particularly American studies which have concluded that there is no difference between treatment initiation between individuals with social anxiety alone and those who also had comorbid diagnoses (χ^2=2.31, p=0.13).

Comorbidity with depression also had a strong influence on the GP's diagnosis.[47] In the comorbid group, 76% were recognised as cases, but only 11% were identified as having an anxiety disorder. Priority is therefore given to the depressive symptomatology by GPs

Treatment

Anxiety symptoms exist on a continuum and many people with milder degrees of anxiety, particularly of recent onset and associated with stressful life events but with little disability will experience an improvement without specific intervention. When the disease is chronic and is associated with disability, most patients who fulfil diagnostic criteria for an anxiety disorder are likely benefit from some form of treatment[75].

This need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid mental disorder or physical illness, the level of disability and impact on social functioning, concomitant medication, and a history of good response to, or poor tolerability of, previous treatment approaches.

As randomized controlled trials are generally performed in rather restricted patient groups with little comorbidity or other features commonly seen in conventional clinical samples, study findings may not necessarily simplify treatment decisions in primary or secondary care.[75] Choice of treatment is affected by the patient characteristics (such as previous response or contraindications), the evidence base supporting its use, patient and physician preference, and the local availability of that proposed intervention.[76] Although there is considerable overlap between effective therapies for the different anxiety disorders there are also differences and separate evidence bases for treating each disorder. For this reason identifying individual disorders is helpful.

In general, treatment of SAD should focus on:

1) acute reduction and control of pathological social anxiety and related phobic avoidance;

2) adequate treatment of depression/comorbid conditions; and
3) long-term management to permit and sustain optimal improvement. Cognitive-behavioural therapies, medication treatments and their combination have all been shown to be effective interventions.[77]

Current Guidelines for managing social phobia are presented in Table 6. The new guidelines from the British Association for Psychopharmacology (BAP) for anxiety disorders notes that with respect to pharmacotherapy there is high level evidence that SSRIs are effective across the range of anxiety disorders at all stages of the condition, and thus are generally suitable for first-line treatment.[78]

It can also be said with some certainty that acute treatment periods of at least 12 weeks are needed to assess efficacy.[79] This is in contrast to common practice in the treatment of depression where shorter treatment periods (6-8 weeks) are generally used. To maintain benefit in those patients who are responding at 12 weeks, drug treatment should be continued for at least 6 more months for GAD, and social anxiety disorder (SAD), and (these time periods are based on available evidence, but it is likely that benefit is maintained for longer than this and the need for continuing treatment needs to be determined on an individual patient basis). This places limitations on the use of benzodiazepines (which are effective for many anxiety disorders), as current recommendations are for short-term use due to potential problems with side effects and dependence. A possible exception is in treatment-resistant cases, where longer-term treatment with benzodiazepines may be warranted.

The ideal outcome of achieving medication-free status may not be a reasonable goal for all patients and should certainly not be pursued at the expense of a patient's well-being.[14]

Table 6: Guidelines for Social Anxiety Disorder or Social Phobia

	British Guidelines[79 80]	Australian Guidelines[81]	Literature
Recognition and diagnosis	Social phobia is often not recognized in primary medical care , where it is often misconstrued as shyness[15]. It can be distinguished from shyness by the levels of personal distress and associated social and occupational impairment .[14] The generalized subtype is associated with greater disability and higher comorbidity [6]. Patients can present with symptoms arising from comorbid conditions (especially depression), rather than with characteristic social anxiety and avoidance.[82] Many patients use alcohol and drugs of misuse in an attempt to relieve symptoms .[83]	Social phobia, also known as social anxiety disorder, is a persistent fear of one or more social or performance situations in which the person is exposed to possible scrutiny by others and fears that they may do something or act in a way that will be humiliating or embarrassing (eg speaking in public). The phobic situation(s) is avoided or is endured with intense anxiety or distress.	Generalised social phobics or those with avoidant personality traits are more likely to benefit from medication taken on a regular basis.
Acute Treatment	Systematic reviews and placebo-controlled RCTs indicate that a range of treatment approaches are efficacious, including CBT, SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), the SNRI venlafaxine, the MAOI phenelzine and the RIMA moclobemide. Some benzodiazepines (bromazepam and clonazepam), anticonvulsants (gabapentin and pregabalin) and the antipsychotic olanzapine are also efficacious in acute treatment. Treatments with unproven efficacy in generalized social phobia include the TCA imipramine, buspirone and the beta blocker atenolol	• Paroxetine 10-60mg daily or other SSRIs • Moclobemide: 450-600mg daily • Phenelzine 15mg, twice daily initially, increasing every 3-4days (depending on adverse effects) to 45-60mg daily in 2 or 3 divided doses by the 7th day. If there is no response after 1-2 weeks, dose can be increased at weekly intervals by increments of 15mg per day, to a max of 45 mg twice a day. • When disabling symptoms which suggest sympathetic overactivity (eg tremors, palpitations, sweating) are anticipated use propranolol 10-40mg daily, 30-60min before social event or performance. Be aware of contraindications withbeta-blockers.	• Some options and their impact are reported below: 1. Phenelzine: established efficacy, the dietary restrictions (i.e., tyramine-free diet) and the risk of antihypertensive crises are difficult for some patients to tolerate[11]. 2. Tricyclic antidepressants appear to lack efficacy.[12] 3. Benzodiazepines: have dependence potential. Patients who take benzodiazepines before social encounters to increase their comfort may develop psychological dependence.[12] 4. Cognitive behavioural therapy should be started at the same time medication begins.[11] 5. In severe social phobia psychopharmacotherapy is

			successful with the use of SSRIs. [84] 6. Also in severe social phobia psychopharmacotherapy is successful with the use of venlafaxine.[84] • Treating the anxiety associated with performance situations involves the use of beta-blocker just before the feared situation.[84]
Long-term treatment	Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24 weeks is associated with an increase in overall treatment response rates.		
Comparative efficacy of pharmacological, psychological and combination treatments	Drug and psychological treatments, delivered singly, have broadly similar efficacy in acute treatment. However, acute treatment with cognitive therapy (group or individual) may be associated with reduced risk of symptomatic relapse at follow-up. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone.		
When initial treatments prove unhelpful	There is no clear evidence for the benefit of dose escalation after an initial non-response. Switching between treatments with proven efficacy may be helpful.		
Duration of Treatment	These note that in acute treatment periods at least 12 weeks treatment are needed to assess efficacy.[79] To main benefit in those patients who are responding at 12 weeks, drug treatment should be continued for at least 6 more months for SAD (and GAD).		

Effects of Treatment with co-morbidities

In practice the presence of marked coexisting depressive symptoms is an important consideration in treatment decisions in primary and secondary medical care. A way of addressing comorbidity is by combining CBT and medication. In one study, the moderately depressed group that received combined treatment did not do better than the groups receiving monotherapies.[61] However, medication and CBT were initiated concurrently, and it is possible that combining medication and therapy sequentially might be a better strategy.[85] Administering medication prior to beginning CBT might improve mood, hopefulness, and motivation, and might also reduce anxiety, so that patients will be more willing to comply with CBT demands to confront feared social situations. Future studies should examine the efficacy of different strategies for combining CBT and medication. It is also possible that some serotonin reuptake inhibitors might be better adjuncts to CBT than others.[86 87]

Results from a 4-year longitudinal study that tracked depression and suicidality in adolescents showed that participants who, in the beginning of the study, had SAD not accompanied by a depressive disorder (MDD or dysthymia) or a depressive disorder not accompanied by SAD differed very little from participants who had no mental disorders with respect to suicidality and incidence of depressive disorders at subsequent assessment points. [42] In contrast, participants who had both depressive disorders and SAD at the beginning of the study experienced greater suicidal ideation and more suicide attempts over the 4-year study than participants who were healthy at the start of the study.

In another study, depressed patients had more severe social anxiety both at pre- and post-treatment, although they improved as much as patients in the other two groups (SAD alone, and SAD with comorbid anxiety disorders). [62]

More data on treatment outcomes with comorbidities is presented in Attachment 8.

Treatment Outcomes

Liebowitz Social Anxiety Scale (LSAS)

The LSAS[88] is designed to assess SAD through evaluation of fear and avoidance. The LSAS is a clinician-administered (interview) scale to evaluate the wide range of social situations within the last 7 days that are typically difficult for individuals with SAD. The LSAS includes 24 items: 13 describe performance situations and 11 describe social interaction situations. Each item is rated with respect to fear (0 to 3 = none, mild, moderate, severe, respectively) and avoidance (0 to 3 = never, occasionally, often, usually, respectively). Thus, the LSAS provides an overall social anxiety severity rating, and additionally scores four subscales: performance fear, performance avoidance, social fear, and social avoidance. Total scores for fear and avoidance as well as total LSAS scores are obtained by adding the scores.

The ratings are based up an interview with the patient and were conducted by the same person at each visit, whenever possible. Only persons accepted by the study sponsor and trained as raters during a co-rating session were allowed to rate patients on the LSAS. The rater sessions were undertaken to increase inter-rater reliability, and were chaired by an experienced rater(s). At these sessions, video tapes were shown of patients with SAD; these patients were rated and the ratings discussed.

The max possible score is 144 of the LSAS[89]. Patients with SAD generally score above 50 points, whilst normal volunteers score below 30 points. Scores between 50-70 may be considered moderate and are associated with distress while scores over 70, and particularly over 90, are considered severe and are associated with functional impairment.[89 90]

As mentioned earlier, an improvement of 10 points on the LSAS has been suggested as showing a clinically relevant improvement[90].

Responders[90]: LSAS: ≥35-50% reduction in score from baseline. Defining responders, as having a reduction in the initial score on the severity scale of 50%, used in other psychiatric conditions and which seems reasonable, has been reported to be useful in some studies in SAD. However, SAD tends to respond more slowly than the conditions where the 50% criterion has proved most useful. The studies indicate that at 12 weeks a 35% reduction in initial severity appears to be a useful measure with approximately half the patients achieving this criterion. This closely corresponds to 31% reduction, which was determined from a study looking at the correlation between outcomes from the analysis of various trials (shown below).[90]

Remission[91]: Keeping in mind that some controversy may exist regarding remission standards for CGI, an analysis of remission for various trials found the correlations between the various scales are reported in Table 7.[43] Given that a normal volunteers scores below 30 points on the LSAS the remission score is appropriate. Consensus conferences addressing this issue have also arrived at remission being defined as LSAS≤30.[92 93]

Therefore in totality the results should be based on more than a change in score of ≥ 10 points and the totality of the evidence should be considered.

Clinical Global Impression (CGI)

The CGI[76] are categorical scales used as both primary (though they are not recommended as primary and are most useful as secondary scales to help judge the clinical relevance of the finding) and secondary efficacy scales and as categorical scales to define responders.[90] CGI consists of two subscales:

- Clinical Global Impressions – Improvement scale (CGI-I):
  This scale evaluates a patients' total improvement from baseline I on a 7 point-scale, regardless of whether the improvement is related to the study product. The assessor rates the patient from 1 (very much improved) to 7 (very much worse)
- Clinical Global Impressions – Severity scale (CGI-S):

This scale evaluates a patient's severity of disease on a 7-point scale based on the investigators total clinical experience with this population. The assessor rates the patient from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

Responders and Remitters on the CGI scale are classified as:

Responders: CGI-I≤ 2 (much or very much improved)[90] or CGI-I ≥50% reduction[91]. These patients have improved but have not yet reached remission.

Remission:[90] CGI-S≤ 2 (normal, not at all ill, or borderline illness). This has been used to define remitters but the level of remission represented by these scores remains controversial.

Sheehan Disability Scale (SDS)

The SDS[94] is a 3-item scale to measure impairment. The items address the impact of symptoms of SAD on work, social life, and family life, within the last 7 days. The rating is based up an interview with the patient. This scale has proved robust in most studies and provides evidence of an improvement is disability in almost all studies where it is used.[90] The SDS has been able to distinguish an effective treatment from placebo, both in the short and long-term studies. Conclusions arrived at consensus conferences identify remission at SDS≤1 on each item (mildly disabled).[92 93]

Duration of Treatment

Acute Treatment: 12 weeks[90]**,** this is also the period required by the European Authorities to determine efficacy of a medication aiming to treat SAD[95].

Long –Term Treatment: 6-12 months[90], **,** this is also the period required by the European Authorities to determine efficacy of a medication aiming to treat SAD[95].

Defining Remission

When defining 'response' to a treatment on a standard rating scale, a ≥50% reduction of scale score this was found to be too conservative, with clinically measurable difference at

a smaller change from baseline being found to be more accurate as can be seen in Table 7.

Table 7: Correlation of Response/Treatment Between Scales[91]

CGI Defined	Corresponding Reductions		
	MDRS	HAM-A	LSAS
Response CGI-I ≥50% reduction	39%	42%	31%
Remission CGI-S ≤2	11 points	9 points	36 points

Longitudinal Evidence

Data from the Harvard/ Brown Anxiety Disorders Research Program, a prospective, naturalistic, longitudinal, multicenter study of adults with a current or past history of anxiety disorders were examined.[96] Probabilities of recovery and recurrence were calculated by using standard survival analysis methods. The long-term clinical course of anxiety disorders over 12 years was observed in order to ascertain the influence of comorbid psychiatric disorders on recovery from or recurrence of panic disorder, generalized anxiety disorder, and social phobia. Social phobia, the most common of the anxiety disorders, was found to be the most chronic; patients with social phobia had a 0.63 probability of remaining in the original intake episode even after 12 years of follow-up. However, patients who did recover from social phobia had a lower rate of recurrence (probability=0.39) over 12 years, compared with patients with panic disorder (with or without agoraphobia), generalized anxiety disorder, or major depressive disorder. These findings suggest that although social phobia is typically a chronic, unremitting disorder, patients with social phobia whose symptoms improve to the point of recovery tend to stay well, relative to patients with other anxiety disorders.

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Attachment 4

DETAILS OF THE LITERATURE SEARCHES CONDUCTED

Table of Contents

List of Tables

The details of the literature searches relevant to Section B of this submission are presented in this Attachment.

Attachment 4 presents the complete documentation of all search strategies, and citations and abstracts identified from the literature searches for smoking cessation studies. The following sources were used to search for relevant data.

1. A search of the electronic databases EMBASE which combines EMBASE and MEDLINE.
2. PubMed was also seartched.
3. A search of all Evidence Based Medicine Database which includes Cochrane DSR, ACP Journal Club, DARE and Central Register of Controlled Trials (CCTR).
4. A search of clinical trial registries through the Australian Clinical Trials Registry (ACTR) and ClinicalTrials.gov .
5. Manual searching of references publications retrieved via the database searches.
6. A search of Lundbeck's internal databases.

Inclusion criteria for clinical evidence

A literature search was undertaken for this submission in order to identify all relevant randomised controlled trials (RCTs) for Social Anxiety Disorder (SAD) and escitalopram (Lexapro®).

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All titles/abstracts were appraised against the inclusion criteria for the submission. If it was clear from the title/abstract that the article did not meet the inclusion criteria, then the paper was excluded. If it appeared from the title/abstract that the study might meet the inclusion criteria, the full text was retrieved for a thorough evaluation. It was then determined whether the paper was to be included or excluded from the submission. Those papers that were included and used as a reference paper in the Main body of the submission are presented in full in the reference folders.

Search strategies for comparative randomised trials

1.1.1 EMBASE and Medline search strategy

Presented in Table 1 is the search strategy employed in the EMBASE+MEDLINE® EMBASE database (EMBAE), all years till 31May 2007. An update of the search from 1/6/2007 to 4/10/2007 showed no additional references, as can be seen in Table 2 (please refer to yellow highlighted rows).

Table 1: Search details for EMBAE+MEDLINE® EMBASE, all years till 31 May 2007[1]

No.	Query	Results	Date
#1	**'generalised anxiety disorder'**/exp AND [english]/lim AND [humans]/lim	1,081	31 May 2007
#2	**'gad'**/exp AND [english]/lim AND [humans]/lim	1,555	31 May 2007
#3	**#1** OR **#2**	2,634	31 May 2007
#4	**'oxazepam'**/exp AND [english]/lim AND [humans]/lim	2,672	31 May 2007
#5	**'diazepam'**/exp AND [english]/lim AND [humans]/lim	21,125	31 May 2007
#6	**#4** OR **#5**	22,306	31 May 2007
#7	(**'hamilton anxiety scale'**/exp OR **'hamilton anxiety scale'**) AND [english]/lim AND [humans]/lim	354	31 May 2007
#8	**'hama'** AND [english]/lim AND [humans]/lim	1,490	31 May 2007
#9	**'ham-a'** AND [english]/lim AND [humans]/lim	307	31 May 2007
#10	**#7** OR **#8** OR **#9**	2,051	31 May 2007
#11	**'escitalopram'**/exp AND [english]/lim AND [humans]/lim	965	31 May 2007
#12	**'lexapro'**/exp AND [english]/lim AND [humans]/lim	965	31 May 2007
#13	**'escitalopram'**/exp AND [english]/lim AND [humans]/lim	965	31 May 2007
#14	**#11** OR **#12**	965	31 May 2007

[1] Relevant search highlighted in yellow

#15	#3 AND #6	125	31 May 2007
#16	#3 AND #6 AND ([article]/lim OR [conference paper]/lim OR [review]/lim) AND [english]/lim AND [humans]/lim	112	31 May 2007
#17	#3 AND #6 AND #10	10	31 May 2007
#18	#10 AND #15	10	31 May 2007
#19	#17 OR #18	10	31 May 2007
#20	#6 AND #10 AND #13	1	31 May 2007
#21	#3 AND #10 AND #14	12	31 May 2007
#22	#3 AND #14	78	31 May 2007
#23	#3 AND #14	78	31 May 2007
#24	'social anxiety disorder'/exp AND [english]/lim AND [humans]/lim	2,436	31 May 2007
#25	'sad' AND [english]/lim AND [humans]/lim	2,315	31 May 2007
#26	'social phobia'/exp AND [english]/lim AND [humans]/lim	2,436	31 May 2007
#27	'generalised social anxiety disorder' AND [english]/lim AND [humans]/lim	4	31 May 2007
#28	#24 OR #25 OR #26 OR #27	4,642	31 May 2007
#29	'liebowitz social anxiety scale' AND [english]/lim AND [humans]/lim	109	31 May 2007
#30	'lsas' AND [english]/lim AND [humans]/lim	76	31 May 2007
#31	#29 OR #30	127	31 May 2007
#32	#29 OR #30 AND ([article]/lim OR [conference paper]/lim OR [review]/lim) AND [english]/lim AND [humans]/lim	125	31 May 2007
#33	#14 AND #28 AND #31	9	31 May 2007

Table 2 Update of Embase+ Medline Searches; 1/06/2007-4/10/2007

No.	Query	Results	Date
#1	'generalised anxiety disorder'/exp/mj AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	38	03 Oct 2007
#2	'gad'/exp/mj AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	5	03 Oct 2007
#3	#1 OR #2	43	03 Oct 2007
#4	esitalopram AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	0	03 Oct 2007
#5	'lexapro'/exp/mj AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	19	03 Oct 2007
#6	#4 OR #5	19	03 Oct 2007
#7	'oxazepam'/exp/mj AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	0	03 Oct 2007
#8	'diazepam'/exp/mj AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	21	03 Oct 2007
#9	#7 OR #8	21	03 Oct 2007
#10	'hamilton anxiety score' AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	0	03 Oct 2007
#11	'hamilton anxiety score' AND [english]/lim AND	0	03 Oct 2007

	[humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py		
#12	**'hama'** AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**49**	**03 Oct 2007**
#13	(**``ham-a``**) AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**11**	**03 Oct 2007**
#14	**#11** OR **#12** OR **#13**	**60**	**03 Oct 2007**
#15	**#3** AND **#6** AND **#9** AND **#14**	**0**	**03 Oct 2007**
#16	**#3** AND **#9** AND **#14**	**0**	**03 Oct 2007**
#17	**#3** AND **#6** AND **#14**	**0**	**03 Oct 2007**
#18	**'social anxiety disorder'**/exp AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**134**	**03 Oct 2007**
#19	**'sad'** AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**68**	**03 Oct 2007**
#20	(**``social phobia``**) AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**145**	**03 Oct 2007**
#21	**'liebowitz social anxiety scale'** AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**5**	**03 Oct 2007**
#22	(**``lsas``**) AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**1**	**03 Oct 2007**
#23	**'generalised social anxiety disorder'** AND [english]/lim AND [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**0**	**03 Oct 2007**
#24	**#18** OR **#19** OR **#20** OR **#23**	**203**	**03 Oct 2007**
#25	**#21** OR **#22**	**5**	**03 Oct 2007**
#26	**#6** AND **#24** AND **#25**	**0**	**03 Oct 2007**

1.1.2 PubMed search strategy

A PubMed search was also conducted and the results are presented in Table 3. Since there was complete overlap between Embase+Medline and Pubmed this search was not re-run for the chronological update.

Table 3: PubMed Search Strategy, 2 June 2007[2]

No.		Result
#2	Search **"Phobic Disorders"[MeSH Major Topic]**	4707
#6	Search **"Anxiety Disorders"[MeSH Major Topic]**	32366
#7	Search **social anxiety disorder**	6960
#8	Search **generalised social anxiety disorder**	42
#9	Search **social phobia**	7394

[2] The numbering is not always consecutive and had to do with errors being made whilst conducting the search.

#10	Search **escitalopram**	2054
#11	Search **lexapro**	10
#12	Search **#2 or #6 or #7 or #8 or #9**	324299
#13	Search **#10 or #11**	2054
#14	Search **#12 and #13**	168
#15	Search **Liebowitz social anxiety scale**	136
#16	Search **LSAS**	92
#17	Search **#15 or #16**	163
#18	Search **#17 and #114**	0
#19	Search **#17 and #14**	12
#20	Search **#17 and #14** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	9

1.1.3 Medline in Process search strategy

Presented in Table 4 is the search strategy employed in the MEDLINE® In-Process Datastar database (MEIP), last 8 weeks to 12 September 2007.

Table 4: Search details for MEDLINE® In-Process Ovid - 8 weeks prior to 26 September 2007

No		Result
1	lexapro.mp. [mp=title, original title, abstract, name of substance word]	0
2	escitalopram.mp. [mp=title, original title, abstract, name of substance word]	34
3	social anxiety disorder.mp. [mp=title, original title, abstract, name of substance word]	31
4	social anxiety disorder.mp. [mp=title, original title, abstract, name of substance word]	31
5	sad.mp. [mp=title, original title, abstract, name of substance word]	93
6	social phobia.mp. [mp=title, original title, abstract, name of substance word]	59
7	4 or 5 or 6	169
8	2 and 7	2

1.1.4 Cochrane library search strategy

The Cochrane Library was searched for systematic reviews, economic evaluations and publications using the search terms for the drugs under evaluation Cochrane DSR,

ACP Journal Club, DARE, and CCTR). A summary of the Cochrane search strategy is presented in Table 5. The search was undertaken 2 June 2007.

Table 5: Search details for Cochrane Library database to 2 June 2007

#	Search strategy	Results
1	'social anxiety disorder'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	109
2	'social phobia'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	333
3	'generalised social anxiety disorder'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	2
4	1 or 2 or 3	395
5	'escitalopram'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	110
6	'lexapro'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	1
7	5 or 6	110
8	'Liebowitz social anxiety scale'.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	54
9	LSAS.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	39
10	8 or 9	59
11	4 and 7 and 10	7

This search was updated 4 October 2007. No additional articles were identified , as can be seen in **Error! Reference source not found.**.

Table 6: Updated Cochrane Search 4 October 2007

#	Search Strategy	Results
1	escitalopram.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	121
2	lexapro.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	1
3	1 or 2	121
4	social anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	110
5	sad.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	288
6	social phobia.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	335
7	liebowitz social anxiety scale.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	56
8	lsas.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	40
9	4 or 5 or 6	661
10	7 or 8	61
11	3 and 9 and 10	7
12	limit 11 to (classical article or clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or conference or congresses or controlled clinical trial or "corrected and republished article" or guideline or journal article or meta analysis or multicenter study or practice guideline or randomized controlled trial or retracted publication or "review" or "review literature") [Limit not valid in: CDSR,ACP Journal Club,DARE; records were retained]	6
13	limit 12 to yr="2007" [Limit not valid in: DARE; records were retained]	0

1.1.5 Clinical trial registers search strategy

Presented in Table 7 are the results from the search of the clinical trials register; Clinical Trials.gov and ACTR:

Table 7: Results of the search of Clinical Trial Registries, 16 May 2007.

#	Search strategy	Results
Clinical Trials.gov	escitalopram [TREATMENT] AND ("Phase IV" OR "Phase III") [PHASE] AND 'social anxiety disorder' [CONDITION]	0
Clinical Trials.gov	escitalopram [TREATMENT] AND ("Phase IV" OR "Phase III") [PHASE] AND 'social phobia' [CONDITION]	0
ACTR	escitalopram	0

1.1.6 Search of HTA databases

A search of the international health technology assessment groups was conducted for systematic reviews, economic evaluations and publications using the search terms for the drugs under evaluation. A summary of the search strategies is presented in Table 8. The search was undertaken 25 September February 2007.

Table 8: Search details for HTA Databases to 25 September 2007

Database	Search	Results
Canadian Agency for Drugs and Technology in Health (CADTH)	Escitalopram, Lexapro	0
National Institute of Clinical Excellence (NICE)	Mental Health (search for SAD)	0
Total		**0**

1.1.7 Search of conference abstracts

A search of the conference abstracts relevant to this field of study was also conducted. This was considered appropriate as the Cochrane Library, as a rule, indexes the abstracts from the Society for Research on Nicotine and Tobacco (SRNT) and the (WCToH). Therefore it was considered appropriate to expand the search to include data presented at the conferences listed in

Table 9.

Table 9: Search details for conference proceedings 1982 to 25 September 2007

Conference	Search	Results
Conference Papers Index	(escitalopram or lexapro) and KW=((social anxiety disorder) or (SAD) or (social phobia))	1

1.1.8 Search of the sponsor's database for Studies

The trials identified by the Sponsor's database are presented in Table 10.

Table 10: Results of the Sponsor's Database for Studies

Study Number	Title	Publication
99270	A double blind, randomised trial comparing the efficacy and safety of fixed dosages of Lu 26-054 and paroxetine with placebo in the treatment of patients with social anxiety disorder	Montgomery SA., Lader M., Nil R., Escitalopram and paroxetine in fixed doses for the treatment of social anxiety disorder (SAD). Nordic Journal of Psychiatry, 2003
		Lader, M., K. Stender, et al. (2004). "Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study." Depression and Anxiety 19(4): 241-248.
		Montgomery SA., Lader M., et al., Escitalopram and paroxetine in fixed doses for the treatment of social anxiety disorder (SAD). 4th Annual Meeting of the Scandinavian College of Neuro-Psychopharmacology, 9-12 April 2003, France
99269	A double blind, randomised, placebo-controlled flexible to fixed-dose prevention study with Lu 26-054 in social anxiety disorder	Montgomery SA., Durr-Pal N., Loft H., Nil R., Escitalopram prevents relapse in patients suffering from social anxiety disorder (SAD), ADAA, 2003
		Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." Journal of Clinical Psychiatry 66(10): 1270-1278.
99012	A double blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 in the treatment of patient with social anxiety disorder	Kasper S., Loft H., Smith JR., Escitalopram is well tolerated in the treatment of social anxiety disorder. Anxiety disorders association of America (ADAA). March 2002.
		Kasper S., Loft H., Nil R., Escitalopram is well tolerated in the treatment of social anxiety disorder. Scandinavian College of Neuropsychopharmacology (SCNP), April

Study Number	Title	Publication
		2002
		Kasper S., Escitalopram is well tolerated in the treatment of social anxiety disorder. American Psychiatric association (APA), May 2002
		Kasper S., Loft H., Nil R., Treatment of social anxiety disorder: Escitalopram is well tolerated and efficacious. Collegium Internationale Neuro-Psychopharmacologicum (CINP), June2002
		Kasper S., Loft H., Smith JR., Escitalopram is efficacious and well tolerated in the treatment of SAD. Association of European Psychiatrists (AEP), May 2002.
		Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study." British Journal of Psychiatry 186(MAR.): 222-226.

1.1.9 Manual searching

A manual search through the references of the retrieved trials and reviews examining RCTs of escitalopram did not identify any additional citations that were relevant to this submission.

1.1.10 Lundbeck trial programme

No additional trials exist.

List of citations and reasons for exclusion

The results from the search of the indexed databases, EMBASE+MEDLINE, PubMed, MEDLINE In-Process, CCT, ACTR, Conference Paper Index, Cochrane Library and the Sponsor's database were combined and duplicate citations were then removed from the list. Any publications identified by manual searching of bibliographies were added to the database. Copies of the abstracts are presented with the citations, where available. Presented below in Table 11 are the results of the literature search. In total 18 citations were identified and reviewed for inclusion.

Table 11: Results of the search for escitalopram clinical trials

	Database	Results
1	EMBASE + Medline	9
2	PubMed	9
3	Medline In Process	2
4	CCTR	0
5	ACTR	0
6	Duplicates from databases (1-6)	(8)
7	Articles excluding duplicates	12
8	Cochrane Library	7
9	Trial registers	0
10	HTA databases and conference proceedings	0
11	Manual searching	0
12	Conferences	1
13	Duplicates from databases 7-13	(3)
14	Articles excluding duplicates	5
15	Sponsor's database ▪ Clinical trial reports ▪ Publications	 3 7
16	Duplicates from 15-16	(7)
17	Articles excluding duplicates	**3**
18	**Total (7+14+17)**	**20**

Results of the literature search

The summary presented in Table 12 is a summary of the literature search results. This summary is presented as a composite of the numbers of citations identified, those included and those excluded, with reasons.

The published 17 citations (the 3 study reports are not included in this list, if they had been the total would be 20) identified in the literature search are listed below in alphabetical order, and reasons for their exclusion is provided in **Table 13**.

s38

Table 12: Summary of identification of direct randomised trials from the literature search

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA[3]	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	9	9	2	0	0	7	11	1	0	0	39
Total number of duplicates	6	1	1			3	8				19
Total number of citations reviewed for inclusion	3	8	1	0	0	4	3	1	0	0	20
Number of citations excluded after title/abstract review:	1	5	1					1			8
• Not an RCT	1	2	1					1			5
• RCT does not include comparator		3									3
• Trial subjects are not representative of the proposed indication relevant/insufficient outcomes											
Number of citations excluded after full text review:	2					4					6
• RCT does not include comparator											
• Other	2					4					6
Number of citations of direct randomised trials included from each database		3									3
Number of direct randomised trials identified for inclusion in this submission	0	3	0	0	0	0	3[4]	0	0	0	6

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration.

[3] The conference presentations relating to the study reports are reported as duplicates. However all 3 study reports are utilised in the submission. See Table 10

[4] There are 3 study reports and the identified PubMed articles that are the representative publications of these trials.

The primary publications relevant to the submission are:

Clinical Reports	Primary Publication
99270 A double blind, randomised trial comparing the efficacy and safety of fixed dosages of Lu 26-054 and paroxetine with placebo in the treatment of patients with social anxiety disorder	Lader, M., K. Stender, et al. (2004). "Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study." Depression and Anxiety 19(4): 241-248.
99269 A double blind, randomised, placebo-controlled flexible to fixed-dose prevention study with Lu 26-054 in social anxiety disorder	Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." Journal of Clinical Psychiatry 66(10): 1270-1278
99012 A double blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 in the treatment of patient with social anxiety disorder	Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study." British Journal of Psychiatry 186(MAR.): 222-226

Listing of the included and excluded citations with reasons for selection

Presented below in **Table 13** are the 17 citations identified and the reasons for inclusion and exclusion (at total of 20 studies were identified but the 3 study reports are not included in the table as these are presented directly above – and because their publications are included in the 17 citations). Full article abstracts for all 17 citations are presented in Appendix 1. This table does not include the 3 study reports (which would bring the total RCTs reviewed to 20). Detailed presentations of all references by search engine are presented in Appendix 2.

Table 13: Summary of Inclusion/Exclusion criteria for Trials

	SAD	Included / Excluded	Reason for Exclusion	Rational
1	Atmaca, M., E. Tezcan, et al. (2004). "Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment." Eur Arch Psychiatry Clin Neurosci 254(4): 231-5.	E	b	
2	Atmaca, M., M. Kuloglu, et al. (2002). "Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings." Hum Psychopharmacol 17(8): 401-5.	E	b	
3	Bandelow, B., D. S. Baldwin, et al. (2006). "What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?" Journal of Clinical Psychiatry 67(9): 1428-1434.	E	a	
4	Bouwer, C. and D. J. Stein (1998). "Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia." J Affect Disord 49(1): 79-82.	E	b	
5	Davidson, J., Pharmacotherapy of social anxiety disorder: What does the evidence tell us? Journal of Clinical Psychiatry, 2006. 67: p. 20-26.	E	a	
6	Dhillon, S., L. J. Scott, et al. (2006). "Escitalopram: A review of its use in the management of anxiety disorders." CNS Drugs 20(9): 763-790.	E	a	
7	Hedges, D. W., B. L. Brown, et al. (2007). "The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: A meta-analysis of double-blind, placebo-controlled trials." Journal of Psychopharmacology 21(1): 102-111.	E	a	Meta-analysis of SSRIs in social anxiety disorder – not all comparators used are appropriate. Lader M. et al (2004) which is included in the meta-analysis is included in this submission.
8	Ipser, J.C., P; Dhansay, Y; Fakier, N; Seedat, S; Stein, DJ, Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews. 2007. 2.	E	a	Meta-analysis of pharmacotherapy in social anxiety disorder – not all comparators used are appropriate. Kasper S (2002) which is included in the meta-analysis is included in this submission as Kasper S (2005).

9	**Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study." British Journal of Psychiatry 186(MAR.): 222-226.**	**I**		
10	**Lader, M., K. Stender, et al. (2004). "Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study." Depression and Anxiety 19(4): 241-248.**	**I**		
11	**Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." Journal of Clinical Psychiatry 66(10): 1270-1278.**	**I**		
12	Montgomery SA. Relapse Prevention in Patients Suffering From Social Anxiety Disorder. in 158th Annual Meeting of the American Psychiatric Association. May 2005. Atlanta, GA.	E		Same as Montgomery (2005)
13	Pallanti, S. and L. Quercioli (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice and Epidemiology in Mental Health 2:35.	E	a	non-randomised open label
14	Stein DJ., Continued escitalopram reduces risk of relapse in people with generalised social anxiety disorder.[comment]. Evidence-Based Mental Health, 2006. 9(2): p. 52.	E	a	Comment
15	Stein, D. J., E. W. Andersen, et al. (2006). "Escitalopram versus paroxetine for social anxiety disorder: An analysis of efficacy for different symptom dimensions." European Neuropsychopharmacology 16(1): 33-38.	E	c	Analyses of different symptom dimensions from Lader et al (2004; study 99270)
16	Stein, D. J., S. Kasper, et al. (2004). "Escitalopram in the treatment of social anxiety disorder: Analysis of efficacy for different clinical subgroups and symptom dimensions." Depression and Anxiety 20(4): 175-181.	E	a	Includes Kasper and Lader which are both included in the submission
17	Stein, D.I., JC; van Balkom, AJ, Pharmacotherapy for social anxiety disorder. Cochrane Database of Systematic Reviews. , 2007. 2.	E	a	All studies reviewed are included in the submission (Kasper et al, 2002).

Appendix 1: Article Abstracts

Atmaca, M., M. Kuloglu, et al. (2002). "Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings." Hum Psychopharmacol **17**(8): 401-5.

The efficacy of irreversible and reversible monoamine oxidase inhibitors (MAOIs) in the treatment of social phobia (SP) is well established. Recently, selective serotonin reuptake inhibitors (SSRIs) have been used more frequently. In the present study, the efficacy and side-effect profile of citalopram, an SSRI, and moclobemide, the only MAOI used in Turkey, were compared. The 71 patients diagnosed with SP according to DSM-III-R were randomly assigned to two subgroups; citalopram (n = 36) or moclobemide (n = 35). The study was an 8-week, randomized, open-label, rater-blinded, parallel-group trial. All patients were assessed by Hamilton anxiety rating (HAM-A), Liebowitz social anxiety (LSAS), clinical global impression-severity of illness (CGI-SI) and clinical global impression-improvement (CGI-I) scales. There was a similar percentage of responders (citalopram 75%, n = 27 and moclobemide 74.3%, n = 26), with a >50% or greater reduction in LSAS total score and ratings of "very much" or "much improved" on the CGI-I. None of the patients withdrew from the study. The results of the present study suggest that citalopram has shown promising results in patients with SP.

Atmaca, M., E. Tezcan, et al. (2004). "Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment." Eur Arch Psychiatry Clin Neurosci **254**(4): 231-5.

A growing body of evidence indicates that oxidative stress is involved in the etiopathogenesis of some psychiatric disorders. In our previous study, we have found that social phobia (SP) seems to be associated with elevated antioxidant enzymes and malondialdehyde (MDA) levels, a lipid peroxidation product. In the present investigation, we sought to determine whether the increased radical burden observed in patients with SP would be attenuated with alleviation of symptoms. Thirty-nine patients diagnosed with generalized SP and 39 healthy controls participated in this study. The measurements of MDA, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) were performed before and after a period of 8 weeks of citalopram treatment. In this period, the patients received citalopram but controls did not. The initial dose of citalopram was 20mg, with 20 mg increments occurring every 2 weeks, to a maximum dose of 60 mg, with the mean daily dose of 38.9 +/- 13.3 mg/day. All patients were evaluated by using Liebowitz Social Anxiety Scale (LSAS). The mean MDA, SOD, GSH-Px and CAT levels of the patient group at baseline were significantly higher than those of controls. Antioxidant enzymes and MDA levels decrease significantly through citalopram treatment. Significant and positive correlation was observed between decrease in the total LSAS scores, and SOD or CAT levels. In conclusion, our

results suggest that, in patients with SP, subchronic treatment with citalopram may decrease antioxidant enzymes and MDA values and that they are state markers of SP because they return to normal values with treatment.

Bandelow, B., D. S. Baldwin, et al. (2006). "What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?" J Clin Psychiatry **67**(9): 1428-34.

OBJECTIVE: Symptom-free remission is a goal for treatment in depression and anxiety disorders, but there is no consensus regarding the threshold for determining remission in individual disorders. We sought to determine these thresholds by comparing, in a post hoc analysis, scores on the Clinical Global Impressions scale (CGI) and disorder-specific symptom severity rating scales from all available studies of the treatment of major depressive disorder, panic disorder, generalized anxiety disorder, and social anxiety disorder with the same medication (escitalopram). We also sought to compare the standardized effect sizes of escitalopram for these 4 psychiatric disorders. DATA SOURCES AND STUDY SELECTION: Raw data from all randomized, double-blind, placebo-controlled, acute treatment studies sponsored by H. Lundbeck A/S (Copenhagen, Denmark) or Forest Laboratories, Inc. (New York, N.Y.), published through March 1, 2004, with patients treated with escitalopram for DSM-IV major depressive disorder (5 studies), panic disorder (1 study), generalized anxiety disorder (4 studies), or social anxiety disorder (2 studies) were compared with regard to the standardized effect sizes of change in CGI score and scores on rating scales that represent the "gold standard" for assessment of these disorders (the Montgomery-Asberg Depression Rating Scale, the Panic and Agoraphobia Scale, the Hamilton Rating Scale for Anxiety, and the Liebowitz Social Anxiety Scale, respectively). DATA SYNTHESIS: In all indications, treatment with escitalopram showed differences from placebo in treatment effect from 0.32 to 0.59 on the CGI-S and CGI-I and standardized effect sizes from 0.32 to 0.50 on the standard rating scales. There were no significant differences among the different disorders. Moderate to high correlations were found between scores on the CGI and the standard scales. The corresponding standard scale scores for CGI-defined "response" and "remission" were determined. CONCLUSION: Comparison of scores on the standard scales and scores on the CGI suggest that the traditional definition of response (i.e., a 50% reduction in a standard scale) may be too conservative.

Bouwer, C. and D. J. Stein (1998). "Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia." J Affect Disord **49**(1): 79-82.

BACKGROUND: There is increasing evidence that social phobia responds to treatment with selective serotonin reuptake inhibitors (SSRIs). However, the efficacy of citalopram, the most selective of the SSRIs, in social phobia has not been well documented. METHODS:

Citalopram was used on an open-label naturalistic basis in 22 social phobia patients presenting for treatment (40 mg daily for 12 weeks). Patients were rated with the Liebowitz Social Anxiety Scale and the Clinical Global Impressions (CGI) scale. RESULTS: Ratings on the Liebowitz Social Anxiety Scale and the CGI were significantly improved after treatment. A total of 86% of patients were responders at week 12. LIMITATION: Open, uncontrolled study. CONCLUSIONS: Citalopram appears to be effective in the treatment of social phobia. A controlled trial is warranted to confirm these data. The role of serotonin in social phobia deserves further study.

Davidson, J. (2006). "Pharmacotherapy of social anxiety disorder: What does the evidence tell us?" Journal of Clinical Psychiatry **67**: 20-26.

The treatment goals for social anxiety disorder (SAD) are to reduce fear, avoidance, physical distress, disability, and comorbidity. This review illustrates some of the primary studies used to evaluate efficacy of treatments for SAD. The selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, fluoxetine, fluvoxamine, and escitalopram and the serotonin-norepinephrine reuptake inhibitor venlafaxine are effective treatments. They have the additional benefit of being able to treat comorbid conditions. For people who do not respond to serotonin reuptake inhibitors, treatment options include benzodiazepines (clonazepam, alprazolam, and bromazepam), a2d calcium-channel blockers (gabapentin and pregabalin), reversible inhibitors of monoamine oxidase A (moclobemide, although agents in this class are not available in the United States), antiepileptics (levetiracetam), and atypical antipsychotics (olanzapine). The irreversible monoamine oxidase inhibitor phenelzine can be considered an effective third-line therapy. Combination treatments may be beneficial, but more research is needed. Benefits of b-blockers (propranolol and atenolol) are limited to performance anxiety. Botulinum toxin A may be an effective augmentation treatment option for severe axillary hyperhidrosis in patients with SAD. Studies show that patients with SAD who are maintained on paroxetine, sertraline, or clonazepam have a low relapse rate.

Dhillon, S., L. J. Scott, et al. (2006). "Escitalopram: A review of its use in the management of anxiety disorders." CNS Drugs **20**(9): 763-790.

Abstract: Escitalopram (Cipralex(registered trademark) Lexapro(registered trademark) Seroplex(registered trademark) Sipralexa(registered trademark)), the therapeutically active S-enantiomer of racemic citalopram (RS-citalopram), is a potent and highly selective serotonin reuptake inhibitor. It is effective and generally well tolerated in the treatment of moderate to severe generalised anxiety disorder (GAD) or social anxiety disorder (SAD), panic disorder (with or without agoraphobia) as well as obsessive-compulsive disorder (OCD). Moreover, escitalopram is at least as effective as paroxetine for the treatment of GAD, SAD or OCD and appears to achieve a more rapid response than racemic citalopram in the management of panic disorder. Generally, it has a more favourable tolerability profile than

paroxetine in terms of fewer discontinuation symptoms. In addition, a favourable pharmacokinetic profile permits once-daily administration of the drug. Additional comparative studies are required to definitively position escitalopram with respect to other SSRIs and venlafaxine. Nevertheless, available clinical data indicate that escitalopram is an effective first-line treatment option for the management of GAD, SAD, panic disorder and OCD. Pharmacological Properties: Escitalopram is unique among SSRIs in that it stabilises its binding to the high-affinity binding site of the serotonin transporter protein via an allosteric effect at the low-affinity binding site. In vivo and in vitro studies have shown escitalopram to be approximately twice as potent as citalopram in inhibiting serotonin reuptake. It is highly selective for the serotonin transporter protein and shows no or very low affinity for other receptors or ion channels. In vivo, escitalopram was four times more potent than citalopram in reducing firing activity of presumed serotonergic neurons in rat brain. Single and multiple once-daily oral doses of escitalopram 10-30 mg/day show linear, dose-proportional pharmacokinetics in healthy volunteers. The steady-state plasma concentration of the drug was reached within 7-10 days. Escitalopram is largely metabolised in the liver, mainly into S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). Cytochrome P450 (CYP) isozymes CYP2C19, 3A4 and 2D6 contribute equally to the metabolism of escitalopram into S-DCT, whereas only CYP2D6 was involved in the second demethylation of S-DCT to S-DDCT. Neither metabolite has significant serotonin reuptake activity in vivo. Escitalopram and its metabolites are excreted primarily via the kidneys, with a small percentage of the drug excreted unchanged. The mean plasma elimination half-life (t1/2) of escitalopram is 27-33 hours. Escitalopram dosage adjustments are recommended in elderly patients and patients with impaired hepatic function, and caution is advised in patients with severe renal impairment. Therapeutic Efficacy: In well designed, double-blind, comparative, 8- to 24-week studies in patients with moderate to severe GAD, escitalopram was more effective than placebo and at least as effective as paroxetine in reducing the mean Hamilton Rating Scale for Anxiety total score (primary efficacy parameter). Escitalopram demonstrated continued efficacy in a 24-week open-label extension study of three 8-week double-blind trials and a (less-than or equal to)76-week placebo-controlled, double-blind, relapse-prevention study. Moreover, in the relapse-prevention study, escitalopram recipients showed a significantly longer time to relapse and reduced risk of relapse than placebo recipients, and fewer escitalopram than placebo recipients relapsed. Escitalopram was also associated with better mental health-related quality of life than placebo in a subgroup of patients from the relapse-prevention study. In two randomised, double-blind, 12- and 24-week studies in patients with moderate to severe SAD, apart from escitalopram 10 mg/day at 12 weeks, escitalopram was significantly more effective than placebo and at least as effective as paroxetine in reducing the mean Liebowitz Social Anxiety Scal total scores (primary efficacy parameter). In a 24-week double-blind, placebo-controlled relapse-prevention study,

escitalopram recipients had a longer time to relapse and reduced risk of relapse compared with placebo recipients, and significantly fewer escitalopram than placebo recipients relapsed. Escitalopram was significantly more effective than placebo in reducing the panic attack frequency (primary efficacy parameter) with a faster onset of action than citalopram in a randomised, double-blind trial in patients with panic disorder. In an open-label study in elderly (>65 years) patients with panic disorder, improvement in panic attack frequency (primary efficacy parameter) and secondary efficacy variables occurred more quickly in escitalopram than citalopram recipients. In patients with OCD, escitalopram 20 mg/day for 12 weeks was more effective than placebo, and at least as effective as paroxetine 40 mg/day, with respect to a mean reduction from baseline in the Yale-Brown Obsessive Scale total score (primary efficacy parameter). In a relapse-prevention study, escitalopram recipients showed a longer time to relapse and a significantly reduced risk of relapse compared with those receiving placebo. In addition, the proportion of patients who relapsed in the escitalopram group was significantly lower than in the placebo group. Tolerability: Escitalopram was generally well tolerated in adult patients with GAD, SAD, panic disorder or OCD. Withdrawal rates due to treatment-emergent adverse events in escitalopram recipients were 6.0-11.8%. The profile of treatment-emergent adverse events was generally similar in escitalopram recipients irrespective of the type of anxiety disorder in placebo-controlled short-term trials. The most common adverse event in escitalopram and placebo recipients was headache (15-25% of patients). Other common adverse events in escitalopram recipients with GAD include nausea (18.2%), ejaculation disorder (14.3%), insomnia (11.9%), fatigue (7.7%), decreased libido (6.8%) and anorgasmia (5.7%). Withdrawal rates during the 12-week open-label period of three relapse-prevention studies were 7.7-20.0%, whereas 2.6-7.9% withdrew from the study during the (less-than or equal to)76-week double-blind period. Furthermore, the overall incidence of adverse events was numerically lower during the double-blind period than the initial 12-week open-label period. Escitalopram recipients generally reported more discontinuation symptoms than placebo recipients after switching to placebo in two fixed-dose studies, whereas patients continuing escitalopram treatment generally reported fewer discontinuation symptoms than those switching to placebo in the relapse-prevention studies. The tolerability profile of escitalopram was generally similar to those of paroxetine or citalopram. However, in one study, paroxetine recipients showed significantly higher rates of withdrawal due to treatment-emergent adverse events than escitalopram recipients, and more paroxetine than escitalopram recipients appeared to experience sexual adverse events (ejaculation disorder [30.0% vs 14.8%], anorgasmia [26.2% vs 5.9%] and decreased libido [22.6% vs 4.9%]). Some discontinuation symptoms were reported in significantly fewer escitalopram than paroxetine recipients, and escitalopram recipients showed significantly lower mean changes in discontinuation emergent signs and symptoms scores than paroxetine recipients. In large analyses of placebo-controlled and

relapse-prevention studies in patients with major depressive disorder or anxiety disorders, there was no indication of increased risk of suicidal behaviour in escitalopram or placebo recipients, with no completed suicides during the first 2 weeks of escitalopram or placebo therapy. Moreover, in an analysis of pharmacovigilance post-marketing surveillance information, escitalopram recipients had a low suicide rate (1.8 per million prescriptions). (copyright) 2006 Adis Data Information BV. All rights reserved.

Hedges, D. W., B. L. Brown, et al. (2007). "The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials." J Psychopharmacol **21**(1): 102-11.

Social anxiety disorder is associated with impairment in social and occupational functioning, significant personal distress and a possible economic burden, resulting in a reduction in quality of life. To understand better the efficacy of selective serotonin reuptake inhibitors in social anxiety disorder, randomized, double-blind, placebo-controlled trials were evaluated. Pubmed and PsychINFO electronic databases were searched for social anxiety disorder, social phobia, selective serotonin reuptake inhibitors, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Fifteen published, randomized, double-blind, placebo-controlled trials of selective serotonin reuptake inhibitors in social anxiety disorder were identified. Design, subject number, drug and dose, trial length, rating instruments, and baseline and end point data were extracted and then verified independently by a second investigator. Effect sizes were calculated from mean changes in drug and placebo groups in the Liebowitz Social Anxiety Scale and the Sheehan Disability Scale, as well as from other scales where available. For the binary data of the Clinical Global Impression of Change scores, Theta log-odds ratios (the effect-size measure appropriate for binary data) were calculated from proportion changes. Effect sizes for the Liebowitz Social Anxiety Scale ranged from -0.029 to 1.214. Effect sizes for the Sheehan Disability Scale ranged from 0.203 to 0.480 for work, 0.237 to 0.786 for social function, and 0.118 to 0.445 for family function. The Theta log-odds ratios for Clinical Global Impression of Change scores ranged from 0.644 to 3.267. Consistent with previous studies, selective serotonin reuptake inhibitors appear more effective than placebo for social anxiety disorder, with improvement extending into social and occupational function.

Ipser, J. C., P; Dhansay, Y; Fakier, N; Seedat, S; Stein, DJ (2007). "Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders." Cochrane Database of Systematic Reviews **2**.

A large proportion of patients with anxiety disorders fail to respond to first-line medication interventions, despite evidence of the effectiveness of these agents.

Objectives

To assess the effects of medication versus placebo augmentation in the treatment of patients with anxiety disorders who have failed to respond adequately to first-line drug therapies.

Search strategy

The Cochrane Depression, Anxiety & Neurosis Group (CCDAN) specialised registers (CCDANCTR-Studies and CCDANCTR-References) were searched on 3/8/2005, MEDLINE (January 1966 to July 2005) and PsycINFO (1966 to 2005, Part A). Unpublished trials were identified through the Controlled Trials database and the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972 to 2005). Additional studies in any language were sought in reference lists of retrieved articles.

Selection criteria

All randomised controlled trials (RCTs) of the medication augmentation of pharmacotherapy for treatment resistant anxiety disorders.

Data collection and analysis

Two raters independently assessed RCTs for inclusion in the review, collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by class of augmentation agent and anxiety disorder. Overall effect estimates were calculated using a random-effects model, heterogeneity was assessed and subgroup/sensitivity analyses were undertaken.

Main results

Twenty eight short-term (average of seven weeks) randomised controlled trials (740 participants) were included in the review, 20 of which investigated augmentation of medication for treatment-resistant obsessive compulsive disorder (OCD). Summary statistics for responder status from nine trials demonstrate overall superiority of a variety of medication agents to placebo (relative risk of non-response (RR) 3.16, 95% CI 1.08 to 9.23). Similarly, symptom severity was significantly reduced in the medication groups, relative to placebo (number of trials (N) = 14, standardised mean difference (SMD) -0.87, 95% CI -1.37 to -0.36). There is no evidence of a difference between medication and placebo in total dropout rate, or in the number of dropouts due to adverse events.

Authors' conclusions

Medication augmentation can be an effective and well-tolerated short-term treatment strategy for non-responders to first-line pharmacotherapy of anxiety disorders. However, any conclusions must be tentative in view of methodological and clinical heterogeneity, and the fact that much of

the relevant database is based on antipsychotic augmentation trials in OCD patients resistant to serotonin reuptake inhibitors (SRIs). Additional data are needed to address several areas, including the efficacy of augmentation over the longer-term, and the value of medication augmentation in comparison to other strategies (eg switching medication, adding psychotherapy).

Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study." Br J Psychiatry **186**: 222-6.

BACKGROUND: Selective serotonin reuptake inhibitors are effective in the treatment of social anxiety disorder and are currently regarded as the pharmacotherapy of choice. AIMS: To investigate the efficacy and tolerability of escitalopram in the treatment of generalised social anxiety disorder. METHOD: Patients with generalised social anxiety disorder were randomised to receive placebo (n=177) or 10-20 mg escitalopram (n=181) in a 12-week, double-blind trial. The primary outcome measure was the mean change from baseline to last assessment in the Liebowitz Social Anxiety Scale (LSAS) total score. RESULTS: The study showed a statistically superior therapeutic effect for escitalopram compared with placebo on the LSAS total score (P=0.005). There were significantly more responders to treatment for escitalopram than for placebo (54% v. 39%; P<0.01). The clinical relevance of these findings was supported by significant reduction in the work and social components of the Sheehan Disability Scale and by the good tolerability of escitalopram treatment. CONCLUSIONS: Escitalopram was efficacious and well tolerated in the treatment of generalised social anxiety disorder.

Lader, M., K. Stender, et al. (2004). "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 **19**(4): 241-8.

Selective serotonin reuptake inhibitors are the pharmacological treatment of choice for the treatment of social anxiety disorder (SAD). The efficacy and tolerability of fixed doses of escitalopram were compared to those of placebo in the long-term treatment of generalised SAD, using paroxetine as an active reference. Patients with a DSM-IV diagnosis of SAD between 18-65 years of age were randomised to 24 weeks of double-blind treatment with placebo (n = 166), 5 mg escitalopram (n = 167), 10 mg escitalopram (n = 167), 20 mg escitalopram (n = 170), or 20 mg paroxetine (n = 169). Based on the primary efficacy parameter, Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (LOCF), a significantly superior therapeutic effect compared to placebo was seen for 5 and 20 mg escitalopram and for all doses for the OC analyses. Further improvement in LSAS scores was seen at Week 24 (OC and LOCF), with significant superiority over placebo for all doses of escitalopram, and 20 mg escitalopram was significantly superior to 20 mg paroxetine. Response to treatment (assessed by a Clinical Global Impression-Improvement score < or = 2) was significantly higher for all active treatments than for placebo at

Week 12. Clinical relevance was supported by a significant decrease in all the Sheehan disability scores, and the good tolerability of escitalopram treatment. It is concluded that doses of 5-20 mg escitalopram are effective and well tolerated in the short- and long-term treatment of generalised SAD.

Montgomery SA (May 2005). Relapse Prevention in Patients Suffering From Social Anxiety Disorder. 158th Annual Meeting of the American Psychiatric Association, Atlanta, GA.

Introduction: Escitalopram is the most selective SSRI, whose efficacy and tolerability in the short-term treatment of SAD has been established. Methods: This study was conducted in outpatients (18-80 years) with a primary diagnosis of generalized SAD (DSM-IV) and an LSAS score >=70. After 12 weeks of open-label treatment (10-20mg/day escitalopram), responders (CGI-I of 1 or 2) were RANDOMized to 24 weeks of escitalopram (n=190) or PLACEBO (n=181) treatment, to assess the relapse rate. The initial dose of 10 mg/ day could be doubled to a maximum of 20 mg/day, if clinically indicated, at Week 2, 4, or 8 of open treatment. Relapse was defined as an increase in LSAS score >=10 or withdrawal due to lack of efficacy. Results: Time to relapse was significantly lower for escitalopram COMPARed to PLACEBO (log-rank: p<0.001), and significantly fewer escitalopram-treated patients relapsed (22% VERSUS 50%, Fisher’s test, p<0.001). Significantly more escitalopram-treated patients completed the study (66% VERSUS 44%, p<0.001). The favorable side-effect profile of escitalopram in long-term treatment was confirmed, with only 4% of escitalopram-treated patients withdrawing due to adverse events. Conclusion: Escitalopram 10-20 mg/day is highly effective in preventing relapse in patients with SAD and well tolerated. References: 1. Lader M, Stender K, Burger V, Nil R: Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: RANDOMized, DOUBLE-BLIND, PLACEBO-controlled, fixeddose study. Depress Anxiety 2004; 19:241-248. 2. Kasper S, Stein DJ, Loft H, Nil R: Escitalopram in the treatment of social anxiety disorder: a RANDOMised, PLACEBO-controlled, flexible-dose study. Br J Psychiatry, in press.

Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." J Clin Psychiatry **66**(10): 1270-8.

OBJECTIVE: Escitalopram has proven efficacy in the short-term treatment of generalized social anxiety disorder (SAD). The present relapse prevention study investigated relapse rates during a 24-week, randomized, double-blind, placebo-controlled period in patients with generalized SAD who had responded to 12-week open-label treatment with escitalopram. METHOD: A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of > or = 70 received 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global

Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalopram (10 or 20 mg/day) (N = 190) or placebo (N = 181), continuing with the dose level administered at the end of the open-label period. Relapse was defined as either an increase in LSAS total score of > or = 10 or withdrawal due to lack of efficacy, as judged by the investigator. The study was conducted from January 2001 to June 2002. RESULTS: Survival analysis of relapse and time to relapse showed a significant advantage for escitalopram compared to placebo (log-rank test: p < .001). The risk of relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients (p < .001), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses. Escitalopram was well tolerated during double-blind treatment of generalized SAD, and only 2.6% of the escitalopram-treated patients withdrew because of adverse events. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram and 8.3% for patients treated with placebo. CONCLUSION: Escitalopram was effective and well tolerated in the long-term treatment of generalized SAD.

Pallanti, S. and L. Quercioli (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice and Epidemiology in Mental Health **2**(-).

Background: Social Anxiety Disorder (SAD) is a common disorder and its high prevalence and lifelong chronicity are such that it represents a substantial public health problem. The observation that serotonergic agents appear to be effective for its treatment suggests that patients may have abnormal serotonergic neurotransmission within the central nervous system. We investigated the efficacy of Escitalopram in treatment resistant patients with SAD. Method: Twenty-nine adult outpatients participated in a 12-week open-label trial of escitalopram. All the subjects had a primary diagnosis of SAD and had failed at least one previous adequate trial of paroxetine. Escitalopram was orally administered starting with a dose of 10 mg/day following a 1-week titration. Results: The escitalopram treatment was characterized by good tolerability (drop-out rate due to intolerance: 10.3%), and 24 subjects completed the study trial. At the end of the 12-week treatment period, 14 subjects (48.3%) were considered as responders on the basis of the Clinical Global Impression-Improvement (CGI-I) (much or very much improved) scale and the Liebowitz Scale for Social Anxiety (LSAS) (reduction >35% compared to baseline). We observed a significant mean reduction in the Sheehan Disability Scale Work (p < .05) and Social (p < .05) subscores, but not in the Family subscore. Conclusion: These data suggest escitalopram has a role in the treatment of resistant SAD, especially in view of the favourable tolerability profile observed in the patients. Controlled studies are required to further investigate these findings and to compare escitalopram with other treatments for this disorder. (copyright) 2006 Pallanti and Quercioli; licensee BioMed Central Ltd.

Stein, D. I., JC; van Balkom, AJ (2007). "Pharmacotherapy for social anxiety disorder." Cochrane Database of Systematic Reviews **2**.

Background

Social phobia (SP), or social anxiety disorder, is a prevalent and disabling disorder. The growing evidence of the disorder's neurobiological basis has stimulated an increased interest in the use of medication in its treatment.

Objectives

To assess the effects of pharmacotherapy for social phobia, and to determine whether particular classes of medication are more effective and/or acceptable than others in its treatment.

Search strategy

We searched the Cochrane Depression, Anxiety & Neurosis Group (CCDAN) specialised register, the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 1, 2004), MEDLINE (1966 to 2003), PsycINFO (1966 to 2003), and reference lists of retrieved articles. We also requested published and unpublished RCTs from SP researchers and pharmaceutical companies.

Selection criteria

All placebo-controlled randomised trials of the pharmacotherapy of SP were considered for the review.

Data collection and analysis

Two raters independently collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by medication group (SSRIs - selective serotonin reuptake inhibitors; MAOIs - Monoamine oxidase inhibitors; moclobemide and brofaromine). Dichotomous and continuous measures were calculated using a random effects model, heterogeneity was assessed, and subgroup/sensitivity analyses were undertaken.

Main results

37 RCTs of a range of medications were included in the analysis (5264 participants), of which 23 were short-term (14 weeks or less). A funnel plot provided evidence of publication bias.

Twenty-six trials demonstrated short-term superiority in treatment response of all medication groups over placebo (N = 3696; relative risk of non-response (RR-non) = 0.64; 95% CI = 0.57, 0.73). However, the SSRIs were significantly more effective than both moclobemide (Qb = 38.61; p

< 0.00001), and, and to a lesser extent, brofaromine (Qb = 2.87; p = 0.09).

Sixteen comparisons of symptom severity showed a statistically significant difference between medication and placebo (weighed mean difference = -18, 95%CI = -25.17, -10.83). This effect was once again most evident for the SSRIs. Medication also reduced SP symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment response was demonstrated by 4 maintenance (RR-non = 0.62; 95% CI = 0.50, 0.77) and 4 relapse prevention (RR of relapse = 0.33; 95% CI = 0.22, 0.49) studies. Two performance anxiety RCTs reported mixed results.

Authors' conclusions

Medication appears effective in treating SP over the short term (particularly amongst the SSRIs), and the long term. Nevertheless, the possibility of publication bias has to be acknowledged. Additional issues for future research include the use of medication in children and adolescents with SP, SP with comorbid psychiatric disorders, and performance anxiety.

Stein, D. J., S. Kasper, et al. (2004). "Escitalopram in the treatment of social anxiety disorder: Analysis of efficacy for different clinical subgroups and symptom dimensions." Depression and Anxiety **20**(4): 175-181.

Escitalopram has demonstrated efficacy for the acute treatment of social anxiety disorder (SAD) in two placebo-controlled trials and for long-term treatment in a relapse-prevention study. Social anxiety disorder is a heterogeneous disorder. This study questions whether this new selective serotonin reuptake inhibitor is effective across different subgroups of patients. Data from two randomised, placebo-controlled, 12-week escitalopram SAD trials were pooled. General linear models were used to determine the efficacy of escitalopram in different patient subgroups. Furthermore, a factor analysis of the primary efficacy scale, the Liebowitz Social Anxiety Scale (LSAS), was undertaken, and a determination made of whether treatment effects were similar for the different symptom dimensions. Escitalopram was effective in both younger and older patients, in male and female patients, and in patients with more and less severe social anxiety symptoms. The LSAS factor analysis showed six factors, which were differentially associated with different areas of disability. Escitalopram was significantly superior to placebo for all six symptom dimensions. The treatment effects of escitalopram were independent of gender, symptom severity and chronicity, and comorbid depressive symptoms. A six-factor model of social anxiety symptoms is supported by the distinctive association between these symptom dimensions and different areas of disability, but did not predict differential response to escitalopram. (copyright) 2005 Wiley-Liss, Inc.

Stein DJ, A. E., Lader M (2006). "Escitalopram versus paroxetine for social anxiety disorder: an analysis of efficacy for different symptom dimensions." European neuropsychopharmacology **16**(1): 33-8.

BACKGROUND: A previous factor analysis of pooled data demonstrated that the Liebowitz Social Anxiety Scale (LSAS) can be divided into six subscales. This paper examines data from a fixed-dose trial of escitalopram versus paroxetine, in order to determine the differential effects of these agents on symptom dimensions in social anxiety disorder (SAD). METHODS: Data from a 24-week randomised, placebo-controlled, comparative study of fixed doses of escitalopram (5 mg, 10 mg, 20 mg) versus paroxetine (20 mg) in SAD were examined. The six factors identified in a previous factor analysis of baseline data from escitalopram studies on the primary efficacy scale, the LSAS, were used to compute subscale scores. These were analysed using analysis of covariance (ANCOVA), and standardised effect sizes were calculated. RESULTS: The combined escitalopram data and the paroxetine data both demonstrated significant superiority to placebo on each of the 6 LSAS factors at week 24 (OC analysis). Escitalopram doses of 5 mg, 10 mg, and 20 mg were generally more effective than placebo for each of the factors. Escitalopram 20 mg was significantly more effective than paroxetine 20 mg on 5 of the 6 symptom dimensions. CONCLUSION: Factor analysis of the LSAS allows for useful secondary analyses that support and extend the primary efficacy analysis of this instrument. The analysis here indicates that different escitalopram doses are effective across the various symptom dimensions of SAD.

Stein DJ. (2006). "Continued escitalopram reduces risk of relapse in people with generalised social anxiety disorder.[comment]." Evidence-Based Mental Health **9**(2): 52.

Appendix 2: Full list of articles from Various Databases

PubMed

Atmaca, M., M. Kuloglu, et al. (2002). "Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings." Hum Psychopharmacol **17**(8): 401-5.

The efficacy of irreversible and reversible monoamine oxidase inhibitors (MAOIs) in the treatment of social phobia (SP) is well established. Recently, selective serotonin reuptake inhibitors (SSRIs) have been used more frequently. In the present study, the efficacy and side-effect profile of citalopram, an SSRI, and moclobemide, the only MAOI used in Turkey, were compared. The 71 patients diagnosed with SP according to DSM-III-R were randomly assigned to two subgroups; citalopram (n = 36) or moclobemide (n = 35). The study was an 8-week, randomized, open-label, rater-blinded, parallel-group trial. All patients were assessed by Hamilton anxiety rating (HAM-A), Liebowitz social anxiety (LSAS), clinical global impression-severity of illness (CGI-SI) and clinical global impression-improvement (CGI-I) scales. There was a similar percentage of responders (citalopram 75%, n = 27 and moclobemide 74.3%, n = 26), with a >50% or greater reduction in LSAS total score and ratings of "very much" or "much improved" on the CGI-I. None of the patients withdrew from the study. The results of the present study suggest that citalopram has shown promising results in patients with SP.

Atmaca, M., E. Tezcan, et al. (2004). "Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment." Eur Arch Psychiatry Clin Neurosci **254**(4): 231-5.

A growing body of evidence indicates that oxidative stress is involved in the etiopathogenesis of some psychiatric disorders. In our previous study, we have found that social phobia (SP) seems to be associated with elevated antioxidant enzymes and malondialdehyde (MDA) levels, a lipid peroxidation product. In the present investigation, we sought to determine whether the increased radical burden observed in patients with SP would be attenuated with alleviation of symptoms. Thirty-nine patients diagnosed with generalized SP and 39 healthy controls participated in this study. The measurements of MDA, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) were performed before and after a period of 8 weeks of citalopram treatment. In this period, the patients received citalopram but controls did not. The initial dose of citalopram was 20mg, with 20 mg increments occurring every 2 weeks, to a maximum dose of 60 mg, with the mean daily dose of 38.9 +/- 13.3 mg/day. All patients were evaluated by using Liebowitz Social Anxiety Scale (LSAS). The mean MDA, SOD, GSH-Px and CAT levels of the patient group at baseline were significantly higher than those of controls. Antioxidant enzymes and MDA levels decrease significantly through citalopram treatment. Significant and positive correlation was observed between decrease in the total LSAS scores, and SOD or CAT levels. In conclusion, our results suggest that, in patients with SP, subchronic treatment with citalopram may decrease antioxidant enzymes and MDA values and that they are state markers of SP because they return to normal values with treatment.

Bandelow, B., D. S. Baldwin, et al. (2006). "What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?" J Clin Psychiatry **67**(9): 1428-34.

OBJECTIVE: Symptom-free remission is a goal for treatment in depression and anxiety disorders, but there is no consensus regarding the threshold for determining remission in individual disorders. We sought to determine these thresholds by comparing, in a post hoc analysis, scores on the Clinical Global Impressions scale (CGI) and disorder-specific symptom severity rating scales from all available studies of the treatment of major depressive disorder, panic disorder, generalized anxiety disorder, and social anxiety disorder with the same medication (escitalopram). We also sought to compare the standardized effect sizes of escitalopram for these 4 psychiatric disorders. DATA SOURCES AND STUDY SELECTION: Raw data from all randomized, double-blind, placebo-controlled, acute treatment studies sponsored by H. Lundbeck A/S (Copenhagen, Denmark) or Forest Laboratories, Inc. (New York, N.Y.), published through March 1, 2004, with patients treated with escitalopram for DSM-IV major depressive disorder (5 studies), panic disorder (1 study), generalized anxiety disorder (4 studies), or social anxiety disorder (2 studies) were compared with regard to the standardized effect sizes of change in CGI score and scores on rating scales that represent the "gold standard" for assessment of these disorders (the Montgomery-Asberg Depression Rating Scale, the Panic and Agoraphobia Scale, the Hamilton Rating Scale for Anxiety, and the Liebowitz Social Anxiety Scale, respectively). DATA SYNTHESIS: In all indications, treatment with escitalopram showed differences from placebo in treatment effect from 0.32 to 0.59 on the CGI-S and CGI-I and standardized effect sizes from 0.32 to 0.50 on the standard rating scales. There were no significant differences among the different disorders. Moderate to high correlations were found between scores on the CGI and the standard scales. The corresponding standard scale scores for CGI-defined "response" and "remission" were determined. CONCLUSION: Comparison of scores on the standard scales and scores on the CGI suggest that the traditional definition of response (i.e., a 50% reduction in a standard scale) may be too conservative.

Bouwer, C. and D. J. Stein (1998). "Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia." J Affect Disord **49**(1): 79-82.

BACKGROUND: There is increasing evidence that social phobia responds to treatment with selective serotonin reuptake inhibitors (SSRIs). However, the efficacy of citalopram, the most selective of the SSRIs, in social phobia has not been well documented. METHODS: Citalopram was used on an open-label naturalistic basis in 22 social phobia patients presenting for treatment (40 mg daily for 12 weeks). Patients were rated with the Liebowitz Social Anxiety Scale and the Clinical Global Impressions (CGI) scale. RESULTS: Ratings on the Liebowitz Social Anxiety Scale and the CGI were significantly improved after treatment. A total of 86% of patients were responders at week 12. LIMITATION: Open, uncontrolled study. CONCLUSIONS: Citalopram appears to be effective in the treatment of social phobia. A controlled trial is warranted to confirm these data. The role of serotonin in social phobia deserves further study.

Hedges, D. W., B. L. Brown, et al. (2007). "The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials." J Psychopharmacol **21**(1): 102-11.

Social anxiety disorder is associated with impairment in social and occupational functioning, significant personal distress and a possible economic burden, resulting in a reduction in quality of life. To understand better the efficacy of selective serotonin reuptake inhibitors in social anxiety disorder, randomized, double-blind, placebo-controlled trials were evaluated. Pubmed and PsychINFO electronic databases were searched for social anxiety disorder, social phobia, selective serotonin reuptake inhibitors, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Fifteen published, randomized, double-blind, placebo-controlled trials of selective serotonin reuptake inhibitors in social anxiety disorder were identified. Design, subject number, drug and dose, trial length, rating instruments, and baseline and end point data were extracted and then verified independently by a second investigator. Effect sizes were calculated from mean changes in drug and placebo groups in the Liebowitz Social Anxiety Scale and the Sheehan Disability Scale, as well as from other scales where available. For the binary data of the Clinical Global Impression of Change scores, Theta log-odds ratios (the effect-size measure appropriate for binary data) were calculated from proportion changes. Effect sizes for the Liebowitz Social Anxiety Scale ranged from -0.029 to 1.214. Effect sizes for the Sheehan Disability Scale ranged from 0.203 to 0.480 for work, 0.237 to 0.786 for social function, and 0.118 to 0.445 for family function. The Theta log-odds ratios for Clinical Global Impression of Change scores ranged from 0.644 to 3.267. Consistent with previous studies, selective serotonin reuptake inhibitors appear more effective than placebo for social anxiety disorder, with improvement extending into social and occupational function.

Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study." Br J Psychiatry **186**: 222-6.

BACKGROUND: Selective serotonin reuptake inhibitors are effective in the treatment of social anxiety disorder and are currently regarded as the pharmacotherapy of choice. AIMS: To investigate the efficacy and tolerability of escitalopram in the treatment of generalised social anxiety disorder. METHOD: Patients with generalised social anxiety disorder were randomised to receive placebo (n=177) or 10-20 mg escitalopram (n=181) in a 12-week, double-blind trial. The primary outcome measure was the mean change from baseline to last assessment in the Liebowitz Social Anxiety Scale (LSAS) total score. RESULTS: The study showed a statistically superior therapeutic effect for escitalopram compared with placebo on the LSAS total score (P=0.005). There were significantly more responders to treatment for escitalopram than for placebo (54% v. 39%; P<0.01). The clinical relevance of these findings was supported by significant reduction in the work and social components of the Sheehan Disability Scale and by the good tolerability of escitalopram treatment. CONCLUSIONS: Escitalopram was efficacious and well tolerated in the treatment of generalised social anxiety disorder.

Lader, M., K. Stender, et al. (2004). "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 **19**(4): 241-8.

Selective serotonin reuptake inhibitors are the pharmacological treatment of choice for the treatment of social anxiety disorder (SAD). The efficacy and tolerability of fixed doses of escitalopram were compared to those of placebo in the long-term treatment of generalised SAD, using paroxetine as an active reference. Patients with a DSM-IV diagnosis of SAD between 18-65 years of age were randomised to 24 weeks of double-blind treatment with placebo (n = 166), 5 mg escitalopram (n = 167), 10 mg escitalopram (n = 167), 20 mg escitalopram (n = 170), or 20 mg paroxetine (n = 169). Based on the primary efficacy parameter, Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (LOCF), a significantly superior therapeutic effect compared to placebo was seen for 5 and 20 mg escitalopram and for all doses for the OC analyses. Further improvement in LSAS scores was seen at Week 24 (OC and LOCF), with significant superiority over placebo for all doses of escitalopram, and 20 mg escitalopram was significantly superior to 20 mg paroxetine. Response to treatment (assessed by a Clinical Global Impression-Improvement score < or = 2) was significantly higher for all active treatments than for placebo at Week 12. Clinical relevance was supported by a significant decrease in all the Sheehan disability scores, and the good tolerability of escitalopram treatment. It is concluded that doses of 5-20 mg escitalopram are effective and well tolerated in the short- and long-term treatment of generalised SAD.

Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." J Clin Psychiatry **66**(10): 1270-8.

OBJECTIVE: Escitalopram has proven efficacy in the short-term treatment of generalized social anxiety disorder (SAD). The present relapse prevention study investigated relapse rates during a 24-week, randomized, double-blind, placebo-controlled period in patients with generalized SAD who had responded to 12-week open-label treatment with escitalopram. METHOD: A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of > or = 70 received 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalo-pram (10 or 20 mg/day) (N = 190) or placebo (N = 181), continuing with the dose level administered at the end of the open-label period. Relapse was defined as either an increase in LSAS total score of > or = 10 or withdrawal due to lack of efficacy, as judged by the investigator. The study was conducted from January 2001 to June 2002. RESULTS: Survival analysis of relapse and time to relapse showed a significant advantage for escitalopram compared to placebo (log-rank test: p < .001). The risk of relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients (p < .001), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses. Escitalopram was well tolerated during double-blind treatment of generalized SAD, and only 2.6% of the escitalopram-treated patients withdrew because of adverse events. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram and 8.3% for patients treated with placebo. CONCLUSION: Escitalopram was effective and well tolerated in the long-term treatment of generalized SAD.

Stein, D. J., E. W. Andersen, et al. (2006). "Escitalopram versus paroxetine for social anxiety disorder: an analysis of efficacy for different symptom dimensions." Eur Neuropsychopharmacol **16**(1): 33-8.

BACKGROUND: A previous factor analysis of pooled data demonstrated that the Liebowitz Social Anxiety Scale (LSAS) can be divided into six subscales. This paper examines data from a fixed-dose trial of escitalopram versus paroxetine, in order to determine the differential effects of these agents on symptom dimensions in social anxiety disorder (SAD). METHODS: Data from a 24-week randomised, placebo-controlled, comparative study of fixed doses of escitalopram (5 mg, 10 mg, 20 mg) versus paroxetine (20 mg) in SAD were examined. The six factors identified in a previous factor analysis of baseline data from escitalopram studies on the primary efficacy scale, the LSAS, were used to compute subscale scores. These were analysed using analysis of covariance (ANCOVA), and standardised effect sizes were calculated. RESULTS: The combined escitalopram data and the paroxetine data both demonstrated significant superiority to placebo on each of the 6 LSAS factors at week 24 (OC analysis). Escitalopram doses of 5 mg, 10 mg, and 20 mg were generally more effective than placebo for each of the factors. Escitalopram 20 mg was significantly more effective than paroxetine 20 mg on 5 of the 6 symptom dimensions. CONCLUSION: Factor analysis of the LSAS allows for useful secondary analyses that support and extend the primary efficacy analysis of this instrument. The analysis here indicates that different escitalopram doses are effective across the various symptom dimensions of SAD.

Embase and Medline

Bandelow, B., D. S. Baldwin, et al. (2006). "What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?" Journal of Clinical Psychiatry **67**(9): 1428-1434.

Objective: Symptom-free remission is a goal for treatment in depression and anxiety disorders, but there is no consensus regarding the threshold for determining remission in individual disorders. We sought to determine these thresholds by comparing, in a post hoc analysis, scores on the Clinical Global Impressions scale (CGI) and disorder-specific symptom severity rating scales from all available studies of the treatment of major depressive disorder, panic disorder, generalized anxiety disorder, and social anxiety disorder with the same medication (escitalopram). We also sought to compare the standardized effect sizes of escitalopram for these 4 psychiatric disorders. Data Sources and Study Selection: Raw data from all randomized, double-blind, placebo-controlled, acute treatment studies sponsored by H. Lundbeck A/S (Copenhagen, Denmark) or Forest Laboratories, Inc. (New York, N.Y.), published through March 1, 2004, with patients treated with escitalopram for DSM-IV major depressive disorder (5 studies), panic disorder (1 study), generalized anxiety disorder (4 studies), or social anxiety disorder (2 studies) were compared with regard to the standardized effect sizes of change in CGI score and scores on rating scales that represent the "gold standard" for assessment of these disorders (the Montgomery-Asberg Depression Rating Scale, the Panic and Agoraphobia Scale, the Hamilton Rating Scale for Anxiety, and the Liebowitz Social Anxiety Scale, respectively). Data Synthesis: In all indications, treatment with escitalopram showed differences from placebo in treatment effect from 0.32 to 0.59 on the CGI-S and CGI-I and standardized effect sizes from 0.32 to 0.50 on the standard rating scales. There were no significant differences among the different disorders. Moderate to high correlations were found between scores on the CGI and the standard scales. The corresponding standard scale scores for CGI-defined "response" and "remission" were determined. Conclusion: Comparison of scores on the standard scales and scores on the CGI suggest that the traditional definition of response (i.e., a 50% reduction in a standard scale) may be too conservative.

Dhillon, S., L. J. Scott, et al. (2006). "Escitalopram: A review of its use in the management of anxiety disorders." CNS Drugs **20**(9): 763-790.

Abstract: Escitalopram (Cipralex(registered trademark) Lexapro(registered trademark) Seroplex(registered trademark) Sipralexa(registered trademark)), the therapeutically active S-enantiomer of racemic citalopram (RS-citalopram), is a potent and highly selective serotonin reuptake inhibitor. It is effective and generally well tolerated in the treatment of moderate to severe generalised anxiety disorder (GAD) or social anxiety disorder (SAD), panic disorder (with or without agoraphobia) as well as obsessive-compulsive disorder (OCD). Moreover, escitalopram is at least as effective as paroxetine for the treatment of GAD, SAD or OCD and appears to achieve a more rapid response than racemic citalopram in the management of panic disorder. Generally, it has a more favourable tolerability profile than paroxetine in terms of fewer discontinuation symptoms. In addition, a favourable pharmacokinetic profile

permits once-daily administration of the drug. Additional comparative studies are required to definitively position escitalopram with respect to other SSRIs and venlafaxine. Nevertheless, available clinical data indicate that escitalopram is an effective first-line treatment option for the management of GAD, SAD, panic disorder and OCD. Pharmacological Properties: Escitalopram is unique among SSRIs in that it stabilises its binding to the high-affinity binding site of the serotonin transporter protein via an allosteric effect at the low-affinity binding site. In vivo and in vitro studies have shown escitalopram to be approximately twice as potent as citalopram in inhibiting serotonin reuptake. It is highly selective for the serotonin transporter protein and shows no or very low affinity for other receptors or ion channels. In vivo, escitalopram was four times more potent than citalopram in reducing firing activity of presumed serotonergic neurons in rat brain. Single and multiple once-daily oral doses of escitalopram 10-30 mg/day show linear, dose-proportional pharmacokinetics in healthy volunteers. The steady-state plasma concentration of the drug was reached within 7-10 days. Escitalopram is largely metabolised in the liver, mainly into S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). Cytochrome P450 (CYP) isozymes CYP2C19, 3A4 and 2D6 contribute equally to the metabolism of escitalopram into S-DCT, whereas only CYP2D6 was involved in the second demethylation of S-DCT to S-DDCT. Neither metabolite has significant serotonin reuptake activity in vivo. Escitalopram and its metabolites are excreted primarily via the kidneys, with a small percentage of the drug excreted unchanged. The mean plasma elimination half-life (t1/2) of escitalopram is 27-33 hours. Escitalopram dosage adjustments are recommended in elderly patients and patients with impaired hepatic function, and caution is advised in patients with severe renal impairment. Therapeutic Efficacy: In well designed, double-blind, comparative, 8- to 24-week studies in patients with moderate to severe GAD, escitalopram was more effective than placebo and at least as effective as paroxetine in reducing the mean Hamilton Rating Scale for Anxiety total score (primary efficacy parameter). Escitalopram demonstrated continued efficacy in a 24-week open-label extension study of three 8-week double-blind trials and a (less-than or equal to)76-week placebo-controlled, double-blind, relapse-prevention study. Moreover, in the relapse-prevention study, escitalopram recipients showed a significantly longer time to relapse and reduced risk of relapse than placebo recipients, and fewer escitalopram than placebo recipients relapsed. Escitalopram was also associated with better mental health-related quality of life than placebo in a subgroup of patients from the relapse-prevention study. In two randomised, double-blind, 12- and 24-week studies in patients with moderate to severe SAD, apart from escitalopram 10 mg/day at 12 weeks, escitalopram was significantly more effective than placebo and at least as effective as paroxetine in reducing the mean Liebowitz Social Anxiety Scal total scores (primary efficacy parameter). In a 24-week double-blind, placebo-controlled relapse-prevention study, escitalopram recipients had a longer time to relapse and reduced risk of relapse compared with placebo recipients, and significantly fewer escitalopram than placebo recipients relapsed. Escitalopram was significantly more effective than placebo in reducing the panic attack frequency (primary efficacy parameter) with a faster onset of action than citalopram in a randomised, double-blind trial in patients with panic disorder. In an open-label study in elderly (>65 years) patients with panic disorder, improvement in panic attack frequency (primary efficacy parameter) and secondary efficacy variables occurred more quickly in escitalopram than citalopram recipients. In patients with OCD, escitalopram 20 mg/day for 12 weeks was more effective than placebo, and at least as effective as paroxetine 40 mg/day, with respect to a mean

reduction from baseline in the Yale-Brown Obsessive Scale total score (primary efficacy parameter). In a relapse-prevention study, escitalopram recipients showed a longer time to relapse and a significantly reduced risk of relapse compared with those receiving placebo. In addition, the proportion of patients who relapsed in the escitalopram group was significantly lower than in the placebo group. Tolerability: Escitalopram was generally well tolerated in adult patients with GAD, SAD, panic disorder or OCD. Withdrawal rates due to treatment-emergent adverse events in escitalopram recipients were 6.0-11.8%. The profile of treatment-emergent adverse events was generally similar in escitalopram recipients irrespective of the type of anxiety disorder in placebo-controlled short-term trials. The most common adverse event in escitalopram and placebo recipients was headache (15-25% of patients). Other common adverse events in escitalopram recipients with GAD include nausea (18.2%), ejaculation disorder (14.3%), insomnia (11.9%), fatigue (7.7%), decreased libido (6.8%) and anorgasmia (5.7%). Withdrawal rates during the 12-week open-label period of three relapse-prevention studies were 7.7-20.0%, whereas 2.6-7.9% withdrew from the study during the (less-than or equal to)76-week double-blind period. Furthermore, the overall incidence of adverse events was numerically lower during the double-blind period than the initial 12-week open-label period. Escitalopram recipients generally reported more discontinuation symptoms than placebo recipients after switching to placebo in two fixed-dose studies, whereas patients continuing escitalopram treatment generally reported fewer discontinuation symptoms than those switching to placebo in the relapse-prevention studies. The tolerability profile of escitalopram was generally similar to those of paroxetine or citalopram. However, in one study, paroxetine recipients showed significantly higher rates of withdrawal due to treatment-emergent adverse events than escitalopram recipients, and more paroxetine than escitalopram recipients appeared to experience sexual adverse events (ejaculation disorder [30.0% vs 14.8%], anorgasmia [26.2% vs 5.9%] and decreased libido [22.6% vs 4.9%]). Some discontinuation symptoms were reported in significantly fewer escitalopram than paroxetine recipients, and escitalopram recipients showed significantly lower mean changes in discontinuation emergent signs and symptoms scores than paroxetine recipients. In large analyses of placebo-controlled and relapse-prevention studies in patients with major depressive disorder or anxiety disorders, there was no indication of increased risk of suicidal behaviour in escitalopram or placebo recipients, with no completed suicides during the first 2 weeks of escitalopram or placebo therapy. Moreover, in an analysis of pharmacovigilance post-marketing surveillance information, escitalopram recipients had a low suicide rate (1.8 per million prescriptions). (copyright) 2006 Adis Data Information BV. All rights reserved.

Hedges, D. W., B. L. Brown, et al. (2007). "The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: A meta-analysis of double-blind, placebo-controlled trials." Journal of Psychopharmacology **21**(1): 102-111.

Social anxiety disorder is associated with impairment in social and occupational functioning, significant personal distress and a possible economic burden, resulting in a reduction in quality of life. To understand better the efficacy of selective serotonin reuptake inhibitors in social anxiety disorder, randomized, double-blind, placebo-controlled trials were evaluated. Pubmed and PsychINFO electronic databases were searched for social anxiety disorder, social phobia, selective serotonin reuptake inhibitors, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Fifteen published, randomized, double-blind, placebo-controlled trials of

selective serotonin reuptake inhibitors in social anxiety disorder were identified. Design, subject number, drug and dose, trial length, rating instruments, and baseline and end point data were extracted and then verified independently by a second investigator. Effect sizes were calculated from mean changes in drug and placebo groups in the Liebowitz Social Anxiety Scale and the Sheehan Disability Scale, as well as from other scales where available. For the binary data of the Clinical Global Impression of Change scores, (theta) log-odds ratios (the effect-size measure appropriate for binary data) were calculated from proportion changes. Effect sizes for the Liebowitz Social Anxiety Scale ranged from -0.029 to 1.214. Effect sizes for the Sheehan Disability Scale ranged from 0.203 to 0.480 for work, 0.237 to 0.786 for social function, and 0.118 to 0.445 for family function. The (theta) log-odds ratios for Clinical Global Impression of Change scores ranged from 0.644 to 3.267. Consistent with previous studies, selective serotonin reuptake inhibitors appear more effective than placebo for social anxiety disorder, with improvement extending into social and occupational function. (copyright) 2007 British Association for Psychopharmacology.

Kasper, S., D. J. Stein, et al. (2005). "Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study." British Journal of Psychiatry **186**(MAR.): 222-226.

Background: Selective serotonin reuptake inhibitors are effective in the treatment of social anxiety disorder and are currently regarded as the pharmacotherapy of choice. Aims: To investigate the efficacy and tolerability of escitalopram in the treatment of generalised social anxiety disorder. Method: Patients with generalised social anxiety disorder were randomised to receive placebo (n=177) or 10-20 mg escitalopram (n=181) in a 12-week, double-blind trial. The primary outcome measure was the mean change from baseline to last assessment in the Liebowitz Social Anxiety Scale (LSAS) total score. Results: The study showed a statistically superior therapeutic effect for escitalopram compared with placebo on the LSAS total score (P=0.005). There were significantly more responders to treatment for escitalopram than for placebo (54% v. 39%; P<01.01). The clinical relevance of these findings was supported by significant reduction in the work and social components of the Sheehan Disability Scale and by the good tolerability of escitalopram treatment. Conclusions: Escitalopram was efficacious and well tolerated in the treatment of generalised social anxiety disorder.

Lader, M., K. Stender, et al. (2004). "Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study." Depression and Anxiety **19**(4): 241-248.

Selective serotonin reuptake inhibitors are the pharmacological treatment of choice for the treatment of social anxiety disorder (SAD). The efficacy and tolerability of fixed doses of escitalopram were compared to those of placebo in the long-term treatment of generalised SAD, using paroxetine as an active reference. Patients with a DSM-IV diagnosis of SAD between 18-65 years of age were randomised to 24 weeks of double-blind treatment with placebo (n = 166), 5 mg escitalopram (n = 167), 10 mg escitalopram (n = 167), 20 mg escitalopram (n = 170), or 20 mg paroxetine (n = 169). Based on the primary efficacy parameter, Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (LOCF), a significantly superior therapeutic effect compared to placebo was seen for 5 and 20 mg escitalopram and for all doses for the OC analyses. Further improvement in LSAS scores was seen at Week 24 (OC and LOCF), with significant superiority over placebo for all doses of

escitalopram, and 20 mg escitalopram was significantly superior to 20 mg paroxetine. Response to treatment (assessed by a Clinical Global Impression-Improvement score (less-than or equal to)2) was significantly higher for all active treatments than for placebo at Week 12. Clinical relevance was supported by a significant decrease in all the Sheehan disability scores, and the good tolerability of escitalopram treatment. It is concluded that doses of 5-20 mg escitalopram are effective and well tolerated in the short- and long-term treatment of generalised SAD. (copyright) 2004 Wiley-Liss, Inc.

Montgomery, S. A., R. Nil, et al. (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." Journal of Clinical Psychiatry **66**(10): 1270-1278.

Objective: Escitalopram has proven efficacy in the short-term treatment of generalized social anxiety disorder (SAD). The present relapse prevention study investigated relapse rates during a 24-week, randomized, double-blind, placebo-controlled period in patients with generalized SAD who had responded to 12-week open-label treatment with escitalopram. Method: A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of (greater-than or equal to) 70 received 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalopram (10 or 20 mg/day) (N = 190) or placebo (N = 181), continuing with the dose level administered at the end of the open-label period. Relapse was defined as either an increase in LSAS total score of (greater-than or equal to) 10 or withdrawal due to lack of efficacy, as judged by the investigator. The study was conducted from January 2001 to June 2002. Results: Survival analysis of relapse and time to relapse showed a significant advantage for escitalopram compared to placebo (log-rank test: $p < .001$). The risk of relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients ($p < .001$), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses. Escitalopram was well tolerated during double-blind treatment of generalized SAD, and only 2.6% of the escitalopram-treated patients withdrew because of adverse events. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram and 8.3% for patients treated with placebo. Conclusion: Escitalopram was effective and well tolerated in the long-term treatment of generalized SAD.

Pallanti, S. and L. Quercioli (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice and Epidemiology in Mental Health **2**(-).

Background: Social Anxiety Disorder (SAD) is a common disorder and its high prevalence and lifelong chronicity are such that it represents a substantial public health problem. The observation that serotonergic agents appear to be effective for its treatment suggests that patients may have abnormal serotonergic neurotransmission within the central nervous system. We investigated the efficacy of Escitalopram in treatment resistant patients with SAD. Method: Twenty-nine adult outpatients participated in a 12-week open-label trial of escitalopram. All the subjects had a primary diagnosis of SAD and had failed at least one previous adequate trial of paroxetine. Escitalopram was orally administered starting with a dose of 10 mg/day following a 1-week titration. Results: The escitalopram treatment was characterized by good tolerability (drop-out rate due to intolerance: 10.3%), and 24 subjects completed the study trial. At the end of the 12-week treatment period, 14 subjects

(48.3%) were considered as responders on the basis of the Clinical Global Impression-Improvement (CGI-I) (much or very much improved) scale and the Liebowitz Scale for Social Anxiety (LSAS) (reduction >35% compared to baseline). We observed a significant mean reduction in the Sheehan Disability Scale Work ($p < .05$) and Social ($p < .05$) subscores, but not in the Family subscore. Conclusion: These data suggest escitalopram has a role in the treatment of resistant SAD, especially in view of the favourable tolerability profile observed in the patients. Controlled studies are required to further investigate these findings and to compare escitalopram with other treatments for this disorder. (copyright) 2006 Pallanti and Quercioli; licensee BioMed Central Ltd.

Stein, D. J., E. W. Andersen, et al. (2006). "Escitalopram versus paroxetine for social anxiety disorder: An analysis of efficacy for different symptom dimensions." European Neuropsychopharmacology **16**(1): 33-38.

Background: A previous factor analysis of pooled data demonstrated that the Liebowitz Social Anxiety Scale (LSAS) can be divided into six subscales. This paper examines data from a fixed-dose trial of escitalopram versus paroxetine, in order to determine the differential effects of these agents on symptom dimensions in social anxiety disorder (SAD). Methods: Data from a 24-week randomised, placebo-controlled, comparative study of fixed doses of escitalopram (5 mg, 10 mg, 20 mg) versus paroxetine (20 mg) in SAD were examined. The six factors identified in a previous factor analysis of baseline data from escitalopram studies on the primary efficacy scale, the LSAS, were used to compute subscale scores. These were analysed using analysis of covariance (ANCOVA), and standardised effect sizes were calculated. Results: The combined escitalopram data and the paroxetine data both demonstrated significant superiority to placebo on each of the 6 LSAS factors at week 24 (OC analysis). Escitalopram doses of 5 mg, 10 mg, and 20 mg were generally more effective than placebo for each of the factors. Escitalopram 20 mg was significantly more effective than paroxetine 20 mg on 5 of the 6 symptom dimensions. Conclusion: Factor analysis of the LSAS allows for useful secondary analyses that support and extend the primary efficacy analysis of this instrument. The analysis here indicates that different escitalopram doses are effective across the various symptom dimensions of SAD. (copyright) 2005 Elsevier B.V. and ECNP. All rights reserved.

Stein, D. J., S. Kasper, et al. (2004). "Escitalopram in the treatment of social anxiety disorder: Analysis of efficacy for different clinical subgroups and symptom dimensions." Depression and Anxiety **20**(4): 175-181.

Escitalopram has demonstrated efficacy for the acute treatment of social anxiety disorder (SAD) in two placebo-controlled trials and for long-term treatment in a relapse-prevention study. Social anxiety disorder is a heterogeneous disorder. This study questions whether this new selective serotonin reuptake inhibitor is effective across different subgroups of patients. Data from two randomised, placebo-controlled, 12-week escitalopram SAD trials were pooled. General linear models were used to determine the efficacy of escitalopram in different patient subgroups. Furthermore, a factor analysis of the primary efficacy scale, the Liebowitz Social Anxiety Scale (LSAS), was undertaken, and a determination made of whether treatment effects were similar for the different symptom dimensions. Escitalopram was effective in both younger and older patients, in male and female patients, and in patients with more and less severe social anxiety symptoms. The LSAS factor analysis showed six factors, which were differentially associated with different areas of disability. Escitalopram

was significantly superior to placebo for all six symptom dimensions. The treatment effects of escitalopram were independent of gender, symptom severity and chronicity, and comorbid depressive symptoms. A six-factor model of social anxiety symptoms is supported by the distinctive association between these symptom dimensions and different areas of disability, but did not predict differential response to escitalopram. (copyright) 2005 Wiley-Liss, Inc.

Medline In Process

Pallanti S., Q. L. (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice & Epidemiology in Mental Health [Electronic Resource]: CP & EMH 2: 35.

BACKGROUND: Social Anxiety Disorder (SAD) is a common disorder and its high prevalence and lifelong chronicity are such that it represents a substantial public health problem. The observation that serotonergic agents appear to be effective for its treatment suggests that patients may have abnormal serotonergic neurotransmission within the central nervous system. We investigated the efficacy of Escitalopram in treatment resistant patients with SAD. METHOD: Twenty-nine adult outpatients participated in a 12-week open-label trial of escitalopram. All the subjects had a primary diagnosis of SAD and had failed at least one previous adequate trial of paroxetine. Escitalopram was orally administered starting with a dose of 10 mg/day following a 1-week titration. RESULTS: The escitalopram treatment was characterized by good tolerability (drop-out rate due to intolerance: 10.3%), and 24 subjects completed the study trial. At the end of the 12-week treatment period, 14 subjects (48.3%) were considered as responders on the basis of the Clinical Global Impression-Improvement (CGI-I) (much or very much improved) scale and the Liebowitz Scale for Social Anxiety (LSAS) (reduction >35% compared to baseline).We observed a significant mean reduction in the Sheehan Disability Scale Work ($p < .05$) and Social ($p < .05$) subscores, but not in the Family subscore. CONCLUSION: These data suggest escitalopram has a role in the treatment of resistant SAD, especially in view of the favourable tolerability profile observed in the patients. Controlled studies are required to further investigate these findings and to compare escitalopram with other treatments for this disorder.

Stein DJ. (2006). "Continued escitalopram reduces risk of relapse in people with generalised social anxiety disorder.[comment]." Evidence-Based Mental Health 9(2): 52.

Evidence Based Medicine Databases

(Cochrane)

Ipser, J. C., P; Dhansay, Y; Fakier, N; Seedat, S; Stein, DJ (2007). "Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders." Cochrane Database of Systematic Reviews **2**.

A large proportion of patients with anxiety disorders fail to respond to first-line medication interventions, despite evidence of the effectiveness of these agents.

Objectives

To assess the effects of medication versus placebo augmentation in the treatment of patients with anxiety disorders who have failed to respond adequately to first-line drug therapies.

Search strategy

The Cochrane Depression, Anxiety & Neurosis Group (CCDAN) specialised registers (CCDANCTR-Studies and CCDANCTR-References) were searched on 3/8/2005, MEDLINE (January 1966 to July 2005) and PsycINFO (1966 to 2005, Part A). Unpublished trials were identified through the Controlled Trials database and the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972 to 2005). Additional studies in any language were sought in reference lists of retrieved articles.

Selection criteria

All randomised controlled trials (RCTs) of the medication augmentation of pharmacotherapy for treatment resistant anxiety disorders.

Data collection and analysis

Two raters independently assessed RCTs for inclusion in the review, collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by class of augmentation agent and anxiety disorder. Overall effect estimates were calculated using a random-effects model, heterogeneity was assessed and subgroup/sensitivity analyses were undertaken.

Main results

Twenty eight short-term (average of seven weeks) randomised controlled trials (740 participants) were included in the review, 20 of which investigated augmentation of medication for treatment-resistant obsessive compulsive disorder (OCD). Summary statistics for responder status from nine trials demonstrate overall superiority of a variety of medication agents to placebo (relative risk of non-response (RR) 3.16, 95% CI 1.08 to 9.23). Similarly, symptom severity was significantly reduced in the medication groups, relative to placebo (number of trials (N) = 14, standardised mean difference (SMD) -0.87, 95% CI -1.37 to -0.36). There is no evidence of a difference between medication and placebo in total dropout rate, or in the number of dropouts due to adverse events.

Authors' conclusions

Medication augmentation can be an effective and well-tolerated short-term treatment strategy for non-responders to first-line pharmacotherapy of anxiety disorders. However, any conclusions must be tentative in view of methodological and clinical heterogeneity, and the fact that much of the relevant database is based on antipsychotic augmentation trials in OCD patients resistant to serotonin reuptake inhibitors (SRIs). Additional data are needed to address several areas, including the efficacy of augmentation over the longer-term, and the value of medication augmentation in comparison to other strategies (eg switching medication, adding psychotherapy).

Kasper S, S. D., Loft H, Nil R (2005). "Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study." The British journal of psychiatry **186**: 222-6.

BACKGROUND: Selective serotonin reuptake inhibitors are effective in the treatment of social anxiety disorder and are currently regarded as the pharmacotherapy of choice. AIMS: To investigate the efficacy and tolerability of escitalopram in the treatment of generalised social anxiety disorder. METHOD: Patients with generalised social anxiety disorder were randomised to receive placebo (n=177) or 10-20 mg escitalopram (n=181) in a 12-week, double-blind trial. The primary outcome measure was the mean change from baseline to last assessment in the Liebowitz Social Anxiety Scale (LSAS) total score. RESULTS: The study showed a statistically superior therapeutic effect for escitalopram compared with placebo on the LSAS total score (P=0.005). There were significantly more responders to treatment for escitalopram than for placebo (54% v. 39%; P<0.01). The clinical relevance of these findings was supported by significant reduction in the work and social components of the Sheehan Disability Scale and by the good tolerability of escitalopram treatment. CONCLUSIONS: Escitalopram was efficacious and well tolerated in the treatment of generalised social anxiety disorder.

Lader M, S. K., Burger V, Nil R (2004). "Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study." Depression and anxiety. **19**(4): 241-8.

elective serotonin reuptake inhibitors are the pharmacological treatment of choice for the treatment of social anxiety disorder (SAD). The efficacy and tolerability of fixed doses of escitalopram were compared to those of placebo in the long-term treatment of generalised SAD, using paroxetine as an active reference. Patients with a DSM-IV diagnosis of SAD between 18-65 years of age were randomised to 24 weeks of double-blind treatment with placebo (n = 166), 5 mg escitalopram (n = 167), 10 mg escitalopram (n = 167), 20 mg escitalopram (n = 170), or 20 mg paroxetine (n = 169). Based on the primary efficacy parameter, Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (LOCF), a significantly superior therapeutic effect compared to placebo was seen for 5 and 20 mg escitalopram and for all doses for the OC analyses. Further improvement in LSAS scores was seen at Week 24 (OC and LOCF), with significant superiority over placebo for all doses of escitalopram, and 20 mg escitalopram was significantly superior to 20 mg paroxetine. Response to treatment (assessed by a Clinical Global Impression-Improvement score < or = 2) was significantly higher for all active treatments than for placebo at Week 12. Clinical relevance was supported by a significant decrease in all the Sheehan disability scores, and the good tolerability of escitalopram treatment. It is concluded

that doses of 5-20 mg escitalopram are effective and well tolerated in the short- and long-term treatment of generalised SAD.

Montgomery SA (May 2005). Relapse Prevention in Patients Suffering From Social Anxiety Disorder. 158th Annual Meeting of the American Psychiatric Association, Atlanta, GA.

Introduction: Escitalopram is the most selective SSRI, whose efficacy and tolerability in the short-term treatment of SAD has been established. Methods: This study was conducted in outpatients (18-80 years) with a primary diagnosis of generalized SAD (DSM-IV) and an LSAS score >=70. After 12 weeks of open-label treatment (10- 20mg/day escitalopram), responders (CGI-I of 1 or 2) were RANDOMized to 24 weeks of escitalopram (n=190) or PLACEBO (n=181) treatment, to assess the relapse rate. The initial dose of 10 mg/ day could be doubled to a maximum of 20 mg/day, if clinically indicated, at Week 2, 4, or 8 of open treatment. Relapse was defined as an increase in LSAS score >=10 or withdrawal due to lack of efficacy. Results: Time to relapse was significantly lower for escitalopram COMPARed to PLACEBO (log-rank: p<0.001), and significantly fewer escitalopram-treated patients relapsed (22% VERSUS 50%, Fisher’s test, p<0.001). Significantly more escitalopram-treated patients completed the study (66% VERSUS 44%, p<0.001). The favorable side-effect profile of escitalopram in long-term treatment was confirmed, with only 4% of escitalopram-treated patients withdrawing due to adverse events. Conclusion: Escitalopram 10-20 mg/day is highly effective in preventing relapse in patients with SAD and well tolerated. References: 1. Lader M, Stender K, Burger V, Nil R: Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: RANDOMized, DOUBLE-BLIND, PLACEBO-controlled, fixeddose study. Depress Anxiety 2004; 19:241-248. 2. Kasper S, Stein DJ, Loft H, Nil R: Escitalopram in the treatment of social anxiety disorder: a RANDOMised, PLACEBO-controlled, flexible-dose study. Br J Psychiatry, in press.

Montgomery SA, N. R., Durr-Pal N, Loft H, Boulenger JP (2005). "A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder." The Journal of clinical psychiatry. **66**(10): 1270-8.

OBJECTIVE: Escitalopram has proven efficacy in the short-term treatment of generalized social anxiety disorder (SAD). The present relapse prevention study investigated relapse rates during a 24-week, randomized, double-blind, placebo-controlled period in patients with generalized SAD who had responded to 12-week open-label treatment with escitalopram. METHOD: A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of > or = 70 received 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalo-pram (10 or 20 mg/day) (N = 190) or placebo (N = 181), continuing with the dose level administered at the end of the open-label period. Relapse was defined as either an increase in LSAS total score of > or = 10 or withdrawal due to lack of efficacy, as judged by the investigator. The study was conducted from January 2001 to June 2002. RESULTS: Survival analysis of relapse and time to relapse showed a significant advantage for escitalopram compared to placebo (log-rank test: p < .001). The risk of

relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients ($p < .001$), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses. Escitalopram was well tolerated during double-blind treatment of generalized SAD, and only 2.6% of the escitalopram-treated patients withdrew because of adverse events. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram and 8.3% for patients treated with placebo. CONCLUSION: Escitalopram was effective and well tolerated in the long-term treatment of generalized SAD.

Stein, D. I., JC; van Balkom, AJ (2007). "Pharmacotherapy for social anxiety disorder." Cochrane Database of Systematic Reviews **2**.

Background

Social phobia (SP), or social anxiety disorder, is a prevalent and disabling disorder. The growing evidence of the disorder's neurobiological basis has stimulated an increased interest in the use of medication in its treatment.

Objectives

To assess the effects of pharmacotherapy for social phobia, and to determine whether particular classes of medication are more effective and/or acceptable than others in its treatment.

Search strategy

We searched the Cochrane Depression, Anxiety & Neurosis Group (CCDAN) specialised register, the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 1, 2004), MEDLINE (1966 to 2003), PsycINFO (1966 to 2003), and reference lists of retrieved articles. We also requested published and unpublished RCTs from SP researchers and pharmaceutical companies.

Selection criteria

All placebo-controlled randomised trials of the pharmacotherapy of SP were considered for the review.

Data collection and analysis

Two raters independently collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by medication group (SSRIs - selective serotonin reuptake inhibitors; MAOIs - Monoamine oxidase inhibitors; moclobemide and brofaromine). Dichotomous and continuous measures were calculated using a random effects model, heterogeneity was assessed, and subgroup/sensitivity analyses were undertaken.

Main results

37 RCTs of a range of medications were included in the analysis (5264 participants), of which 23 were short-term (14 weeks or less). A funnel plot provided evidence of publication bias.

Twenty-six trials demonstrated short-term superiority in treatment response of all medication groups over placebo (N = 3696; relative risk of non-response (RR-non) = 0.64; 95% CI = 0.57, 0.73). However, the SSRIs were significantly more effective than both moclobemide ($Qb = 38.61$; $p < 0.00001$), and, and to a lesser extent, brofaromine ($Qb = 2.87$; $p = 0.09$).

Sixteen comparisons of symptom severity showed a statistically significant difference between medication and placebo (weighed mean difference = -18, 95%CI = -25.17, -10.83). This effect was once again most evident for the SSRIs. Medication also reduced SP symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment response was demonstrated by 4 maintenance (RR-non = 0.62; 95% CI = 0.50, 0.77) and 4 relapse prevention (RR of relapse = 0.33; 95% CI = 0.22, 0.49) studies. Two performance anxiety RCTs reported mixed results.

Authors' conclusions

Medication appears effective in treating SP over the short term (particularly amongst the SSRIs), and the long term. Nevertheless, the possibility of publication bias has to be acknowledged. Additional issues for future research include the use of medication in children and adolescents with SP, SP with comorbid psychiatric disorders, and performance anxiety.

Stein DJ, A. E., Lader M (2006). "Escitalopram versus paroxetine for social anxiety disorder: an analysis of efficacy for different symptom dimensions." European neuropsychopharmacology **16**(1): 33-8.

BACKGROUND: A previous factor analysis of pooled data demonstrated that the Liebowitz Social Anxiety Scale (LSAS) can be divided into six subscales. This paper examines data from a fixed-dose trial of escitalopram versus paroxetine, in order to determine the differential effects of these agents on symptom dimensions in social anxiety disorder (SAD). METHODS: Data from a 24-week randomised, placebo-controlled, comparative study of fixed doses of escitalopram (5 mg, 10 mg, 20 mg) versus paroxetine (20 mg) in SAD were examined. The six factors identified in a previous factor analysis of baseline data from escitalopram studies on the primary efficacy scale, the LSAS, were used to compute subscale scores. These were analysed using analysis of covariance (ANCOVA), and standardised effect sizes were calculated. RESULTS: The combined escitalopram data and the paroxetine data both demonstrated significant superiority to placebo on each of the 6 LSAS factors at week 24 (OC analysis). Escitalopram doses of 5 mg, 10 mg, and 20 mg were generally more effective than placebo for each of the factors. Escitalopram 20 mg was significantly more effective than paroxetine 20 mg on 5 of the 6 symptom dimensions. CONCLUSION: Factor analysis of the LSAS allows for useful secondary analyses that support and extend the primary efficacy analysis of this instrument. The analysis here indicates that different escitalopram doses are effective across the various symptom dimensions of SAD.

Conference Papers Index

Sep 25 18:42:46 EDT 2007
CSA
Subject Area: Natural Sciences
Query: KW=(escitalopram or lexapro) and KW=((social anxiety disorder) or SAD or (social phobia))

Record 1 of 1

DN: Database Name
International Pharmaceutical Abstracts
TI: Title
Pharmacotherapy of social anxiety disorder: What does the evidence tell us?
AU: Author
Davidson, JR
SO: Source
Journal of Clinical Psychiatry, vol. 67, pp. 20-26, 2006
DE: Descriptors
Rational therapy: paroxetine; Anxiety disorders: paroxetine; Antidepressants: paroxetine; Rational therapy: sertraline; Anxiety disorders: sertraline; Antidepressants: sertraline; Rational therapy: fluoxetine; Anxiety disorders: fluoxetine; Antidepressants: fluoxetine; Rational therapy: fluvoxamine; Anxiety disorders: fluvoxamine; Antidepressants: fluvoxamine; Rational therapy: escitalopram; Anxiety disorders: escitalopram; Antidepressants: escitalopram; Rational therapy: venlafaxine; Anxiety disorders: venlafaxine; Antidepressants: venlafaxine; Rational therapy: clonazepam; Anxiety disorders: clonazepam; Anxiolytics, sedatives andhypnotics: clonazepam; Rational therapy: alprazolam; Anxiety disorders: alprazolam; Anxiolytics, sedatives and hypnotics: alprazolam; Rational therapy: bromazepam; Anxiety disorders: bromazepam; Anxiolytics, sedatives and hypnotics: bromazepam; Rational therapy: gabapentin; Anxiety disorders: gabapentin; Anticonvulsants: gabapentin; Rational therapy: pregabalin; Anxiety disorders: pregabalin; Anticonvulsants: pregabalin; Rational therapy: moclobemide; Anxiety disorders: moclobemide; Monoamine oxidase inhibitors: moclobemide; Rational therapy: levetiracetam; Anxiety disorders: levetiracetam; Anticonvulsants: levetiracetam; Rational therapy: olanzapine; Anxiety disorders: olanzapine; Antipsychotic agents: olanzapine; Rational therapy: propranolol; Anxiety disorders: propranolol; Sympatholytic agents: propranolol; Rational therapy: atenolol; Anxiety disorders: atenolol; Sympatholytic agents: atenolol; Rational therapy: botulinum toxin A; Anxiety disorders: botulinum toxin A; Skeletal muscle relaxants: botulinum toxin A; Anxiety disorders: prophylaxis; Paroxetine: anxiety disorders; Sertraline: anxiety disorders; Fluoxetine: anxiety disorders; Fluvoxamine: anxiety disorders; Escitalopram: anxiety disorders; Venlafaxine: anxiety disorders; Clonazepam: anxiety disorders; Alprazolam: anxiety disorders; Bromazepam: anxiety disorders; Gabapentin: anxiety disorders; Pregabalin: anxiety disorders; Moclobemide: anxiety disorders; Levetiracetam: anxiety disorders; Olanzapine:

anxiety disorders; Propranolol: anxiety disorders; Atenolol: anxiety disorders; Botulinum toxin A: anxiety disorders; Human

AB: Abstract

The treatment goals for social anxiety disorder (SAD) are to reduce fear, avoidance, physical distress, disability, and comorbidity. This review illustrates some of the primary studies used to evaluate fficacy of treatments for SAD. The selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, fluoxetine, fluvoxamine, and escitalopram and the serotonin-norepinephrine reuptake inhibitor venlafaxine are effective treatments. They have the additional benefit of being able to treat comorbid conditions. For people who do not respond to serotonin reuptake inhibitors, treatment options include benzodiazepines (clonazepam, alprazolam, and bromazepam), a2d calcium-channel blockers (gabapentin and pregabalin), reversible inhibitors of monoamine oxidase A (moclobemide, although agents in this class are not available in the United States), antiepileptics (levetiracetam), and atypical antipsychotics (olanzapine). The irreversible monoamine oxidase inhibitor phenelzine can be considered an effective third-line therapy. Combination treatments may be beneficial, but more research is needed. Benefits of b-blockers (propranolol and atenolol) are limited to performance anxiety. Botulinum toxin A may be an effective augmentation treatment option for severe axillary hyperhidrosis in patients with SAD. Studies show that patients with SAD who are maintained on paroxetine, sertraline, or clonazepam have a low relapse rate.

Lundbeck Database

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Montgomery SA., Lader M., et al., (2003) Escitalopram and paroxetine in fixed doses for the treatment of social anxiety disorder (SAD). 4th Annual Meeting of the Scandinavian College of Neuro-Psychopharmacology, 9-12 April 2003, France