B.2 Listing of all direct randomised trials

B.2.1 Direct randomised trials: search results

Table B.2.1 summarises the search results for direct randomised trials.

Table B.2.1:[b]Summary of identification of direct randomised trials from the search of the published literature[c]

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA[d]	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	9	9	2	0	0	7	10	1	0	0	39
Total number of duplicates	6	1	1			3	7				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[e]	0	0	0	6

ACTR = Australian Clinical Trials Registry, CT = Clinical Trials, EBM Databases (Includes: CDSR = Cochrane Database of Systematic Reviews, CENTRAL = Cochrane Central Register of Controlled Trials, CSA = Conference Papers Index, DARE = Database of Abstracts of Reviews of Effects), MIP = Medline-In-Process

[b] Tables B2.1 and B2.2 of the Guidelines have been combined into this table to account for the duplicates and the final number of RCTs included in this submission.
[c] Same as Table 12 in Attachment 4.
[d] The conference presentations relating to the study reports are reported as duplicates. However all 3 study reports are utilised in the submission.
[e] There are 3 study reports and the identified PubMed articles that are the representative publications of these trials.

B.2.2 Master list of trials

Table B.2.2 provides a list of trials (and associated reports) presented in the submission.

Table B.2.2:Trials (and associated reports) presented in the submission

Trial ID	Report	Study Included in Original Submission
99270	Integrated Clinical Study Report: 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 (Report No. 266-311, 2002; dated 14 March 2003).	Yes
	Lader et al, 2004:[1] Lader M, Stender K, Burger V, Nil R. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study. Depression and Anxiety 2004;19(4):241-248.	
	Montgomery et al 2003(abstract)[2] 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 (a)	
	Montgomery et al 2003(abstract)[3] 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	
99012	Integrated Clinical Study Report: A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 in the treatment of patients with social anxiety disorder (Report No. 226/311, 2000; dated 18 July 2002)	No New Study
	Kasper et al 2005[4]: Kasper S, Stein DJ, Loft H, Nil R. Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study. British Journal of Psychiatry 2005;186(MAR.):222-226.	

	Kasper et al, 2002a[5] 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 et al 2002b[6] Kasper S., Loft H., Nil R., Escitalopram is well tolerated in the treatment of social anxiety disorder. Scandinavian College of Neuropsychopharmacology (SCNP), April 2002	
	Kasper et al 2002c[7] Kasper S., Escitalopram is well tolerated in the treatment of social anxiety disorder. American Psychiatric association (APA), May 2002	
	Kasper et al 2002d[8] Kasper S., Loft H., Nil R., Treatment of social anxiety disorder: Escitalopram is well tolerated and efficacious. Collegium Internationale Neuro-Psychopharmacologicum (CINP), June2002	
	Kasper et al 2002e[9] Kasper S., Loft H., Smith JR., Escitalopram is efficacious and well tolerated in the treatment of SAD. Association of European Psychiatrists (AEP), May 2002.	
99269	Integrated Clinical Study Report: A double-blind, randomised, placebo-controlled, flexible-to fixed-dose relapse prevention study with Lu 26-054 in Social Anxiety Disorder (Report No. 226/311, 2000; dated 18 July 2002)	No New Study
	Montgomery et al 2005[10]: Montgomery SA, Nil R, Durr-Pal N, Loft H, Boulenger JP. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. Journal of Clinical Psychiatry 2005;66(10):1270-1278.	
	Montgomery et al 2005[11]: Relapse Prevention in Patients Suffering From Social Anxiety Disorder. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26.	

All study details and results are taken from the Clinical Study Reports (rather than the published papers) as these contain the most comprehensive details and results for the studies. The details reported in the cited published papers have been compared with the study reports and any discrepancies are detailed in the relevant part of Section B of the submission.

B.2.3 Exclusion of trials

All trials identified in the literature search and excluded from the submission are listed in Table B.2.3 (this is based on Table 11 in Attachment 4; where the full list and details of inclusion or exclusion can be found).

Table B.2.3:Reasons to exclude each direct randomised trial from the submission

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
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.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
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.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
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	Review	Not an RCT	Table 11; Attachment 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.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
Davidson, J., Pharmacotherapy of social anxiety disorder: What does the evidence tell us? Journal of Clinical Psychiatry, 2006. 67: p. 20-26.	Review	Not an RCT	Table 11; Attachment 4
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.	Review	Not an RCT	Table 11; Attachment 4

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
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.	Meta-analysis of all SSRIs for SAD. The study that included escitalopram is Lader M. et al (2004) which is included in the current submission.	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.	Table 11; Attachment 4
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.	Meta-analysis of pharmacotherapy for SAD. The study that included escitalopram is Kasper (2002), which is included in the current submission.	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).	Table 11; Attachment 4
Montgomery SA. Relapse Prevention in Patients Suffering From Social Anxiety Disorder. in 158th Annual Meeting of the American Psychiatric Association. May 2005. Atlanta, GA.	Same as Montgomery 05	Poster presentation of Montgomery 05	Table 11; Attachment 4
Pallanti, S. and L. Quercioli (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice and Epidemiology in Mental Health 2:35.	Open label, non-randomised	This was a 12 week open trial of escitalopram treatment for patients who had failed other treatments.	Table 11; Attachment 4

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
Stein, D.I., JC; van Balkom, AJ, Pharmacotherapy for social anxiety disorder. Cochrane Database of Systematic Reviews, 2007. 2.	Review article.	All studies reviewed are included in the submission (Kasper et al, 2002).	Table 11; Attachment 4
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.	Re-analysis of Lader et al (2004; Study 99270) looking at different symptom dimensions	Lader et al (2004) is included in the submission	Table 11; Attachment 4

TableB.2.4 summarises the key design and population characteristics of the three identified trials, and also the main primary and secondary outcomes.

TableB.2.4:Comparative summary of characteristics of direct randomised trials

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
Included trials					
99270	RCT, DB, MN, MC, FD	placebo escitalopram: 5, 10, 20mg/day paroxetine: 20mg/day 24 weeks	N=840 • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • SDS subscale ≥5 • Exhibited fear or avoidance in at lease four social situations (derived from baseline LSAS) • Age: 18-65	Efficacy from the baseline to wk12 is LSAS total score using LOCF Safety AEs, DESS checklist, clinical safety laboratory tests, ECGs, vital signs, weight, and physical examinations	• Change from baseline to each visit in LSAS total score • Change from baseline to final assessment in LSAS subscale (fear/anxiety, avoidance) score • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with CGI-I score ≤ 2 per visit • Proportion of patients with CGI-S score ≤ 2 per visit • Change from baseline to each visit in SDS items 1-3 score • Assessment of depression status – change from baseline to each visit in MADRS total score
99012	RCT, DB	placebo escitalopram: 10- 20mg/day 12 weeks	N=358 • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • CGI-S score≥4 • Has a score ≥2 on at least 4	Efficacy Change from the baseline to final assessment of the LSAS total score using LOCF Safety AEs, clinical safety laboratory tests, ECGs, vital signs and physical	• Change from baseline to each visit in LSAS total score • Change from baseline to last assessment in LSAS subscale (fear/anxiety, avoidance) total score • CGI-S score per visit • Change from baseline to each visit in CGI-S score

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
			items of both the fear and avoidance questions on the LSAS rating at screening and at baseline • Exhibited fear or avoidance in at lease four social situations (derived from baseline LSAS) • Age: 18-65	examinations	• CGI-I score per visit • Proportion of patients with CGI-I score ≤ 2 • Change from baseline to each visit in SDS items 1-3 score • Assessment of depression status – change from baseline to each visit in MADRS total score
99269	RCT, DB, MN, MC, Flexible to fixed dose 12 wk open label and a 24 wk double-blind period	placebo escitalopram: 10- 20mg/day	N=517 open label N=372 DB period • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • SDS subscale ≥5 • Exhibited fear or avoidance in at lease four or more social situations (derived from baseline LSAS) • Age: 18-80	<u>Efficacy</u> Time to relapse in the double-blind period <u>Safety</u> AEs, DESS checklist, clinical safety laboratory tests, ECGs, vital signs, weight, and physical examinations	LSAS CGI-I CGI-S SDS

AE = adverse events; C-O = cross-over; DB = double-blind; DBP = diastolic blood pressure; ITT = intention to treat; MC = multicentre; MN = multinational; PG = parallel group; PP = per protocol analysis; RCT = randomised controlled trial; LOCF= last observation carried forward

B.3 Assessment of the measures taken by investigators to minimise bias in the direct randomised trials

Summary

The three key studies were all studies providing the highest level of evidence. They were randomised, double-blind, parallel-group, multicentre direct comparisons of escitalopram and placebo. Randomisation was provided off-site by a third party, identical study product was provided for each group and patients, investigators and assessors were fully blinded treatment assignment. Full details of the adequacy of randomisation and blinding are provided. Intention-to-treat (last observation carried forward) analysis was used, with full details of patient follow-up provided.

All the information provided in Section B.3 was sourced from the Clinical Study Reports for Study 99270, Study 99012 and Study 99269. These reports are provided in electronic form on the CD-ROM labelled Clinical Study Reports and References. Hard copies of the Study Reports are also provided.

B.3.1 Randomisation

The patients in the studies were all randomised, following a run-in period. As Study 99269 was a relapse prevention study, all patients received open-label escitalopram for 12-weeks prior to randomisation. With this type of study all patients have to receive treatment to allow them to respond to treatment so that the efficacy of the antidepressant agent with regard to relapse prevention can be compared to placebo in the double-blind phase of the study.

Patients admitted to the double-blind period in all three studies were randomly allocated to either placebo or escitalopram according to a randomisation code generated by Lundbeck. Randomisation numbers and study product were prepared, equally assigned to each treatment group (2 groups in 99269, 99012 and 5 groups in 99270). Block randomisation was used in all the studies, to ensure that equal numbers

of patients entered each treatment group. At each centre the 4-digit randomisation number was to be assigned consecutively, starting with the lowest number available.

B.3.2 Blinding

The studies were all double-blind. The study products were encapsulated tablets for oral administration in Studies 99270 and 99269. In Study 99012 identical active and placebo tablets were used. Patients took either one or two tablets daily, equivalent to escitalopram 10mg or 20mg daily in the active group. All tablets were oval, white, scored and film-coated (not specified in 99269). All capsules were identical. The randomisation code was not broken in Studies 99270 or 99012. In Study 99269 the randomisation code was broken for one patient, after the patient had stopped treatment with placebo.

B.3.3 Adequacy of follow-up

Studies 99270 and 99012

The following analysis sets were defined *a priori*:

- All-patients-randomised set (APRS) – all patients randomised into the study
- All-patients treated set (APTS) – all randomised patients who took at least one dose of double-blind study product
- Full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the LSAS total score
- Per-protocol set (PPS) – all randomised patients who had no major protocol violations (as pre-defined in the Statistical Analysis Plan), who received double-blind study product at least up to Week 4, and who had at least one post-baseline assessment of the LSAS total score at or after Week 4.

All efficacy analyses were conducted on the FAS. Note that the primary study outcome is a continuous variable and it is therefore necessary to have at least one

post-baseline assessment to allow a valid result to be recorded for that patient. All safety analyses were conducted on the APTS.

In both studies all efficacy analyses, including the primary analysis of the change in LSAS total score over the study period was based on the FAS using last observation carried forward (LOCF).

Study 99269

The following analysis sets were defined *a priori*:

- All-patients treated set (APTS) – all patients enrolled in the open-label period who took at least one dose of study product
- All-patients-randomised set (APRS) – all patients randomised into the study
- Full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product.
- Per-protocol set (PPS) – all randomised patients in the FAS who did not relapse or withdraw at or before Day 7 and omitting all subsequent assessments for patients committing major protocol violations.

All efficacy analyses were conducted for the FAS and, when considered relevant, also for the PPS. All safety analyses were based on the APTS and the FAS for the open-label and double-blind periods, respectively.

The primary analysis of efficacy consisted of a log-rank test on the FAS comparing the time to relapse for the escitalopram and the placebo groups. Actual treatment days were used in the analysis, which was supplemented with Kaplan-Meier plots.

A summary of the measures taken to minimise bias in the key studies is presented in TableB.3.1.

TableB.3.1:Summary of the measures undertaken to minimise bias in the direct randomised trials

Trial ID	Concealment of randomisation[a]	Blinding			Basis of analysis[b]
		Participants	Investigators	Outcomes assessors	
99270	B (p. 27)	Yes (p. 21)	Yes (p. 21)	Yes (p. 21)	E[c] (p. 39, 41)
99012	B (p. 25)	Yes (p. 20)	Yes (p. 20)	Yes (p. 20)	E[c] (p. 36, 39)
99269	B (p. 27)	Yes (p.21)	Yes (p.21)	Yes (p.21)	E[d] (p. 41, 43)

All page references are for the relevant Study Report.
a A = central telephone randomisation service; B = third-party randomisation service (eg pharmacy, pharmaceutical company);
C = sequentially labelled, fully opaque, sealed envelopes
b D = intention-to-treat (all randomised participants: specify how the analysis dealt with missing data); E = all treated participants (specify how the analysis dealt with missing data); F = per protocol participants; G = other (specified)
c The study population consisted of all patients randomised to treatment who took at least one dose of double-blind study medication and who had at least one valid post-baseline assessment of the primary efficacy variable (LSAS total score). Last observation carried forward (LOCF) methodology was used for missing data. All safety analyses were conducted on all patients who took at least one dose of study medication
d. The study population (efficacy and safety) consisted of all patients randomised to treatment who took at least one dose of double-blind study medication. Last observation carried forward (LOCF) methodology was used for missing data.

Details of the flow of patients through the direct randomised trials are presented in TableB.3.2.

TableB.3.2:Flow of participants through the direct randomised trials

Trial ID • Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Dis-continued	Analysed
99270[a]					
• Escitalopram 10mg	168	1 (0.6%)	7 (4.2%)	60 (35.9%)	164 (97.6%)[b]
• Escitalopram 20mg	170	0 (0%)	7 (4.1%)	54 (31.8%)	163 (95.9%)[b]
• Placebo	166	0 (0%)	5 (3.0%)	54 (32.5%)	165 (99.4%)
99012					
• Escitalopram	181	0 (0%)	8 (4.4%)	36 (19.9%)	177 (97.8%)
• Placebo	177	0 (0%)	5 (2.8%)	32 (18.1%)	176 (99.4%)
99269					
• Escitalopram	190	0 (0%)	3 (1.6%)	64 (33.7%)	190 (100%)
• Placebo	182	1 (0.6%)	2 (1.1%)	101 (55.5%)	181 (99.5%)

a. Information on the escitalopram 5mg daily and paroxetine treatment arms are not presented, as they are not relevant to this submission. Full details are available in the Clinical Study Report provided.
b. The published paper[12] reports that there are n=162 patients in the escitalopram 10mg and 20mg arms full analysis set population. It is unclear why this differs from the numbers reported in the Clinical Study Report.

Source:
Study 99278 - Panel 7 p.45, Panel 9 p.47
Study 99012 - Panel 6 p.42, Panel 7 p.43
Study 99269 - Panel 10 p.48, Panel 11 p.49

Source Documents

The study reports for the three direct randomised trials are the source documents for all information in this section. The page references for all the information are provided under or in TableB.3.1and TableB.3.2.

B.4 Characteristics of the direct randomised trials

Summary

This resubmission included two new studies: Study 99012 and 99269. This meant that the effective duration of therapy for assessment was 48 weeks (24 weeks for Study 99270 and an additional 24 weeks from the relapse prevention study 99269); a total of 70 weeks of data for SAD patients on escitalopram. s38

The key randomised, controlled studies (Study 99270, 99012 and 99269 all included patients diagnosed with moderate to severe SAD whose lives were severely disrupted because of fear and avoidance of normal social situations. Patients did not have other psychiatric co-morbidities.

The studies were all parallel group, randomised controlled trials of 12 week (Study 99012) or 24 week (Study 99270) duration. Study 99269 was a relapse prevention study with patients receiving 12 weeks of open-label escitalopram, with responders then randomised to receive a further 24 weeks therapy with either escitalopram or placebo. Patients were randomised to either a fixed dose of escitalopram or placebo (Study 99270), or a flexible dose of escitalopram dose (Study 99012 and 99269). Full details of the interventions received are presented in Section B.4.2, including details of the actual escitalopram doses taken.

The baseline characteristics of patients (age, sex, race, duration and onset of SAD) across the studies and in the treatment arms within studies were all similar.

The characteristics of patients included in the key randomised, controlled trials are presented in Section B.4. The eligibility criteria are detailed followed by the baseline demographic and clinical characteristics of the patients. The study designs are explained, including the daily dose of the interventions received in each treatment group (escitalopram and placebo) and the duration of the trials. All trials have been

completed. Full details of each study are available in the Study Report provided, with clear cross-referencing in this submission to the relevant pages and tables.

A summary of the trial characteristics for the key studies included in this submission (Studies 99270, 99012 and 99269) is provided in TableB.4.1.

TableB.4.1:Summary of the characteristics of the included trials (Study 99270, 99012 and 99269)

Trial ID	Design / Duration	Size	Location	Dosage regimen	Trial population
99270	Randomised, double-blind, placebo-controlled, parallel group, fixed dose study comparing 3 ESC doses, paroxetine and placebo - 1 week run-in - 24 week randomised phase - 2 week placebo run-out period	840 patients ESC 10 167 ESC 20 170 Placebo 166	47 centres in 11 countries in Europe, including the UK	Relevant study arms: ESC 10mg once daily ESC 20mg once daily Placebo once daily Other study arms: ESC 5mg daily Paroxetine 20mg daily	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities
99012	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study comparing ESC and placebo - 1 week run-in - 12 week randomised phase	358 patients ESC 181 Placebo 177	41 centres in 8 countries in Europe (including UK), Canada, South Africa	- ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 4. - Placebo once daily	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities
99269	Randomised, double-blind, placebo-controlled, parallel group study, flexible dose, relapse prevention study comparing ESC and placebo - 12 week open label period - 24 week randomised, double-blind period	372 patients ESC 190 Placebo 182	76 centres in 11 countries in Europe (including UK), Canada, South Africa	Open-label period: - Initially ESC 10 once daily, which could be increased to 20mg once daily if required. Double-Blind period: - ESC 10 or 20mg once daily (i.e. dose patient was on in open-label phase) - Placebo	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS, CGI-S scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities

CGI-S = Clinical Global Impression – Severity; ESC = escitalopram; LSAS = Liebowitz Social Anxiety Scale; SDS = Sheehan Disability Scale

B.4.1 Selection of the study population

The key studies included adult patients with SAD diagnosed based on DSM-IV criteria. These patients had a Liebowitz Social Anxiety Score (LSAS) of 70 or more. The LSAS is designed to assess SAD through evaluation of fear and avoidance in social situations. A minimum entry score of at least 70 in SAD investigational drug studies is recommended to ensure that patients have moderate to severe SAD (European College of Neuropsychopharmacology (ECNP) Guidelines, 2003[13]). For study inclusion patients also had to experience fear and avoidance in at least four distinct social situations (based on LSAS baseline scores) to ensure that patients had the more severe generalised form of SAD[13].

Patients were excluded from study entry if they suffered from other psychiatric disorders or co-morbidities. While patients with SAD often do suffer from co-morbidities such as alcohol/substance abuse and depression, it is usual to exclude or control for the confounding variable (i.e. the co-morbidity) which may affect the results. The ECNP Guidelines recommend that "*In all cases the primary diagnosis should be SAD and patients with other recent or current psychiatric diagnoses should be excluded"*[13].

The ECNP Guidelines further state that "*In studies that include a putative or potential antidepressant, patients suffering from concomitant major depression as well as those with a history of major depression over the previous 3-6 months, should be excluded. Some "depressive symptoms" are part of SAD. However current depressive symptoms should nevertheless be restricted to a mild level, with a maximum permitted score on a depression rating scale below that normally used to include patients into depression studies. The results of these studies may then be generalisable to the population with SAD without concerns of an indirect effect via depression*"[13]. The Montgomery and Åsberg Depression Rating Scale (MADRS) was administered to patients in order to exclude patients with depression from the key studies.

The inclusion and exclusion criteria for the direct randomised trials are presented in TableB.4.2.

TableB.4.2: Eligibility criteria in the direct randomised trials

Trial ID	Inclusion criteria	Exclusion criteria
99270	Age: 18-65 years	Any other Axis I diagnosis that was considered the primary disorder or the predominant disorder (over the last 6 months).
	Patient was an outpatient	Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study.
	Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD	Patient had a baseline MADRS total score ≥18.
	Patient had a total LSAS score ≥70	Patient had an alcohol or drug abuse problem, as defined in DSM-IV.
	Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS)	Patient suffered from mania or hypomania or had a history thereof, as defined in DSM-IV.
	Patients were otherwise healthy	Patient suffered from body dysmorphic disorder, as defined in DSM-IV.
	Gave informed consent and willing to attend study appointments in the correct time windows	Patient had an Axis II Cluster B diagnosis: antisocial personality disorder, borderline personality disorder, histrionic personality, or narcissistic personality disorder.
	Patient had a score ≥5 on one or more of the SDS subscales	Patient suffered from MDD, panic disorder, or obsessive compulsive disorder, as defined in DSM-IV.
		Patients with schizophrenia, as defined in DSM-IV, or any other psychotic disorder or history thereof.
		Female patients of child bearing potential who were pregnant or breastfeeding or not using adequate contraception.
		Patients suffering from eating disorders, as defined in DSM-IV.
		Patients suffering from mental retardation or other cognitive disorder.
99012	Age: 18-65 years	Any other Axis I diagnosis that was considered the primary diagnosis.
	Patient was an outpatient	Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study.
	Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD	Patient had a baseline MADRS total score >19.
	Patient had a total LSAS score ≥70 and a CGI-S rating of ≥4 at baseline.	Patient had an alcohol or drug abuse problem, as defined in DSM-IV within 6 months prior to screening.
	Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS). At least 2 of these were required to involve interpersonal interactions.	Patient had an Axis II Cluster A diagnosis: personality disorder or borderline or antisocial personality disorder.

Trial ID	Inclusion criteria	Exclusion criteria
	Patients scored at least 2 on at least 4 items of the fear and avoidance questions on the LSAS rating at screening and baseline. Patients were otherwise healthy Gave informed consent and willing to attend study appointments in the correct time windows	Patient suffered from mania or hypomania, body dysmorphic disorder, schizophrenia or any other psychotic disorder, or eating disorders as defined in DSM-IV. Female patients of child bearing potential who were pregnant or breastfeed or not using adequate contraception. Patients suffering from mental retardation or other cognitive disorder. Patients using any of the listed disallowed therapies. Patients with a lack of response to citalopram treatment for SAD at a dose and duration normally adequate to show a response (previous and current episodes included). Patient at serious risk of suicide (investigators opinion) Patients with hypersensitivity to citalopram or with a history of severe drug allergy or hypersensitivity. Patients had a serious illness (according to the list provided). Patients unlikely to comply with the study protocol or was considered unsuitable (investigator's opinion). Patient had a positive drug screen result at screening. Patient was rated <3 (mildly ill) on the CGI-S scale at Visit 1 and 2.
99269	Age: 18-80 years Patient was an outpatient Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD Patient had a total LSAS score ≥70 Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS) Patients were otherwise healthy Gave informed consent and willing to attend study appointments in the correct time windows Patient had a score ≥5 on one or more of the SDS subscales	Any other Axis I diagnosis that was considered the primary disorder or the predominant disorder (over the last 6 months). Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study. Patient had a baseline MADRS total score ≥18. Patient had an alcohol or drug abuse problem, as defined in DSM-IV. Patient suffered from mania or hypomania or had a history thereof, as defined in DSM-IV. Patient suffered from body dysmorphic disorder, as defined in DSM-IV. Patient had an Axis II Cluster B diagnosis: antisocial personality disorder, borderline personality disorder, histrionic personality, or narcissistic personality disorder. Patient suffered from MDD, panic disorder, or obsessive compulsive disorder, as defined in DSM-IV. Patients with schizophrenia, as defined in DSM-IV, or any other psychotic disorder or history thereof.

Trial ID	Inclusion criteria	Exclusion criteria
		Female patients of child bearing potential who were pregnant or breastfeeding or not using adequate contraception. Patients suffering from eating disorders, as defined in DSM-IV. Patients suffering from mental retardation or other cognitive disorder. Patients using any of the listed disallowed therapies. Patients with a lack of response to previous treatment for SAD with SSRI. Patient at serious risk of suicide (investigators opinion or scored ≥5 points on item 10 of MADRS) Patients with hypersensitivity to citalopram and/or escitalopram or with a history of severe drug allergy or hypersensitivity. Patients had a serious illness (according to the list provided). Patients unlikely to comply with the study protocol or was considered unsuitable (investigator's opinion).

Source: 99269 Study Report p. 23-25.
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; LSAS = Liebowitz Social Anxiety Scale; MADRS = Montgomery and Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale

B.4.2 Trial dosage regimens

Two of the studies (99012 and 99269) used flexible doses of escitalopram, with patients commencing on 10mg daily and investigators able to increase the dose to 20mg daily (see Section B.4.4 – Study Design for full details). The actual escitalopram doses used in the flexible dose studies (the average daily dose) are presented following TableB.4.3 below. Study 99270 compared three fixed dosages of escitalopram, paroxetine 20mg daily and placebo. Only the relevant treatment arms (i.e. escitalopram 10mg and 20mg daily and placebo) are reported in the submission.

The Australian Approved Product Information (Attachment 1) for escitalopram use in SAD recommends commencing with 10mg daily, increasing to a maximum of 20mg daily if necessary. The study dosages reported are all within this approved range.

TableB.4.3 summarises the interventions compared in the included studies.

TableB.4.3: Interventions compared by the direct randomised trials

Trial ID	Treatment	Dosage regimen	Duration of treatment median (range)	Duration of follow-up Median (range)
99270[a]	ESC 10mg	ESC 10mg/day (1 capsule morning or evening[b]) for 24 weeks	168 days (1-217 days)[c]	NR
	ESC 20mg	ESC 20mg/day (1 capsule morning or evening[b]) for 24 weeks	168 days (1-202 days)[c]	NR
	Placebo	Placebo once daily (1 capsule morning or evening[b]) for 24 weeks	168 days (10-196 days)[c]	NR
99012	ESC	Escitalopram 10mg (1 tablet) once daily. After weeks 4, 6 or 8 the daily dose could be increased to 20mg daily or left at 10mg daily. Dosage could be decreased from 20mg daily to 10mg daily in the event of adverse events. The total double-blind treatment period was 12 weeks.	84 days (1-109 days)[c]	NR
	Placebo	Placebo (1 capsule) once daily. After weeks 4, 6 or 8 the daily dose could be increased to 2 tablets daily or left at 1 tablet daily. Dosage could be decreased from 2 tablets daily to 1 tablet daily in the event of adverse events. The total double-blind treatment period was 12 weeks.	84 days (2-99 days)[c]	NR
99269	ESC	ESC 10 or 20mg (1 tablet once daily, preferably in the morning) for 24 weeks[d].	168 days (7-194 days)[e]	NR
	Placebo	Placebo (1 tablet once daily, preferably in the morning) for 24 weeks[d]	112 days (5-190 days)[e]	NR

ESC = escitalopram; NR = not reported
Source:
Study 99270 – p. 26, Table 25;
Study 99012 – p. 20, 24, 25, Table 15
Study 99269 - p. 2, 26, Table 30;

a. the escitalopram 5mg daily treatment arm is not presented as it is not an approved dosage; the paroxetine 20mg daily arm, is also not presented as it not a comparator
b. at the same time every day, either morning or evening.
c. "All patients treated set" (APTS) population, i.e. all randomised patients who took at least one dose of double-blind study medication.
d. Patients received 12 weeks of open-label escitalopram – initially 10mg daily which could be increased to 20mg daily at Week 2, 4 or 8. The open-label period was designed to detect responders to escitalopram treatment. In the double-blind period patients were randomised to receive either escitalopram at the same dose that they were taking at the end of the open-label period or placebo, both once daily.
e. "Full analysis set" (FAS) population, i.e. all randomised patients who took at least done dose of double-blind study medication (the definition for FAS used in this study differs from that used in the other two studies).

B.4.3 Doses used in the clinical trials

Study 99270

Study 99270 used fixed doses of escitalopram or placebo as described in Table B.4.3.

Study 99012

There was a 1-week, single-blind run-in period with placebo, followed by a 12-week, double-blind treatment period with escitalopram or placebo. The initial dose of escitalopram was 10mg daily. At Week 4, 6 or 8 investigators had the option of doubling a patient's dosage of study product from 10mg to 20mg, if his/her response had been unsatisfactory or if there was an aggravation of the disorder based on the Clinical Global Impression Severity (CGI-S) score. Investigators could decrease the dosage to the original dosage at any time if there were adverse events.

The percentages of patients in each treatment group who had their dosage of study drug doubled from 10 to 20mg at Week 4, 6 or 8 were 68% for the escitalopram group and 69% for the placebo group (APTS population, i.e. all randomised patients who took at least one dose of double-blind study product). Of these, 4% of escitalopram-treated patients and 2% of placebo-treated patients had their dosage of study drug reduced to 10mg after dose increase. The majority of patients had their dosage doubled at Week 4 (escitalopram 61%, placebo 65%). (Source – Study Report 99012 p. 50 and Table 16). TableB.4.4 below reports the mean daily doses used in each treatment arm during the study. At the end of the treatment period patients on escitalopram were taking a mean dose of 17.1mg daily.

TableB.4.4:Doses used in Study 99012 (APTS population)

Week	ESC			Placebo	
	N	Mean capsules/day	Mean mg/day	N	Mean capsules/day
1	177	1.0	10.0	173	1.0
2	169	1.0	10.0	171	1.0
3	165	1.0	10.0	167	1.0
4	163	1.1	10.5	164	1.1
6	161	1.6	16.2	162	1.7
8	158	1.7	17.0	157	1.7
12	149	1.7	17.1	152	1.7

Source: Study Report 99012 Table 16
APTS = all patients treated set, i.e. patients who received at least one dose of study product.

Study 99269

All patients received escitalopram 10mg daily during the initial 12 week open-label period. The dosage could be increased to 20mg daily if clinically indicated at Week 2, 4 or 8. As the study was designed to assess relapse to escitalopram, only patients who responded to treatment in the open-label phase were then randomised into the double-blind phase that followed. Of those randomised, 139 escitalopram patients (out of 190 patients, or 73%) received 20mg daily and 141 placebo patients (out of 181, or 78%) received 2 placebo tablets daily[10]. This equates to a mean daily dose of escitalopram of 17.3mg.

B.4.4 Study design

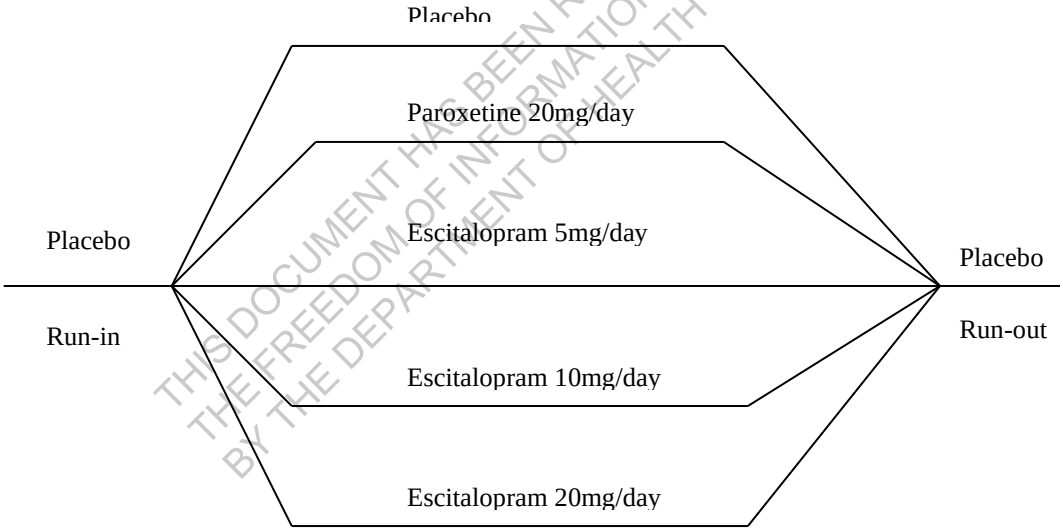
The efficacy and safety of escitalopram in SAD was investigated in three placebo-controlled clinical studies conducted as part of a comprehensive clinical development program:

a) A long-term fixed dose study (10mg or 20mg/day) – **Study 99270**
b) A shorter-term flexible dose (10-20mg/day) study - **Study 99012**
c) A flexible dose relapse prevention study – **Study 99269**

a) Study 99270

This was a multicentre, fixed-dose, randomised, double-blind, placebo-controlled, active-reference study with five parallel treatment groups. The study consisted of a 1-week single-blind placebo run-in period after which patients were randomised in a (1:1:1:1:1 ratio) to 24 weeks of double-blind treatment with fixed doses of escitalopram (5, 10 or 20mg/day), paroxetine (20mg/day) or placebo. The paroxetine arm results are not presented in this submission as it is not a comparator. The escitalopram 5mg daily treatment results are also not presented, as this is not an approved dosage for SAD in Australia. Patients who completed double-blind treatment entered a 2-week single-blind run-out period during which they received placebo. The overall study design is presented in Figure B.4.1.

Figure B.4.1: Overall study design (Study 99270)



Rationale for study design:

A double-blind, placebo controlled design is an expected design for investigating the efficacy and safety profile of a medication for this type of indication. The duration of 12 weeks for the acute treatment period was chosen since clinically and statistically significant improvements in SAD have been seen with other SSRIs within a 12-week

treatment period[14 15 16]. The treatment extension to 24 weeks was included to demonstrate whether the acute treatment effects were sustained, and to evaluate the response to therapy after an additional 12 weeks of treatment.

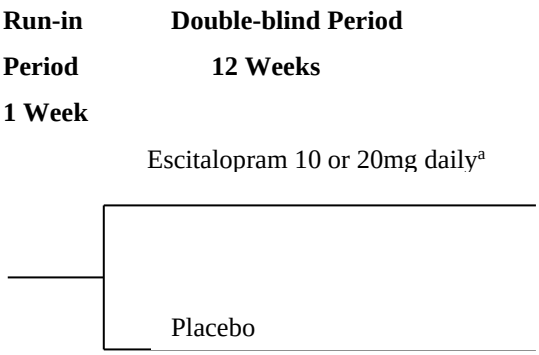
A one-week, single-blind, placebo run-in period allowed for the exclusion of patients who responded (Clinical Global Impression – Improvement (CGI-I) score of 1 or 2) to placebo therapy as well as washout psychoactive medication, which had been taken prior to screening and which may have influenced social behaviour. It also provided time for the assessment of clinical safety laboratory test results and electrocardiograms (ECGs). A two-week, single-blind, placebo run-out period was included to examine potential treatment withdrawal reactions.

b) Study 99012

This study was a multinational, randomised, double-blind, parallel-group, placebo controlled flexible-dose study. There was a one-week single-blind run-in period with placebo, followed by a 12-week, double-blind treatment period with escitalopram or placebo. The initial dose of escitalopram was 10mg daily. At Week 4, 6 or 8 investigators had the option of doubling a patient's dosage of study product from 10 to 20mg daily if his/her response had been unsatisfactory or if there was an aggravation of the disorder based on the Clinical Global Impression - Severity (CGI-S) score. Investigators could decrease the dosage to the original dosage at any time after the increase in dosage if there was an adverse event.

The overall study design is presented in Figure B.4.2.

Figure B.4.2:Overall study design (Study 99012)



a. All patients were dosed with 10mg/day at the start of the double-blind period. The dose could be increased to 20mg/day at Week 4, 6 or 8.

Rationale for study design:

A double-blind, placebo-controlled design is the 'gold standard' design for investigating the efficacy and safety profile of a compound for this type of indication. The treatment duration of 12 weeks was chosen since clinically and statistically significant improvements in SAD have been seen with other SSRIs within a 12-week treatment period[14 15 16].

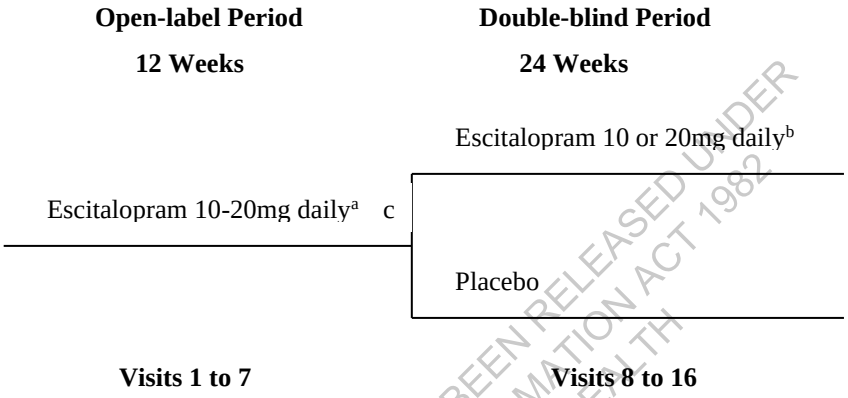
The dose of 10-20mg/day of escitalopram was chosen since it was expected that it would be equivalent to the dose range of 20-40mg/day of citalopram already shown to be effective in open-label studies of this disorder (consistent with the PBPA Therapeutic Relativities and the escitalopram Approved Product Information). A placebo run-in period allowed both the opportunity to exclude patients who respond to placebo therapy to be excluded and washout psychoactive medication which had been taken prior to screening and which may influence social behaviour. The one-week duration also provided time for assessment of laboratory test results and ECGs.

b) Study 99269

This multinational, multicentre study consisted of a 12-week open-label period with flexible doses of escitalopram doses and a 24-week randomised, double-blind, parallel-group, fixed dose comparison of escitalopram and placebo in the prevention

of relapse of SAD. Throughout the double-blind period the investigators evaluated relapse symptoms. Relapse was defined either as a Liebowitz Social Anxiety Scale (LSAS) total score ≥10 points greater than that at randomisation; or as withdrawal of the patient from the study due to unsatisfactory treatment response (lack of efficacy), as judged by the investigator. The overall study design is presented in Figure B.4.3.

Figure B.4.3:Overall study design (Study 99269)



a. All patients were dosed with 10mg/day at study start. The dose could be increased to 20mg/day at Week 2, 4 or 8.
b. The patients remained on the dose to which they responded during the open-label period.
c. Response was defined as a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale. Non-responders left the study.

Rationale for study design:

The open-label period was included to detect responders to escitalopram treatment. The duration of 12 weeks was chosen since clinically and statistically significant improvements in SAD have been seen within a 12-week period[14 15 16]. The double-blind, placebo-controlled design is widely accepted for examining relapse prevention. In addition, treatment of patients for a total of 9 months provides long-term tolerability and safety data.

Summary of the key aspects of the identified trials

While all three studies provide useful information on the overall efficacy of escitalopram, Study 99269 is a relapse prevention study and thus the design is markedly different to that of the other two studies. Therefore, while the study is considered a key study and provides important information on whether patients continue to respond to escitalopram therapy, the results of this study cannot be combined to give an overall assessment of effect (i.e. meta-analysed) with the other two studies. Full details of the meta-analysis undertaken are provided in Section B.5.3.

B.4.5 Subject characteristics

Subject characteristics in the treatments arms were generally similar, both within and across studies. The key subject characteristics are discussed below. TableB.4.5 presents the baseline characteristics of participants in the treatment arms in the three key direct randomised trials.

Age, Sex, Race

Patients' mean age in the different treatment groups in the 3 studies ranged from 36-39 years. SAD has an early age of onset, of around 15 years of age and is usually associated with a long a particularly prolonged duration prior to diagnosis and treatment with the prevalence of SAD tending to decline in the elderly[13]. Generally, there was a higher prevalence of SAD in females. From the literature review there was approximately a 1:5 to a 1:2 ratio or males to females (these figures vary from country to country: see Attachment 2). In Australia the prevalence of SAD was 3% for females and 2.4% for males.[17]

SAD onset

The age of SAD onset was consistent in all of the studies and treatment arms within studies, ranging from 15-18 years. This is also consistent with the age of onset generally reported[13]. SAD usually develops in adolescence, though it may be many years later that patients are formally diagnosed. As the mean patient age was 36-39

years in the studies, the mean duration of SAD was 19-20 years. The onset of SAD rarely occurs after the age of 25.[18]

Level of impairment at baseline

The mean LSAS total score ranged from 92 to 96. In study 99270 the baseline LSAS values in the escitalopram 10mg group was numerically similar, but statistically significantly lower (p=0.028) than in the placebo group. In the relapse prevention study (Study 99269), the patients' mean baseline LSAS score prior to them receiving 12 weeks of open-label escitalopram was similar to baseline values in the other studies. After 12 weeks of open-label escitalopram therapy (i.e. prior to being randomised to receive 24 weeks of either escitalopram or placebo) the patients' mean LSAS Total Score had significantly improved to around 42.

The LSAS was used to assess the level of impairment of patients at baseline and the efficacy of therapy with active treatment. The maximum possible score is 144 of the LSAS[19]. 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. In the studies a score of greater than or equal to 82 on the LSAS is classified as severe SAD (LSAS>70 is considered severe), thus with a mean score of 92-96 points in the current studies the patients are classified as having severe SAD associated with functional impairment.

The baseline MADRS total score was used to ensure that patients met the exclusion criteria of MADRS>18. MADRS total scores were used to assess the level of depressive symptoms still present in the study population even though patients with major depressive disorder were excluded. Patients in all groups and studies demonstrated a low level of depressive symptoms at baseline, based on the MADRS. In studies 99270 and 99012 all patient groups had a mean score of <8. In Study 99269 the mean scores were <4, as patients had received 12 weeks of open-label escitalopram at baseline.

TableB.4.5: Baseline characteristics of participants in the direct randomised trials

99270	ESC 10mg	ESC 20mg	Placebo
Mean age (years)	37.2	37	37
Sex (% male)	42.5	47.1	48.8
Race (%):			
Caucasian	98.8	100	100
Black	0	0	0
Asian	0.6	0	0
Other	0.6	0	0
Mean BMI (kg/m²)	23.9	23.8	24.1
Mean age of SAD onset (years)	16.9	17.5	17.9
Mean duration of SAD (years)	20.3	19.5	19.2
Mean LSAS Total Score (SD)	92 (15)	94 (14)	96 (14)
Mean MADRS Total Score (SD)	6.84 (4.35)	7.31 (4.68)	7.56 (4.80)
99012	**ESC**	**Placebo**	
Mean age (years)	39	36	
Sex (% male)	55.8	53.1	
Race (%):			
Caucasian	90.6	91.5	
Black	3.9	3.4	
Asian	2.8	1.7	
Other	2.8	3.4	
Mean BMI (kg/m²)	25	25	
Mean age of SAD onset (years)	15[a]	15[a]	
Mean duration of SAD (years)	24[a]	21[a]	
Mean LSAS Total Score (SD)	96 (17)	95 (16)	
Mean MADRS Total Score (SD)	7.59 (4.48)	7.50 (4.37)	
99269	**ESC**	**Placebo**	
Mean age (years)	36.6[b]	38.3	
Sex (% male)	54.2	51.4	
Race (%):			
Caucasian	94.7	95	
Black	4.2	2.2	
Asian	0	0.6	
Other	1.1	2.2	
Mean BMI (kg/m²)	24.2	24.2	
Mean age of SAD onset (years)	17.2	17.9[c]	
Mean duration of SAD (years)	19.2	20.4	
Mean LSAS Total Score (SD)			
Baseline I -Prior to open-label phase	95 (16)	94 (14)	
Baseline II – Prior to randomised therapy			
	44 (21)	43 (20)	
Mean MADRS Total Score (SD)	3.21 (3.14)	3.34 (3.51)	

BMI = body mass index; NR = not reported
Study 99270 Study Report – Tables 11, 12, 15, 27 (FAS data) – Other data is for the "All patients treated" population (APTS).
Study 99012 Study Report – Tables 6, 7- All data is for the "All patients treated" population (APTS).
Study 99269 Study Report – Tables 13, 14, 15, 32, - All data is for the "Full analysis set" population (FAS), immediately prior to randomisation into the double-blind period (called Baseline II in the study report)

a. Data reported in the Kasper et al. publication4. In the Study Report (p. 54-55) the following information is provided: "At baseline, the two treatment groups were statistically significantly unbalanced with respect to duration of SAD (p=0.021). When adjusting for the covariate "duration of SAD" in the model (p=0.39), the statistically significant difference of escitalopram relative to placebo was slightly higher than in the primary analysis with an estimate of –7.8 points (p=0.003). No statistically significant interaction between duration of SAD and treatment was found at the 10% level of significance (p=0.20). No statistically significant interaction between treatment and age of SAD onset was found."
b. Reported as 36 years in the Montgomery et al.[10] publication, with the same range quoted as in the Study Report.
c. Reported as 17 years in the Montgomery et al.[10] publication

Source documents

Data provided in this section is taken from the Study Reports provided. Page and/or table references are provided under the tables or in text.

B.5 Outcome measures and analysis of the direct randomised trials

Summary

The methods of analysis of the primary and secondary study outcomes are fully presented. In studies 99270 and 99012 the primary outcome was mean change from baseline to study endpoint in the Liebowitz Social Anxiety Scale (LSAS). This outcome was analysed using analysis of covariance (ANCOVA). Study 99269 investigated the relapse of patients following successful escitalopram therapy, with time to relapse as the primary study outcome.

The LSAS is considered a gold standard, patient-relevant outcome in assessing the impact of therapy in SAD. s38 A change of (minus) 10 points on the LSAS has been suggested in the literature as showing a clinically relevant improvement.

Other patient-relevant outcomes such as changes in the Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression – Severity (CGI-S) scales, Sheehan Disability Scale (SDS) and adverse event information are also reported in the studies and in this submission.

Details of the meta-analyses undertaken for this submission are provided in this section and in Attachment 5. Two of the three key studies (Study 99270 and 99012) have been meta-analysed to give an overall treatment effect at Week 12. Due to significant differences in study design, the results of one study (Study 99269) cannot validly be meta-analysed with the other two and thus the results for this study are presented separately in Section B.6.

The primary and secondary outcomes for the three key studies are presented in Section B.5.1 and B.5.2. Full details of the analyses undertaken are provided, including the meta-analysis of two of the key trials. The clinical importance of the outcomes measured in the trials is reviewed.

B.5.1 Primary outcomes

The primary outcomes, methods of statistical analysis and information on the sample size calculations in the three randomised, controlled trials are presented in TableB.5.1 below.

TableB.5.1:Primary outcomes and statistical analyses in the key studies

Trial ID	Definition of primary outcome	Method of primary statistical analysis
99270	Change from Baseline to Week 12 (LOCF) in LSAS total score	A general linear model for ANCOVA adjusting for centres and baseline LSAS total score was applied. An overall treatment comparison was made; if the overall F-test proved significance at the 5% significance level, then pairwise tests for differences between each of the ESC groups and placebo were performed. The appropriateness of the final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups, and evaluating the potential influence of covariates. Adjustment of p-values in multiple testing (pairwise comparison) was carried out in the primary analysis and where appropriate in the secondary analyses using Fisher's Protected Least Significance Difference (LSD) multiple Comparison Procedure. **Sample size calculation:** A standardised effect size in the two relevant ESC arms (10mg, 20mg) of 0.292 and 0.375 points, respectively was used in the sample size calculations to provide 80% power to detect a significant difference in the primary outcome at a 5% level of significance. An estimate of the standard deviation of the change in LSAS total score was set to 24 based on a previous Lundbeck Study.
99012	Change from baseline to last assessment of the LSAS total score	The primary efficacy analysis was based on a general linear model for ANCOVA with factors for treatment group, collective centres and with baseline score as a covariate. The appropriateness of the final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups, and evaluating the potential influence of covariates. **Sample size calculation:** A signal-to-noise ratio of 0.40 at a significance level of 5% was used in the sample calculation to provide 90% power to detect a significant different in mean change from baseline to final assessment of the LSAS total score between the ESC and placebo treatment groups. The signal-to-noise ratio is the treatment difference (mean change from baseline for ESC versus placebo) divided by the pooled standard deviation.
99269	Time to relapse[a] in the double-blind period of the study.	A log-rank test compared the time to relapse for the ESC and placebo groups. Actual treatment days were used in the analysis, which was supplemented with Kaplan-Meier plots. The appropriateness and robustness of the primary analysis was further studied by investigating a possible effect of collective centres, and of a collective centres by treatment interaction. This was done by applying stratified log-rank test, Cox's proportional hazard model, and accelerated failure time models. Analyses taking the interval censored nature of the survival times into account were performed using accelerated failure time models. **Sample size calculation:** A non-relapse withdrawal rate of 15% and a cumulative relapse rate at Week 24 of 30% for ESC and 55% for placebo was used in the sample size calculation to provide 90% power to demonstrate the difference in relapse rate between the ESC and placebo groups at a 5% level of significance.

ANCOVA = analysis of covariance, ESC = escitalopram, FAS = LOCF = last observation carried forward
Study 99270 – p. 39, 40, 41.
Study 99012 – p. 36, 37, 38
Study 99269 – p. 41, 42, 43
a. Relapse defined either as a LSAS total score ≥10 points greater than that at randomisation; or as withdrawal of the patient from the study due to unsatisfactory treatment response (lack of efficacy), as judged by the investigator.

B.5.2 Secondary outcomes

All secondary outcomes and the statistical analysis methods used in the three direct randomised, controlled trials are presented in Table B.5.2 below.

The results of secondary outcomes not considered patient-relevant are not presented in this submission. See Section B.5.3.3 for a full listing of patient-relevant secondary outcomes that are reported in Section B.6 in this submission (and meta-analysed if sufficient data is available).

A full list of secondary outcomes that are not considered patient-relevant is also provided in Section B.5.3.3. The results of all secondary outcomes are available in the individual Study Reports provided

TableB.5.2:Secondary outcomes and analyses in the key studies

Trial ID	Definition of secondary outcome	Method of statistical analysis
99270	• Change from baseline to each visit in LSAS total score • Proportion of patients with a ≥50% reduction in LSAS total score from baseline to visit • Change from baseline to last assessment in LSAS subscales (fear/ anxiety, avoidance) scores • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with a CGI-I score ≤2 per visit • Proportion of patients with a CGI-S score ≤2 per visit • Change from baseline to each visit in SDS items 1-3 score • Change from baseline to each visit in MADRS total score. • AEs in the ESC and placebo groups • DESS score	The LSAS total score per visit, the change from baseline to each visit in LSAS subscales (fear/ anxiety avoidance) score, CGI-S and SDS (family, social and work) scores were analysed by ANCOVA using the model described for the primary analysis and applying nominal visits. Adjustment of p-values in multiple testing (pairwise comparison) was carried out in the primary analysis and where appropriate in the secondary analyses using Fisher's Protected Least Significance Difference (LSD) multiple Comparison Procedure. In the secondary analyses, pairwise comparisons were only performed if the overall F-test was significant at the 5% level.
99012	• Change from baseline to each visit in LSAS total score • Change from baseline to last assessment in LSAS subscales (fear/ anxiety, avoidance) scores • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with a CGI-I score ≤2 per visit • Change from baseline to each visit in SDS items 1-3 score • Change from baseline to each visit in MADRS total score • AEs in the ESC and placebo groups	Analyses of LSAS total scores were performed on OC, using repeated measures techniques to model and compare the treatment groups over all assessment points simultaneously. The LSAS total score per visit, the change from baseline to visit of the LSAS subscales (fear/ anxiety, avoidance) score and the SDS total score were analysed by ANCOVA (using the model described for the primary endpoint) and applying nominal visits. The CGI-S and CGI-I scores were analysed in the same way, however the final CGI-S and CGI-I scores were also analysed using the non-parametric Cochran-Mantel-Haenszel mean score statistic with modified ridit scores. Between group comparisons of the proportion of patients considered to be treatment responders were performed using Chi-squared and Fisher's exact tests for the CGI-I score ≤2 per visit
99269	• LSAS total score • Change from baseline(s) in the LSAS total score • LSAS avoidance and fear/anxiety subscale score • SDS items (work, social life and family life) • Change from baseline of the SDS items • CGI-S score • CGI-S change from baseline • CGI-I score in open-label period • Change from baseline to each visit in MADRS total score. • AEs in the ESC and placebo groups • DESS score	All secondary efficacy parameters were analysed by visit using ANCOVA (OC and LOCF) adjusting for study centre and baseline values.

ANCOVA = analysis of covariance
Source: Study 99270 – p. 41, 42; Study 99012 – p. 38, 39; Study 99269 – p.43, 44,

B.5.3 Analysis of the trial data

A large number of primary and secondary outcomes have been analysed in the three key studies. In addition, the results of patient-relevant outcomes have been meta-analysed as described in Section B.5.3.2. The primary and patient-relevant secondary outcomes have been meta-analysed (if sufficient data is available) and reported in this submission.

B.5.3.1 Analysis of the individual studies

The method of analysis of the primary and secondary outcomes of the three key studies has been provided in Section B.5.2. A large number of clinical outcomes were assessed. The clinical importance of these outcomes is discussed in Section B.5.4.

Study 99270 and 99269 both had 24-week (double-blind) active treatment periods, while Study 99012 had a 12-week active treatment period. Data is reported at study endpoint (Week 24) and at Week 12 (where available) for Study 99270 and 99269.

The Clinical Study Reports contain results for mean change from baseline for the continuous outcomes (e.g. LSAS, SDS Scores) as well as adjusted mean change from baseline (using ANCOVA) for the same outcome. As **adjusted** mean change was specified in the analysis for the primary and secondary outcomes, these results are reported in the individual study results in Section B.6. However the (unadjusted) change values are used for the meta-analysis. This leads to slight differences in the values reported for the individual studies and in the individual study meta-analysis data.

B.5.3.2 Meta-analyses undertaken

A meta-analysis combining the results of two of the key studies (Study 99270 and Study 99012) has been undertaken. See Attachment 5 for full details of study methodology and results. Some key issues in the design and conduct of the meta-analysis are highlighted below.

Excluded study (Study 99269)

Study 99269 has not been meta-analysed with the other two key studies. It is not possible to validly combine the results of the three direct comparative studies, due to significant differences in the objectives and design of Study 99269 compared with the other two key studies, leading to different patient populations being randomised to active treatment.

Study 99269 was a relapse prevention study. The trial was undertaken in order to determine the rate of patient relapse following successful treatment of SAD. All patients who met the eligibility criteria received open-label escitalopram for 12 weeks prior to study randomisation. Only patients who responded to therapy were randomised to continue in the relapse prevention study (since in order to be able to relapse, a patient must have responded to treatment). Thus the patients entering the randomised active treatment phase of this study were a "responder sub-population" of the patients with SAD who were initially eligible to enter the study. This is a different total patient population to that of Study 99270 and 99012. Due to the significant differences in the patient population randomised in Study 99269 (the relapse prevention study), compared with the other treatment studies, the results could not validly be combined in a meta-analysis.

Escitalopram treatment arms combined in the meta-analysis

Study 99270 was a fixed-dose study comparing three doses of escitalopram - 5mg, 10mg and 20mg daily – with placebo. Study 99012 was a flexible dose study with patients taking escitalopram 10mg to 20mg daily or placebo. Patients in this study took a mean daily dose of 17.1mg at Week 12. The meta-analysis combined the results of the fixed dose escitalopram 20mg daily treatment arm in Study 99270 with the flexible dose escitalopram arm in Study 99012, as these were the most similar study treatment arms that could be combined.

Treatment time-point analysed

Study 99012 had a 12 week active treatment phase. Study 99270 had a 24 week active treatment phase, with most outcomes also being reported after the first 12 weeks. The 12 week outcome data for each of the two studies was combined in the meta-analysis. This is important, as patients generally continued to improve from

weeks 12-24 in the two 24 week studies. Thus the results of the meta-analysis are likely to underestimate the true value of escitalopram therapy. Section B.6 for details of 12 and 24 week responses in Study 99270 and 99269.

B.5.3.3 Outcomes analysed in the meta-analysis and/or individual studies and reported in Section B.6

There are a large number of secondary outcomes reported in Study 99270 and Study 99012.TableB.5.3lists the outcomes that have been meta-analysed and/or reported in the individual studies with the results presented in Section B.6 of the submission.

TableB.5.3: Patient-relevant outcome results reported in Section B.6

Patient-relevant outcome	Trial ID			
	Meta-analysis (of Study 99270 & 99012)	Study 99270	Study 99012	Study 99269
Time-point analysed and reported[a]	**Week 12[b]**	**Week 12 & 24**	**Week 12**	**Week 12 & 24**
Primary outcome				
Change in mean LSAS Total Score	√	√	√	√[c]
Time to relapse	NA	NA	NA	√
Secondary efficacy outcomes				
Proportion of patients with a ≥50% reduction in LSAS score	NR	√	NR	NR
CGI-I Score	√	√	√	NR
Number and % patients with CGI-I≤2 (CGI-I responders)	√	√	√	NR
Change in mean CGI-S Score	√	√	√	√
Number and % patients with CGI-S≤2	NR	√	NR	NR
Change in SDS Work Scores	√	√	√	√
Change in SDS Social Scores	√	√	√	√
Change in SDS Family Scores	√	√	√	√
Change in MADRS total score	√	√	√	√
Secondary safety outcomes				
Total study withdrawals	√	√	√	√ Week 24 only
Study withdrawals - due to lack of efficacy	√	√	√	√ Week 24 only
Study withdrawals – due to AEs	√	√	√	√ Week 24 only
Patients with TEAEs	√	√	√	√ Week 24 only
TEAEs reported in ≥5% of patients	NR	NR	√	√ Week 24 only

Key:
√ = outcome reported in the Study Report or analysed in the meta-analysis and results presented in Section B.6
NA = not available – not a pre-defined study outcome, therefore data not collected
NR = not reported – data not reported for that outcome
Notes:
All change outcomes are change from baseline
a. Study 99012 had 12 weeks of randomised treatment. The other two studies had 24 weeks of randomised treatment. The meta-analysis was conducted using 12 week data (i.e. the longest timepoint available for both the analysed studies)
b. Data also reported at Week 4 and Week 8 for the primary outcome and CGI-responders (i.e. CGI-I≤2)
c. Change in mean LSAS Score was a secondary endpoint in Study 99012

TableB.5.4 lists the study outcomes reported in the individual studies that have not been meta-analysed or reported in Section B.6 for the reason stated.

TableB.5.4:Secondary outcome results that are not presented in Section B.6 (with reasons)

Secondary outcomes	Trial ID			Reason
	Study 99270	Study 99012	Study 99269	
Change from baseline to each visit in LSAS Score	√	√		Change from baseline to Week 12 and Week 24 (i.e. study mid and/or endpoint) results reported, rather than per visit
Proportion of patients with a ≥50% reduction in LSAS score at each visit	√			
CGI-I Score per visit	√	√		
Number and % patients with CGI-I≤2 at each visit	√	√		
CGI-S Score per visit	√	√	√	
Number and % patients with CGI-S≤2 at each visit	√			
Change from baseline to each visit in MADRS Score	√	√	√	
Change in CGI-S score per visit	√	√	√	
Change from baseline to last assessment in LSAS single items	√		√	Total Score results reported. Subscale results are difficult to interpret meaningfully.
Change in mean LSAS Avoidance Sub-scale Score	√	√	√	
Change in mean LSAS Fear/Anxiety Sub-scale Score	√	√	√	
Change in LSAS single items	√	√		
CGI-I score in open-label period			√	Randomised, double-blind phase results reported
Total adverse events	√	√	√	Treatment-emergent AEs and AEs leading to withdrawal reported
DESS score	√		√	Looks at discontinuation effects after completion of active treatment

Key:
√ = results for this outcome available in the Study Report, however the results are not presented in Section B.6 for the reasons provided

B.5.4 Clinical importance of the outcomes used in the studies

Liebowitz Social Anxiety Scale (LSAS)

Change in mean LSAS Total Score is the primary outcome in Study 99270 and 99012. While a variety of measurement scales have been developed to quantify the severity of SAD, the most widely used scale is the LSAS. It has been able to establish efficacy in a large number of placebo-controlled studies in SAD and is currently viewed as the gold standard[13]. s38

An improvement of 10 points on the LSAS has been suggested as showing a clinically relevant improvement[13]. This is also in line with the clinically relevant difference between drug and placebo for licensing approval.[20]

Clinical Global Impression– Improvement (CGI-I)

CGI-I score results are secondary study outcomes in the studies. The CGI-I scale has been used to identify responders to therapy, specifically patients reporting a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale have been defined as responding to therapy. While this global scale is not recommended as a primary scale, it may be useful as a secondary scale to help judge the clinical relevance of the finding[13]. This was consistent with the pre-specified magnitude identified in the trials.

B.5.5 Measurement scales used as primary and secondary outcomes in the studies

Liebowitz Social Anxiety Scale (LSAS)

The LSAS[21] 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 upon 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 maximum possible score is 144 of the LSAS[19]. 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.[13,19]

As mentioned earlier, an improvement of 10 points on the LSAS has been suggested as showing a clinically relevant improvement[13]. However this should not be viewed in isolation and proportion of patients responding and importantly remitting should be considered to be at the very least of equivalent importance.

Responders[13]: 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).[13]

Remission[22]: Keeping in mind that some controversy may exist regarding remission standards for CGI, an analysis of remission for various trials found the following correlations between the various scales.

CGI Defined	Corresponding Reductions	
	MDRS	LSAS
Response CGI-I ≥50% reduction	39%	31%
Remission CGI-S ≤2	11 points	36 points

Given that a normal volunteers scores below 30 points on the LSAS the remission score suggested is not unreasonable. Indeed, consensus conferences addressing this issue have also arrived at remission being defined as LSAS≤30.[23 24]

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[25] 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.[13] CGI consists of two subscales:

- Clinical Global Impressions – Improvement scale (CGI-I):
  This scale evaluates a patients' total improvement from baseline 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)[13] or CGI-I ≥50% reduction[22]. These patients have improved but have not yet reached remission.

Remission:[13] CGI-S≤ 2 (normal, not at all ill, or borderline illness)..

Sheehan Disability Scale (SDS)

The SDS[26] 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.[13] 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).[23 24]

Montgomery and Åsberg Depression Rating Scale (MADRS)

The MADRS[27] consists of 10 items, each rated on a scale from 0 (*no symptoms*) to 6 (*severe symptoms*). All the items are core symptoms of a depressive episode and thus measure the severity of a depressive episode for the previous 7 days.

The symptoms rated are: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.

The MADRS is based on a clinical interview with the patient beginning with general questions about symptoms and gradually becoming more detailed to allow for a precise rating of depression severity.

Source documents

All study data provided in Section B.5 comes from the Study Reports provided (Study 99270, 99012 and 99269). Page and/or table references are provided under the tables or in text. .

B.6 Systematic overview of the results of the direct randomised trials

Summary

The results of the randomised, controlled, double-blind studies demonstrate that escitalopram treatment significantly reduces the severity of Social Anxiety Disorder, compared with placebo and improved patient functioning. s38

Mean improvement in LSAS Total Score was the primary study outcome in the two treatment studies and a key secondary outcome in the relapse-prevention study. In all studies escitalopram significantly improved the mean LSAS total score compared with placebo. In addition, the percentage of patients defined as responders (based on both the LSAS and CGI-I scales) and remitters (based on the CGI-S scale) were significantly greater with escitalopram. The improvements seen were both statistically significant and clinically meaningful, demonstrating the clear benefit of escitalopram to this severely incapacitated patient group.

Figure B.6.1 depicts the timelines for the various trials. It outlines the level of information provided over a 36 week trial program for patients being treated with SAD. It clearly depicts, together with Table B.6.1 that there is a clinically superior effect with escitalopram.

. As can be seen a statistically different outcomes is observed in the primary and secondary outcomes. These differences are determined to be clinically relevant, as will be shown in the following sections.

Figure B.6.1: Clinical trials for SAD

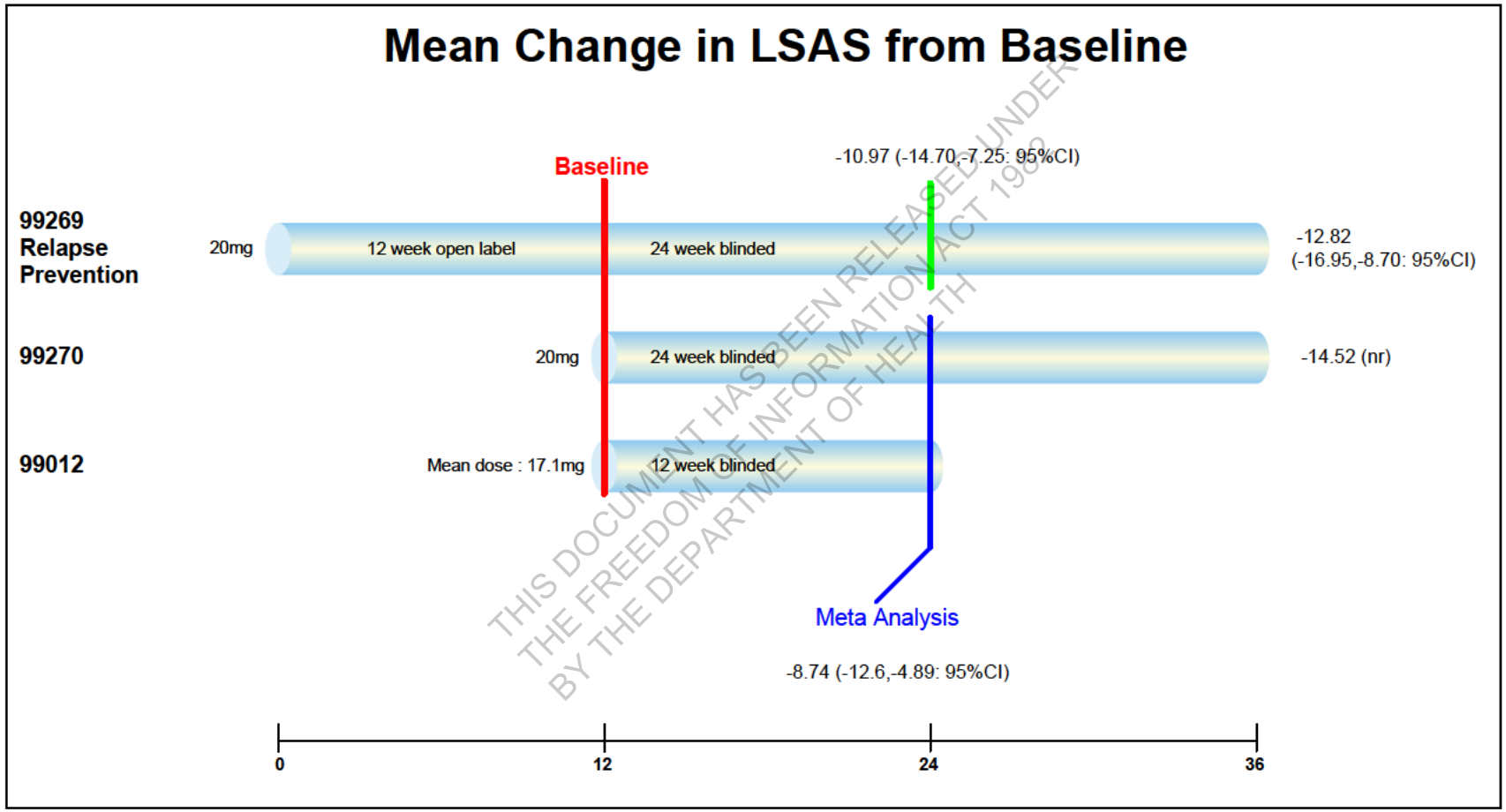


Table B.6.1: Summary results of primary outcome and meta-analysis

		99270			99012		99269 Relpase Prevention	
		Escitalopram 10mg	Escitalopram 20mg	Placebo	Escitalopram $\bar{x}$=17.1mg	Placebo	Escitalopram	Placebo
	n reporting data / N (%)	164/168 (98)	163/170 (96)	165/166 (99)	177/181 (98)	176/177 (99)	189/190 (99.5)	179/181 (99)
Unadjusted	**Mean LSAS total score (SD) at:**							
	Open Label	[redacted]					94.24 (15.72)	93.88 (14.09)
	Baseline	92.38 (14.93)	93.98 (13.99)	96.00 (14.46)	96.32 (17.35)	95.44 (16.35)	44.28 (20.84)	43.16 (19.94)
	Week 12	59.36 (26.81)	55.35 (28.76)	67.44 (26.81)	62.25 (30.67)	68.82 (29.70)	37.95 (22.41)	48.80 (26.53)
	Week 24 (endpoint)	52.57 (29.12)	46.17 (31.55)	62.72 (30.16)	[redacted]		35.71 (24.27)	48.50 (26.87)
	Mean change LSAS from baseline (SD) at:							
	Week 12	-33.02 (24.19	-38.63 (27.56)	-28.56 (22.84)	-34.07 (25.81)	-26.62 (26.09)	-6.20 (16.43)	5.54 (19.81)
	Week 24	-39.80 (28.31)	-47.80 (30.78)	-33.28 (26.55)	[redacted]		-8.43 (19.08)	5.24 (21.27)
	Difference of mean changes (95% CI), escitalopram versus placebo: Results from Meta-analysis at 12 weeks	[redacted]	-8.74 (-12.60, -4.89)				[redacted]	
	Difference of mean changes (95% CI), escitalopram versus placebo at 24 weeks	-6.92 (n.r.)	-14.52 (n.r)	[redacted]				
Adjusted	**Adjusted* mean change LSAS from baseline (SE) at:**							
	Week 12	-34.55 (1.96)	-39.79 (1.97)	-29.48 (1.95)	-34.45	-27.16	-6.13 (1.56)	4.85 (1.65)
	Week 24	-41.50 (2.17)	-49.13 (2.13)	-34.04 (2.17)	[redacted]		-8.28 (1.73)	4.55 (1.82
	Difference of adjusted* mean change LSAS (95% CI) - escitalopram versus placebo:							
	Week 12	-5.07 (-10.32, 0.18)	-10.31 (-15.56, -5.06)	[redacted]	7.29 (-12.37, -2.21)	[redacted]	-10.97 (-14.70, -7.25)	[redacted]
	Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25))	[redacted]	[redacted]		-12.82 (-16.95, -8.70)	[redacted]

Full details of the results of the included studies are provided in this section and in Attachment 6. The results are presented in the following sub-sections:

B.6.1 Primary outcome result – Change in mean LSAS Total Score

- For Study 99270 and 99012, presented individually
- Meta-analysis of Study 99270 and 99012 (at Week 12)

B.6.2 Results of the primary outcome for Study 99269 – relapse-prevention study

B.6.3 Results of key secondary efficacy results for the individual studies (provided in full in Attachment 6)

B.6.4 Results of the meta-analysis of key secondary outcomes (Study 99270 and 99012) at Week 12

B.6.5 Results of key secondary safety results for the individual studies (provided in full in Attachment 6)

B.6.6 Summary of efficacy and safety data

Change in mean LSAS total score is the primary outcome for Study 99270 and 99269.

s47E(d) This is followed by the primary outcome results of the relapse-prevention study (time to relapse). The results of the meta-analysis of the key secondary outcomes are presented next. Individual study key secondary efficacy and safety results are then presented, with full details available in Attachment 6.

The results of Study 99270 and 99012 demonstrate the efficacy and safety of escitalopram in the treatment of SAD. The results of the relapse prevention study

(Study 99269) demonstrate the continued efficacy and safety of escitalopram treatment in patients who have been initially successfully treated with escitalopram.

All results are sourced from the Clinical Study Reports, with Table and page references provided. Copies of the Clinical Study Reports have been provided with the submission.

B.6.1 Primary outcome – Mean change in LSAS Total Score

The primary outcome in Study 99270 and 99012 was mean change in LSAS Total Score. The results are presented individually for each study. s38 This is followed by the results of the meta-analysis of this outcome for Study 99270 and 99012 at Week 12.

B.6.1.1 Study 99270, Study 99012 and Study 99269 (Mean change in LSAS Total Score)

Study 99270 had a 24-week active treatment period. Data is reported at Week 12 and 24 to allow comparison with Study 99012 which was of 12 weeks duration (see Table B.6.2). Both mean change and adjusted mean change data is reported, as adjustment using ANOVA was the pre-specified method of analysis in the individual studies, with adjustment leading to only very small differences in the adjusted versus unadjusted results.

Table B.6.2: Results of primary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99270

Outcome Time point	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source (Study Report)
n reporting data / N (%)	164/168 (98)	163/170 (96)	165/166 (99)	Table 27
Mean LSAS total score (SD) at:				
Baseline	92.38 (14.93)	93.98 (13.99)	96.00 (14.46)	
Week 12	59.36 (26.81)	55.35 (28.76)	67.44 (26.81)	
Week 24 (endpoint)	52.57 (29.12)	46.17 (31.55)	62.72 (30.16)	
Mean change from baseline (SD) at:				Table 29
Week 12	-33.02 (24.19	-38.63 (27.56)	-28.56 (22.84)	
Week 24	-39.80 (28.31)	-47.80 (30.78)	-33.28 (26.55)	
Adjusted* mean change from baseline (SE) at:				Table 32
Week 12	-34.55 (1.96)	-39.79 (1.97)	-29.48 (1.95)	
Week 24	-41.50 (2.17)	-49.13 (2.13)	-34.04 (2.17)	
Difference of adjusted* mean changes (95% CI) - escitalopram versus placebo:				
Week 12	-5.07 (-10.32, 0.18)	-10.31 (-15.56, -5.06)		
Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25))		

SE = Standard error (least squares estimate)
* Using ANCOVA

The difference of the adjusted mean change in LSAS total score at Week 24 was –7.45 (95% CI –13.29, -1.62) in the escitalopram 10mg group and –15.09 (95% CI –20.92, -9.25) in the escitalopram 20mg group, both compared with placebo. The improvement in LSAS score was statistically significant for escitalopram 20mg at Week 12. The benefit of escitalopram continued to increase over time, and by Week 24 achieved statistical significance in both escitalopram groups.

The final (i.e. 12 week) primary outcome results for Study 99012 are presented in TableB.6.3 below.

TableB.6.3:Results of primary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99012

Outcome Time point	Escitalopram[a]	Placebo	Source (Study Report)
n reporting data / N (%)	177/181 (98)	176/177 (99)	Table 18
Mean LSAS total score (SD):			
Baseline	96.32 (17.35)	95.44 (16.35)	
Week 12	62.25 (30.67)	68.82 (29.70)	
Mean change from baseline (SD) at:			Table 20
Week 12	-34.07 (25.81)	-26.62 (26.09)	
Adjusted[b] mean change from baseline[c] at:			Table 23
Week 12	-34.45	-27.16	
Difference of adjusted[b] mean change (95% CI) - escitalopram versus placebo:			
Week 12	-7.29 (-12.37, -2.21)		

SE = Standard error (least squares estimate)
a. Flexible dose study, mean escitalopram study dose at Week 12 was 17.1mg daily
b. using ANCOVA
c. SD/SE values not reported

At the end of the 12 week study period, escitalopram provided a significant improvement in the primary study outcome, compared with placebo.

Study 99269 was a 24-week randomised, double-blind, relapse prevention study. Prior to randomisation all patients received open-label escitalopram for 12 weeks. Patients that responded to therapy were then randomised into the double-blind, active treatment phase of the study. While time to relapse was the primary study outcome, a secondary outcome of importance was the improvement in LSAS total score. These results are presented in TableB.6.4 below.

TableB.6.4:Results of secondary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99269

Outcome Time point	Escitalopram[a]	Placebo	Source (Study Report)
n reporting data / N (%)	189/190 (99.5)	179/181 (99)	
Mean LSAS total score (SD):			
Open-label phase Baseline	95.11 (15.65) (n=190)	96.24 (14.35) (n=181)	Table 32
Baseline (prior to randomisation)	44.28 (20.84)	43.16 (19.94)	Table 61
Week 12	37.95 (22.41)	48.80 (26.53)	
Week 24	35.71 (24.27)	48.50 (26.87)	
Mean change from baseline (SD) at:			
Week 12	-6.20 (16.43)	5.54 (19.81)	Table 63
Week 24	-8.43 (19.08)	5.24 (21.27)	
Adjusted mean change from baseline (SE) at:			
Week 12	-6.13 (1.56)	4.85 (1.65)	
Week 24	-8.28 (1.73)	4.55 (1.82	Table 65
Difference of adjusted[b] mean change (95% CI) -- escitalopram versus placebo:			
Week 12	-10.97 (-14.70, -7.25)		
Week 24	-12.82 (-16.95, -8.70)		

SE = Standard error (least squares estimate)
a. Flexible dose study, mean escitalopram study dose was 17.3mg daily
b. using ANCOVA

Patients in the relapse-prevention study had lower (i.e. improved) LSAS total Scores at baseline compared with those in the two treatment studies (Study 99270 and 99012) as they had received 12 weeks of open-label therapy with escitalopram. Prior to the 12 weeks open-label escitalopram therapy, the patients' baseline LSAS scores were similar to the baseline scores seen in the treatment studies (Study 99270 and 99012)

At Week 12 and 24 after randomisation to escitalopram or placebo, patients in the escitalopram group had an improvement in mean LSAS Total Score compared with patients receiving placebo. Patients had a difference in the adjusted mean change of –10.97 (95% CI –14.70 to –7.25) at Week 12, compared with placebo. Further improvement occurred at Week 24 with a difference of –12.82 (95% CI –16.95 to –8.70) between escitalopram therapy and placebo. This difference was both statistically significant and clinically meaningful, with both point estimates exceeding the clinically important difference of –10 (see Section B.5.4 for details).

Of note, patients continued to improve from the time they received open-label escitalopram until the final assessment at Week 24, after a total of 36 weeks of escitalopram therapy.

B.6.1.2 Meta-analysis

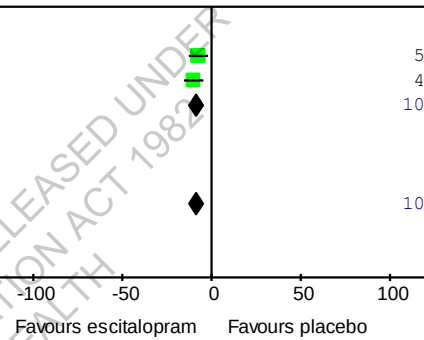
The meta-analysis combines the primary outcome results for Study 99270 and 99012 (**using the unadjusted change data**) at Week 4, 8 and 12. The data utilised for 99270 was 20mg arm of escitalopram patients, given that the mean dose for 99012 was 17.1mg. The data is presented below with full details of the study methodology available in Attachment 5. As Study 99012 was only of 12 weeks duration, the longest time-point that could be meta-analysed was 12 weeks. The results of Study 99270 (and Study 99269) demonstrate that patients receiving escitalopram continue to improve during Week 12 to Week 24 of therapy. Therefore the results of the meta-analysis underestimate the true value of escitalopram therapy, i.e. that occurring beyond 12 weeks of therapy. The results of Study 99269 could not be meta-analysed with the other two studies due to significant differences in study design, leading to differing patient populations.

The results of the meta-analysis were conducted for the duration of 4, 8 and 12 weeks. Only the 12 week data is presented here, all results are presented in Attachment 5. The 12 week data is presented in Figure B.6.2.

Figure B.6.2:Results of primary outcome (mean change in LSAS total score, LOCF) at Week 12 – meta-analysis of Study 99270 and 99012

Review: Escitalopram (Lexapro) - SAD
Comparison: 01 Change in Mean LSAS Total Score (FAS LOCF) - primary endpoint
Outcome: 03 Change in Mean LSAS Total Score (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

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							
99012	177	-34.07(25.81)	176	-26.62(26.09)		50.62	-7.45 [-12.86, -2.04]
99270	163	-38.63(27.56)	165	-28.56(22.84)		49.38	-10.07 [-15.55, -4.59]
Subtotal (95% CI)	340		341			100.00	-8.74 [-12.60, -4.89]
Test for heterogeneity: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%							
Test for overall effect: Z = 4.45 (P < 0 00001)							
Total (95% CI)	340		341			100.00	-8.74 [-12.60, -4.89]
Test for heterogeneity: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%							
Test for overall effect: Z = 4.45 (P < 0 00001)							



Source: Meta-analysis Report - Attachment 5

The weighted mean change in the LSAS total score continued to increase from Week 4 to Week 12. At Week 12 the difference in the weighted mean change was -8.74 (95% CI -12.60, -4.89). This is a statistically significant improvement in LSAS total score in the escitalopram group, compared with placebo. Importantly, the 95% confidence intervals include the value 10, the clinically important improvement in LSAS Total Score described in Section B.5.4. Based on the results of the 24 week treatment and relapse-prevention studies, it would be expected that escitalopram treated patients would continue to improve beyond the 12 week meta-analysis period reported.

B.6.2 Relapse-prevention Study 99269 - primary outcome result (time to relapse)

Study 99269 was a relapse prevention study. All patients received 12 weeks of open-label escitalopram, with responders then randomised to receive 24 weeks of escitalopram or placebo. The primary study outcome was time to relapse. The results are presented in TableB.6.5 and graphically in Figure B.6.3.

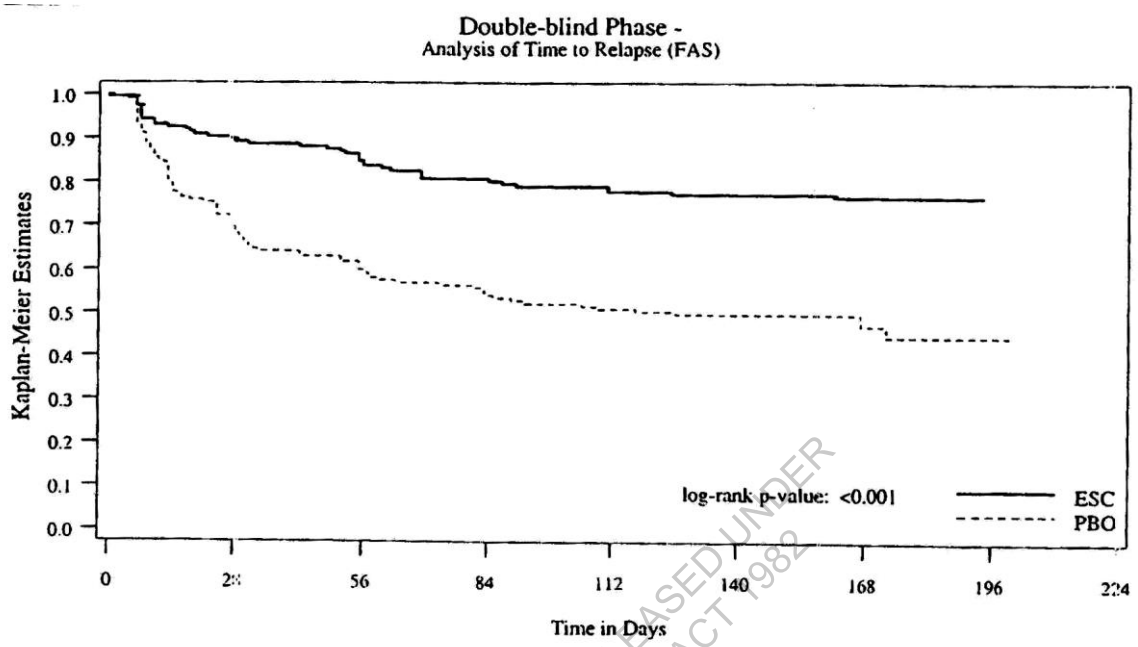
Due to the relatively few relapses in the escitalopram group, median survival times could not be estimated satisfactorily. Instead descriptive mean survival times have been presented.

TableB.6.5: Analysis of time to relapse (Study 99269)

Treatment	n / N (%)	No. of relapses	% Relapsed	Mean survival days
Escitalopram Placebo	190/190 (100) 181/182 (99.5)	42 91	22.1 50.3	135.3 103.5
Log-rank P value	**Hazard Ratio (Cox)**	**Standard Error**	**Cox-Model P-value**	
5.0E-09	2.83 (NR)	1.21	2.7E-08	

Source – Table 42
NR.: not reported

Figure B.6.3: Analysis of time to relapse (Study 99269)



The results of the primary analysis show a clear beneficial effect of escitalopram relative to placebo, with more than twice as many patients in the placebo group relapsing. (Hazard Ratio 2.83, log rank test, p<0.001). This study demonstrates the benefit of escitalopram in reducing the risk of relapse once patients have responded to therapy.

B.6.3:Secondary outcome results for the individual studies - efficacy

The key secondary efficacy results are summarised in this section and presented for the individual studies in full in Attachment 6. A summary list of these efficacy outcomes and the studies in which they are available is presented in TableB.6.6 below.

TableB.6.6: Key secondary efficacy results for the individual studies presented in Attachment 6

	Study 99270	Study 99012	Study 99269
Time-point analysed and reported[a]	**Week 12 & 24**	**Week 12**	**Week 12 & 24**
Secondary efficacy outcomes			
Proportion of patients with a ≥50% reduction in LSAS score	√	NR	NR
CGI-I Score	√	√	NA
Number and % patients with CGI-I≤2 (CGI-I responders)	√	√	NA
Change in mean CGI-S Score	√	√	√
Number and % patients with CGI-S≤2	√	NR	NR
Change in SDS Work Scores	√	√	√
Change in SDS Social Scores	√	√	√
Change in SDS Family Scores	√	√	√
Change in MADRS total score	√	√	√

Key:
√ = outcome reported in the Study Report and results presented in Section B.6.4
NA = not available – not a pre-defined study outcome, therefore data not collected
NR = not reported – data not reported for that outcome
CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; ESC = escitalopram, LSAS = Liebowitz Social Anxiety Scale, MADRS = Montgomery and Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale.
Notes:
a. All change outcomes are change from baseline

Summary of key secondary efficacy outcome results

Studies 99270 and 99269 were both of 24 weeks duration (randomised, double-blind phase) Results of the secondary efficacy outcomes demonstrate that patients continue to gain benefit from escitalopram beyond 12 weeks and up to at least 24 weeks of therapy. Patients on escitalopram showed a significantly greater response to therapy (based on significant improvements in % patients with a ≥50% reduction in LSAS, CGI-I scores, % patients with CGI-I≤2 and CGI-S scores). Measures of functional impairment (SDS) also showed benefits with escitalopram therapy.

Study 99270 also compared two different daily doses of escitalopram (10mg and 20mg) over 24 weeks of therapy. The benefits of therapy were greater with escitalopram 20mg daily in all the efficacy outcomes, compared with escitalopram 10mg daily.

The results of the key secondary outcomes measures that are markers of disease severity and improvement with therapy (i.e. % patients with ≥50% improvement in LSAS Score, CGI-I Score and % patients with a CGI-I or CGI-S Score ≤2) are presented for Study 99270 and Study 99012 in TableB.6.7 below. In all cases escitalopram significantly improved patient outcomes.

The Sheehan Disability Scales (SDS) scores (Work, Social and Family) were also statistically significantly improved in Study 99270 at Weeks 12 and 24. At Week 12 in Study 99012 there were statistically significant improvements in SDS Work and Social Scores, with a trend towards improvement in the Family Score. The SDS is a measure of functional disability in SAD in the three key affected areas.

TableB.6.7: Summary results of secondary efficacy outcomes – Study 99270 and Study 99012 (% patients with ≥50% reduction in LSAS, Clinical Global Impression – Improvement, % patients with CGI-I and CGI-S≤2)

	Study 99270		Study 99012
Outcome	**Escitalopram 10mg**	**Escitalopram 20mg**	
% of patients with ≥50% reduction in LSAS total score			
Mean % difference (95% CI) esc vs placebo			NR
Week 12	8.7 (-0.6, 18.0)	18.7 (8.9, 28.4)	
Week 24:	17.2 (7.0, 27.5)	27.3 (17.1, 37.6)	
Relative Risk* (95% CI) esc vs placebo at:			NR
Week 12	1.42 (0.97, 2.08)	1.91 (1.34, 2.72)	
Week 24	1.61 (1.20, 2.15)	1.96 (1.49, 2.59)	
NNT* (95% CI) vs placebo at:			NR
Week 12	11 (6, 167)	5 (4, 11)	
Week 24	6 (4, 14)	4 (3, 6)	
CGI-I[a]			
Difference of adjusted mean CGI-I Score esc vs placebo (95% CI) at:			
Week 12	-0.21 (-0.43, 0.01)	-0.32 (-0.55, -0.10)	-0.37 (-0.59, -0.16)
Week 24	-0.21 (-0.45, 0.02)	-0.48 (-0.72, -0.25)	-
% Patients with CGI-I ≤2			
Difference in % patients with CGI-I ≤2 esc vs placebo (95% CI) at:			
Week 12	13.7 (3.0, 24.4)	20.8 (10.2, 31.3)	15.6 (5.3, 25.9)
Week 24	7.6 (-3.1, 18.4)	19.6 (9.3, 30.0)	-
Relative Risk* (95% CI) esc vs placebo at:			
Week 12	1.33 (1.06, 1.67)	1.50 (1.21, 1.87)	1.40 (1.12, 1.77)
Week 24	1.15 (0.94, 1.41)	1.39 (1.16, 1.67)	-
NNT* (95% CI) esc vs placebo at:			
Week 12	7 (4, 33)	5 (3, 10)	6 (4, 19)
Week 24	13 (5, 32)	5 (3, 11)	-
Patients with CGI-S≤2			
Difference in % patients with CGI-S ≤2 esc vs placebo (95% CI) at:			NR
Week 12	11.1 (2.7. 19.4)	13.7 (5.1, 22.2)	
Week 24	17.8 (8.3, 27.3)	26.6 (16.9, 36.4)	
Relative Risk* (95% CI) esc vs placebo at:			NR
Week 12	1.83 (1.14, 2.94)	2.03 (1.27, 3.22)	
Week 24	1.92 (1.33, 2.77)	2.37 (1.67, 3.38)	

	Study 99270		Study 99012
Outcome	Escitalopram 10mg	Escitalopram 20mg	
NNT* (95% CI) esc vs placebo at:			NR
Week 12	9 (5, 37)	7 (5, 20)	
Week 24	6 (4, 12)	4 (3, 6)	

CGI-I = Clinical Global Impression – Improvement, CGI-S= Clinical Global Impression – Severity, esc = escitalopram, LSAS = Liebowitz Social Anxiety Scale, NR = not reported
* calculated value

The key secondary efficacy outcomes for the relapse-prevention Study 99269 are presented in full in Attachment 6. The proportion of patients with ≥50% reduction in LSAS Total Score was not reported, while CGI-I was not measured in this study. There was a statistically significant improvement in CGI-S total score and in all the SDS scores (Work, Social, Family) at both Weeks 12 and 24 in Study 99269.

B.6.3 Meta-analysis of key secondary outcomes

Revman format results for the meta-analysis of the key secondary outcomes of the treatment studies (Study 99270 and 99012) are presented in Figure B.6.4 to Figure B.6.14 below. Results are presented at 12 weeks, with CGI-I ≤2 (sometimes called CGI-I responders) 12 weeks. The meta-analysis presented in Attachment 5 also contains results reported at 4 and 8 weeks.

It is important to note that Study 99270 was of 24 weeks duration, so the meta-analysed results do not reflect the value of escitalopram during the second 12 weeks of study treatment. In addition, due to differences in study design the relapse-prevention study (Study 99269) could not be validly meta-analysed with the other two treatment studies. Study 99269 also provides data on the use of escitalopram for 24 weeks, rather than the 12 weeks reported in the meta-analysis. See Section B.6.4 for the 24 week study results.

Summary of meta-analysis results

Results for the meta-analysis are reported in Figure B.6.4 to Figure B.6.14. Escitalopram was statistically significantly superior to placebo for all efficacy outcomes relating to reduced severity of SAD at Week 12 (CGI-I Score, % patients

with CGI≤2 also called 'remitters', CGI-S). The percentage of patients with CGI-I≤2 (or CGI-I 'responders', patients who are rated as 'very much or 'much' improved on the CGI-I scale) was 50% greater with escitalopram at 12 weeks (RR 1.46; 95% CI 1.24, 1.71). Two functional disability measures on the Sheehan Disability Scale (SDS) – work and social scores - also showed a statistically significant benefit for escitalopram, with the exception being the SDS Family score (where there was a trend towards significance).

The MADRS score was not an efficacy endpoint, but rather an assessment of depressive status. While escitalopram was superior to placebo at week 12, the MADRS score seen throughout the studies in all treatment groups was below the recognised cut-off for a depressive episode (i.e. <8), indicating that benefits seen with escitalopram were due to treatment of SAD, rather than co-morbid depression.

Patients receiving escitalopram had a higher rate of treatment-emergent adverse events than placebo and more adverse events leading to withdrawal, as would be expected of an active treatment compared with placebo. However with escitalopram there was a significant 62% reduction in patients withdrawing from the studies due to lack of efficacy (RR 0.38, 95% CI 0.21, 0.67).

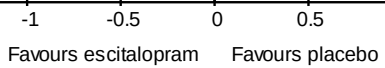
Clinical Global Impression – Improvement (CGI-I)

Results from the meta-analysis are presented in Figure B.6.4 to Figure B.6.6.

Figure B.6.4: CGI Improvement (LOCF) – 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 05 CGI Improvement (FAS LOCF) - a change characteristic - secondary endpoint
Outcome: 01 CGI Improvement (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

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							
99012	177	2.55(1.05)	175	2.93(1.07)		53.99	-0.38 [-0.60, -0.16]
99270	162	2.38(1.16)	165	2.71(1.05)		46.01	-0.33 [-0.57, -0.09]
Subtotal (95% CI)	339		340			100.00	-0.36 [-0.52, -0.19]
Test for heterogeneity: Chi² = 0 09, df = 1 (P = 0.76), I² = 0%							
Test for overall effect: Z = 4.30 (P < 0.0001)							
Total (95% CI)	339		340			100.00	-0.36 [-0.52, -0.19]
Test for heterogeneity: Chi² = 0 09, df = 1 (P = 0.76), I² = 0%							
Test for overall effect: Z = 4.30 (P < 0.0001)							



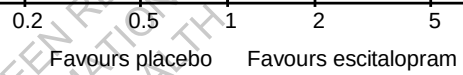
Source: Meta-analysis Report - Attachment 1

Figure B.6.5: Number and Percentage of Patients with CGI-I ≤2 (LOCF), also called 'responders' - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 06 Number of Patients with CGI-I <=2 (FAS LOCF) - secondary endpoint
Outcome: 03 Number of Patients with CGI-I <=2 (FAS LOCF) - 12 weeks

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
99012	96/177	68/176		47.37	1.40 [1.12, 1.77]
99270	101/163	68/165		52.63	1.50 [1.21, 1.87]
Total (95% CI)	340	341		100.00	1.46 [1.24, 1.71]

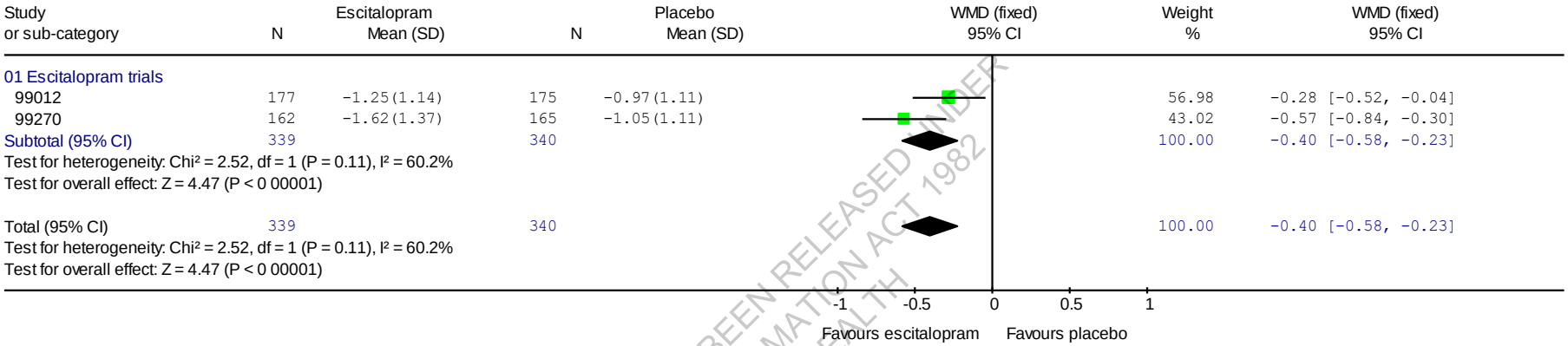
Total events: 197 (Escitalopram), 136 (Placebo)
Test for heterogeneity: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%
Test for overall effect: Z = 4.64 (P < 0.00001)



Source: Meta-analysis Report - Attachment 5

Figure B.6.6: Change in CGI Severity (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 04 Change in CGI Severity (FAS LOCF) - secondary endpoint
Outcome: 01 Change in CGI Severity (FAS LOCF) - "Head-to-Head" comparison - 12 weeks



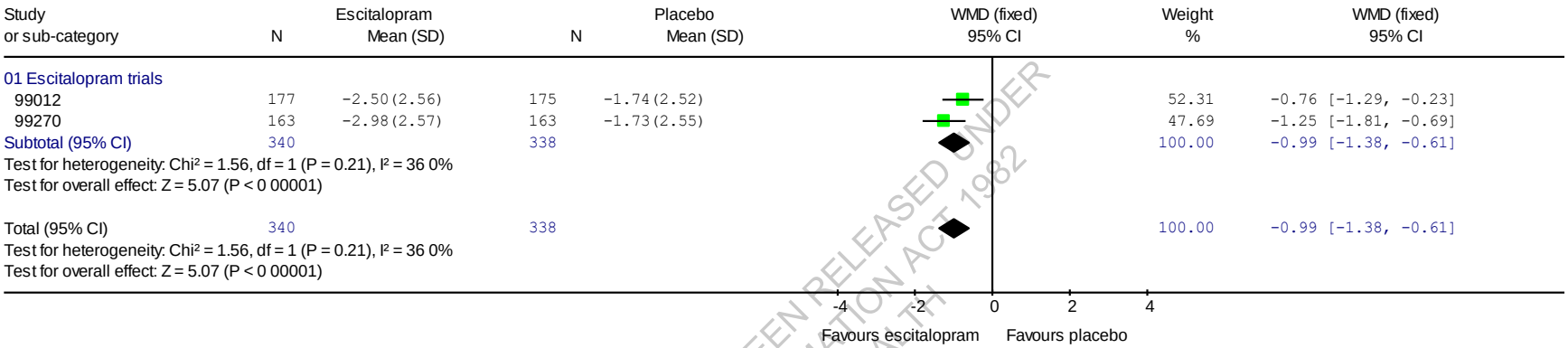
Source: Meta-analysis Report - Attachment 5

Sheehan Disability Scale (SDS)

Results from the meta-analysis are presented in Figure B.6.7 to Figure B.6.9.

Figure B.6.7: Change in SDS Work Scores (LOCF) - 12 weeks

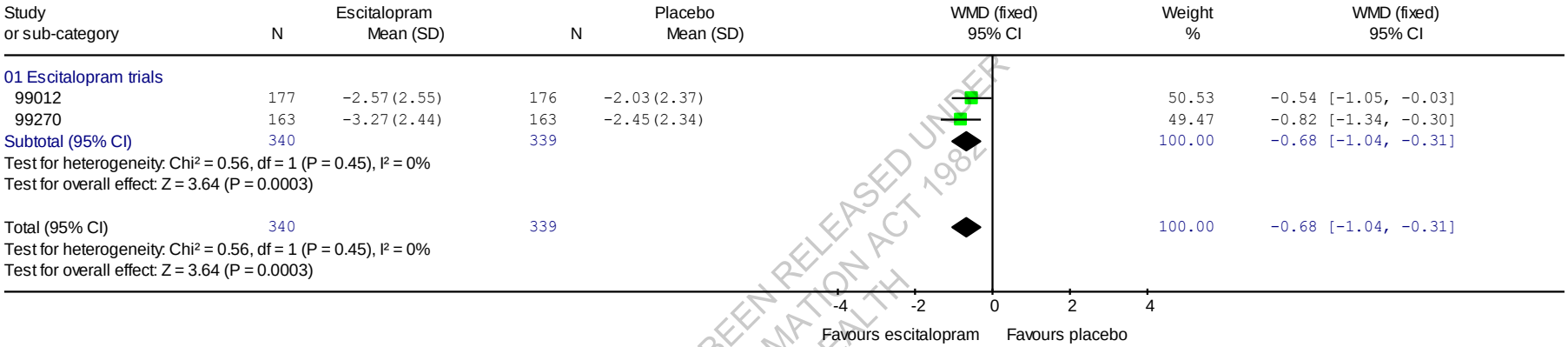
Review: Escitalopram (Lexapro) - SAD
Comparison: 07 Change in SDS Work Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Work Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks



Source: Meta-analysis Report - Attachment 5

Figure B.6.8: Change in SDS Social Scores (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 08 Change in SDS Social Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Social Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

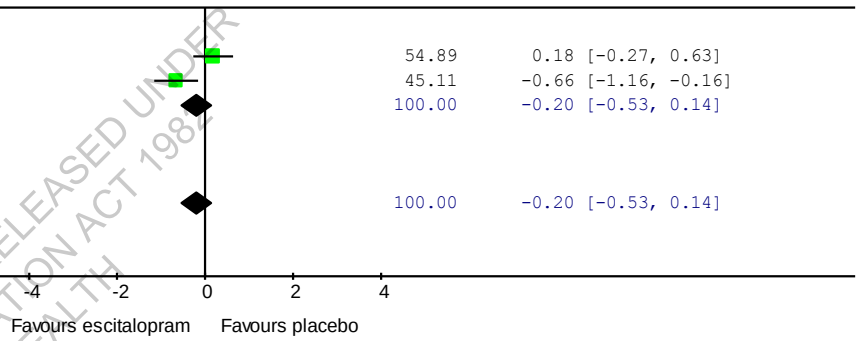


Source: Meta-analysis Report - Attachment 5

Figure B.6.9: Change in SDS Family Scores (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 09 Change in SDS Family Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Family Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

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							
99012	177	-1.44(2.05)	176	-1.62(2.27)		54.89	0.18 [-0.27, 0.63]
99270	163	-2.00(2.41)	163	-1.34(2.17)		45.11	-0.66 [-1.16, -0.16]
Subtotal (95% CI)	340		339			100.00	-0.20 [-0.53, 0.14]
Test for heterogeneity: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%							
Test for overall effect: Z = 1.17 (P = 0.24)							
Total (95% CI)	340		339			100.00	-0.20 [-0.53, 0.14]
Test for heterogeneity: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%							
Test for overall effect: Z = 1.17 (P = 0.24)							



Source: Meta-analysis Report - Attachment 5

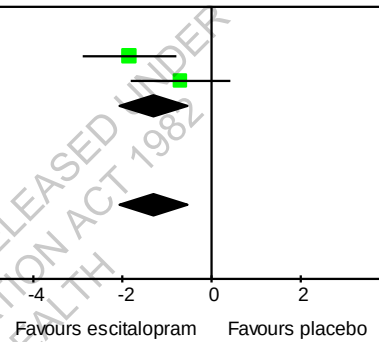
Montgomery and Åsberg Depression Rating Scale (MADRS)

Results from the meta-analysis are presented in Figure B.6.10.

Figure B.6.10: Change in MADRS Total Score (LOCF) - secondary endpoint - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 10 Change in MADRS Total Score (FAS LOCF) - secondary endpoint
Outcome: 01 Change in MADRS Total Score (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

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							
99012	175	-2.44(5.05)	170	-0.60(4.89)		53.06	-1.84 [-2.89, -0.79]
99270	159	-2.76(5.09)	158	-2.06(5.04)		46.94	-0.70 [-1.82, 0.42]
Subtotal (95% CI)	334		328			100.00	-1.30 [-2.07, -0.54]
Test for heterogeneity: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%							
Test for overall effect: Z = 3 35 (P = 0 0008)							
Total (95% CI)	334		328			100.00	-1.30 [-2.07, -0.54]
Test for heterogeneity: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%							
Test for overall effect: Z = 3 35 (P = 0 0008)							



Source: Meta-analysis Report - Attachment 5

s22 [redacted]

B.6.6 Summary of efficacy and safety

Change in mean LSAS total score was the primary outcome for Study 99270 and 99012, and a secondary outcome in Study 99269. s47E(d) [redacted] The LSAS is widely used in treatment studies, is sensitive, validated and considered the gold standard measure of treatment success in SAD. An improvement of 10 points on the LSAS (i.e. a mean Total Score difference of –10) is considered a clinically relevant treatment improvement[13]. Responders (based on LSAS criteria) have been defined as having a greater than or equal to 35-50% reduction in LSAS Total Score[13]. Similarly, a CGI-I score of $\leq$ 2 has also been used to define a responder to therapy, while a CGI-S score <2 suggests remission[13]. ***On all of these important response measures, escitalopram was shown to significantly improve patient outcomes, compared with the comparator.***

The improvement in LSAS scores seen in all three studies was statistically significant. The benefit of escitalopram was evident after 12 weeks of therapy and continued to increase from 12 to 24 weeks of therapy. In Study 99270, treatment with escitalopram 20mg daily resulted in a difference in mean LSAS total score change of -15.09 (95% CI -20.92, -9.25) at Week 24, while at 24 weeks in Study 99269 there was a difference of –12.82 (95% CI –16.95, -8.70), both compared with placebo. In all

three studies at both 12 and 24 weeks, a difference in mean improvement of –10 in LSAS Total Score fell within the 95% CIs for this outcome, providing a high level of confidence that a clinically meaningful result was obtained.

Responders to therapy, defined as either a 50% or greater reduction in LSAS total score or CGI-I ≤2, were also significantly greater with escitalopram. In Study 99270 at endpoint, 17.2% (95% CI 7.0%, 27.5%) of patients receiving escitalopram 10mg daily and 27.3% (95% CI 17.1%, 37.6%) more patients responded to escitalopram (based on LSAS criteria), compared with the comparator. Improvements in CGI-I responders also occurred. The percentage of CGI-S remitters (i.e. patients with a score of ≤2 on the CGI-S) were significantly greater with escitalopram. Eighteen percent (risk difference 17.8%, 95% CI 8.3%, 27.3%; escitalopram 10mg daily) and 27% (risk difference 26.6%, 95% CI 16.9%, 36.4%; escitalopram 20mg daily) more patients achieved remission at study endpoint, versus the comparator, based on CGI-S improvements.

Thus, escitalopram consistently improved patient outcomes on all key, patient-relevant efficacy outcome measures. This included mean improvement in the LSAS scale Total Score (≥10 point improvement) and percentage of responders (based on LSAS criteria), as well as responders based on CGI-I criteria. In addition, significantly more patients achieved remission (based on CGI-S criteria) with escitalopram. The results of the randomised, controlled, double-blind 24 week treatment studies presented demonstrate that therapy with escitalopram provides statistically significantly superior treatment (compared with placebo), across a range of outcomes, that is also clinically meaningful and relevant.

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B.8 Interpretation of the clinical evidence

Summary

Social Anxiety Disorder is a severe, disabling condition with significant negative patient impact on social functioning leading to educational, social and financial disadvantage. Information on the importance of pharmacotherapy in improving the lives of patients with SAD is presented.

The patients in the trials had been sufferers of SAD for 20-24 years and the mean age of onset was 15-18 years. This sample of patients closely mirrors the epidemiological evidence (see Attachment 2). At 12 weeks a greater proportion of these patients responded to treatment (when compared to placebo) and at 24 weeks an even larger response was seen. This was reinforced by the relapse prevention study. As would be expected, and shown in other studies, duration of treatment was important, with greater improvements seen over time.

Escitalopram provides superior efficacy and similar safety to the main comparator (placebo). A modelled economic evaluation is presented in Section C. This assessment is based on three well designed and conducted direct comparative randomised, controlled studies. The key study outcome (improvement in the LSAS Total Score) was significantly improved in the escitalopram treatment groups, compared with placebo in all studies.

The percentage of patients responding to therapy (based on LSAS and CGI-I criteria) and achieving remission (based on CGI-S criteria) were also significantly greater with escitalopram, demonstrating the overall superiority of escitalopram therapy across a range of patient-relevant outcomes. s22

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B.8.2 Assessment of the trial evidence for escitalopram in SAD

B.8.2.1 The level of the evidence

A comprehensive literature review was undertaken, with full details provided in Section B.1 and B.2. The three studies identified in the literature search and presented in the submission are all double-blind, randomised, controlled, multicentre, parallel-group **direct** comparisons between escitalopram and comparator (placebo). This is generally considered the highest level of clinical evidence available.

B.8.2.2 The quality of the evidence

The studies were well designed, conducted and reported, with full details provided in the Clinical Study Reports provided. Full details of the methods of randomisation, and blinding are provided in this submission. Randomisation was by a third party service (the pharmaceutical company). Blinding was maintained throughout the studies, with identical study products provided for each treatment group.

The basis of the analysis was 'intent to treat', based on all randomised patients with one valid post-baseline assessment of the primary outcome (a continuous variable). In all cases the results are presented using Last Observation Carried Forward methodology. The flow of participants through each of the studies is clearly identified in Section B.3.

Thus, the level of evidence provided in the submission is high, with the three studies presented all well conducted, randomised, controlled, double-blind, parallel group studies that provide a direct comparison with the comparator.

B.8.2.3 The statistical precision of the evidence

Efficacy and safety result data presented in Subsection B.6 for the individual direct randomised trial results and the pooled analyses was able to provide a high level of statistical precision. The primary efficacy results were presented as the difference between escitalopram and placebo in mean change from baseline to study endpoint in LSAS Total Score (with 95%CI). Secondary efficacy endpoints were presented as difference in mean change from baseline to endpoint with 95% CIs (continuous data), with dichotomous data also being reported as a relative risk (with 95% CI) and NNT (with 95% CI). Safety results were presented with relative risk (with 95%CI) and risk difference (with 95%CI).

B.8.2.4 The size of the effect

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all studies, treatment with escitalopram resulted in statistically and clinically significant improvements in LSAS Total Score, compared with placebo at

study endpoint. The clinical patient relevance of the improvements is discussed in Section B.8.5 below.

In the fixed-dose treatment Study 99270 at Week 24 the difference of the adjusted mean change was –7.45 (95% CI –13.29, -1.62) in the escitalopram 10mg group and –15.09 (95% CI –20.92, -9.25) in the escitalopram group, both compared with placebo.

In the flexible-dose treatment Study 99012 at Week 12 (study endpoint) the difference was –7.29 (95% CI –12.37, -2.21). In this study the mean dose of escitalopram was 17.1mg daily.

When meta-analysed the non-adjusted mean change between escitalopram versus placebo was -8.74 (95% CI -12.60, -4.89) at 12 weeks. This also needs to be considered in light of the final data point at 24 week mean change being -14.52. These results are depicted in summary table Table B.6.1.

The 24 weeks results, as expected, show a higher difference in the adjusted mean change in LSAS Total Score in the flexible-dose relapse prevention study –12.82 (95% CI –16.95, -8.70) for escitalopram (mean daily dose 17.3mg). The primary outcome in the relapse prevention study was time to relapse. The mean time to relapse was significantly greater, with a mean survival time of 135 days with escitalopram, compared with 103.5 days for placebo (Cox Hazard Ratio 2.83, P = 2.7E-08). **More than twice as many patients receiving placebo relapsed (91 with placebo versus 42 with escitalopram.**

Secondary Study Outcomes

The results of the key secondary outcomes (proportion of patients with ≥50% improvement in LSAS (LSAS responders), Clinical Global Impression – Improvement and Severity (CGI-I, CGI-S), % patients with CGI-I≤2 (CGI responders) and % patients with CGI-S≤2 (CGI-S remitters)) all improved with escitalopram therapy, with most improvements also being of statistical significance. The proportion of LSAS responders (patients with ≥50% change in LSAS Total Score) in Study 99270 was 17% greater with escitalopram 10mg daily (17.2%; 95%

risk difference CI 7.0, 27.5) and 27% greater with escitalopram 20mg daily (risk difference 27.3%; 95% CI 17.1%, 37.6%), compared with placebo at Week 24.

The CGI ≤2 (CGI responders) from the meta-analysis at 12 weeks confirms that patients are 46% more likely to respond on escitalopram than placebo at 12 weeks. This was slightly lower at 24 weeks at 39% but the difference was not statistically different. This can be seen in the summary Table B.8.1.

What is also clear is the consistency in the results reported across various outcome measures in terms of NNT, responders and remitters. Overall indicating that the body of evidence suggests that escitalopram is clinically significant.

Table B.8.1: Summary of secondary outcomes

(95% CI)			**Study 99270**		**Study 99012**
		week	**Escitalopram 10mg**	**Escitalopram 20mg**	**Escit. $\bar{x}$ =17.1mg**
NNT vs placebo					
	≥50% LSAS	*12*	**11** (6, 167)	**5** (4, 11)	
		24	**6** (4, 14)	**4** (3, 6)	
	CGI-I<2	*12*	**7** (4, 33)	**5** (3, 10)	**6** (4, 19)
		24	**13** (5, 32)	**5** (3, 11)	
	CGI-S<2	*12*	**9** (5, 37)	**7** (5, 20)	
		24	**6** (4, 12)	**4** (3, 6)	
Relative Risk vs placebo					
	≥50% LSAS	*12*	**1.42** (0.97, 2.08)	**1.91** (1.34, 2.72)	
		24	**1.61** (1.20, 2.15)	**1.96** (1.49, 2.59)	
	CGI-I<2	*12*	**1.33** (1.06, 1.67)	**1.50** (1.21, 1.87)	**1.40** (1.12, 1.77)
		Meta analysis 12		**1.46 (1.24, 1.71)**	
		24	**1.15** (0.94, 1.41)	**1.39** (1.16, 1.67)	
	CGI-S<2	*12*	**1.83** (1.14, 2.94)	**2.03** (1.27, 3.22)	
		24	**1.92** (1.33, 2.77)	**2.37** (1.67, 3.38)	
Difference in % of patients achieving vs placebo					
	≥50% LSAS	*12*	**8.7** (-0.6, 18.0)	**18.7** (8.9, 28.4)	
		24	**17.2** (7.0, 27.5)	**27.3** (17.1, 37.6)	
	CGI-I<2	*12*	**13.7** (3.0, 24.4)	**20.8** (10.2, 31.3)	**15.6** (5.3, 25.9)
		24	**7.6** (-3.1, 18.4)	**19.6** (9.3, 30.0)	
	CGI-S<2	*12*	**11.1** (2.7. 19.4)	**13.7** (5.1, 22.2)	
		24	**17.8** (8.3, 27.3)	**26.6** (16.9, 36.4)	

More patients receiving escitalopram had treatment-emergent adverse events, with the risk statistically significantly greater in two out of three of the studies. Total patients withdrawals in the two treatment groups were similar, as were withdrawals due to adverse events, with no statistically significant differences between the treatment groups in all studies. Patient withdrawals due to lack of efficacy were significantly reduced with escitalopram compared with placebo in the studies at week 24 (Study 99270: escitalopram 10mg RR 0.53, 95% CI 0.30 to 0.96, escitalopram 20mg RR 0.38, 95% CI 0.20 to 0.75; Study 99269: RR 0.43, 95% CI 0.30 to 0.62). In Study 99012 at Week 12 there was a non-significance trend in favour of escitalopram (RR 0.36, 95% CI 0.12, 1.10).

B.8.2.5 The clinical importance and patient-relevance of the effectiveness and safety outcomes

Liebowitz Social Anxiety Scale (LSAS)

Change in mean LSAS Total Score is the primary outcome in Study 99270 and 99012. While a variety of measurement scales have been developed to quantify the severity of SAD, the most widely used scale is the LSAS. It has been able to establish efficacy in a large number of placebo-controlled studies in SAD and is currently viewed as the gold standard[13]. s38 An improvement of at least 10 points on the LSAS has been suggested as showing a clinically relevant improvement, while patients demonstrating a ≥35-50% reduction in LSAS have been defined as treatment responders[13]. Study 99270 reported patients achieving a ≥50% reduction, rather than the potentially more relevant and easier to obtain ≥35%, i.e. the 'hurdle' to achieve response was perhaps higher in this study than necessary.

Interpreting the data for these disorders and determining the clinical significance of the results achieved can be complex.

The patients in the trials had been sufferers of SAD for 20-24 years and the mean age of onset was 15-18 years. This sample of patients closely mirrors the epidemiological evidence (see Attachment 2). Patients entering into the trials had a mean LSAS at baseline ranging between 95.44 to 96.32, thereby, classifying patients as having ***severe SAD***, (i.e. significant impairment). At the end of 12 weeks patients on escitalopram achieved a mean LSAS score ranging from 55.35-62.25 and at 24 weeks 32.28-39.80 (all results were statistically significantly better than placebo). Clinically, this translates into a patient improving from severe to moderate (and associated with less distress) or mild forms of SAD. Given that normal volunteers scored LSAS<30 the results achieved by patients on escitalopram suggests a clinically significant improvement.

The mean improvement, in LSAS scores in all three studies is statistically significant. The benefit of escitalopram was evident after 12 weeks of therapy and continued to increase from 12 to 24 weeks of therapy. In Study 99270, treatment with escitalopram 20mg daily resulted in a difference in an adjusted mean LSAS total score change of -15.09 (95% CI -20.92, -9.25) at 24 weeks, while at 24 weeks in Study 99269 there was a benefit of –12.82 (95% CI –16.95, -8.70), both compared with placebo.

These results were also seen in the unadjusted mean change from baseline, on which the meta-analysis was conducted. When meta-analysed the mean change between escitalopram versus placebo was -8.74 (95% CI -12.60, -4.89) at 12 weeks. This also needs to be considered in light of the 24 week mean change being -14.52 for study 99270. In all three studies and the meta-analysis at both 12 and 24 weeks, a difference in mean improvement of –10 on the LSAS fell within the 95% CIs for this outcome, providing a high level of confidence that a clinically meaningful result was obtained. In Study 99279, 17 to 27% more patients responded to therapy, based on the LSAS responders definition (risk difference 17.2%, 95% CI 7.0%, 27.5% with escitalopram 10mg daily; risk difference 27.3%, 95% CI 17.1%, 37.6% with escitalopram 20mg daily), both compared with placebo at Week 24.

The further improvement in the response to treatment on the LSAS scale between 12 and 24 weeks seen in these studies suggest that the 12 weeks short-term efficacy

results underestimate the fuller response to treatment observed with prolonged treatment to six months. Other available clinical trial evidence indicates that further mean improvement in the symptoms of SAD as measured on the LSAS total score beyond six months is likely[13]. Thus it would be expected that improvement much greater than a 10 point change on the LSAS scale would be seen if treatment duration was extended, given that statistically and clinically significant improvements of 11 points (Study 99269) and 15 points (escitalopram 20mg daily, Study 99270) were seen in the 24 week studies.

Clinical Global Impression– Improvement (CGI-I) and Severity (CGI-S)

CGI-I score results are secondary study outcomes in all the studies. The CGI-I scale has been used to identify responders to therapy, specifically patients reporting a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale have been defined as responding to therapy. Patients reporting a CGI-S score of ≤2 have been defined as remitters (i.e achieving disease remission). While these global scales are not recommended as primary scales, they may be useful as a secondary scale to help judge the clinical relevance of the finding[13].

The percentage of patients with CGI-I≤2 was greater with escitalopram than placebo in the two treatment studies in which it was measured. In the meta-analysis of Study 99270 and 99012 there was a 46% improvement with escitalopram compared with placebo (RR 1.46, 95% CI 1.24, 1.71). Significant improvement in response beyond 12 weeks did not occur. In Study 99270 remission based on the CGI-S scale was also assessed, with significantly more patients achieving remission at Weeks 12 and 24 with both 10mg and 20mg escitalopram daily. The improvement was 83-92% greater from Weeks 12-24 with escitalopram 10mg compared with placebo (Week 12: RR 1.83, 95% CI 1.14, 2.94; Week 24: RR 1.92, 95% CI 1.33, 2.77). A 103-137% greater improvement was seen with escitalopram 20mg daily (Week 12: RR 2.03, 95% CI 1.27, 3.22; Week 24: 2.37, 95% CI 1.67, 3.38; both versus placebo)

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The impact of co-morbidities on the effectiveness of treatment

The clinical trials excluded patients with co-morbidities, as recommended in clinical trials guidelines for SAD[13]. However approximately 50%-82.3% of patients with social phobia have comorbid mental, drug or alcohol problems.[28 29] 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.[30] Studies have shown that alcohol-related disorders occur twice as often in those affected by SAD than in those without.[18 31] Social phobia usually precedes alcohol abuse and about 20% of those treated for alcohol-related disorders have SAD.[32] 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[18 33]
- Social phobia may be a risk factor for other mental health issues[16 34] and is also associated with a more severe course and character of subsequent depressive illness[35]
- The presence of comorbidity in social phobia has been associated with an increased lifetime incidence of suicidal ideation and suicide attempts.[18]
- 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[36].

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.[37] 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.[38] 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.[39] 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.

Attachment 8 presents the clinical trial evidence (1 trial) regarding escitalopram treating people with SAD and comorbidities (with depression being the largest co-morbidity). Many of the symptoms of SAD overlap with those of depression and other anxiety disorders[40]. 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 therefore, 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.[41]

Table B.8.2 and Table B.8.3 present details regarding Olie et al (07).

Table B.8.2: Clinical Trial: Anxiety with comorbid depression

	Study Characteristics	Patient Characteristics	Outcomes Measured	Aims of Study
Olie JP et al 2007[42]	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	Primary: MADRS Secondary HAM-A CGI-I CGI-S AEs	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. To evaluate the safety and tolerability of Escitalopram in this patient population. To assess correlations between physician and patient measures of efficacy.

Table B.8.3: Details of Trial[42]

	% Co-morbidities	Population with Anxiety	HAM-A≥20
Olie JP et al (2007)[42]	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	N=423

Outcomes from the trial are presented in and Table B.8.4:

Table B.8.4: Outcomes from Trial[42]

	MADRS (Primary)	HAMA	Responders ≥50% reduction HAMA % (CI)	Remitters HAMA<7	Responders CGI-I≤2
Change in patients with no anxiety	20.5	13.8			
Change in patients with ≥1 anxiety	18.3[i]	15.5[ii]			
All patients		10.8	69% (65.6-72.2%)	38.1% (34.7-41.6%)	70.8% (67.5-74%)

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

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

Conclusions:[42]

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 score 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.

Evidence 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 1 trial utilising escitalopram, it would seem that patients with at least one anxiety disorder and comorbid depression has a greater improvement in Hamilton Anxiety Scale (HAMA) score than those without comorbid anxiety (Table B.8.4). This would seem to indicate 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 HAMA. As SAD in the main randomised, controlled trials was measured with LSAS it is hard to draw a conclusion on this measure.

B.8.2.6 The consistency of results over the three trials presented

The results in the three studies presented were generally consistent. All efficacy outcomes improved with escitalopram therapy, with most results achieving statistical significance. This was particularly evident with the primary outcome, difference in mean change in LSAS Total Score. There was generally a greater improvement with escitalopram 20mg daily compared with 10mg daily (Study 99270). Results achieved at 24 weeks were generally greater than those achieved after 12 weeks of therapy (Study 99270 and 99012).

Study 99012 was a relapse prevention study and thus the study design differed from the other two treatment studies. Prior to randomisation into this study, patients had received open-label escitalopram for 12 weeks, with responders then randomised to receive either escitalopram or placebo. Despite this difference in study design, the results occurring in this study were generally consistent with the other two studies (in which all patients were randomised to therapy, not specifically responders).

B.8.2.7 Classification of the therapeutic profile of escitalopram

Escitalopram has been demonstrated to be therapeutically superior to the comparator placebo, in Section B.6 and B.8, due to greater comparative effectiveness. The comparative safety is considered similar/non-inferior. While treatment-emergent adverse events are greater with escitalopram than placebo (as would be expected of an active treatment), total patient withdrawals and withdrawals due to adverse events are similar in the treatment studies. Withdrawals due to lack of efficacy were statistically significantly greater with placebo in the two longer term studies, in the 12 week meta-analysis and there was a strong trend towards significance in the 12 week study.

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PRODUCT INFORMATION

LEXAPRO® FILM-COATED TABLETS
LEXAPRO® ORAL SOLUTION

NAME OF THE MEDICINE

Escitalopram oxalate

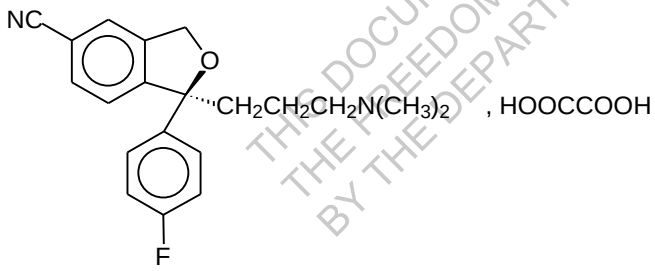
Chemical name:
S(+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrogen oxalate.

CAS number:
219861-08-2

Molecular formula:
$C_{20}H_{21}FN_2O$, $C_2H_2O_4$

Molecular weight:
414.42

Structural formula:



DESCRIPTION

Escitalopram is the active enantiomer (S-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

Lexapro 10 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "L" on one side.

Lexapro 20 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "N" on one side.

Lexapro tablets contain the following excipients: cellulose - microcrystalline, silica - colloidal anhydrous, talc - purified, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

Lexapro oral solution is a clear, nearly colourless to yellowish solution. It contains the following excipients: sodium hydroxide and purified water.

PHARMACOLOGY

Pharmacological actions

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake (*in vitro* IC_{50} 2nM).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective Serotonin Reuptake Inhibitor (SSRI). On the basis of *in vitro* studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing properties of the S-enantiomer in citalopram.

In healthy volunteers and in patients escitalopram did not cause clinically significant changes in vital signs, ECGs, or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30% of parent compound levels after oral dosing and is about 5-fold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing).

While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80%).

Distribution
The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%.

Metabolism
Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28 - 31% and < 5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination
The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0% of escitalopram is eliminated unchanged in urine and 9.6% as the S-demethylcitalopram metabolite based on 20 mg escitalopram data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Reduced hepatic function
In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Reduced renal function
While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Elderly patients (> 65 years)
Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients.

Gender
In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism
It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Lexapro should not be used for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and obsessive-compulsive disorder in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major Depression

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

Two fixed-dose studies and one flexible-dose study have shown escitalopram in the dose range 10 - 20 mg/day to be more efficacious than placebo in the treatment of depression.

All three studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression–Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20 mg/day as compared to 10 mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4, or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible-dose study with a similar design, the primary analysis did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open-label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined as a decrease of the MADRS total score to ≤ 12.

Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26% vs. 40%; hazard ratio=0.56, p=0.013).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary endpoint (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open-label 12-month study. The efficacy of escitalopram was maintained throughout the study, as measured by the MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment, and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

Generalised Anxiety Disorder (GAD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of Generalised Anxiety Disorder was demonstrated in three 8-week placebo-controlled flexible-dose studies (10 to 20 mg per day) and one 12-week fixed-dose, active-reference (paroxetine 20 mg/day), study (5, 10 and 20 mg per day).

In the four studies, the mean HAM-A total scores at baseline ranged from 22.1 to 27.7 and the CGI-S scores were 4.2 or higher, indicating significant GAD symptomatology.

In all three placebo-controlled, flexible-dose studies, escitalopram was significantly better than placebo at endpoint on the primary efficacy measure (mean change from baseline to endpoint in HAM-A total score), and the results were supported by secondary efficacy measures.

In the fixed-dose study, over a 12-week period, escitalopram in doses of 10 and 20 mg/day was statistically significantly more effective than placebo on the primary measure of efficacy, with an effect size at least as high as that of the reference treatment paroxetine. The 5 mg dose of escitalopram was numerically, but not statistically significantly, superior to placebo. 10 mg escitalopram was statistically significantly superior to the reference treatment paroxetine (LOCF) based on the HAM-A and CGI-I.

Table 1

Study	**Mean Treatment Difference in Change from Baseline in HAM-A Total Scores (LOCF) [95% CI]**	
	8 weeks	**12 weeks**
Flexible-dose		
ESC to PBO	-1.6* [-3.2 ; -0.0]	-
Flexible-dose		
ESC to PBO	-1.48* [-2.83; -0.13]	-
Flexible-dose		
ESC to PBO	-3.49*** [-4.93; -2.04]	-
Fixed-dose		
ESC5 to PBO	-	-1.29 [-3.13; 0.54]
ESC10 to PBO	-	-2.56** [-4.40; -0.73]
ESC20 to PBO	-	-2.15* [-3.99; -0.31]
PAR20 to PBO	-	-0.51 [-2.33; 1.32]
ESC20 to PAR20	-	-1.65# [-3.49; 0.20]

*p≤0.05; **p≤0.01; ***p≤0.001; #p≤0.05 *versus* PAR

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

In the pooled analysis of these three placebo-controlled, flexible-dose studies of similar design, the mean change from baseline in HAM-A total score improved statistically significantly (LOCF) over time in the escitalopram group relative to the placebo group. The separation from placebo was first observed at week 1 and continued through to the end of the study (week 8). The treatment difference to placebo at week 8 was –2.3 in favour of escitalopram ($p \leq 0.01$).

The results of the primary analysis (pooled data) were supported by secondary LOCF analyses (pooled data), where escitalopram was statistically significantly superior to placebo on the HAM-A psychic anxiety subscale score ($p \leq 0.001$), the HAM-A item 1 (anxious mood) score ($p \leq 0.001$), and the HAM-A item 2 (tension) score ($p \leq 0.01$). Escitalopram was also more effective than placebo on the CGI-S score ($p \leq 0.01$) and on the CGI-I score at week 8 ($p \leq 0.001$). The results on the HAD anxiety subscale, the HAM-A somatic subscale, the HAM-D anxiety scale, the Covi Anxiety Scale (OC), and the QoL (OC) also showed superior efficacy of escitalopram relative to placebo at week 8 ($p \leq 0.05$).

The long-term efficacy of escitalopram in the treatment of GAD is based on the results from the double-blind active comparator study, an open-label extension study and a double-blind, randomised, placebo-controlled relapse prevention study.

The active comparator study demonstrated numerically superior efficacy of escitalopram over paroxetine both on the primary efficacy measure (mean change from baseline in HAM-A total score) and on the secondary efficacy measures (mean change from baseline in HAM-A psychic anxiety, CGI-S, QoL, HAM-A somatic anxiety, HAM-A item 1 (anxious mood), HAM-A item 2 (tension), HAM-D anxiety and Covi scores, and mean CGI-I score) at week 24. For all but one (QoL) of the efficacy measures, a further improvement was seen from week 8 to week 24. In the primary efficacy analysis, the extra improvement in mean HAM-A total score over the last 16 weeks of treatment was 2.3 points for escitalopram compared with 1.6 points for paroxetine.

Further evidence of long-term efficacy is provided by an open-label extension study, which showed a beneficial effect of continued treatment with escitalopram. In this study, escitalopram treatment was associated with additional improvement beyond the response observed during the initial 8 weeks of treatment in the lead-in studies. The mean change in HAM-A total score from baseline (final visit of the lead-in study) to week 24 (LOCF) was -3.8, with greater improvement observed in patients who were switched from placebo in the lead-in study to escitalopram in the extension study (4.9 points versus 2.7 points for those previously treated with escitalopram). Similar positive results were seen in the analyses of secondary efficacy measures.

Escitalopram 20 mg/day significantly reduced the risk of relapse in a 24- to 76-week randomised continuation study in 373 patients who had responded during the initial 12-week open-label treatment.

Social Anxiety Disorder (SAD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of SAD was demonstrated in three placebo-controlled clinical studies. A short-term, flexible-dose (10 to 20 mg/day) study, a long-term,

fixed-dose (5, 10, and 20 mg/day), active-reference (paroxetine 20 mg/day) study, and a relapse prevention study.

Approximately two-thirds of patients in the studies were markedly or severely ill (score of 5 or 6 on the CGI-S) and one-third were moderately ill (score of 4 or less on the CGI-S). The mean baseline LSAS total score ranged from 92 to 96 in the three studies.

In the short-term, flexible-dose study, over a 12-week period, escitalopram was statistically significantly better than placebo on the primary, and almost all the secondary measures of efficacy (see Table 2).

In the placebo-controlled, active-reference study, escitalopram was effective both in the short- and in the long-term (see Table 2), with an effect size at least as high as that of the reference treatment paroxetine (escitalopram 20 mg/day was significantly superior to the reference treatment paroxetine 20 mg/day from week 16 and onwards (OC)). Thus, continued treatment with escitalopram improves treatment response. At week 24 of the study, all three doses of escitalopram also produced significant improvements in the LSAS subscale scores for fear/anxiety and avoidance, the CGI-I score (except for the 10 mg dose of escitalopram), the CGI-S score, and the SDS subscale scores for work, social life, and family life.

Table 2

Study	**Mean Treatment Difference in Change from Baseline in LSAS Total Scores (LOCF) [95% CI]**	
	12 weeks	**24 weeks**
Short-term, flexible-dose		
ESC to PBO	-7.29** [-12.37; -2.21]	-
Long-term, fixed-dose		
ESC5 to PBO	-9.18*** [-14.40; -3.95]	-10.46*** [-16.27; -4.66]
ESC10 to PBO	-5.07† [-10.32; 0.18]	-7.45** [-13.29; -1.62]
ESC20 to PBO	-10.31*** [-15.56; -5.06]	-15.09*** [-20.92; -9.25]
PAR20 to PBO	-9.83*** [-15.04; -4.61]	-11.82*** [-17.62; -6.03]
ESC20 to PAR20	-	-3.26 [-9.07; 2.54]

*p≤0.05; **p≤0.01; ***p≤0.001; †p=0.059

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

The beneficial effect of long-term treatment with escitalopram was also reflected in the analyses of responders and remitters in this study. The analyses showed a further increase both in the proportion of responders and in the proportion of remitters from week 12 to week 24, especially in the escitalopram 20 mg group. At week 24, a statistically significantly greater proportion of responders and remitters were seen in all three escitalopram dose groups (except for the proportion of responders in the 10 mg group) than in the placebo group (p≤0.01) (see Tables 3 and 4).

Table 3

Long-term, fixed-dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	41	50
ESC5	61***	67**
ESC10	55*	58
ESC20	62***	70***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 4

Long-term, fixed-dose study	**Remitters (CGI-S ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	13	19
ESC5	29***	39***
ESC10	24*	37***
ESC20	27**	46***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

In the relapse prevention study, the primary efficacy analysis showed a statistically significantly superior effect of escitalopram relative to placebo on the time to relapse of SAD (log-rank test, p≤0.001). Furthermore, patients treated with escitalopram had fewer protocol-defined relapses than those treated with placebo. In addition, patients treated with escitalopram showed a further improvement in mean LSAS total score during the double-blind period, while patients treated with placebo showed deterioration. Escitalopram was also statistically significantly superior to placebo at week 24 on all the secondary efficacy measures in this study: the LSAS total score, the LSAS subscale scores for fear/anxiety and avoidance, the CGI-S score, and the SDS subscale scores for work, social life, and family life (p≤0.001).

Obsessive-Compulsive Disorder (OCD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

Efficacy of escitalopram in the treatment of OCD was investigated in two clinical trials, a 24-week placebo-controlled, fixed-dose study (with efficacy assessments at week 12 and week 24) and a 16 + 24-week placebo-controlled relapse prevention study.

Patients included in these studies were male and female outpatients aged 18 – 65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a pre-defined minimum score of 20 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approx. 27, indicating significant OCD symptomatology. A structured clinical interview, the

Mini International Neuropsychiatric Interview (MINI), was used to assist in the diagnosis and to exclude relevant psychiatric comorbidities. In order to avoid the confounding variable of significant concomitant depression, patients with more than mild depressive symptoms, i.e. a score of 22 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS), were excluded. To ensure a relatively homogenous population with OCD, patients currently diagnosed with any other psychiatric disorders as per Axis I of DSM-IV-TR or any clinically significant unstable medical illness were also excluded.

Results at week 12 of the 24-week placebo-controlled, fixed-dose study are shown in Tables 5 and 6. In the short-term (**12 weeks**), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

Table 5

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 12 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-1.97 [-3.97; 0.02]
ESC20 to PBO	-3.21* [-5.19; -1.23]

*p≤0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Furthermore, escitalopram 20 mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10 mg/day and escitalopram 20 mg/day were significantly more efficacious than placebo on the Y-BOCS subscale of obsessions as well as on the NIMH-OCS total score, CGI-I score and CGI-S score.

Table 6

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]**				
	Y-BOCS Obsessional Subscore	**Y-BOCS Compulsive Subscore**	**NIMH-OCS Score**	**CGI-I Score**	**CGI-S Score**
ESC10 to PBO	-1.15* [-2.20; -0.10]	-1.01 [-2.04; 0.01]	-1.01** [-1.70; -0.33]	-0.36* [-0.66; -0.06]	-0.41* [-0.72; -0.09]
ESC20 to PBO	-2.05*** [-3.10; -1.01]	-1.34** [-2.37; -0.32]	-1.40*** [-2.08; -0.72]	-0.53*** [-0.83; -0.23]	-0.64*** [-0.95; -0.33]

*p≤0.05; **p≤0.01; ***p≤0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Results after **24 weeks** showed that both escitalopram 10 mg/day (p<0.05) and escitalopram 20 mg/day (p<0.01) were significantly more efficacious than placebo as measured by the primary outcome measure, the Y-BOCS total score, as well as on the secondary subscales of Y-BOCS (obsessions and rituals) and the NIMH-OCS score (escitalopram 10 mg/day (p<0.01) and escitalopram 20 mg/day (p<0.001)).

Table 7

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 24 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-2.56* [-4.93; -0.20]
ESC20 to PBO	-3.55** [-5.90; -1.20]

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

The beneficial efficacy of long-term treatment with escitalopram was also demonstrated by the analyses of responders and remitters in this study as shown in Tables 8 and 9.

Table 8

Long-term (24 weeks) fixed-dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	38.9	38.1
ESC10	50	58*
ESC20	57.9*	56.1*

ESC (10 or 20 mg) vs PBO: *p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 9

Long-term (24 weeks) fixed-dose study	**Remitters (CGI-S ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	11.5	26.5
ESC10	24.1*	41.1*
ESC20	28.1**	38.6

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Maintenance of efficacy and prevention of relapse were investigated in the relapse prevention study. This 24-week relapse prevention study was preceded by a 16-week open-label period with patients initially receiving escitalopram 10 mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20 mg/day. If dose-limiting adverse effects occurred, it was permissible to decrease the dose to 10 mg/day. Thus the dose of escitalopram was flexible at 10 - 20 mg/day from week 2 to 12. Subsequently, the dose was fixed at the dose received at the end of week 12 until week 16 to allow stabilisation of the patient on this dose. Responders to treatment were defined as patients with a decrease in Y-BOCS total score from baseline by ≥ 25% at week 16, and remitters were defined as Y-BOCS ≤ 10. See Table 10 for responder and remitter rates at the end of the 16-week open-label phase.

Table 10

Relapse prevention study (16-week open-label, flexible-dose phase)	**Responders (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF) (%)**	**Remitters (Y-BOCS ≤ 10) (APTS I, LOCF) (%)**
ESC	74.4	34.0

ESC = escitalopram 10 & 20 mg

Responders at the end of the above 16-week open-label treatment phase (escitalopram 10 mg: 30 responders; escitalopram 20 mg: 133 responders) entered the 24-week randomised, double-blind placebo-controlled relapse prevention phase. Both escitalopram 10 mg/day (p=0.014) and 20 mg/day (p<0.001) showed significantly fewer relapses as seen in Table 11.

Table 11

Relapse prevention study (24-week double-blind phase)		**n**	**Number of relapses**	**% relapsed**
10 mg dose group	ESC10	30	3	10.00*
	PBO	20	7	35.00
20 mg dose group	ESC20	133	35	26.32**
	PBO	137	74	54.01
10 - 20 mg dose group	ESC	163	38	23.31**
	PBO	157	81	51.59

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo

INDICATIONS

Treatment of major depression.
Treatment of social anxiety disorder (social phobia).
Treatment of generalised anxiety disorder.
Treatment of obsessive-compulsive disorder.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in Lexapro (see DESCRIPTION).

Monoamine Oxidase Inhibitors - Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see Interactions with other medicines). Some cases presented with features resembling serotonin syndrome (see ADVERSE EFFECTS).

Escitalopram should not be used in combination with a MAOI. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing escitalopram treatment before starting a MAOI or RIMA.

Pimozide - Concomitant use in patients taking pimozide is contraindicated (see Interactions with other medicines).

PRECAUTIONS

Clinical worsening and suicide risk - The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16-week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive-compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants

compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia/psychomotor restlessness - The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage **-** Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Lexapro should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia **-** Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Especially elderly patients seem to be a risk group.

Seizures **-** The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see ***Preclinical safety***).

Diabetes **-** In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania - SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (electroconvulsive therapy) - There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advised.

Effects on ability to drive and use machines - Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Discontinuation - Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 - 3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see DOSAGE AND ADMINISTRATION).

Cardiac disease - Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

Impaired hepatic function - In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should therefore be reduced (see Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Impaired renal function - Escitalopram is extensively metabolised and excretion of unchanged drug in urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Preclinical safety - High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 8-fold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive

heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experiences with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Effects on fertility

No fertility studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Use in pregnancy

Category C.

No relevant epidemiological data or well controlled studies in pregnant women are available for escitalopram. SSRIs have had limited use in pregnancy without a reported increase in birth defects.

Neonates should be observed if maternal use of Lexapro continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Neonates exposed to Lexapro, other SSRIs (Selective Serotonin Reuptake Inhibitors), or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (< 24 hours) after delivery.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced foetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold that anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring were decreased at a relative systemic exposure level ca. 5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Use in lactation
It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4 - 5.1% (below the notional 10% level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

Paediatric use (children and adolescents < 18 years)
The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the elderly (> 65 years)
Escitalopram AUC and half-life were increased in subjects ≥ 65 years of age compared to younger subjects in a single-dose and a multiple-dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see DOSAGE AND ADMINISTRATION).

Carcinogenicity
No carcinogenicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity
No genotoxicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

Interactions with other medicines
MAOIs - Co-administration with MAO inhibitors may cause serotonin syndrome (see CONTRAINDICATIONS).

Pimozide - Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs - Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, *Hypericum perforatum* (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan - There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines affecting the central nervous system - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold - SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

Hepatic enzymes - Escitalopram has a low potential for clinically significant drug interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A4, and a weak inhibitor of 2D6.

Effects of other drugs on escitalopram in vivo

The pharmacokinetics of escitalopram was not changed by co-administration with ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Co-administration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine, fluvoxamine, lansoprazole, and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Effects of escitalopram on other drugs in vivo

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a twofold increase in the plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc) – Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Lexapro.

Alcohol - The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo-controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

Treatment Emergent Adverse Events with an Incidence of ≥ 1% in placebo-controlled trials

Figures marked with * in the table below indicate adverse reactions where the incidence with escitalopram is statistically significantly different from placebo (p<0.05).

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
GASTROINTESTINAL SYSTEM DISORDERS		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*
mouth dry	74 (4.1)	152 (5.8)*
constipation	42 (2.3)	71 (2.7)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
dyspepsia	30 (1.7)	33 (1.3)
flatulence	15 (0.8)	31 (1.2)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
PSYCHIATRIC DISORDERS		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*
nervousness	13 (0.7)	25 (1.0)
dreaming abnormal	18 (1.0)	41 (1.6)
impotence [gs]	4 (0.6)	22 (2.2)*
RESPIRATORY SYSTEM DISORDERS		
upper respiratory tract infection	91 (5.1)	96 (3.6)
coughing	18 (1.1)	24 (0.9)
rhinitis	81 (4.8)	146 (5.5)
sinusitis	24 (1.3)	46 (1.7)
pharyngitis	44 (2.5)	57 (2.2)
yawning	3 (0.2)	58 (2.2)*
bronchitis	31 (1.7)*	26 (0.9)
BODY AS A WHOLE - GENERAL DISORDERS		
influenza-like symptoms	65 (3.6)	87 (3.3)
fatigue	62 (3.5)	230 (8.7)*
back pain	61 (3.4)	74 (2.8)
SKIN AND APPENDAGES DISORDERS		
sweating increased	27 (1.5)	145 (5.5)*
MUSCULOSKELETAL SYSTEM DISORDERS		
arthralgia	22 (1.2)	27 (1.0)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
REPRODUCTIVE DISORDERS, FEMALE		
anorgasmia [gs]	3 (0.3)	47 (2.9)*
METABOLIC AND NUTRITIONAL DISORDERS		
weight increase	20 (1.1)	45 (1.7)
REPRODUCTIVE DISORDERS, MALE		
ejaculation disorder [gs]	3 (0.5)	48 (4.7)*
ejaculation failure [gs]	1 (0.2)	27 (2.7)*
CARDIOVASCULAR DISORDERS		
hypertension	24 (1.3)*	13 (0.5)
HEART RATE AND RHYTHM DISORDERS		
palpitation	15 (0.8)	30 (1.1)
SECONDARY TERMS		
inflicted injury (unintended injury)	22 (1.2)	23 (0.8)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg escitalopram treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day escitalopram treated patients was greater (86%). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown below.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day Lexapro, or 20 mg/day Lexapro

Adverse Event	Placebo (n=311)	10 mg/day Lexapro (n=310)	20 mg/day Lexapro (n=125)
Insomnia	4%	7%	14%
Diarrhoea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	< 1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*adverse events with an incidence rate of at least 5% in either escitalopram group and with an incidence rate in the 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group.

Vital Sign Changes
Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG Changes
Electrocardiograms from escitalopram, racemic citalopram, and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically relevant changes in pulse rate for any one treatment group. In all treatment groups (including placebo), there was a small increase in the mean adjusted QTcB interval: 1.8 msec for escitalopram and 2.0 msec for racemic citalopram, compared to 1.7 msec for placebo. Neither escitalopram nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Weight Changes
Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes
In clinical studies, there were no signals of clinically important changes in either various serum chemistry, haematology, and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either *uncommon events* or *serious adverse events from ongoing trials* and observed during (but not necessarily caused by) treatment with Lexapro, please see Other Events Observed during the Premarketing Evaluation of Lexapro.

<u>Other Events Observed during the Premarketing Evaluation of Lexapro</u>

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients.

Application Site Disorders
Uncommon: otitis externa, cellulitis.

Body as a Whole
Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar.

Cardiovascular Disorders, General
Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and Peripheral Nervous System Disorders
Uncommon: ataxia, dysaesthesia, dysequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal System Disorders
Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and Vestibular Disorders
Uncommon: deafness, earache, ear disorder, otosalpingitis, tinnitus.

Heart Rate and Rhythm Disorders
Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders
Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders
Uncommon: abnormal glucose tolerance, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperlipaemia, thirst, weight decrease, xerophthalmia.

Musculoskeletal System Disorders
Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.

Myo-, Endo- and Pericardial and Valve Disorders
Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm
Uncommon: female breast neoplasm, ovarian cyst, uterine fibroid.

Platelet, Bleeding and Clotting Disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison Specific Terms
Uncommon: sting.

Psychiatric Disorders
Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression

aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red Blood Cell Disorders
Uncommon: anaemia hypochromic, anaemia.

Reproductive Disorders / Female
Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive Disorders / Male
Uncommon: ejaculation delayed, prostatic disorder.

Resistance Mechanism Disorders
Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory System Disorders
Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and Appendages Disorders
Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary Terms
Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Special Senses Other, Disorders
Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, vision blurred.

Urinary System Disorders
Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (Extracardiac) Disorders
Uncommon: cerebrovascular disorder, flushing, hot flush [gs], ocular haemorrhage, peripheral ischaemia, varicose vein, vein disorder, vein distended.

Vision Disorders
Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.

White Cell and Reticuloendothelial System Disorders
Uncommon: leucopenia.

In addition the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs):

Disorders of metabolism and nutrition – hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological disorders – convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and inco-ordination).

Skin disorders - ecchymoses, angioedema.

Furthermore a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below:

Cardiovascular disorders - postural hypotension.

Hepatobiliary disorders - abnormal liver function tests.

Neurological disorders - movement disorders.

Psychiatric disorders - mania, panic attacks.

Renal and urinary disorders - urinary retention.

Reproductive disorders - galactorrhoea.

Other Events Observed During the Postmarketing Evaluation of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

DOSAGE AND ADMINISTRATION

Adults
Escitalopram is administered as a single oral dose and may be taken with or without food. The oral solution can be mixed with water, orange juice or apple juice.

Major depression
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily.

Usually 2 - 4 weeks are necessary for antidepressant response, although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is required. Therefore, treatment of a depressive episode should be continued for a minimum of 6 months.

Social anxiety disorder
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily. Social anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Generalised anxiety disorder
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily. Generalised anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Obsessive-compulsive disorder
The recommended starting dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily.

Long-term treatment has been studied for a maximum of 40 weeks. Patients responding to a 16-week open-label treatment phase were randomised to a 24-week placebo-controlled relapse prevention phase, receiving 10 or 20 mg escitalopram daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (> 65 years of age)
A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg (one 10 mg tablet or 1 mL of the oral solution) is the recommended maximum maintenance dose in the elderly (see Pharmacokinetics and PRECAUTIONS).

Children and adolescents (< 18 years of age)
Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see PRECAUTIONS).

Reduced hepatic function
An initial dose of 5 mg (half a 10 mg tablet or 0.5 mL of the oral solution) daily for the first two weeks of treatment is recommended. Depending on individual patient response, the

dose may be increased to 10 mg (one 10 mg tablet or 1 mL of the oral solution) (see PRECAUTIONS).

Reduced renal function
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) (see PRECAUTIONS).

Poor metabolisers of CYP2C19
For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg (half a 10 mg tablet or 0.5 mL of the oral solution) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet or 1 mL of the oral solution) (see Pharmacokinetics and Interactions with other medicines under PRECAUTIONS).

Discontinuation
Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Toxicity
Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms. No fatalities or sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800 mg).

Symptoms
Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation)), and electrolyte/fluid balance conditions.

Treatment
There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Lexapro tablets
- Film-coated tablets containing 10 mg or 20 mg escitalopram (as oxalate).
- Blister packs of 28 tablets.

Lexapro solution
- Oral solution containing 10 mg/mL escitalopram (as oxalate).
- 28 mL solution in brown glass bottle with a screw cap with childproof closure and syringe.

Storage conditions

Lexapro tablets:	Store below 30°C.
Lexapro solution:	Store below 25°C. Store the opened oral solution below 25°C. Discard after 3 months.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine

DATE OF APPROVAL

Date of TGA approval: 27 April 2007

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ATTACHMENT 2

EPIDEMIOLOGY OF GENERALISED ANXIETY DISORDER (GAD)

Table of Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	
GAD	Generalized Anxiety Disorder
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
LASA	Longitudinal Aging Study Amsterdam
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

GAD Overview

Generalized anxiety disorder (GAD) is characterized by chronic and uncontrollable worrying and somatic anxiety, such as tension, hypervigilance and insomnia [1] The sufferer knows that the worry is excessive or unrealistic but feels unable to control it. The worry is associated with symptoms such as restlessness, fatigue, difficulty concentrating, irritability, muscle tension or sleep disturbance.[2] GAD is highly associated with other psychiatric disorders, and this comorbidity increases the economic and personal burden and severity of the disorder[1 3 4].

A re-analysis of the National Comorbidity Survey Replication that introduced a measure of severity, showed that GAD severity predicts the onset of secondary disorders, with more severe GAD associated with a higher risk of secondary disorders (comorbidities).[5]

Some of the symptoms associated with GAD are as follows (3 of these symptoms. Of at least moderate severity, should be present for a diagnosis)[6]:

- Restlessness or feeling 'on edge'
- Easily tired
- Concentration difficulties or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling or staying asleep or unsatisfying sleep)

These symptoms were also commonly reported in a Hong Kong study[7], where the three most commonly reported symptoms were:

- ''easily tired'',
- ''easily irritable'' and
- ''difficult to concentrate''.

Over half of the GAD subjects reported palpitations and bowel problems.[7] GAD subjects were more likely than sub-threshold GAD subjects to report ten of the eleven symptoms

examined, depressed mood for two or more weeks, suicidal ideation, cigarette smoking and alcohol use[7]. Other concerns were over finances, work performance and studies.

An American study[8] found that in a sample of primary care patients (N=1,029), approximately 1 in 10 met the criteria for GAD (DSM-IV) and these patients were more likely to suffer from somatic pain.

The following case study describes a GAD patient:

"The patient is a 54-year-old man who has been worrying excessively about activities of daily living in general and his health in particular for several years. He recently read about leukaemia and asked his primary physician to perform a bone marrow aspiration to rule out the disease. A hypochondriac, he fears that his minor physical ailments (such as headaches, coughing and sneezing) are masking a deadly disease. He is also convinced that his 33 year old son, who is mildly overweight, is going to die soon of heart disease, and he is doing his utmost to convince his son to lose the excess weight.

The patient is a successful businessman, husband and father of several children; an athlete; a pointer –even a decorated war veteran. Despite his achievements, however, the patient feels "miserable" and "tortured" by his persistent worries. He anticipates and dreads poor outcomes of even routine activities. He feels he cannot go to the movies because he might be unable to get a parking spot. He is convinces that people disregard him because he is short. He believes his wife is entirely unsympathetic to his plight. He now seeks medical advice."[9]

Clinical Features

GAD is categorised as an independent disorder.[10] The clinical diagnostic criteria for GAD are provided in Table 1.

Table 1 Diagnostic Criteria for Generalised Anxiety Disorder[11]

DSM IV Criteria for the Anxiety Disorders: Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not, for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not, for the past 6 months). Note: Only one item is required in children.

- restlessness or feeling keyed up or on edge
- being easily fatigued
- difficulty concentrating or mind going blank
- irritability
- muscle tension
- sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, eg, the anxiety or worry is not about having a panic attack (as in Panic Disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during post-traumatic stress disorder.

E. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a Pervasive Developmental Disorder.

Aetiology of GAD and worry

A generic model of GAD proposed by Barlow incorporates biological, psychological and environmental factors (an abridged version of the model is presented in Figure 1).[12] Barlow conceptualizes GAD as anxious apprehension and, suggests that it is the 'basic' anxiety disorder.

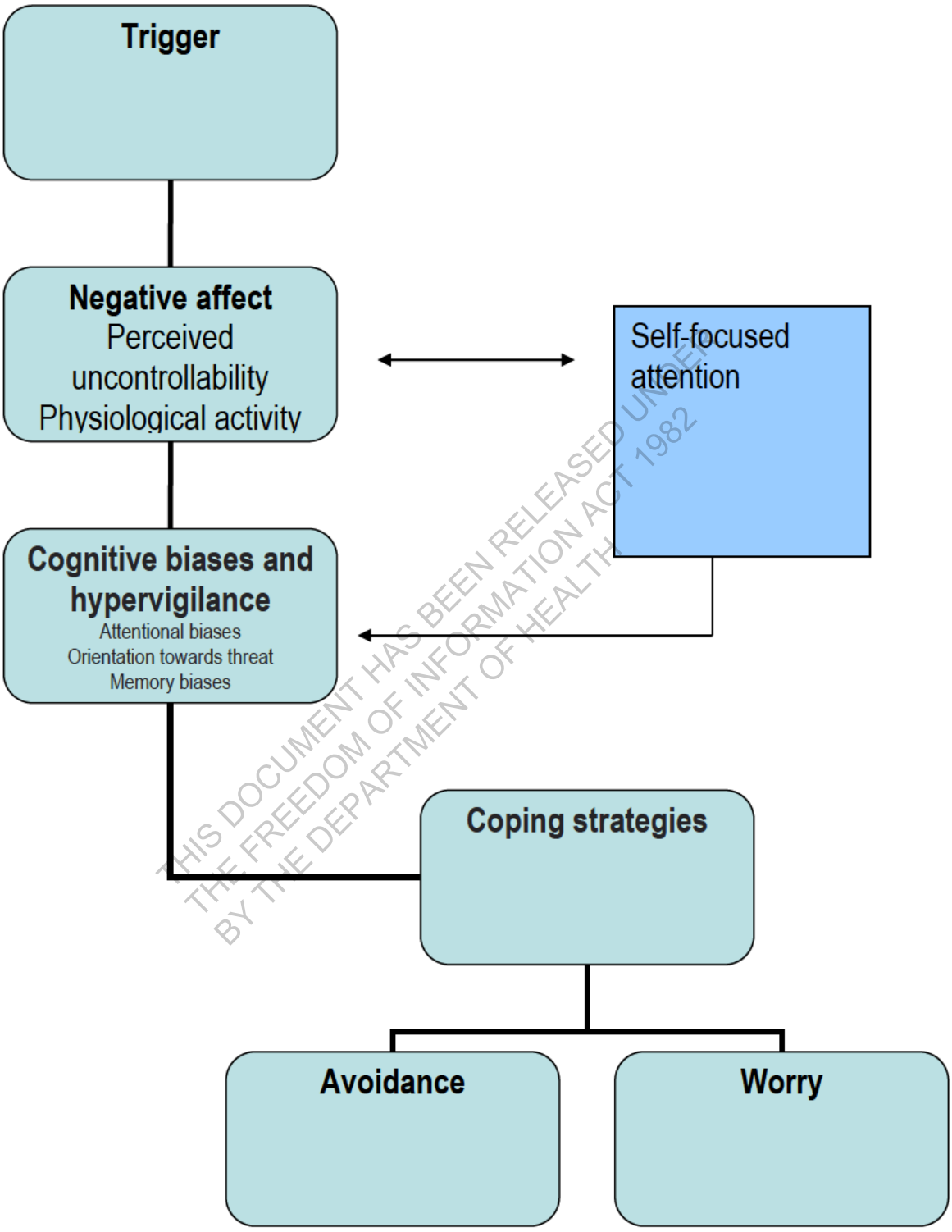
The model suggests that an individual has biological and psychological vulnerabilities which, if triggered will result in negative affect.[12] The negative affect is characterized by a sense of uncontrollability and is accompanied by supportive physiology and activation of specific brain circuits (e.g. the behavioural inhibition system). The individual becomes self-focused (e.g. on their physiological arousal) and hypervigilant for threat, which results in attempts to cope with the anxiety. Predominant coping strategies are behavioural avoidance or worry in an attempt to solve problems and reduce negative affect. It is important to note that behavioural avoidance is quite common in GAD: one study reported that 65% of patients avoided specific triggering stimuli, with social situations being most common.[13]

Results from the twin studies suggest a modest role for genetics with an estimated heritability of approximately 30–40% for both men and women (vs 70% heritability for major depression).[14] It should be noted that the largest proportion of the variance in liability for GAD is due to individual environmental factors.

Early environmental factors that are considered to be important in the development of GAD are:[6]

- Insecure attachment in childhood which is adulthood develop into beliegs that the world is a dangerous place, worry becomes an effective coping strategy.
- A traumatic childhood experience
- Parental separation
- Lack of opportunity for social interactions
- Modeling of a relative who has an anxiety disorder.

Figure 1Process of anxious apprehension[12]



Epidemiology

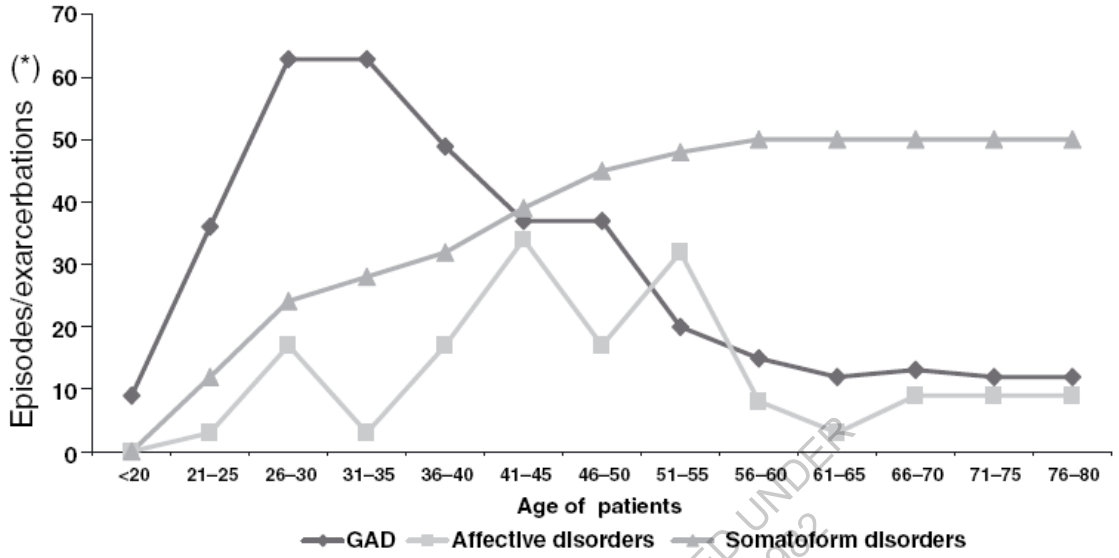
In general, anxiety disorders develop relatively early in life.[15] In 80–90% of cases, the disorder manifests before the age of 35, and the time between 10 and 25 years seems to be a high-risk period for the development of anxiety disorders. With GAD, the average first manifestation is between 25 and 30 years. GAD is the only anxiety disorder to show increased prevalence in the elderly.

In a 40 year longitudinal study of GAD patients (DSM-II-R) the course of the disorder was followed.[16] Between 1950-61, 512 people were admitted to the Lopez Neuropsychiatric Research Institute in Spain. A total of 370 of the original patients were contacted in 1984-2000 and of those 209 agreed to participate in the study. They were interviewed and 65 were diagnosed with GAD during the period of 1984-88. These patients were followed up during 1997-2000 (n=59).

The mean age of onset of GAD was 25.6 years and the mean episode length was 7.4 months; periods of remission or total remission of anxiety symptoms was uncommon.[16] There is however evidence to suggest that unlike other anxiety disorders, GAD is most common among older age groups.[17] See Figure 2 which shows that the majority of cases are in the 25-35 age group.

Social phobia (12%) and simple phobia (70%) were present before the appearance eof GAD, whilst the rest of the comorbid disorders usually emerged afterwards.[16] The course of development is presented in Figure 2.[16] It can be seen that, anxiety disorders peaked during the third and fourth decades of life and decreased thereafter. From age 30 the somatoform disorders emerged, together with major depression and alcohol dependence; finally, from age 50, dysthymia appeared. USD (undifferentiated somatoform disorder) was very frequent as a chronic clinical condition. The main symptoms recorded were somatic complaints about pain, and gastrointestinal and cardiopulmonary symptoms. These complaints had caused patients to see a doctor, and their worry about symptoms was not considered uncontrolled.

Figure 2 Course of patients with generalized anxiety disorder. [16]



(*) Percentage of patients with episodes or exacerbations of psychiatric disorders

Notes:

Affective disorders: major depression or dysthymia

Somatoform disorders: somatization disorder, hypochondria or undifferentiated somatoform disorder (USD)

The study found that :

(i) a low percentage of subjects were chronically affected by GAD after age 50;

(ii) with age, GAD tends to be replaced by somatizations (USD); and

(iii) worse prognosis was determined by lack of regular compliance, gender (female) and early onset of GAD.

In relation to the natural history of the disorder and the replacement, with age, of GAD by somatoform disorders, these results are in line with those of classic works. [18] The replacement of GAD by undifferentiated somatization disorder (USD) could be interpreted from two different points of view.[19] USD in these patients could reflect a change in the way they cope with anxiety. It has been suggested that in addition to the classic fight-or-flight reaction to chronic stress, the aged respond in a way that is more adaptative (freeze-reaction). The freeze response would not necessarily produce anxiety, but the elderly would be more likely to focus on their somatic state.[20] From an alternative

point of view, USD may constitute a minor form of GAD in older subjects . Older adults report more worries about health and fewer concerns about work compared with younger adults. Also, habituation to anxiety can decrease the number and severity of anxiety symptoms. Therefore, GAD in older patients could be characterized by vague and persistent complaints about health with mild levels of anxiety. These clinical symptoms could lead to a diagnosis of undifferentiated somatization disorder in older subjects [21 22].

Generally GAD has been associated with various medical conditions.[23 24] The susceptibility to comorbid conditions differs between male and female sufferers. Among males, particularly high rates were found for dermatologic (75%), arthritic (27%), and cardiac problems (20%), and among females, gastrointestinal problems (63%), allergies (52%), back pain (50%), migraine (42%), metabolic disorders (27%), and neurologic disorders (8%).[23 24] Similar results were observed in a French study though the rates were lower[25]. To secure successful remission, therefore, physician treatment choices must address not only the symptoms of GAD, but also current or probable comorbidities and any underlying causality.

Prevalence

Interpreting the epidemiological evidence[26]

Stage 1

Many of the earliest studies were based on DSM-III criteria (APA, 1980). DSM-III defined GAD as 1 month of persistent anxiety accompanied by associated symptoms from three of four categories.[5] DSM-III allowed GAD to be diagnosed only if patients did not meet the criteria for any other anxiety or affective disorder. It also separated generalised anxiety disorder from panic disorder. This was considered to create confusion because GAD was a residual category.[27]

Stage 2

DSM-III-R changed the requirements to 6 months of worry along with 6 of 18 associated symptoms to improve the validity of separation from normal anxiety and from anxiety that occurs secondary to other mental disorders (American Psychiatric Association, 1987).[5] An example of how this change has impacted on the estimation of the prevalence of GAD is shown by relaxing the requirement of excessive worry more days than not occurring for at least 6 months (requirement for DSM-III-R) to 1 month (requirement for DSM-III). A re-analysis of the National Comorbidity Survey Replication using this change showed that prevalence increased by about 50-60%.[5]

Stage 3

DSM-IV made further changes aimed at sharpening the characterization of GAD by requiring that worry be excessive and uncontrollable (American Psychiatric Association, 1994). DSM-IV also stipulated that the worry in GAD must be associated with at least three of six symptoms of tension and vigilance, and cause significant distress or impairment.[5] An example of how this change has impacted on the estimation of the prevalence of GAD is shown by relaxing the requirement of **excessiveness of worry** in DSM-IV, re-analysis of the National Comorbidity Survey Replication showed that prevalence increased by about 40%.[5] The authors also found that increasingly broader definitions of GAD are associated with decreasing rates of co-morbidity. One of the criticisms levelled at DSM-IV is that the 6-month duration and excessive-worry requirements, appear to miss individuals who suffer from significant generalized anxiety, and who also have an elevated risk of developing additional disorders. This has been found in other studies, with concerns that patients suffering from symptoms of GAD are being excluded inappropriately.[28] [29]

The changes seen in the classification of GAD and the epidemiologic evidence that eventuated suggest that GAD is a common disorder that, although often comorbid with other mental disorders, does not have a rate of comorbidity that is higher than those found in most other anxiety or mood disorders.[30]

The above description of the changes in DSM from III to IV, leave little doubt that GAD is now classified as a severe disorder that produces significant distress or impairment.

Table 2 summarises the key features of DSM-III, DSM-III-R and DSM-VI. The key differences in DSM changes from DSM-III-R to DSM-VI being[31]:

- "unrealistic/excessive anxiety and worry about two or more life circumstances" in the DSM-III-R to "excessive (but not unrealistic) anxiety and worry about more than one life circumstance" in the DSM-IV to which "difficulties to control the worry" was added.
- In the DSM-IV, the ancillary symptoms were further reduced and involve only 3 of 6 symptoms, selected from the categories of motor tension and vigilance, whereas the autonomic category was deleted.
- With associative features, "mild depressive symptoms are common," according to the DSM-III and DSM-III-R, whereas in the DSM-IV, in addition to depressive symptoms, the severity of which is unspecified, symptoms of muscle tension and somatic symptoms were added.
- Finally, impairment, which in the DSM-III and DSM-III-R was considered "only mild," is considered in the DSM-IV as "producing significant distress or impairment".

Therefore it is clear from this evidence that DSM-IV defined GAD patients are a severe group of GAD patients. Further DSM-IV defined patients are a more restrictive group of patients that would not include a large proportion of DSM-III-R patients. This is the key reason why the submission will look at DSM-IV patients alone, given that these were the basis of the Escitalopram trial.

Table 2 Shift in Criteria to Diagnose GAD[31]

Criteria	DSM-III	DSM-III-R	DSM-IV
Anxiety	Persistent anxiety	Unrealistic/excessive anxiety and worry (apprehensive expectation) about two or more life circumstances	**Excessive anxiety and worry (apprehensive expectation) about a number of events or activities; difficult to control (includes overanxious disorder of childhood)**
Duration	1 months	6 months	6 months
Ancillary symptoms	Unspecified number of symptoms from three of four categories	≥ 6 of 18 specified symptoms	**≥ 3 of 6 specified symptoms**
Symptoms and symptom categories	Apprehensive expectation	Motor tension (n = 4)	Restlessness/mental tension
	Motor tension	Autonomic (n = 9)	Fatigue
	Autonomic	Vigilance (n = 5)	Poor concentration
	Vigilance		Irritability
			Muscle tension
			Sleep disturbance
Associated features	Mild depression symptoms	Mild depressive symptoms	Muscle tension
			Somatic symptoms
			Depressive symptoms
			Exaggerated startle response
Impairment in social and occupational functioning	Rarely more than mild	Rarely more than mild	**Significant distress and impairment**
Exclusions	Not caused by another mental disorder such as depression or schizophrenia	Anxiety/worry, unrelated to another disorder (e.g., panic)	Anxiety/worry, unrelated to another disorder (e.g., panic)
		Does not occur during mood disorder or psychotic disorder	Does not occur during mood disorder or psychotic disorder
		Not organic (e.g., hyperthyroidism, caffeine intoxication)	Not organic (e.g., hyperthyroidism, caffeine intoxication)
		Not substance abuse related	Not substance abuse related

A summary of the prevalence data is presented in Table 3 Lifetime Prevalence of GAD. The lifetime prevalence ranged from 2.3-5.1% and 0.4-5.7% for DSM -III-R and DSM-IV respectively.

Australian Prevalence

In 1997 in Australia, 9.7% (1,299,900) people suffered an anxiety disorder, usually social phobia, generalised anxiety disorder or post-traumatic stress disorder.[32 33] The 12 month prevalence of GAD in Australia was 3.1% (females 3.7% and males 2.4%). This is within the range (thought the lower range) of that reported in the literature for other countries.

Table 3 Lifetime Prevalence of GAD

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
Iceland[34]	31.1%			
Cristchurch NZ[35]	21.7			
LASA[36] N=3,056 (55-85 years)	7%			
NCS (USA)[3] N=8,098 (15-54 years)		5.1%		
Nemesis (Netherlands)[37] N=7,076 (18-64 years)		2.3%		
Oslo (Norway)[38] N=2,066 (18-65 years)		4.5%		
ICPE[39]		All: 3.9% F: 5.2% M: 2.7%		
NCS-Replication[40]			5.7%	3.1%
Midlife in the US Survey[41]				3.3%
GADIS[42] N=13,677				8.3%
NESARC[43] N=43,093 (Age>18 years)			All: 4.1% F:5.4% M:2.8%	All: 2.1% F:2.8% M:1.3%

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
Hong Kong[7] N=3,304 (15-60 years)				4.1%[1]
US _Primary Care N=1,029				10.1%
EDSP (Germany) [44] N=3,021 (14-24 years) *Baseline Results*			All: 0.8%	All: 0.5%
Bremer Jugenstudie (Germany)[45] N=1,935 (12-17 years)			0.4%	0.2%
Dresdener Studie (Germany)[46] N=3,021 (18-25 years)			2.4%	
TACOS (Germany)[47] N=4,075 (18-64 years)			0.8%	
NSMHW (Australia) [32 33] (N=10,641 >18 years				**3.1%**
ESEMed[48] N=21,425 (>18 years)			2.8%	1.0%
South Florida Study (USA)[49] N=1,803 (19-21 years)			1.4%	
GHS-MHS (Germany)[50] N=4,181 (18-65 years)				1.5%
Germany[51] N=7,124 (18-64 years)				1.5%
Morocco[52]				4.3% F: 91.1%
NZ[53] N=1,037				12%
Range	**7-31.1%**	**2.3-5.1%**	**0.4-5.7%**	**0.2-10.1%**

[1] 6 month prevalence

Co-morbidity

A New Zealand study found that of those followed from 1972 till 2005, 42% of those diagnosed with GAD, had co-morbid depression, where GAD preceded the depression.[53] They conclude that this comorbidity seemed to be associated with substantial health burden, as indicted by recurrent course, mental health service use and suicide attempt.

The ESEMeD study showed that patients with GAD were 32.7 times more likely to develop depression, 12.5 times more likely to have SAD and 1.5 times more likely to abuse alcohol (10.2 times more likely to be alcohol dependant).[54]

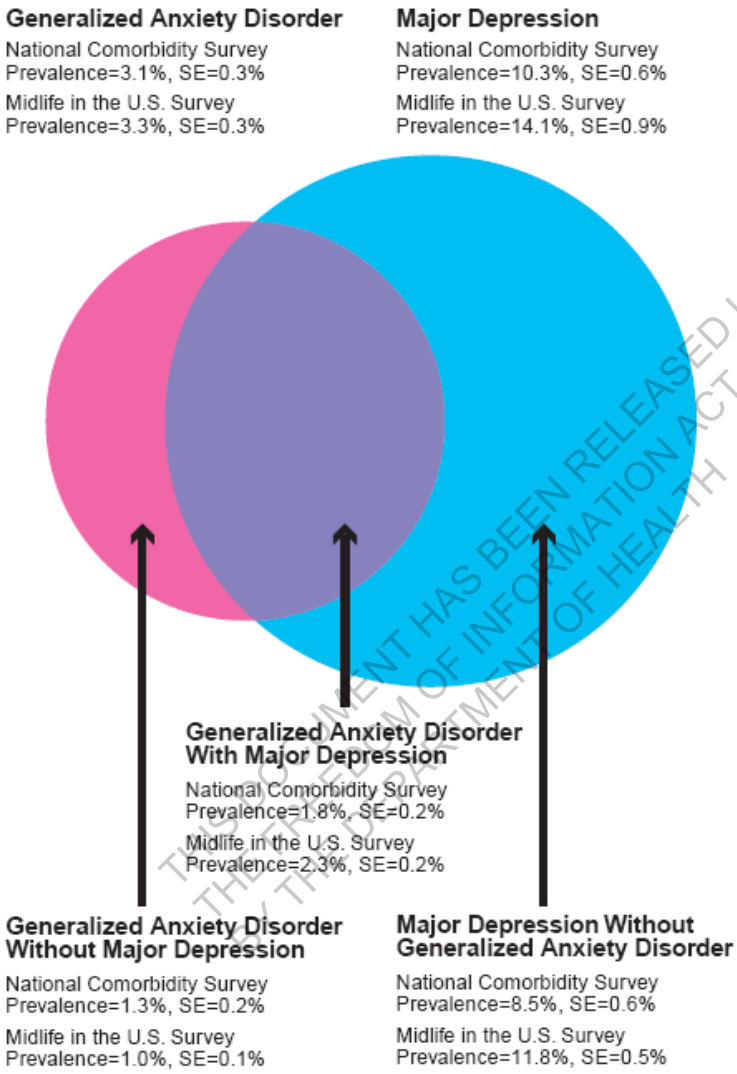
Table 4 Lifetime Co-morbidities with GAD

	Population	Any Co-morbidity		Major Depression		Agoraphobia		Alcholism		SAD	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
DSN-III											
LASA[36]	N=3,056 (55-85 years)			15%							
DSM-III-R											
NCS (USA)[3 55 56]	N=8,098 (15-54 years)	66.3%	90.4%	38.6%	62.4%	26.7%	25.7%	11.2%	37.6%	23.2%	34.4%
France	N=1,042 (18-65 years)	>60%		27.7%				25%			
DSM-IV											
NESARC[43]	General Age>18 years N=43,093	89.8%									
US -Primary Care[8]	N=1,029			69.7%				11.1%			
NZ[53]	General N=1,037				63-88%						
Germany[51]	18-64 years N=7,124	93.1%		70.6%							
NSMHW (Australia)[57]	**General N=10,641 >18 years**	**67.8%**		**44.9%**							
USA[51]	N=9,282 >18 years	85%									
GADIS[42]	GP N=13,677			4.2%							
ICPE Survey[39]	N=20,189		88.3%		60.9%		20.7%				34%
Range DSM IV		**66.3-**	**88.3-**	**4.2-70.6%**	**60.9-88%**	**26.7%**	**20.7-**	**11.1-25%**	**37.6%**	**23.2%**	**34-34.4%**

	Population	Any Co-morbidity		Major Depression		Agoraphobia		Alcholism		SAD	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
		93.1%	90.4%				25.7%				

Figure 3 shows the rate of comorbidities based on two studies and the overlap that exists.[41]

Figure 3 Prevalence and Comorbidity of Generalized Anxiety Disorder and Major Depression at 12 Months in Two National General Population Surveys[41]



Impact on Impairment

A central issue of debate is whether generalized anxiety is itself associated with impairment or disability, or whether the impairment in individuals with GAD is due entirely to other co-morbid disorders.[43] Epidemiological studies have addressed this question by assessing the comparative disability of GAD and major depressive episodes (MDE). In these studies[39 41] the separate and joint effects of GAD and MDE were evaluated by comparing the disability of pure GAD, pure MDE, and the two conditions when co-morbid. No significant differences in disability were found between pure GAD and pure MDE, and two of the three surveys found that individuals with co-morbid GAD-MDE had significantly greater disability than those with either pure GAD or pure MDE.

These findings have led researchers to conclude that the status of GAD as an independent disorder is at least as strongly supported as it is for MDE.[30 43]

It used to be thought that GAD, in the absence of other disorders, was associated with a low level of disability.[58] 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.[10] The NCS and the "Midlife Development in the United States Survey" both state that the level of impairment related to GAD is considerable and equivalent to that of MD. [41] In fact, a combined analysis of these two surveys revealed that even GAD with no comorbidity is associated with marked impairments in psychosocial functioning equivalent to those caused by MD. [41]

A similar conclusion was arrived at in the analysis of the Australian NSMHWH. [57] 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.

Diagnosis

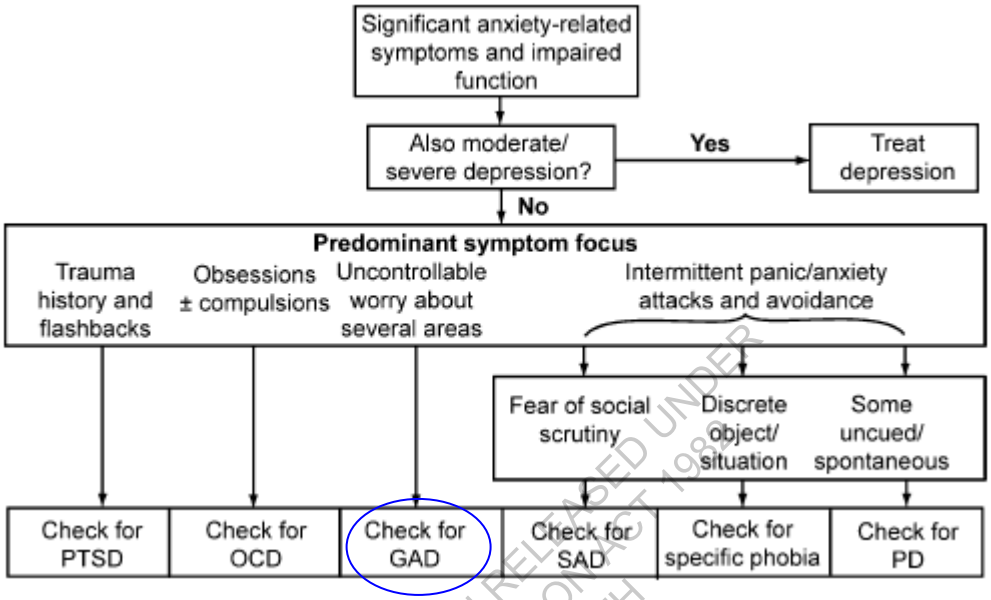
Some useful questions to ask in establishing a diagnosis of GAD[59]

- Are you a worrier?
- Do you think that you worry excessively?
- When things are going well do you still find things to worry about?
- Once you start to worry do you find it hard to stop?
- How much does worry interfere with your life?
- How long has worrying like this been a problem?

Excessive worry accompanied by significant symptoms of muscle tension, autonomic arousal and hypervigilance must be present for at least 6 months for a diagnosis of GAD to be made.

The following (Figure 4) depicts the latest diagnostic algorithm for exploring anxiety disorder issued by the British Association for Psychopharmacology:[60]

Figure 4 Diagnostic algorithm for exploring anxiety disorders[60]



Treatment

GAD follows a chronic course and may be either constant or fluctuating. Patients typically suffer symptoms for a number of years before being diagnosed and effectively treated, with retrospective studies suggesting symptoms may wax and wane for up to 20 years.[61-63] The Harvard/Brown Anxiety Research Program (HARP), a naturalistic, longitudinal study that assessed patients, with PD, PDA, SP, and GAD, at 6–12- month intervals for of 8 years, showed that the likelihood of these anxiety patients experiencing full remission was modest and more likely to occur during the first 2 years of the study. In addition, this study indicated that GAD patients continued remitting late into the study period.[64] This tends to support the idea of GAD having an episodic pattern in which periods of remission and recurrence are evident for many years.[65]

Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated a continued lack of treatment for many individuals with GAD.[43]

Approximately 50-59% of individuals with GAD received no treatment, [7] [43] with an average 2-year lag between onset and first treatment.[43]

A New Zealand study that followed a birth cohort to the age of 32 found that of the patients diagnosed as having pure GAD, 35% only had received mental health services and 19% psychiatric medication[66]. For patients with GAD and comorbid MDD these figures were higher with 57% accessing mental health services and 39% psychiatric medication.[66] Similar results were found in the ESEMeD study where for any anxiety around 36% of individuals had consulted any type of formal health services in the previous 12 months.[67] Overall approximately 30-39% of GAD patients receive appropriate treatment,[67] [58] [66] this was as low as 11% in the UK National Surveys of Psychiatric Morbidity.[68]

In summary, having examined all the evidence the data shows that 11-50% of patients diagnosed with GAD are treated.

The UK National Surveys of Psychiatric Morbidity study also identified that the factors influencing treatment with antidepressants are the number of psychiatric symptoms, marital status, age and employment status. It is clear that by far the strongest influence is that of symptomatic severity, with the most severe category over four times as likely as the least severe to receive antidepressants.[67]

There are a variety of agents that can be used to treat GAD. Figure 1 shows the onset of effect of different anxiolytic drugs (benzodiazepines, buspirone and antidepressants).[69] It can be seen that although benzodiazepines have a rapid anxiolytic effect (without onset worsening) there are major concerns surrounding long-term use of these. **Indeed some argue for the theory that antidepressants affect predominantly psychological symptoms whereas benzodiazepines affect predominantly somatic symptoms in patients with GAD.[70]**

Adverse effects on discontinuation with benzodiazepines are more frequent than with other drugs, and these may be caused by recurrence or rebound (recurrence with increased intensity) of the original anxiety symptoms, or by drug withdrawal effects.[71] [72] The benzodiazepine withdrawal syndrome is potentially serious, but is generally mild and self-limiting (up to 6 weeks). As a guide benzodiazepines may be used for 2–4 weeks to cover the onset worsening caused by some antidepressants, or on an occasional basis before exposure to a feared situation. [59] [60] [73] [74]

In order to assess the magnitude of the withdrawal syndrome some evidence is provided by a Canadian study which examined 30 consecutive inpatients admitted for assistance from their benzodiazepine detoxification.[75] These patients were long-term users of benzodiazepines (≥1 months, $\bar{x}$=86 months). Of all patients 20% were diagnosed with GAD. These patients were assessed as above therapeutic dose users. Another study assessed 131 long-term, therapeutic dose users (daily use >3 months; $\bar{x}$=3 years) who had entered an outpatient treatment program for discontinuations of benzodiazepines.[75] These patients tended to shift their use of medication from an as-prescribed to an as-needed pattern. The majority of patients (91%) had made at least one attempt to decrease their dose or stop their use of benzodiazepines, and all who had done so reported experiencing symptoms upon attempting to discontinuation. Of the patients admitted 33% had GAD.

Studies of the long-term efficacy of benzodiazepines have reported the development of tolerance or loss of effect over time in the treatment of anxiety. Additionally, a high relapse rate (65%) is observed in the 6-month period following benzodiazepine discontinuation after short-term treatment.[76]

Figure 5Onset of effect of different anxiolytic drugs[69]

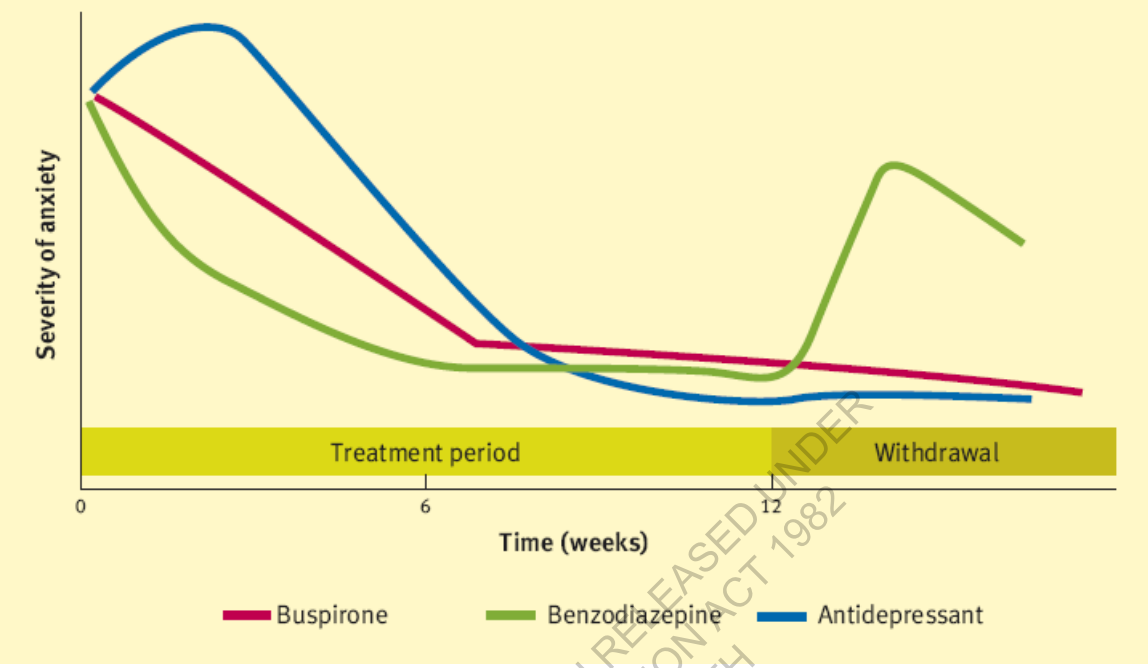


Table 5 Guidelines for Social Anxiety Disorder or Social Phobia

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
Recognition and diagnosis	Although generalized anxiety disorder (GAD) is amongst the most common mental disorders in primary care, and is associated with increased use of health services, it is often not recognized: possibly because only a minority of patients present with anxiety symptoms (most patients with present with physical symptoms), and doctors tend to overlook anxiety unless it is a presenting complaint . The disability associated with GAD is similar to that with major depression.[78] Patients with 'comorbid' depression and GAD have a more severe and prolonged course of illness and greater functional impairment,[41] and a greater chance of being recognized as having mental health problems, though not necessarily as having GAD[10 79].	Some of the symptoms associated with GAD are as follows (3 of these symptoms. Of at least moderate severity, should be present for a diagnosis): • Restlessness or feeling 'keyed up' or 'on edge' • Being easily fatigued • Difficulty concentrating or mind 'going blank' • Irritability • Muscle tension • Sleep disturbance (difficulty falling or staying asleep or restless unsatisfying sleep)	The accurate diagnosis of panic disorder or generalised anxiety disorder is central to the effective management of these conditions. It is acknowledged that frequently there are other conditions present, such as depression, that can make the presentation and diagnosis confusing. An algorithm has been developed to aid the clinician in the diagnostic process, and to identify which guideline is most appropriate to support the clinician in the management of the individual patient.
Acute Treatment	Systematic reviews and placebo-controlled RCTs indicate that some SSRIs (escitalopram, paroxetine and sertraline), the SNRI venlafaxine, some benzodiazepines (alprazolam and diazepam), the tricyclic imipramine, and the [5-HT.sub.1A] partial agonist buspirone are all efficacious in acute treatment. Other compounds with proven efficacy include the antipsychotic trifluoperazine, the antihistamine hydroxyzine, the anticonvulsant pregabalin, and the sigma-site ligand	• Treatment with benzopiazepine for up to 2 weeks followed by a gradual reduction of dose to zero within 6 weeks. Subsequent use should be on an 'as required basis'. • Diazepam 2-5mg orally up to twice a day or • Diazepam 5-10mg at night or • Oxazepam 15-30mg orally, as a single dose, up to twice a day	• support and information • problem solving • benzodiazepines 2-4 weeks • sedating antihistamines • self help Note level of evidence differs

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
	opipramol. Treatments with unproven efficacy in GAD include the beta-blocker. There have been few comparator-controlled studies, and most reveal no significant differences in efficacy between active compounds: however, escitalopram (20 mg/day) has been found significantly superior to paroxetine (20 mg/day), and venlafaxine (75-225 mg/day) superior to fluoxetine (20-60 mg/day) on some outcome measures in patients with comorbid GAD and major depression. Psychological symptoms of anxiety may respond better to antidepressant drugs than to benzodiazepines.		
Long-term treatment	Double-blind studies indicate that continuing with SSRI or SNRI treatment is associated with an increase in overall response rates: from 8 to 24 weeks with escitalopram or paroxetine; from 4 to 12 weeks with sertraline and from 8 to 24 weeks with venlafaxine. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (escitalopram or paroxetine), compared to switching to placebo, for up to six months.	These should be nonpharmacological as pharmacological treatments have statistically significant, but clinically modest effects. Some agents used: • Venlafaxine • Buspirone • paroxetine	• psychological therapy – CBT, conditions apply • pharmacological therapy (antidepressant medication) • SSRIs should be offered • reviewed at 2, 4, 6 and 12 weeks • duration - 12 weeks • if not responding at 12 weeks switch to other SSRI, conditions apply • if responding at 12 weeks continue treatment for another 6 months • venlafaxine initiated only by specialist mental health practitioners, including GPs with a special interest in mental health • self-help

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
			•
Comparative efficacy of pharmacological, psychological and combination treatments	Drug or psychological treatments, delivered singly, have broadly similar efficacy in acute treatment. Relapse rates are lower with cognitive behaviour therapy than with other forms of psychological treatment, but the comparative efficacy of drug and psychological approaches over the long term is not established. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone.	Recommended primary treatments for GAD are nonpharmacological. Initial treatment should include listening to the patient, counselling and the teaching of relaxation techniques, personal and interpersonal strategies and coping skills.	• Cognitive and behavioural techniques combined had greater effect sizes than the individual interventions. • In the short term, cognitive and behavioural techniques were as effective as pharmacological therapies, but evidence is lacking for long term effectiveness. • The Gould meta-analysis found no difference in treatment outcomes for men and women.
When initial treatments prove unhelpful	There is no clear evidence for an increase in response with dose escalation after an initial non-response to a lower dose. Switching between treatments with proven efficacy may be helpful.		Switching to another SSRI
Duration of Treatment	12 weeks initial response, if responding at least another 6 months.		12 weeks initial response, if responding at least another 6 months.

Effects of Treatment with co-morbidities

For a full analysis of treatment with comorbid GAD refer to Attachment 8. Recent epidemiological data suggests that the impact of comorbidity in clinical outcomes is no greater in GAD than in other anxiety disorders.[80] Moreover, comorbidities such as major depression do not appear to change the course of GAD.[80] There are also data supporting the notion that psychotherapy may have an additional impact in the comorbid conditions associated with GAD.[81]

Epidemiologic studies have demonstrated the negative implications of comorbidity for course of illness.[82 83] 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 one year was half the annual rate for GAD alone.[84] 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.[85]

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 score 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.

The conclusions from two open-label studies that examined patients with comorbidities are reported below: :[86 87]

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 score 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.[88] 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.

Treatment Outcomes

Like other mental disorders, the placebo response rate may range from 20% to over 50% and what contributes to this is not always clear from study reports.[74]

Hamilton Anxiety Scale (HAMA)

This scale rates the patient's level of anxiety based on feelings of anxiousness, tension and depression; any phobias, sleep disturbance, or difficulty in concentrating, the presence of genitourinary, cardiovascular, respiratory, autonomic or somatic symptoms, and the interviewer's assessment of the patient's appearance and behaviour during the interview are also rated.

The HAMA was developed to quantify the severity of symptoms of anxiety and is widely used to evaluate anxiety in clinical studies.

The Hamilton Anxiety Scale consists of 14 items, each defined by a series of symptoms; 1) anxious mood, 2) tension, 3) fears, 4) insomnia, 5) intellectual, 6) depressed mood, 7) somatic complaints: muscular, 8) somatic complaints: sensory, 9) cardiovascular symptoms, 10) respiratory symptoms, 11) gastrointestinal symptoms, 12) genitourinary symptoms, 13) autonomic symptoms, and 14) behaviour at interview.

Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (very severe). The sum (total score) indicates the severity of anxiety; less than 12 is normal, 18 mild anxiety (and the lowest threshold at which medication is usually prescribed), 25 moderate anxiety, and 30 severe anxiety.[89]

Typically in clinical trials response is determined for a ≥50% reduction in HAM-A and remission is defined by patients with a HAM-A<10 or a HAM-A<8[90], both of which is within the range of normal anxiety as determined by HAM-A<12.[89]

Consensus conferences proposed that for GAD, remission is defined as HAM-A≤7-10 functional impairment is SDS≤1 on each item and a HAM-D score of ≤7.[91 92]

HAMA Psychic Anxiety Subscale

The HAMA psychic anxiety subscale is derived from the HAMA scale and consists of the sum of the following items: item 1 (anxious mood), item 2 (tension), item 3 (fears), item 4 (insomnia), item 5 (intellectual), item 6 (depressed mood), and item 14 (behaviour at the interview).

HAMA Somatic Anxiety Subscale

The HAMA somatic anxiety subscale is derived from the HAMA scale and consists of the sum of the following items: item 7 (somatic, muscular), item 8 (somatic, sensory),

item 9 (cardiovascular), item 10 (respiratory), item 11 (gastrointestinal), item 12 (genitourinary) and item 13 (other autonomic symptoms).

Hamilton Depression Rating Scale

This 17-item scale rated the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety (psychic and somatic), and agitation; level of insight; patterns of insomnia (early, middle, late); loss of interest in work and other activities; weight loss, hypochondriasis psychomotor retardation; genital symptoms, gastrointestinal somatic symptoms and general somatic symptoms. Each item was scored on 3-, 4- or 5-point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

(Source: SCT-MD-05 Study Report p. 16)

Hospital Anxiety and Depression Scale (HAD)

The HAD scale is completed by the patient and comprises two subscales: one which measures depression (D-scale) and one which measures anxiety (A-scale). Each subscale consists of seven items, with four possible response alternatives (scored from 0 to 3, with 0 reflecting the most enjoyment/least anxiety). The D-scale consists of HAD items 1, 3, 5, 8, 10, 11 and 13, and the A-scale consists of HAD items 2, 4, 6, 7, 9, 12 and 14. Patients fill in the scores that most accurately reflect the way they had felt over the previous days. Scores for the depression and anxiety subscales are calculated separately.

(Source: Study Report for 99815 p.33)

Clinical Global Impression (CGI)

The CGI[93] 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 patient's 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[94]. These patients have improved but are usually not considered as having 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.

Quality of Life Questionnaire (QOL)

This 16-item patient-rated questionnaire is derived from the Quality of Life, Enjoyment, and Satisfaction Questionnaire. Patients answered questions based on their satisfaction during the previous two weeks regarding mood, health, activities of daily living, and interpersonal relationships on a 5-point scale. Unlike the other efficacy ratings, higher scores on this scale reflect improved function.
(Source: SCT-MD-05 Study Report p. 16)

Sheehan Disability Scale (SDS)

The SDS[1] 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 may also be helpful in indicating the relevance of improvement. It has been shown to be efficient in demonstrating significant differences in improvement in function from the patients' perspective. Since GAD is associated with considerable impairment of function the SDS may provide a useful comment on the functional relevance of the treatment.[90]

Duration of Treatment

Acute Treatment: 12 weeks**,** this is also the period required to determine efficacy of a medication aiming to treat GAD.[60 74]

Long –Term Treatment: for patients responding at 12 weeks, an additional 6 months, at least**,** is recommended.[60 74]

Defining Response and Remission

When defining 'response' to a treatment on a standard rating scale, a score which equates to ≥50% reduction on the scale has been found to be too conservative, with a clinically measurable difference being seen at a smaller reduction from baseline as can be seen in Table 6.

Table 6 Correlation of Response/Treatment Between Scales[94]

CGI Defined	Corresponding Reductions		
	MADRS	HAM-A	LSAS
Response CGI-I ≥50% reduction	≥39%	≥42%	≥31%
Remission CGI-S ≤2	≤11 points	≤ 9points	≤36 points

The HAM-A of ≤ 9points full well within the range arrived at the consensus conferences.[91 92]

List of References

1. Nutt DJ, Ballenger JC, Sheehan D, Wittchen HU. Generalized anxiety disorder: Comorbidity, comparative biology and treatment. *International Journal of Neuropsychopharmacology* 2002;5(4):315-325.
2. McManus FV. Assessment of anxiety. *Psychiatry* 2007;6(4):149-155.
3. Kessler RC MK, Zhao S, et al. . Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. . *Arch Gen Psychiatry* 1994;51:8-19.
4. Ormel J, Vonkorff, M., Ustun, T. B., Pini, S., Korten, A. & Oldehinkel, T. Common mental disorders and disability across cultures: results from the WHO Collaborative Study on Psychological Problems in General Health Care. *Journal of the American Medical Association* 1994;272:1741–1748.
5. Ruscio AM, Chiu WT, Roy-Byrne P, Stang PE, Stein DJ, Wittchen HU, et al. Broadening the definition of generalized anxiety disorder: Effects on prevalence and associations with other disorders in the National Comorbidity Survey Replication. *Journal of Anxiety Disorders* 2007;21(5):662-676.
6. Fisher PL. Psychopathology of generalized anxiety disorder. *Psychiatry* 2007;6(5):171-175.
7. Lee S, Tsang A, Chui H, Kwok K, Cheung E. A community epidemiological survey of generalized anxiety disorder in Hong Kong. *Community Mental Health Journal* 2007;43(4):305-319.
8. Olfson M, Gameroff MJ. Generalized anxiety disorder, somatic pain and health care costs. *General Hospital Psychiatry* 2007;29(4):310-316.
9. Wise TN. Anxiety disorders: Guidelines for effective primary care therapy. *Consultant* 2004;44(3):409-414.
10. Wittchen HU. Generalized anxiety disorder: Prevalence, burden, and cost to society. *Depression and Anxiety* 2002;16(4):162-171.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed., Text Revision ed. Washington DC: American Psychiatric Association, 2000.
12. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *Am Psychol* 2000;55:1248–63.
13. Butler G GM, Hibbert G, et al. . Anxiety management: developing effective strategies. . *Behav Res Ther* 1987;25:517–22.
14. Hettema JM NM, Kendler KS. . A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry* 2001;158:1568–78.
15. Andrade L C-AJ, Berglund P, et al. . Cross-national comparisons of the prevalences and correlates of mental disorders. WHO International Consortium in Psychiatric Epidemiology. *Bull World Health Organ* 2000;78:413–26.
16. Rubio G, Lopez-Ibor JJ. Generalized anxiety disorder: A 40-year follow-up study. *Acta Psychiatrica Scandinavica* 2007;115(5):372-379.
17. Lieb R, Becker E, Altamura C. The epidemiology of generalized anxiety disorder in Europe. *European Neuropsychopharmacology* 2005;15(4):445-452.
18. Ernst K. Die Prognose der Neurosen. *Monogr. Neurol. Psychiat* Berlin, 1959.

19. Lo´pez-Ibor JJ Jr. Nosological status of endogenous anxiety: anxious thymopathy revisited. *Psychopathology* 1985;18:133–139.
20. Jarwik LF RD. Anxiety, aging and the third emergency reaction. . *J Gerontol* 1979;34:197–200.
21. Diefenbach GJ HD, Feigon S et al. . Minor GAD: Characteristics of subsyndromal GAD in older adults. *Behav Res Ther* 2003;41:481–487.
22. Rickels K RM. Overview and clinical presentation of generalized anxiety disorder. . *Psychiatr Clin North Am* 2001;24:1–17.
23. Bowen RC, Senthilselvan, A., Barale, A., . Physical illness as an outcome of chronic anxiety disorders. . *Can. J. Psychiatry* 2000;45:459–464.
24. Harter MC, Conway, K.P., Merikangas, K.R. Associations between anxiety disorders and physical illness. *Eur. Arch. Psychiatry Clin. Neurosci.* 2003;253:313–320.
25. Souetre E. et al. Cost of Anxiety Disorders: Impact of Comorbidity. *Journal of Psychosomatic Research* 1994;38(Suppl. 1):151-160.
26. Brunello N, Den Boer JA, Judd LL, Kasper S, Kelsey JE, Lader M, et al. Social phobia: Diagnosis and epidemiology, neurobiology and pharmacology, comorbidity and treatment. *Journal of Affective Disorders* 2000;60(1):61-74.
27. Barlow DH WJ. DSM-IV and beyond: what is generalized anxiety disorder?. [Review]. *Acta Psychiatrica Scandinavica* 1998;393(Supplementum):23-29.
28. Angst J, Gamma A, Bienvenu OJ, Eaton WW, Ajdacic V, Eich D, et al. Varying temporal criteria for generalized anxiety disorder: Prevalence and clinical characteristics in a young age cohort. *Psychological Medicine* 2006;36(9):1283-1292.
29. Kessler RC, Brandenburg N, Lane M, Roy-Byrne P, Stang PD, Stein DJ, et al. Rethinking the duration requirement for generalized anxiety disorder: Evidence from the National Comorbidity Survey Replication. *Psychological Medicine* 2005;35(7):1073-1082.
30. Kessler R C et al. The epidemiology of generalised anxiety disorder. *Psychiatr Clin North Am* 2001;24(1).
31. Rickels K. and Rynn M. Overview and Clinical Presentation of Generalized Anxiety Disorder. *Psychiatr Clin North Am* 2001;24(1).
32. Australian Bureau of Statistics. Mental Health in Australia: A Snapshot, 2004-05. 2006(4824.0.55.001).
33. Australian Institute of Health and Welfare. Mental health: A Report Focusing on Depression: 1998. *National Health Priority Areas Report*: Commonwealth Department of Health and Aged Care, 1999.
34. Stefanssan JG, Lindal, E., Bjornsson, J. K. & Guomundsdottir, A. Lifetime prevalence of specific mental disorders among people born in Iceland in 1931. *Acta Psychiatrica Scandinavica* 1991;84:142–149.
35. Wells JE, Bushnell, J. A., Hornblow, A. R., Joyce, P. R. & Oakley-Brown, M. A. . Christchurch Psychiatric Epidemiology Study, part 1. Methodology and lifetime prevalences for specific psychiatric disorders. . *Australian and New Zealand Journal of Psychiatry* 1989;23:3315–3326.
36. van Balkom AJLM. et al. Comorbidity of the anistey disorders in a community based older populations in The Netherlands. *Acta Psychiatr Scand* 2000;101:37-45.

37. Bijl RV RA, van Zessen G. . Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol* 1998;33:587–95.
38. Kringlen E TS, Cramer V. . A Norwegian psychiatric epidemiological study. *Am J Psychiatry* 2001;158:1091–98.
39. Kessler RC, Andrade LH, Bijl RV, Offord DR, Demler OV, Stein DJ. The effects of co-morbidity on the onset and persistence of generalized anxiety disorder in the ICPE surveys. *Psychological Medicine* 2002;32(7):1213-1225.
40. Kessler RC CW, Demler O, Merikangas KR, Walters EE. . *Arch Gen Psychiatry* 2005;62(617–627).
41. Kessler R C DRL, Berglund. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. . *Am J Psychiatry* 1999;156:1915-1923
42. Ansseau M, Fischler B, Dierick M, Mignon A, Leyman S. Prevalence and impact of generalized anxiety disorder and major depression in primary care in Belgium and Luxemburg: The GADIS study. *European Psychiatry* 2005;20(3):229-235.
43. Grant BF, Hasin DS, Stinson FS, Dawson DA, Ruan WJ, Goldstein RB, et al. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychological Medicine* 2005;35(12):1747-1759.
44. Wittchen HU NC, Lachner G. . Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. *Psychol Med.* 1998;28(1):109-26
45. Essau CA KN, Oetermann F, Conradt J. . Häufigkeit und Komorbidität von Angststörungen bei Jugendlichen: Ergebnisse der Bremer Jugendstudie. *Verhaltenstherapie* 1998;8:180–87.
46. Becker ES TV, Neumer S, Soeder U, Krause P, Margraf J. Praevalenz von psychischen und psychiatrischen Stoerungen bei jungen Frauen aus der Allgemeinbevoelkerung: Ergebnisse der Dresdener Studie. In: Heess-Erler G MR, Kirch W, editor. Regensburg: Roderer, 2000.
47. Meyer C RH, Hapke U, Dilling H, John U. . Lebenszeitprävalenz psychischer Störungen in der erwachsenen Allgemeinbevölkerung. Ergebnisse der TACOS - Studie. . *Nervenarzt* 2000;70:535–42.
48. Alonso J. et al. (The ESEMeD/MHEDEA 2000 Investigators). 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004;109(Suppl. 420):28-37.
49. Turner RJ GA. Psychiatric and substance use disorders in South Florida: racial/ethnic and gender contrasts in a young adult cohort. *Arch Gen Psychiatry* 2002;59:43–50.
50. Jacobi F WH-U, Hölting C. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychol Med* 2004;34:597–611.
51. Carter RM WH, Pfister H, Kessler RC. . One year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. *Depress Anxiety* 2001;13 78-88.

52. Kadri N MA, Samir El Gnaoui, Soumia Berrada and, Moussaoui D. Prevalence of anxiety disorders: a population-based epidemiological study in metropolitan area of Casablanca, Morocco. *Annals of General Psychiatry* 2007;6:6.
53. Moffitt TE, Harrington H, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, et al. Depression and generalized anxiety disorder: Cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry* 2007;64(6):651-660.
54. The ESEMeD/MHEDEA 2000 Investigators. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004;109(Suppl. 420):28-37.
55. Wittchen HU, Zhao, S., Kessler, R.C., Eaton, W.W., . DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 1994;51:355–364.
56. Noyes R. Comorbidity in gneralised anxiety disorder. *Psychiatr Clin North Am* 2001;24:41-55.
57. Hunt C IC, Andrews G. . DSM-IV generalized anxiety disorder in the Australian national survey of mental health and well-being. . *Psychol Med* 2002;32:649-59.
58. Allgulander C. Generalized anxiety disorder: What are we missing? *European Neuropsychopharmacology* 2006;16(SUPPL. 2):S101-S108.
59. Durham RC. Treatment of generalized anxiety disorder. *Psychiatry* 2007;6(5):183-187.
60. Anderson I. The new guidelines from the British Association for Psychopharmacology for anxiety disorders. *International Journal of Psychiatry in Clinical Practice* 2006;10(SUPPL. 3):10-17.
61. Keller M.B. The long-term clinical course of generalized anxiety disorder. *J. Clin. Psychiatry* 2002;63(Suppl. 8):11–16.
62. Brawman-Mintzer O, Lydiard, R.B.,. Generalized anxiety disorder: issues in epidemiology. *J. Clin. Psychiatry* 1996;57(Suppl. 7):3–8.
63. Bruce SE, Machan, J.T., Dyck, I., Keller, M.B., . Infrequency of "pure" GAD: impact of psychiatric comorbidity on clinical course. *Depress Anxiety* 2001;14:219–225.
64. Yonkers KA, Dyck IR, Keller MB. An eight-year longitudinal comparison of clinical course and characteristics of social phobia among men and women. *Psychiatric Services* 2001;52(5):637-643.
65. Rickels K, Schweizer, E.,. The clinical course and long-term management of generalized anxiety disorder. *J. Clin. Psychopharmacol* 1990;10(Suppl):101S–110S.
66. Moffitt TE, Caspi A, Harrington H, Milne BJ, Melchior M, Goldberg D, et al. Generalized anxiety disorder and depression: Childhood risk factors in a birth cohort followed to age 32. *Psychological Medicine* 2007;37(3):441-452.
67. Alonso J. et al. (The ESEMeD/MHEDEA 2000 Investigators). Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004;109(Suppl. 420):21-27.
68. Bebbington PE ea. Neurotic disorders and the receipt of psychiatric treatment. *Psychol Med* 2000;30:1369-1376.

69. Nash J, Nutt D. Psychopharmacology of anxiety. *Psychiatry* 2007;6(4):143-148.
70. Rocca P FV, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. *Acta Psychiatrica Scandinavica* 1997;95(5):444-450.
71. Rickels K DR, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Archives of general psychiatry.* 1993;50(11):884-95.
72. Dinan T. Therapeutic options: Addressing the current dilema. *Eur Neuropsychopharmacol* 2006;16:s119-127.
73. Baldwin DS, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. *International Journal of Neuropsychopharmacology* 2005;8(2):293-302.
74. NICE Guidelines. Clinical Guidelines for the Management of Anxiety: Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care, 2004.
75. Busto UE. Romach MK. Sellers EM. Multiple Drug Use and Psychiatric Comorbidity in Patients Admitted to the Hospital With Severe Benzodiazepine Dependence. *J of Clin Psychopharmacology* 1996;16(1):51-57
76. Mahe V. BA. Long-term pharmacological treatment of generalised anxiety disorder. *Int. Clin. Psychopharm* 2000;15:99-105.
77. Therapeuitc Guidelines. *Psychotropic*. Melbourne: Therapeuitc Guidelines, 2003.
78. Wittchen HU, Fuetsch M, Sonntag H, Muller N, Liebowitz M. Disability and quality of life in pure and comorbid social phobia. Findings from a controlled study. *European Psychiatry* 2000;15(1):46-58.
79. Weiller E BJC, Maier W, Lecrubier Y. Prevalence and recognition of anxiety syndromes in five European primary care settings. A report from the WHO study on Psychological Problems in General Health Care. . *Br J Psychiatry* 1998;34(Suppl):18-23
80. Hunt CJ. The current status of the diagnostic validity and treatment of generalized anxiety disorder. *Current Opinion in Psychiatry* 2002;15(2):157-62.
81. Borkovec TD RA. Psychotherapy for generalized anxiety disorder. *Journal of Clinical Psychiatry* 2001;62(Suppl 11):15-19.
82. Wittchen H.U et al. Anisety disorders: similarities and differences in treated and untreated groups. *Br J Psychiatry* 1991;159:23-33.
83. Angst JaVM. The natural history of anxiety disorders. *Acta Psychiatr Scand* 1991;84:446-52.
84. Yonkers K A DIR, Warshaw M, Keller M B. Factors predicting the clinical course of generalised anxiety disorder. . *Br J Psychiatry* 2000;176:544-549
85. Brown C. et al. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. *Am J Psychiatry* 1996;153:1293-1300.
86. 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.
87. Mohamed S, Osatuke K, Aslam M, Kasckow J. 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):201-209.

88. Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004;19(4):234-40.
89. Lundbeck Australia. Glossary of terms, 2006.
90. Montgomery S LY, Baldwin D, Kasper S, Lader M, Nil R, et al. ECNP Consensus Meeting, March 2003. Guidelines for the investigation of efficacy in social anxiety disorder. . *Eur Neuropsychopharmacol* 2004;14:425-433.
91. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and ansiety. *J Clin Psychiatry* 1999;60(Suppl 22):29-34.
92. Ballenger JC. Treatment of anxiety disorders to remission. *J Clin Psychiatry* 2001;62(Suppl 12):5-9.
93. Haynes R B DPJ, Guyatt G H. Physicians' and patients' choices in evidence based practice. *BMJ* 2002;324:1350.
94. Bandelow B. Defining response and remission in anxiety disorders: Toward an integrated approach. *CNS Spectrums* 2006;11(SUPPL. 12):21-28.
95. Stein DJ. et al. Which factors predict placebo response in ansiety disoerders and major depression? An analysis of placebo controlled studies of escitalopram. *J Clin Psychiatry* 2006;67:1741-1746.
96. Verisiani M. et al. Pharmaotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry* 1992;161:353-360.

ATTACHMENT 4

DETAILS OF THE LITERATURE SEARCHES CONDUCTED FOR ESCITALOPRAM GAD SUBMISSION

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

ABS	Australian Bureau of Statistics
ACTR	Australian Clinical Trial Register
AHA	American Heart Association
AIHW,	Australian Institute of Health and Welfare;
CADTH	Canadian Agency for Drugs and Technology in Health
CENTRAL	Central Register of Controlled Trials
CSR	Clinical Study Report
DARE	Database of Abstracts of Reviews of Effects
DoH	Department of Health
DoHA	Department of Health & Aging
EBM Databases	Includes all Cochrane Library Datasets, including CENTRAL, DARE, Cochrane DSR, ACP Journal Club
HTA	Health technology assessment
mRCT	metaRegister of Clinical Trials
NICE	National Institute of Clinical Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Schedule
RCT	Randomised controlled clinical trial
RPBS	Repatriation Pharmaceutical Benefits Schedule
TGA	Therapeutic Goods Administration

1.1 Introduction

The details of the literature searches relevant to Section B of this submission are presented in this Attachment.

Attachment 2 presents the complete documentation of all search strategies, and citations and abstracts identified from the literature searches for genralised ansiety disorder studies. The following sources were used to search for relevant data.

1. A search of the electronic databases EMBASE+Medline, PubMed and MEDLINE In-Process.
2. A search of the EBM Databases: Cochrane Central Register of Controlled Trials (CENTRAL), DARE, Cochrane DSR and ACP Journal Club.
3. A search of clinical trial registries through the Australian Clinical Trials Registry (ACTR) and ClinicalTrials.gov.
4. Manual searching of references publications retrieved via the database searches.
5. Conference Papers Index,
6. Health Technology Assessment databases (NICE)
7. A search of Lundbeck's internal databases.

1.2 Inclusion criteria for clinical evidence

A literature search was undertaken for this submission in order to identify all relevant randomised controlled trials (RCTs) for Generalised Anxiety Disorder (GAD) and escitalopram (Lexapro®).

Included studies were RCTs of GAD or escitalopram (Lexapro®). s38, s47E(d) The choice of which benzodiazepine would be appropriate as a comparator was determined by the PBS Listing for each. As can be seen below only diazepam and oxazepam (benzodiazepines) had a general listing that supported their TGA indication for treatment of "anxiety disorders". All other benzodiazepines were PBS Authority Listed for other indications and specific groups.

If there were no head to head RCTs comparing Escitalopram to a benzodiazepine then an indirect comparison between escitalopram and benzodiazepines, using placebo as a common comparator would be undertaken. The search would identify benzodiazepine studies for DSM-IV defined GAD that had a placebo arm.

s22

s22

Additional Search terms included, following discussion with the PBB was:

- Hamilton Anxiety Scale (HAMA or HAM-A), as the most appropriate scale to use

The classification for GAD used was DSM-IV. After extensive review of the literature it was concluded that DSM-IV defined patients are a more restrictive group of patients that would not include a large proportion of DSM-III-R or DSM-III patients. This is the key reason why the submission will look at DSM-IV patients alone, given that these were the basis of the Escitalopram trial.

Table 1: TGA Approved and PBS Reimbursed Indications

	TGA Approved Indications	PBS Indication
N05 Psycholeptics		
N05B Anxiolytics		
N05BA Benzodiazepine derivatives		
Diazepam	VALIUM is indicated for the management of **anxiety disorders or for the short term relief of the symptoms of anxiety**. Anxiety or tension associated with the stress of	General Listing

	everyday life usually does not require treatment with an anxiolytic.	
	In acute alcohol withdrawal, VALIUM may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. VALIUM is a useful adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation) to muscles, bones and joints. It can also be used to combat spasticity due to upper motor neuron lesions such as cerebral palsy and paraplegia, as well as in athetosis and stiff-man syndrome. Intravenous VALIUM is useful in controlling status epilepticus and the spasms of tetanus.	
Oxazepam	Management of **anxiety disorders or for the short-term relief of the symptoms of anxiety**. Anxiety associated with depression is also responsive to oxazepam therapy. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. The physician should periodically reassess the usefulness of the drug for the individual patient. Alcoholics with acute tremulousness, confusional state or anxiety associated with alcohol withdrawal are responsive to therapy.	General Listing
Alprazolam	**Anxiety. Short-term symptomatic treatment of anxiety including treatment of anxious patients with some symptoms of depression.** *Panic disorder (DSM-III-R).* The treatment of panic disorder with or without some phobic avoidance, and for blocking or attenuation of panic attacks and phobias in patients who have agoraphobia with panic attacks.	Authority Required: Panic disorder where other treatments have failed or are inappropriate.
Bromazepam	Symptomatic relief of tension, anxiety and agitation. Anxiety and tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.	Authority Required: Patients with refractory phobic or anxiety states

N06 Psychoanaleptics
N06A Antidepressants

N06AA Non-selective monoamine reuptake inhibitors

Amitriptyline Hydrochloride	For the treatment of major depression.
Clomipramine Hydrochloride	For the treatment of major depression; obsessive-compulsive disorders and phobias in adults; cataplexy associated with narcolepsy.
Dothiepin Hydrochloride	For the treatment of major depression.
Doxepin Hydrochloride	For the treatment of major depression.
Imipramine Hydrochloride	Major depression. Nocturnal enuresis (from the age of 5 years onwards and provided the possibility of organic causes has first been excluded).
Nortryptyline Hydrochloride	Major depression.

N06AB Selective serotonin reuptake inhibitors

Escitalopram Oxalate	Treatment of major depression. Treatment of social anxiety disorder (social phobia). **Treatment of generalised anxiety disorder.**
Citalopram Hydrobromide	Treatment of major depression.
Fluoxetine Hydrochloride	Major depression Obsessive Compulsive Disorder. Premenstrual Dysphoric Disorder (PMDD) as defined by DSM-IV criteria.
Fluvoxamine Maleate	Is indicated for the treatment of major depression in adults. MOVOX (fluvoxamine maleate) is also indicated for the treatment of Obsessive Compulsive Disorder (OCD) in children aged 8 years and older, adolescents, and adults.
Paroxetine Hydrochloride	Major depression and for the prevention of relapse of depressive symptoms; Obsessive Compulsive Disorder and for the prevention of relapse of OCD; Panic Disorder and for the prevention of relapse of Panic Disorder; Social Anxiety Disorder/Social Phobia; and **Generalised Anxiety Disorder.** Posttraumatic Stress Disorder

Sertraline Hydrochloride	ZOLOFT (sertraline hydrochloride) is indicated for the treatment of major depression, obsessive compulsive disorder (OCD) and panic disorder. ZOLOFT (sertraline hydrochloride) is indicated for the treatment of social phobia (social anxiety disorder) and the prevention of its relapse. ZOLOFT (sertraline hydrochloride) is indicated for the treatment of premenstrual dysphoric disorder (PMDD) as defined by DSM-IV criteria.
N06AF Monoamine oxidase inhibitors, non-selective	
Phenelzine Sulfate	Treatment of major depression.
Tranylcypromine Sulfate	Treatment of major depression.
N06AG Monoamine oxidase type A inhibitors	
Moclobemide	Treatment of major depression.
N06AX Other antidepressants	
Lithium Carbonate	Acute episodes of mania and hypomania, and for the prophylaxis of recurrent manic depressive illness.
Mianserin Hydrochloride	For the treatment of major depression.
Mirtazapine	Treatment of major depression including relapse prevention.
Reboxetine Mesilate	for the treatment of major depression and is effective in preventing the relapse of depressive symptoms.
Venlafaxine Hydrochloride	Major Depression, including prevention of relapse and recurrence where appropriate. **Generalised Anxiety disorder.** Social Anxiety Disorder. Panic Disorder, including prevention of relapse.

All trials not meeting these requirements were excluded. Prior to conducting the literature searches, entry criteria were defined for the inclusion and exclusion of papers, as follows:

- **Only RCTs were included;**
- **Reviews, editorials and animal studies were excluded;**
- s47E(d) **, and**
- **The population in the trials had to be DSM IV.**

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.

1.3 Search strategies for comparative randomised trials

1.3.1 EMBASE and Medline search strategy

Presented in Table 2 is the search strategy employed in the EMBASE+MEDLINE® EMBASE database (EMBASE), all years till 31May 2007.

Table 2: Search details for EMBASE+MEDLINE® EMBASE, all years till 31 May 2007

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
#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

Search #19: Generalised anxiety disorder and benzodiazepines and HAMA

Search #20: Generalised anxiety disorder and escitalopram and HAMA and benzodiazepines

Search #21: Generalised anxiety disorder and escitalopram and HAMA

1.3.2 PubMed search strategy

A PubMed search was also conducted and the results are presented in

Table 3, Table 4 and Table 5. A summary is provided below. Since there was complete overlap between Embase+Medline and Pubmed this search was not re-run for the chronological update.

	Number of Studies Identified
GAD + Escitalopram+ HAMA	11
GAD + HAMA + benzodiazpepines	24
GAD+Escitalopram+HAMA+ benzodiazpepines	0

Table 3: Generalised anxiety disorder and escitalopram and HAMA: Search details for PubMed all years till 18 May 2007

Search	Most Recent Queries	Time	Result
17	Search #16 and #15 Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase	16:21:58	11

	III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans		
16	Search hamilton anxiety score or HAMA or HAM-A Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:20:37	1641
15	Search #14 and #13 Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:18:27	32
14	Search #6 and #10 Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:16:39	1837
13	Search #11 or #8 Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:15:36	989
12	Search #11 and #8 Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:15:14	9
11	Search lexapro Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:14:23	9
10	Search generalised anxiety disorder or GAD or generalized anxiety disorder Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:13:09	3644
9	Search 'generalised anxiety disorder' or 'GAD' or g'eneralized anxiety disorder' Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:12:09	23
8	Search escitalopram Limits: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Journal Article, Multicenter Study, Humans	16:10:52	989
7	Search escitalopram	16:08:50	2049
6	Search "Anxiety Disorders"[MeSH Major Topic]	16:07:47	32249

Table 4: Generalised anxiety disorder HAMA benzodiazepines: Search details for PubMed all years till 2June 2007

#	Most Recent Queries	Time	Result
27	Search **#26 or #25 or #18 or #19** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:12:28	24
26	Search **#25 and #17** Limits: **English, Clinical Trial, Meta-**	17:08:53	3

	Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans	
25	Search **#24 and #23** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:07:03 13
24	Search **#20 or #21** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:06:35 1699
23	Search **#1 or #22** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:05:40 578
22	Search **gad** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:04:59 529
21	Search **"Diazepam"[MeSH Major Topic]** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:04:15 1582
20	Search **"Oxazepam"[MeSH Major Topic]** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:03:18 134
19	Search **#16 and #17** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:01:33 1
18	Search **#14 and #17** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	17:00:11 13
17	Search **"Hamilton anxiety scale" or "HAM-A" or "HAMA"** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	16:55:59 593
16	Search **"Anxiety Disorders"[MeSH] AND "Oxazepam"[MeSH]** Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**	16:53:09 19
14	Search **"Anxiety Disorders"[MeSH] AND**	16:49:56 214

	"Diazepam"[MeSH] Limits: **English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Conference, "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Comparative Study, Controlled Clinical Trial, Multicenter Study, Humans**		
13	Search **"Anxiety Disorders"[MeSH] AND "Diazepam"[MeSH]**	16:47:19	410
7	Search **"Phobic Disorders"[MeSH Major Topic]**	16:41:45	4693
6	Search **"Anxiety Disorders"[MeSH Major Topic]**	16:37:41	32247
1	Search **generalised anxiety disorder**	16:29:16	252

Table 5: Generalised anxiety disorder and escitalopram and HAMA and benzodiazepines: Search details for PubMed all years till 2June 2007

Search	Most Recent Queries	Time	Result
#43	Search **#38 and #39 and #40 and #23** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:25:22	0
#42	Search **#38 and #39 and #40 and #26** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:24:34	0
#41	Search **#38 and #39 and #40 and #25** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:24:15	0
#40	Search **#34 or #35 or #36** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:22:44	1038
#39	Search **#32 or #33** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:22:09	551
#38	Search **#30 or #31 or #37** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:21:01	7404
#37	Search **GAD** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:18:31	486
#36	Search **HAMA** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:18:10	282
#35	Search **HAM-A** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:17:50	177
#34	Search **Hamilton Anxiety Scale** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:17:31	750
#33	Search **lexapro** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:17:02	6
#32	Search **escitalopram** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:16:40	551
#23	Search **"Diazepam"[MeSH Major Topic]** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:16:19	1332
#25	Search **"Oxazepam"[MeSH Major Topic]** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:15:36	116
#31	Search **generalised anxiety disorder** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	07:14:46	93
#30	Search **"Anxiety Disorders"[MeSH Major Topic]** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial,**	07:14:07	7159

	Review, English	
#28	Search **("Anxiety Disorders"[Mesh]) and diazepam** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	04:04:40 237
#27	Search **("Anxiety Disorders"[Mesh])** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	04:04:08 8814
#20	Search **#17 and #14** Limits: **Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English**	01:23:30 9
#19	Search **#17 and #14**	01:19:12 12
#18	Search **#17 and #114**	01:19:02 0
#17	Search **#15 or #16**	01:18:02 163
#16	Search **LSAS**	01:17:21 92
#15	Search **Liebowitz social anxiety scale**	01:17:00 136
#14	Search **#12 and #13**	01:16:39 168
#13	Search **#10 or #11**	01:16:13 2054
#12	Search **#2 or #6 or #7 or #8 or #9**	01:15:22 34299
#11	Search **lexapro**	01:12:20 10
#10	Search **escitalopram**	01:11:54 2054
#9	Search **social phobia**	01:11:18 7394
#8	Search **generalised social anxiety disorder**	01:10:43 42
#7	Search **social anxiety disorder**	01:10:15 6960
#6	Search **"Anxiety Disorders"[MeSH Major Topic]**	01:09:36 32366
#2	Search **"Phobic Disorders"[MeSH Major Topic]**	01:07:45 4707

Update of Embase+ Medline Searches; 1/06/2007-4/10/2007

A summary of the first and final Embase + Medline search is presented below:

	Search 31 May	**Search 1/06/2007 to 04/10/07**
Escitalopram vs placebo	11	0
Benzodiazepines	24	0
Diazepam and Oxazepam		
Escitalopram and Diazepam and Oxazepam	0	0

The results of the search are presented in Table 6 .

Table 6 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**[1]
#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 [humans]/lim AND [01-06-2007]/sd NOT [04-10-2007]/sd AND [2007]/py	**0**	**03 Oct 2007**
#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**

1.3.3 Medline in Process search strategy

There were no articles identified for escitalopram and 1 article for diazepam/oxazepam. The search strategy is presented in Table 7, last 8 weeks to 26 September 2007.

[1] Please note that the search was conducted 4/10/07 in Australia but the recorded date on the result sheet was 03/10/07 presumably because of the time difference between Australia and the other coutry the database resides in.

Table 7: Search details for MEDLINE® In-Process Ovid - 8 weeks prior to 26 September 2007

#		Results
Escitalopram		
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	general anxiety disorder.mp. [mp=title, original title, abstract, name of substance word]	3
4	gad.mp. [mp=title, original title, abstract, name of substance word]	89
5	3 or 4	91
6	2 and 5	0
Diazepam and Oxazepam		
1	general anxiety disorder.mp. [mp=title, original title, abstract, name of substance word]	3
2	gad.mp. [mp=title, original title, abstract, name of substance word]	89
3	diazepam.mp. [mp=title, original title, abstract, name of substance word]	170
4	oxazepam.mp. [mp=title, original title, abstract, name of substance word]	7
5	3 or 4	173
6	1 or 2	91
7	5 and 6	1

1.3.4 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 8. The search was undertaken 2 June 2007.

Table 8: Search details for Cochrane Library database to 2 June 20072

#	Search History	Results
1	general anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	8
2	gad.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	249
3	hamilton anxiety scale.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	211
4	HAMA.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	119
5	1 or 2	256
6	3 or 4	292
7	5 and 6	32
8	escitalopram.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	121

[2]Rrelevant search highlighted.

9	lexapro.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	1
10	8 or 9	121
11	7 and 10	6
12	diazepam.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	3299
13	oxazepam.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	322
14	12 or 13	3542
15	7 and 14	5
16	7 and 10 and 14	0

Summary of references identified:

Escitalopram (#11): 6

Benzodiazepines (#15): 5

Escitalopram and benzodiazepines (#16): 0

Updated search conducted 4 October 2007 and results are presented in Table 9 – The relevant searches are highlighted in yellow.

Table 9 Update EBM Search, 4 Oct 2007

#	Search History	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
14	general$ anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	476
15	gad.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	249
16	14 or 15	555
17	hamilton anxiety score.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	5
18	hama.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	119
19	ham-a.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	792
20	17 or 18 or 19	906
21	3 and 16 and 20	7
22	limit 21 to (classical article or clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or conference or congresses or consensus development conference or controlled clinical trial or "corrected and republished article" or guideline or journal article or meta analysis or multicenter study or randomized controlled trial or retracted publication or "review" or "review literature" or review, academic) [Limit not valid in: CDSR,ACP Journal Club,DARE; records were retained]	7
23	limit 22 to yr="2007" [Limit not valid in: DARE; records were retained]	0
24	diazepam.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	3299
25	oxazepam.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	322
26	24 or 25	3543
27	16 and 20 and 26	10
28	limit 27 to (classical article or clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or conference or congresses or consensus development conference or controlled clinical trial or "corrected and republished article" or guideline or journal article or meta analysis or multicenter study or practice guideline or published erratum or randomized controlled trial or	10

	retracted publication or "review" or "review literature" or review, academic) [Limit not valid in: CDSR,ACP Journal Club,DARE; records were retained]	
29	limit 28 to yr="2007" [Limit not valid in: DARE; records were retained]	1

There was only one result in this search in DARE:

Database	EBM Reviews - Database of Abstracts of Reviews of Effects
Accession Number	00125498-100000000-01700
Author	Centre for Reviews and Dissemination
Institution	NHS Centre for Reviews and Dissemination. University of York, York, U.K.
Title	Long-term pharmacological treatment of generalized anxiety disorder (Structured abstract).
Source	Database of Abstracts of Reviews of Effects. Issue 3, 2007.
Reviewed Source	Abstract and Commentary for:Mahe V, Balogh A. Long-term pharmacological treatment of generalized anxiety disorder. International Clinical Psychopharmacology. 2000;15(2):99-105.
Date of Most Recent Amendment	2001
Publication Type	Miscellaneous
Keywords	Anti-Anxiety Agents/tu (therapeutic use); Anxiety Disorders/dt (drug therapy); Anxiety Disorders/ps (psychology); Benzodiazepines/tu (therapeutic use); Chronic Disease; Prognosis; Recurrence
External Accession Number	DARE-20003680

However this was an article previously identified and was not considered again.

1.3.5 Clinical trial registers search strategy

Presented in Table 10 are the results from the search of the clinical trials register;

Clinical Trials.gov and ACTR:

Table 10: Results of the search of Clinical Trial Registries, 27 and 28 September

#	Search strategy	Results
Escitalopram		
Clinical Trials.gov	*escitalopram or lexapro [ALL-FIELDS] AND general anxiety disorder [ALL-FIELDS]*	4
ACTR[3]	*escitalopram*	0
Benzodiazepines		
Clinical Trials.gov[3]	*diazepam [ALL-FIELDS] AND general anxiety disorder [ALL-FIELDS]*	2
Clinical Trials.gov	*oxazepam [ALL-FIELDS] AND general anxiety disorder [ALL-FIELDS]*	1
ACTR[4]	*diazepam*	0
ACTR	*oxazepam*	0
Escitalopram and Benzodiazepines		
Clinical Trials.gov	(escitalopram AND or AND lexapro) [ALL-FIELDS] AND diazepam [ALL-FIELDS]	0
Clinical Trials.gov	*(escitalopram AND or AND lexapro) [ALL-FIELDS] AND oxazepam [ALL-FIELDS]*	1
ACTR	*Diazepam and escitalopram*	0
ACTR	*Oxazepam and escitalopram*	0

1.3.6 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 11. The search was undertaken 26 September February 2007.

Table 11: Search details for HTA Databases to 25 September 2007

Database	Search	Results
National Institute of Clinical Excellence (NICE)	Mental Health (search for GAD)	0
Total		**0**

1.3.7 Search of conference abstracts

A search of the conference abstracts relevant to this field of study was also conducted. Therefore it was considered appropriate to expand the search to include data presented at the conferences listed in Table 12.

[3] Searched 16 May
[4] Searched 30 May

Table 12: Search details for conference proceedings 1982 to 25 September 2007

Conference	Search	Results for Conference Papers[5]
Conference Papers Index	(escitalopram or lexapro) and KW=((general anxiety disorder) or (GAD))	1
Conference Papers Index	KW=(diazepam or oxazepam) and KW=((general anxiety disorder	0
Conference Papers Index	KW=(diazepam or oxazepam) and KW=((general anxiety disorder) and (escitalopram or lexapro)	0

1.3.8 Search of the sponsor's database for Studies

Trials identified by the Sponsor's database are presented in Table 13.

Table 13: Results of the Sponsor's Database for Studies

Study Number	Publication
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	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.
SCT-MD-17	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, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. *Journal of Clinical Psychiatry* 2005;66(11):1441-1446
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, Huusom AKT, Maehlim E. Escitalopram and Paroxetine compared to placebo in the treatment of generalized anxiety disorder (GAD). 17th Congress of Neuropsychopharmacology, Sweden, October 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
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., I. Florea, and A.K. Huusom, Prevention of relapse in generalized anxiety disorder by escitalopram treatment. Int J Neuropsychopharmacol, 2006. 9(5): p. 495-505.

[5] This database includes other publication types but was searched only for the conference paper abstracts

1.3.9 Manual searching

Escitalopram

A manual search through the references of the retrieved trials and reviews examining RCTs of escitalopram did not identify any references relevant to this submission

Benzodiazepines (Diazepam and Oxazepam)

A manual search through the references of the retrieved trials and reviews examining RCTs of escitalopram identified several references relevant to this submission. These are presented in Appendix 6.

1.4 List of citations and reasons for exclusion

Escitalopram

The summary for the escitalopram literature search results is presented in Table 14. This summary is presented as a composite of the numbers of citations identified, those included and those excluded, with reasons.

s22

The 25 citations identified in the literature search (these do not include the study reports) are listed below in alphabetical order, and reasons for their exclusion provided in Table 17. A detailed presentation of their abstracts is presented in Appendix 1.

A detailed presentation of all references retrieved in the individual searches is presented in Appendix 2 (study reports not included).

Table 14: Summary of identification of direct and indirect randomised trials from the literature search: Escitalopram

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA[6]	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	12	11	0	4	0	6	12	1	0	0	46
Total number of duplicates		7				5	8	1			21
Total number of citations reviewed for inclusion	12	4	0	4	0	1	4	0	0		25
Number of citations excluded after title/abstract review:	9	4		4		1					18
• Not an RCT	7	2				1					10
• RCT does not include comparator	2	2		2							6
• Trial subjects are not representative of the proposed indication				2							2
Number of citations excluded after full text review:											
• RCT does not include comparator											
• Trial subjects are not representative of the proposed indication											
Number of citations of direct randomised trials included from each database	3										7
Number of direct randomised trials identified for inclusion in this submission	3	0	0	0	0	0	4	0	0	0	7

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration.

[6] Three of the study reports have corresponding publications: these are all included in the submission but are counted only once.

Escitalopram and Benzodiazepines

The summary for the escitalopram and benzodiazepine literature search results is presented in Table 15. This summary is presented as a composite of the numbers of citations identified, those included and those excluded, with reasons.

s22

The published citation identified in the literature search is listed below in alphabetical order, and reasons for its exclusion is provided in Table 18. The abstract is presented in Appendix 3.

A detailed presentation of all references retrieved in the individual searches is presented in Appendix 4.

Table 15: Summary of identification of direct randomised trials from the literature search: Escitalopram and Benzodiazepines

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	1			1							2
Total number of duplicates	0										
Total number of citations reviewed for inclusion	1			1							2
Number of citations excluded after title/abstract review:	1			1							2
• Not an RCT											
• RCT does not include comparator											
• Trial subjects are not representative of the proposed indication	1										
Number of citations excluded after full text review:											
• RCT does not include comparator											
• Trial subjects are not representative of the proposed indication											
Number of citations of direct randomised trials included from each database											
Number of direct randomised trials identified for inclusion in this submission	0			0							0

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration.

Benzodiazepines

The summary for the benzodiazepine literature search results is presented in Table 16 for DSM IV. This summary is presented as a composite of the numbers of citations identified, those included and those excluded, with reasons.

s22

The published citations identified in the literature search are listed below in alphabetical order, and reasons for their exclusion provided in **Table 19** DSM IV (60 citations). A detailed presentation of their abstracts is presented in Appendix 5.

A detailed presentation of all references retrieved in the individual searches is presented in Appendix 6.

Table 16: Summary of identification of indirect randomised trials from the literature search for Benzodiazepines: DSM-IV

	Embase and Medline	PubMed	MEIP[7]	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	10	24	1	3	0	6	0	0	0	20	64
Total number of duplicates		3				1				0	4
Total number of citations reviewed for inclusion	10	21	1	3	0	5	0	0	0	20	60
Number of citations excluded after title/abstract review:	5	11	1	3	0	2				6	28
• Not an RCT		4	1			2				5	12
• RCT does not include comparator	1	7								1	9
• Trial subjects are not representative of the proposed indication	4			3	0						7
Number of citations excluded after full text review:	4	10				3				14	31
• RCT does not include comparator	2					0					2
• Trial subjects are not representative of the proposed indication	2	10				3				14	29
Number of citations of direct randomised trials included from each database	1										1
Number of direct randomised trials identified for inclusion in this submission	1	0	0	0	0	0	0	0	0	0	1

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration.

[7] This article has yet to be published and only access was an abstract that presented no data. This abstract is referred to in the submission but is not used extensively as it is uncertain as to what trials were utilised in the meta-analysis.

1.5 Listing of the included and excluded citations with reasons for selection

Presented below are the citations identified and the reasons for inclusion and exclusion.

Escitalopram: Table 17

Escitalopram and Benzodiazepines: Table 18

Benzodiazepines: Evidence is presented for DSM-IV in Table 19.

Legends Followed:

a	not a randomised trial
b	not an appropriate comparator
c	not a relevant population

Table 17: Summary of Inclusion/Exclusion criteria for Escitalopram Trials

		Included / Excluded	Reason for Exclusion	Rationale
1	**Allgulander, C., I. Florea, and A.K. Huusom, Prevention of relapse in generalized anxiety disorder by escitalopram treatment. Int J Neuropsychopharmacol, 2006. 9(5): p. 495-505.**	**I**		Study report 99769
2	**Baldwin D.S., et al. Escitalopram and paroxetine in the treatment of generalised anxiety disorder. British Journal of Psychiatry. 2006. 189. 262-272**	**I**		Study report 99815
3	Bandelow, B., et al., 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, 2006. 67(9): p. 1428-34.	E	a	
4	Bielski, R.J., A. Bose, and C.C. Chang, A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry, 2005. 17(2): p. 65-9.	E	b	
5	Blank, S., et al., Outcomes of late-life anxiety disorders during 32 weeks of citalopram treatment. J Clin Psychiatry, 2006. 67(3): p. 468-72.	E	b	
6	Bristol-Myers Squibb, Study of Pexacerfont (BMS-562086) in the Treatment of Outpatients With Generalized Anxiety Disorder. 2007.	E	b	
7	**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.**	**I**		**Study report SCT-MD-07**
8	**Davidson, J.R.T., A. Bose, and Q. Wang, Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. Journal of Clinical Psychiatry, 2005. 66(11): p. 1441-1446.**	**I**		**Study report SCT-MD-17**

9	Dhillon, S., L.J. Scott, and G.L. Plosker, Escitalopram: A review of its use in the management of anxiety disorders. CNS Drugs, 2006. 20(9): p. 763-790.	E	a	relevant trials mentioned in submission
10	Goodman, W.K., A. Bose, and Q. Wang, Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord, 2005. 87(2-3): p. 161-7.	E	a	trial population mentioned refeers to Davidson et al, 2002, 2004 and data on file, 2002 which are all incudled in the submission .
11	Grant, J.E. and M.N. Potenza, Escitalopram treatment of pathological gambling with co-occurring anxiety: An open-label pilot study with double-blind discontinuation. International Clinical Psychopharmacology, 2006. 21(4): p. 203-209.	E	a	
12	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	
13	Lenze, E.J., et al., Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. Am J Psychiatry, 2005. 162(1): p. 146-50.	E	b	
14	Menza, M.A., R.D. Dobkin, and H. Marin, An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder [3]. Journal of Clinical Psychopharmacology, 2007. 27(2): p. 207-210.	E	a, b	
15	Mohamed, S., et al., Escitalopram for comorbid depression and anxiety in elderly patients: A 12-week, open-label, flexible-dose, pilot trial. Am J Geriatr Pharmacother, 2006. 4(3): p. 201-9.	E	a	no comparator arm

16	National Institute of Mental Health (NIMH), Drug Therapy for Generalized Anxiety Disorder Among the Elderly. 2006, July, Clinical Trials.	E	a	
17	New York State Psychiatric Institute. , F.L., Cognitive-Behavioral Therapy and Lexapro for GAD	E	a	
18	Sanofi-Aventis, An Eight-Week Study to Evaluate the Efficacy and Safety of Saredutant in Patients With Generalized Anxiety Disorder	E	b	
19	Stein, D.J., H.F. Andersen, and W.K. Goodman, Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes. Ann Clin Psychiatry, 2005. 17(2): p. 71-5.	E	a	Subgroup analysis examined; original studies included in analysis - based on Goodman
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.	E	a	
21	Thase, M.E., Treatment of anxiety disorders with venlafaxine XR. Expert Review of Neurotherapeutics, 2006. 6(3): p. 269-282.	E	b	
22	Varia, I. and F. Rauscher, Treatment of generalized anxiety disorder with citalopram. Int Clin Psychopharmacol, 2002. 17(3): p. 103-7.	E	a	

Table 18: Summary of Inclusion/Exclusion criteria for Escitalopram and Benzodiazepine Trials

		Included / Excluded	Reason for Exclusion
1	Prasko, J., et al., Influence of personality disorder on the treatment of panic disorder - Comparison study. Neuroendocrinology Letters, 2005. 26(6): p. 667-674.	E	c
2	HF, S.I., Discontinuation of Antipsychotics and Antidepressants Among Patients With BPSD. 2006.	E	c

Table 19: Summary of Inclusion/Exclusion criteria for Benzodiazepine Trials: DSM-IV

	GAD Benzo HAMA DSM-IV	Included / Excluded	Reason for Exclusion	Comments
1	Andreatini, R., et al., Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother Res, 2002. 16(7): p. 650-4.	E	c	DSM-III- R
2	Ansseau, M., et al., Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder. Psychopharmacology (Berl), 1991. 104(4): p. 439-43.	E	c	DSM-III-R
3	Ban, T.A. and M.M. Amin, Clobazam: uncontrolled and standard controlled clinical trials. Br J Clin Pharmacol, 1979. 7 Suppl 1: p. 135S-138S.	E	a	
4	Basile, A.S., A.S. Lippa, and P. Skolnick, GABAA receptor modulators as anxioselective anxiolytics. Drug Discovery Today: Therapeutic Strategies, 2006. 3(4): p. 475-481.	E	a	
5	Bobon, D.P., et al., Time-blind videotaped evaluation of injectable diazepam, lorazepam and placebo. Acta Psychiatr Belg, 1978. 78(4): p. 619-34.	E	c	
6	Borison, RL, Albrecht, JW, Diamond, BI. Efficacy and safety of a putative anxyiolitic agent: Ipsapirone. Psychopharmacology Bulletin. 1990;6(26):207-209	E	c	DSM-III
7	Boyer, WF, Feighner, JP. A placebo-controlled double-blind multicenter trial of two doses of ipsapirone versus diazepam in generalized anxiety disorder. International Clinical Psychopharmacology 1993;8:173-76	E	c	DSM-III
8	Brawman-Mintzer, O., R.G. Knapp, and P.J. Nietert, Adjunctive risperidone in generalized anxiety disorder: A double-blind, placebo-controlled study. Journal of Clinical Psychiatry, 2005. 66(10): p. 1321-1325.	E	b	
9	Casacalenda N et al. Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. Canadian Journal of Psychiatry. 1998. 43(7): 722	E	c	DSM-III

10	Centre for Reviews and Dissemination, A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder (Structured abstract). Database of Abstracts of Reviews of Effects, 2007(2).	E	a	
11	Centre for Reviews and Dissemination, Long-term pharmacological treatment of generalized anxiety disorder (Structured abstract). Database of Abstracts of Reviews of Effects, 2007(2).	E	a	
12	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. 2.	E	c	Review, DSM-III; used to identify indiviudal trials
13	Coak, AL; Reilly, J; Morris, S. Thioridazine for anxiety and depressive disorders. Cochrane Database of Systematic Reviews. 2, 2007.	E	c	DSM-III
14	Cohn, J, Rickels, K. A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. Current Medical Research and Opinion 1989;11(5):304-20	E	c	M-A; DSM-III; relevant studies already included
15	Cooper, S.J., et al., Beta 2-adrenoceptor antagonism in anxiety. Eur Neuropsychopharmacol, 1990. 1(1): p. 75-7.	E	c	DSM-III
16	Cutler, N.R., J.M. Hesselink, and J.J. Sramek, A phase II multicenter dose-finding, efficacy and safety trial of ipsapirone in outpatients with generalized anxiety disorder. Prog Neuropsychopharmacol Biol Psychiatry, 1994. 18(3): p. 447-63.	E	b	
17	DeMartinis, N, Runn, M, Rickels, K, mandos, L. Prior Benzodiazepine Use and Buspirone Response in the Treatment of Generalized Anxiety Disorder. The Journal of Clinical Psychiatry 2000;61(2): 91-94	E	c	
18	Downing, R.W. and K. Rickels, Early treatment response in anxious outpatients treated with diazepam. Acta Psychiatr Scand, 1985. 72(6): p. 522-8.	E	b	single arm study
19	Ebadi, M. and Y. Hama, Dopamine, GABA, cholecystokinin and opioids in neuroleptic-induced tardive dyskinesia. Neuroscience and Biobehavioral Reviews, 1988. 12(3-4): p. 179-187.	E	b	

20	Falissard, B., Statistical considerations about the question of a selection of discriminating centres in the analysis of clinical trial. In response to the paper: "A method for controlling for a high response rate in a comparison of venlafaxine XR and diazepan in the short-term treatment of patients with generalised anxiety disorder". Eur Psychiatry, 2003. 18(4): p. 188-9.	E	a	
21	Fontaine, R., et al., Bromazepam and diazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations. J Clin Psychopharmacol, 1983. 3(2): p. 80-7.	E	c	DSM III
22	Fontaine, R., et al., Comparison of withdrawal of buspirone and diazepam: a placebo controlled study. Prog Neuropsychopharmacol Biol Psychiatry, 1987. 11(2-3): p. 189-97.	E	a	
23	Fontaine, R., G. Chouinard, and L. Annable, Bromazepam and diazepam in generalized anxiety: A placebo-controlled study of efficacy and withdrawal. Psychopharmacology Bulletin, 1984. 20(1): p. 126-127.	E	c	DSM III
24	Fontaine, R., G. Chouinard, and L. Annable, Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. Am J Psychiatry, 1984. 141(7): p. 848-52.	E	a	
25	Forest Laboratories, Initiating Acamprosate Within Versus Post-Detoxification in the Rehabilitative Treatment of Alcohol Dependence.	E	c	trial not completed, inappropriate patient population
26	Gao, K., et al., Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: A review. Journal of Clinical Psychiatry, 2006. 67(9): p. 1327-1340.	E	b	antipsychotics
27	Goldberg, H.L. and R. Finnerty, Comparison of buspirone in two separate studies. J Clin Psychiatry, 1982. 43(12 Pt 2): p. 87-91.	E	c	DSM III
28	**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): p. 182-187.**	**I**		DSM IV

29	Heideman J, van Rijswijk E, van Lin N, de Loos S, Laurant M, Wensing M, van de Lisdonk E, Grol R. Interventions to improve management of anxiety disorders in general practice: a systematic review.British Journal of General Practice. 2005;55(520):867-874	E	a	Review
30	Jacobson, A.F., et al., Comparison of buspirone and diazepam in generalized anxiety disorder. Pharmacotherapy, 1985. 5(5): p. 290-6.	E	c	no placebo; DSM-III
31	Jesinger, D.K. and N. Gostick, Anxiety neurosis in general practice. A double-blind comparative study of diazepam and clovoxamine, a novel inhibitor of noradrenaline and serotonin reuptake. Int Clin Psychopharmacol, 1989. 4(4): p. 301-11.	E	b	
32	Kapczinski, F.L., MS; Souza, JS; Cunha, A; Schmitt, R Antidepressants for generalized anxiety disorder. Cochrane Database of Systematic Reviews, 2007. 2.	E	b	M-A
33	King Pharmaceuticals Research and Development, A Study on the Effectiveness and Safety of Diazepam Injection (Vanquix™) for Patients With Epilepsy That Receive Antiepileptic Drugs, But Still Experience Acute Repetitive Seizures (Bouts or Clusters of Seizures) That Require Treatment. 2007.	E	c	trial not completed, inappropriate patient population
34	Llorca, P.M., et al., Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: A 3-month double-blind study. Journal of Clinical Psychiatry, 2002. 63(11): p. 1020-1027.	E	b	bromazepam
35	Mahe V. et al., Long-term pharmacological treatment of generalized anxiety disorder. International Clinical psychopharmacology. 2000;15(2):99-105	E	a	M-A; individual stuides included in analysis
36	Martin JL., S.-P.M.F.T.M.-S.E.S.T.G.C., Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. Journal of Psychopharmacology, 2007. 21(7): p. 774-82.	E	a	MA - not published
37	Meoni, P., D. Hackett, and M. Lader, Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder. Depression and Anxiety, 2004. 19(2): p. 127-132.	E	a, b	Re-analysis of 5 prior trials

38	Mitte K, Noack P, Steil R, Hautzinger M. Ameta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. Journal of Clinical Psychopharmacology. 2005;25(2):141-150	E	a	DSM-III
39	Miyasaka, L.A., AN; Soares, BGO Valerian for anxiety disorders. Cochrane Database of Systematic Reviews, 2007. 2.	E	c	Review; only Andreatini relevant and this is DSM-III-R
40	Murphy, S.M., R. Owen, and P. Tyrer, Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Br J Psychiatry, 1989. 154: p. 529-34.	E	b	diazepam, buspirone, no placebo
41	Pecknold, J.C., et al., Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. Can J Psychiatry, 1989. 34(8): p. 766-71.	E	c	DSM-III
42	Pecknold, JC, Familamiri, P, Chang, H, Wilson, R, Alarcia, J, Mc-Clure, J. Buspirone: Anxiolytic?. Progress in Neuro-psychopharmacol-ogy & Biological Psychiatry 1985;9:638-642	E	c	DSM-III
43	Pomara, N., et al., Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder. Psychopharmacology (Berl), 2005. 178(1): p. 1-8.	E	c	measurement of cortisol
44	Pourmotabbed, T., et al., Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder. J Clin Psychopharmacol, 1996. 16(3): p. 202-7.	E	c	DSM-III -R
45	Power KG et al, "A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo, alone and in combination, the the treatment fo generalized anxiety disorder. J. anxiety disorder. 1990. 4(4):267-292	E	c	DSM-III
46	Rickels, K., et al., Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry, 1993. 50(11): p. 884-95.	E	c	DSM-III
47	Rickels, K., et al., Buspirone and diazepam in anxiety: a controlled study. J Clin Psychiatry, 1982. 43(12 Pt 2): p. 81-6.	E	c	DSM-III
48	Rickels, K., et al., Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial. J Clin Psychopharmacol, 1997. 17(4): p. 272-7.	E	c	DSM-III

49	Rickels, K., N. DeMartinis, and B. Aufdembrinke, A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. J Clin Psychopharmacol, 2000. 20(1): p. 12-8.	E	c	DSM-III -R
50	Rocca, P., et al., Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand, 1997. 95(5): p. 444-50.	E	b	no placebo
51	Ross, CA,Matas, M. A Clinical Trial of Buspirone and Diazepam in the Treatment of Generalized Anxiety Disorder. Canandian Journal of Psychiatry 1987;32:351-355	E	c	buspirone and diazepam, no placebo
52	Rynn, M., et al., Early response and 8-week treatment outcome in GAD. Depression and Anxiety, 2006. 23(8): p. 461-465.	E	c	DSM-III
53	Schwartz, T.L. and N. Nihalani, Tiagabine in anxiety disorders. Expert Opinion on Pharmacotherapy, 2006. 7(14): p. 1977-1987.	E	a	GABA
54	Shah, L.P., et al., A controlled double blind clinical trial of buspirone and diazepam in generalised anxiety disorder. Indian Journal of Psychiatry. Vol, 1990. 32(2): p. 166-169.	E	b	
55	Strand, M., et al., A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam. J Clin Psychiatry, 1990. 51 Suppl: p. 40-5.	E	b	buspirone and oxazepam
56	Tyrer, P. and R. Owen, Anxiety in primary care: is short-term drug treatment appropriate? J Psychiatr Res, 1984. 18(1): p. 73-8.	E	a	DSM-III, crossover trial
57	Tyrer, P., et al., The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years. Br J Psychiatry, 1993. 162: p. 219-26.	E	c	DSM-III
58	Tyrer, P., et al., The Nottingham study of neurotic disorder: comparison of drug and psychological treatments. Lancet, 1988. 332(8605): p. 235-40.	E	c	DSM-III
59	University of Utah, P.C.s.M.C.F., Intranasal Midazolam Versus Rectal Diazepam for Treatment of Seizures. 2006.	E	c	trial not completed, inappropriate patient population

60	Wingerson, D.K., et al., Effect of benzodiazepines on plasma levels of homovanillic acid in anxious patients and control subjects. Psychiatry Res, 1996. 65(1): p. 53-9.	E	b	intravenous diazepam, plasma HVA levels

Appendix 1: Article Abstracts for Escitalopram

1. Allgulander, C., I. Florea, et al. (2006). "Prevention of relapse in generalized anxiety disorder by escitalopram treatment." International Journal of Neuropsychopharmacology **9**(5): 495-505.

Escitalopram has demonstrated a robust and dose-dependent efficacy in the treatment of generalized anxiety disorder (GAD) for up to 3 months. In the present study, the efficacy and tolerability of escitalopram in the prevention of relapse in GAD was investigated. A total of 491 patients with a primary diagnosis of GAD and a Hamilton Anxiety (HAMA) total score (greater-than or equal to)20 received 12 wk of open-label treatment with a fixed dose of escitalopram (20 mg/d). Of these, 375 patients responded (HAMA total score (less-than or equal to)10) and were randomized to double-blind treatment with 20 mg/d escitalopram (n=187) or placebo (n=188). Treatment was continued for 24-76 wk unless the patient relapsed or was withdrawn for other reasons. Relapse was defined as either an increase in HAMA total score to (greater-than or equal to)15, or lack of efficacy, as judged by the investigator. The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, p<0.001). The risk of relapse was 4.04 times higher for placebo-treated patients than for escitalopram-treated patients; the proportion of patients who relapsed was statistically significantly higher in the placebo group (56%) than in the escitalopram group (19%) (p<0.001). Escitalopram was well tolerated and 7% of the escitalopram-treated patients withdrew due to adverse events, vs. 8% of the placebo patients. The incidence of discontinuation symptoms with escitalopram during tapered withdrawal was low; the symptoms primarily being dizziness (10-12%), nervousness (2-6%), and insomnia (2-6%). Escitalopram 20 mg/d significantly reduced the risk of relapse and was well tolerated in patients with GAD. Copyright (copyright) 2005 CINP.

2. Baldwin D.S. (2006). "Escitalopram and paroxetine in the treatment of generalised anxiety disorder." British Journal of Psychiatry **189**: 262-272.

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?" 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.

4. Bielski, R. J., A. Bose, et al. (2005). "A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder." Annals of Clinical Psychiatry **17**(2): 65-69.

Background. This study compared the efficacy and tolerability of escitalopram, a newer SSRI, with paroxetine in the treatment of generalized anxiety disorder (GAD). Methods. Patients with DSM-IV-defined GAD were randomized to receive 24 weeks of double-blind flexible-dose treatment with either escitalopram (10-20 mg/day) or paroxetine (20-50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in Hamilton Anxiety Scale (HAMA) scores was the primary efficacy-variable. Results. Mean baseline HAMA scores for the escitalopram (N=60) and paroxetine (N=61) groups were 23.7 and 23.4, respectively. After 24 weeks of treatment, mean changes in HAMA scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p=0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6% vs. 22.6%; p=0.02). The frequency of treatment-emergent adverse events was higher with paroxetine vs. escitalopram: overall (88.7% vs. 77.0%), insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30.0% vs. 14.8%), anorgasmia (26.2% vs. 5.9%), and decreased libido

(22.6% vs. 4.9%). Conversely, diarrhea and upper respiratory tract infection were reported more with escitalopram than paroxetine (21.3% vs. 8.1%, and 14.8% vs. 4.8%, respectively). Conclusions. These results support the use of escitalopram as a first-line treatment for GAD. Copyright (copyright) Taylor & Francis Inc.

5. Blank, S., E. J. Lenze, et al. (2006). "Outcomes of late-life anxiety disorders during 32 weeks of citalopram treatment." J Clin Psychiatry **67**(3): 468-72.

BACKGROUND: Anxiety disorders are common in later life, but little is known about the long-term benefits and risks of pharmacotherapy. METHOD: 30 patients aged 60 years and older, with a DSM-IV anxiety disorder, entered a 32-week trial of citalopram. Data gathered at baseline and follow-up included anxiety symptoms using Hamilton Rating Scale for Anxiety (HAM-A) scores, quality of life using the Medical Outcomes Study 36-item Short Form (SF-36), and sleep using the Pittsburgh Sleep Quality Index (PSQI). Data analysis consisted of mixed-effect repeated measures models of HAM-A scores and pre-post comparison of SF-36 and PSQI scores. RESULTS: 30 persons entered treatment; most (27/30) had a primary DSM-IV diagnosis of generalized anxiety disorder (2 had panic disorder; 1 had posttraumatic stress disorder). Three subjects discontinued study medication due to side effects, 5 were terminated because of nonresponse, and 5 dropped out of the study for other reasons; thus, 17 subjects (57%) completed 32 weeks of treatment. Subjects' HAM-A scores improved significantly, with continuing improvements up until about 20 weeks of treatment. On the basis of a criterion of reduction in HAM-A to < 10 during the trial, 60% (18/30) of subjects were responders. Those who completed the 32-week trial had significant improvements in sleep and quality of life-including social functioning, vitality, mental health, and role difficulties due to emotional problems. CONCLUSIONS: In this 32-week study of citalopram for elderly persons with anxiety disorders, 60% responded. Those who received a full course of treatment experience significant improvements in quality of life and sleep quality.

6. 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.

7. Davidson, J. R. T., A. Bose, et al. (2005). "Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder." Journal of Clinical Psychiatry **66**(11): 1441-1446.

Introduction: Generalized anxiety disorder (GAD) is a chronic disorder that requires long-term treatment. Escitalopram has previously been shown to be effective and well tolerated in the acute treatment of GAD. Method: Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted of escitalopram in moderate-to-severe GAD (DSM-IV criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10-20 mg/day). Data were collected from September 20, 2000, to August 15, 2002. Results: Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The mean Hamilton Rating Scale for Anxiety (HAM-A) score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continuing improvement on all anxiety and quality-of-life (QOL) scores. Of those completing 24 weeks of treatment, 92.0% were responders (Clinical Global Impressions-Improvement scale score < 2), and the mean HAM-A score in the completer analysis was 6.9; using the last observation carried forward (LOCF), 75.9% were responders, and the mean HAM-A score in the LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. No clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed. Conclusion: These results support the long-term tolerability and effectiveness of escitalopram in the treatment of GAD.

8. 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).

9. Goodman, W. K., A. Bose, et al. (2005). "Treatment of generalized anxiety disorder with escitalopram: Pooled results from double-blind, placebo-controlled trials." Journal of Affective Disorders **87**(2-3): 161-167.

Background: Escitalopram 10 mg/day is an effective and well-tolerated antidepressant. Three randomized controlled trials recently evaluated the safety and efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD). Methods: The trial designs were virtually identical, allowing data to be pooled across studies. Male and female outpatients, ages 18-80 years, with DSM-IV-defined GAD were randomized to double-blind treatment with escitalopram or placebo for 8 weeks. Escitalopram dose was fixed at 10 mg/day for the first 4 weeks, after which increases to 20 mg/day were permitted. The primary efficacy variable was the mean change from baseline in total Hamilton Anxiety Scale (HAMA) score. Results: Approximately 850 patients were randomized to double-blind treatment. In each individual study, escitalopram was significantly superior to placebo ($p<0.05$) as measured by change from baseline in HAMA score. By-visit analyses of data pooled across studies revealed significantly greater improvement ($p<0.05$) in the escitalopram group beginning at week 1 or 2 and continuing through week 8 for all primary and secondary efficacy variables. The mean change in HAMA total score from baseline to endpoint also was significantly greater for patients maintained at escitalopram 10 mg/day than for those receiving placebo. Escitalopram was generally well tolerated. Limitations: The studies included in this analysis were of short-term duration and excluded patients with significant medical and psychiatric comorbidities, such as major depressive disorder. Conclusion: Results from the individual trials and the pooled analysis demonstrate that escitalopram is effective and well tolerated for the treatment of GAD.

10. Grant, J. E. and M. N. Potenza (2006). "Escitalopram treatment of pathological gambling with co-occurring anxiety: An open-label pilot study with double-blind discontinuation." International Clinical Psychopharmacology **21**(4): 203-209.

Although co-occurring disorders are common in pathological gambling (PG), investigations of the response to pharmacotherapy in individuals with PG and co-occurring psychiatric symptomatology are limited. Thirteen subjects with DSM-IV PG and co-occurring anxiety were treated in a 12-week open-label trial of escitalopram. Subjects were assessed with the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; primary outcome measure), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impressions scale (CGI), and measures of psychosocial functioning and quality of life. Those subjects who 'responded' (defined as a 30% or greater reduction in PG-YBOCS total score at endpoint) were offered inclusion in an 8-week double-blind discontinuation phase. PG-YBOCS scores decreased from a mean of 22.2 (plus or minus) 4.5 at baseline to 11.9 (plus or minus) 10.7 at endpoint (P = 0.002) and 61.5% were responders. Scores on the HAM-A decreased by 82.8% over the 12-week period (mean of 15.9 (plus or minus) 3.2 at baseline to a mean of 2.8 (plus or minus) 3.6 at endpoint) (P < 0.001). On the CGI, 38.5% of subjects (n = 5) were 'very much improved' and 23.1% (n = 3) were 'much improved' by study endpoint. The Sheehan Disability Scale, Perceive Stress Scale and Quality of Life Inventory all showed improvement (P (less-than or equal to) 0.001, P = 0.002 and P = 0.029, respectively). The mean end-of-study dose of escitalopram was 25.4 (plus or minus) 6.6 mg/day. Of three subjects assigned to escitalopram during the discontinuation phase, none reported statistically significant worsening of gambling symptoms. However, one subject assigned to placebo reported that gambling symptoms returned within 4 weeks. Open-label escitalopram treatment was associated with improvements in gambling and anxiety symptoms and measures of psychosocial functioning and quality of life. Larger, longer, placebo-controlled, double-blind studies are needed to evaluate further the safety and tolerability of escitalopram in the treatment of PG and co-occurring anxiety. (copyright) 2006 Lippincott Williams & Wilkins.

11. 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).

12. Lenze, E. J., B. H. Mulsant, et al. (2005). "Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial." Am J Psychiatry **162**(1): 146-50.

OBJECTIVE: Anxiety disorders are highly prevalent in elderly persons. However, to date, the efficacy of selective serotonin reuptake inhibitors (SSRIs) for the treatment of anxiety disorders in this age group has not been established. METHOD: Thirty-four participants age 60 and older with a DSM-IV anxiety disorder (mainly generalized anxiety disorder) and a Hamilton Anxiety Rating Scale score of 17 or higher were randomly assigned under double-blind conditions to either citalopram or placebo. Response was defined as a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Improvement scale or a 50% reduction in the Hamilton anxiety scale score. Response and side effects with citalopram and placebo were compared by using chi-square tests and linear modeling. RESULTS: Eleven (65%) of the 17 citalopram-treated participants responded by 8 weeks, versus four (24%) of the 17 placebo-treated participants. The most common and problematic side effect in the citalopram group was sedation. CONCLUSIONS: The authors believe this to be the first prospective controlled study to test the efficacy of an SSRI in the management of anxiety disorders among the elderly. These results support the efficacy of citalopram in late-life anxiety disorders. They need to be replicated in a larger study group.

13. Menza, M. A., R. D. Dobkin, et al. (2007). "An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder [3]." Journal of Clinical Psychopharmacology **27**(2): 207-210.

14. 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.

15. 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.

16. Stein, D. J., D. S. Baldwin, et al. (2006). "Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram." Journal of Clinical Psychiatry **67**(11): 1741-1746.

Background: The placebo response rate has increased in several psychiatric disorders and is a major issue in the design and interpretation of clinical trials. The current investigation attempted to identify potential predictors of placebo response through examination of the placebo-controlled clinical trial database for escitalopram in 3 anxiety disorders and in major depressive disorder (MDD). Method: Raw data from placebo-controlled studies (conducted from 2002 through the end of 2004) of escitalopram in patients meeting DSM-IV criteria for MDD and anxiety disorders (generalized anxiety disorder [GAD], social anxiety disorder [SAD], panic disorder) were used. Potential predictors examined were type of disorder, location of study, dosing regimen, number of treatment arms, gender of patients, and duration and severity of disorder. Results: Placebo response (defined as the percent decrease from baseline in the reference scale) was higher in GAD and MDD studies conducted in Europe ($p < .0001$ and $p = .0006$, respectively) and was not associated with gender or duration of episode. In GAD, the placebo response rate was higher in a European fixed-dose study, which also had more treatment arms. In SAD and in U.S. specialist-treated MDD, a higher placebo response rate was predicted by decreased baseline disorder severity. Conclusion: Additional work is needed before definitive recommendations can be made about whether standard exclusion criteria in clinical trials of antidepressants, such as mild severity of illness, maximize medication-to-placebo differences. This analysis in a range of anxiety disorders and MDD suggests that there may be instances in which the predictors of placebo response rate themselves vary across different conditions.

17. Thase, M. E. (2006). "Treatment of anxiety disorders with venlafaxine XR." Expert Review of Neurotherapeutics **6**(3): 269-282.

When venlafaxine was introduced in 1994, it was the first of the newer generation antidepressants to be classified as a serotonin norepinephrine reuptake inhibitor (SNRI). An extended release (XR) formulation of venlafaxine, introduced in 1997, subsequently received regulatory approval for treatment of three anxiety disorders: generalized anxiety disorder, social anxiety disorder and panic disorder. Although less extensively studied, venlafaxine XR also appears to have efficacy for two other anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder. In contrast to the treatment of depression, for which meta-analyses suggest an efficacy advantage relative to selective serotonin reuptake inhibitors (SSRIs),

evidence of differential efficacy has not yet been established for any of the anxiety disorders. The overall tolerability profile of venlafaxine XR is generally comparable to that of the SSRIs, although there is greater incidence of noradrenergically mediated side effects (i.e., dry mouth and constipation), as well as a dose-dependent risk of treatment-emergent high blood pressure. Concerns about safety in overdose have also recently emerged. Despite these caveats, venlafaxine XR is an effective and generally well-tolerated option for treatment of anxiety disorders. (copyright) 2006 Future Drugs Ltd.

18. Varia, I. and F. Rauscher (2002). "Treatment of generalized anxiety disorder with citalopram." Int Clin Psychopharmacol **17**(3): 103-7.

Serotonin reuptake inhibitors (SSRI), such as venalafaxine and paroxetine, are used in the treatment of generalized anxiety disorder (GAD). Patients with GAD frequently have comorbid psychiatric disorders, such as depression. SSRIs are effective in the treatment of a variety of anxiety disorders and depression. Citalopram, a newer SSRI used in the treatment of depression, has not been studied for GAD. This is the first report of the use of citalopram, the most selective SSRI, for the treatment of GAD in a retrospective case observation study. Thirteen patients diagnosed with GAD were treated with citalopram at an academic outpatient clinic. The main outcome measures were the Hamilton Rating Scale for Anxiety (HAM-A), Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impressions of Severity (CGI-S; at baseline) and Improvement (CGI-I). The mean age of the patients was 38 years. The mean dose of citalopram at endpoint was 33 mg/day (range 10-60 mg/day). After 12 weeks of treatment with citalopram, all 13 patients experienced full or partial improvement in GAD and depressive symptoms leading to meaningful improvement in social and occupational functioning. Mean baseline HAM-A scores (mean+/-SEM) decreased from 22.2+/-1.3 to 6.2+/-0.9 after citalopram treatment. The mean CGI-I score was 1.8+/-0.2 with 11 of the 13 patients responding (CGI-I of 1 or 2). These data suggest that citalopram may be an effective treatment for GAD. Several patients who had failed previous treatment with other SSRIs responded to citalopram, suggesting that a second SSRI, such as citalopram, may be beneficial in this population. A larger placebo-controlled study of citalopram is warranted in GAD.

Appendix 2: Full list of articles from Various Databases for Escitalopram

1 EMBASE and MEDLINE

Allgulander, C., I. Florea, et al. (2006). "Prevention of relapse in generalized anxiety disorder by escitalopram treatment." International Journal of Neuropsychopharmacology **9**(5): 495-505.

Escitalopram has demonstrated a robust and dose-dependent efficacy in the treatment of generalized anxiety disorder (GAD) for up to 3 months. In the present study, the efficacy and tolerability of escitalopram in the prevention of relapse in GAD was investigated. A total of 491 patients with a primary diagnosis of GAD and a Hamilton Anxiety (HAMA) total score (greater-than or equal to)20 received 12 wk of open-label treatment with a fixed dose of escitalopram (20 mg/d). Of these, 375 patients responded (HAMA total score (less-than or equal to)10) and were randomized to double-blind treatment with 20 mg/d escitalopram (n=187) or placebo (n=188). Treatment was continued for 24-76 wk unless the patient relapsed or was withdrawn for other reasons. Relapse was defined as either an increase in HAMA total score to (greater-than or equal to)15, or lack of efficacy, as judged by the investigator. The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, p<0.001). The risk of relapse was 4.04 times higher for placebo-treated patients than for escitalopram-treated patients; the proportion of patients who relapsed was statistically significantly higher in the placebo group (56%) than in the escitalopram group (19%) (p<0.001). Escitalopram was well tolerated and 7% of the escitalopram-treated patients withdrew due to adverse events, vs. 8% of the placebo patients. The incidence of discontinuation symptoms with escitalopram during tapered withdrawal was low; the symptoms primarily being dizziness (10-12%), nervousness (2-6%), and insomnia (2-6%). Escitalopram 20 mg/d significantly reduced the risk of relapse and was well tolerated in patients with GAD. Copyright (copyright) 2005 CINP.

Bielski, R. J., A. Bose, et al. (2005). "A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder." Annals of Clinical Psychiatry **17**(2): 65-69.

Background. This study compared the efficacy and tolerability of escitalopram, a newer SSRI, with paroxetine in the treatment of generalized anxiety disorder (GAD). Methods. Patients with DSM-IV-defined GAD were randomized to receive 24 weeks of double-blind flexible-dose treatment with either escitalopram (10-20 mg/day) or paroxetine (20-50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in Hamilton Anxiety Scale (HAMA) scores was the primary efficacy-variable. Results. Mean baseline HAMA scores for the escitalopram (N=60) and paroxetine (N=61) groups were 23.7 and 23.4, respectively. After 24 weeks of treatment, mean changes in HAMA scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p=0.13).

Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6% vs. 22.6%; p=0.02). The frequency of treatment-emergent adverse events was higher with paroxetine vs. escitalopram: overall (88.7% vs. 77.0%), insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30.0% vs. 14.8%), anorgasmia (26.2% vs. 5.9%), and decreased libido (22.6% vs. 4.9%). Conversely, diarrhea and upper respiratory tract infection were reported more with escitalopram than paroxetine (21.3% vs. 8.1%, and 14.8% vs. 4.8%, respectively). Conclusions. These results support the use of escitalopram as a first-line treatment for GAD. Copyright (copyright) Taylor & Francis Inc.

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.

Davidson, J. R. T., A. Bose, et al. (2005). "Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder." Journal of Clinical Psychiatry **66**(11): 1441-1446.

Introduction: Generalized anxiety disorder (GAD) is a chronic disorder that requires long-term treatment. Escitalopram has previously been

shown to be effective and well tolerated in the acute treatment of GAD. Method: Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted of escitalopram in moderate-to-severe GAD (DSM-IV criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10-20 mg/day). Data were collected from September 20, 2000, to August 15, 2002. Results: Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The mean Hamilton Rating Scale for Anxiety (HAM-A) score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continuing improvement on all anxiety and quality-of-life (QOL) scores. Of those completing 24 weeks of treatment, 92.0% were responders (Clinical Global Impressions-Improvement scale score < 2), and the mean HAM-A score in the completer analysis was 6.9; using the last observation carried forward (LOCF), 75.9% were responders, and the mean HAM-A score in the LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. No clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed. Conclusion: These results support the long-term tolerability and effectiveness of escitalopram in the treatment of GAD.

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).

Goodman, W. K., A. Bose, et al. (2005). "Treatment of generalized anxiety disorder with escitalopram: Pooled results from double-blind, placebo-controlled trials." Journal of Affective Disorders **87**(2-3): 161-167.

Background: Escitalopram 10 mg/day is an effective and well-tolerated antidepressant. Three randomized controlled trials recently evaluated the safety and efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD). Methods: The trial designs were virtually identical, allowing data to be pooled across studies. Male and female outpatients, ages 18-80 years, with DSM-IV-defined GAD were randomized to double-blind treatment with escitalopram or placebo for 8 weeks. Escitalopram dose was fixed at 10 mg/day for the first 4 weeks, after which increases to 20 mg/day were permitted. The primary efficacy variable was the mean change from baseline in total Hamilton Anxiety Scale (HAMA) score. Results: Approximately 850 patients were randomized to double-blind treatment. In each individual study, escitalopram was significantly superior to placebo ($p<0.05$) as measured by change from baseline in HAMA score. By-visit analyses of data pooled across studies revealed significantly greater improvement ($p<0.05$) in the escitalopram group beginning at week 1 or 2 and continuing through week 8 for all primary and secondary efficacy variables. The mean change in HAMA total score from baseline to endpoint also was significantly greater for patients maintained at escitalopram 10 mg/day than for those receiving placebo. Escitalopram was generally well tolerated. Limitations: The studies included in this analysis were of short-term duration and excluded patients with significant medical and psychiatric comorbidities, such as major depressive disorder. Conclusion: Results from the individual trials and the pooled analysis demonstrate that escitalopram is effective and well tolerated for the treatment of GAD. (copyright) 2005 Elsevier B.V. All rights reserved.

Grant, J. E. and M. N. Potenza (2006). "Escitalopram treatment of pathological gambling with co-occurring anxiety: An open-label pilot study with double-blind discontinuation." International Clinical Psychopharmacology **21**(4): 203-209.

Although co-occurring disorders are common in pathological gambling (PG), investigations of the response to pharmacotherapy in individuals with PG and co-occurring psychiatric symptomatology are limited. Thirteen subjects with DSM-IV PG and co-occurring anxiety were treated in a 12-week open-label trial of escitalopram. Subjects were assessed with the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; primary outcome measure), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impressions scale (CGI), and measures of psychosocial functioning and quality of life. Those subjects who 'responded' (defined as a 30% or greater reduction in PG-YBOCS total score at endpoint) were offered inclusion in an 8-week double-blind discontinuation phase. PG-YBOCS scores decreased from a mean of 22.2 (plus or minus) 4.5 at baseline to 11.9 (plus or minus) 10.7 at endpoint ($P = 0.002$) and 61.5% were responders. Scores on the HAM-A decreased by 82.8% over the 12-week period (mean of 15.9 (plus or minus) 3.2 at baseline to a mean of 2.8 (plus or minus) 3.6 at endpoint) ($P < 0.001$). On the CGI, 38.5% of subjects ($n = 5$) were 'very much improved' and 23.1% ($n = 3$) were

'much improved' by study endpoint. The Sheehan Disability Scale, Perceive Stress Scale and Quality of Life Inventory all showed improvement (P (less-than or equal to) 0.001, P = 0.002 and P = 0.029, respectively). The mean end-of-study dose of escitalopram was 25.4 (plus or minus) 6.6 mg/day. Of three subjects assigned to escitalopram during the discontinuation phase, none reported statistically significant worsening of gambling symptoms. However, one subject assigned to placebo reported that gambling symptoms returned within 4 weeks. Open-label escitalopram treatment was associated with improvements in gambling and anxiety symptoms and measures of psychosocial functioning and quality of life. Larger, longer, placebo-controlled, double-blind studies are needed to evaluate further the safety and tolerability of escitalopram in the treatment of PG and co-occurring anxiety. (copyright) 2006 Lippincott Williams & Wilkins.

Menza, M. A., R. D. Dobkin, et al. (2007). "An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder [3]." Journal of Clinical Psychopharmacology **27**(2): 207-210.

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.

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.

Stein, D. J., D. S. Baldwin, et al. (2006). "Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram." Journal of Clinical Psychiatry **67**(11): 1741-1746.

Background: The placebo response rate has increased in several psychiatric disorders and is a major issue in the design and interpretation of clinical trials. The current investigation attempted to

identify potential predictors of placebo response through examination of the placebo-controlled clinical trial database for escitalopram in 3 anxiety disorders and in major depressive disorder (MDD). Method: Raw data from placebo-controlled studies (conducted from 2002 through the end of 2004) of escitalopram in patients meeting DSM-IV criteria for MDD and anxiety disorders (generalized anxiety disorder [GAD], social anxiety disorder [SAD], panic disorder) were used. Potential predictors examined were type of disorder, location of study, dosing regimen, number of treatment arms, gender of patients, and duration and severity of disorder. Results: Placebo response (defined as the percent decrease from baseline in the reference scale) was higher in GAD and MDD studies conducted in Europe ($p < .0001$ and $p = .0006$, respectively) and was not associated with gender or duration of episode. In GAD, the placebo response rate was higher in a European fixed-dose study, which also had more treatment arms. In SAD and in U.S. specialist-treated MDD, a higher placebo response rate was predicted by decreased baseline disorder severity. Conclusion: Additional work is needed before definitive recommendations can be made about whether standard exclusion criteria in clinical trials of antidepressants, such as mild severity of illness, maximize medication-to-placebo differences. This analysis in a range of anxiety disorders and MDD suggests that there may be instances in which the predictors of placebo response rate themselves vary across different conditions.

Thase, M. E. (2006). "Treatment of anxiety disorders with venlafaxine XR." Expert Review of Neurotherapeutics **6**(3): 269-282.

When venlafaxine was introduced in 1994, it was the first of the newer generation antidepressants to be classified as a serotonin norepinephrine reuptake inhibitor (SNRI). An extended release (XR) formulation of venlafaxine, introduced in 1997, subsequently received regulatory approval for treatment of three anxiety disorders: generalized anxiety disorder, social anxiety disorder and panic disorder. Although less extensively studied, venlafaxine XR also appears to have efficacy for two other anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder. In contrast to the treatment of depression, for which meta-analyses suggest an efficacy advantage relative to selective serotonin reuptake inhibitors (SSRIs), evidence of differential efficacy has not yet been established for any of the anxiety disorders. The overall tolerability profile of venlafaxine XR is generally comparable to that of the SSRIs, although there is greater incidence of noradrenergically mediated side effects (i.e., dry mouth and constipation), as well as a dose-dependent risk of treatment-emergent high blood pressure. Concerns about safety in overdose have also recently emerged. Despite these caveats, venlafaxine XR is an effective and generally well-tolerated option for treatment of anxiety disorders. (copyright) 2006 Future Drugs Ltd.

2 PubMed

Allgulander, C., I. Florea, et al. (2006). "Prevention of relapse in generalized anxiety disorder by escitalopram treatment." Int J Neuropsychopharmacol **9**(5): 495-505.

Escitalopram has demonstrated a robust and dose-dependent efficacy in the treatment of generalized anxiety disorder (GAD) for up to 3 months. In the present study, the efficacy and tolerability of escitalopram in the prevention of relapse in GAD was investigated. A total of 491 patients with a primary diagnosis of GAD and a Hamilton Anxiety (HAMA) total score>or=20 received 12 wk of open-label treatment with a fixed dose of escitalopram (20 mg/d). Of these, 375 patients responded (HAMA total score<or=10) and were randomized to double-blind treatment with 20 mg/d escitalopram (n=187) or placebo (n=188). Treatment was continued for 24-76 wk unless the patient relapsed or was withdrawn for other reasons. Relapse was defined as either an increase in HAMA total score to >or=15, or lack of efficacy, as judged by the investigator. The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, p<0.001). The risk of relapse was 4.04 times higher for placebo-treated patients than for escitalopram-treated patients; the proportion of patients who relapsed was statistically significantly higher in the placebo group (56%) than in the escitalopram group (19%) (p<0.001). Escitalopram was well tolerated and 7% of the escitalopram-treated patients withdrew due to adverse events, vs. 8% of the placebo patients. The incidence of discontinuation symptoms with escitalopram during tapered withdrawal was low; the symptoms primarily being dizziness (10-12%), nervousness (2-6%), and insomnia (2-6%). Escitalopram 20 mg/d significantly reduced the risk of relapse and was well tolerated in patients with GAD.

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.

Bielski, R. J., A. Bose, et al. (2005). "A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder." Ann Clin Psychiatry **17**(2): 65-9.

BACKGROUND: This study compared the efficacy and tolerability of escitalopram, a newer SSRI, with paroxetine in the treatment of generalized anxiety disorder (GAD). METHODS: Patients with DSM-IV-defined GAD were randomized to receive 24 weeks of double-blind flexible-dose treatment with either escitalopram (10-20 mg/day) or paroxetine (20-50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in Hamilton Anxiety Scale (HAMA) scores was the primary efficacy variable. RESULTS: Mean baseline HAMA scores for the escitalopram (N = 60) and paroxetine (N = 61) groups were 23.7 and 23.4, respectively. After 24 weeks of treatment, mean changes in HAMA scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p = 0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6% vs. 22.6%; p = 0.02). The frequency of treatment-emergent adverse events was higher with paroxetine vs. escitalopram: overall (88.7% vs. 77.0%), insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30.0% vs. 14.8%), anorgasmia (26.2% vs. 5.9%), and decreased libido (22.6% vs. 4.9%). Conversely, diarrhea and upper respiratory tract infection were reported more with escitalopram than paroxetine (21.3% vs. 8.1%, and 14.8% vs. 4.8%, respectively). CONCLUSIONS: These results support the use of escitalopram as a first-line treatment for GAD.

Blank, S., E. J. Lenze, et al. (2006). "Outcomes of late-life anxiety disorders during 32 weeks of citalopram treatment." J Clin Psychiatry **67**(3): 468-72.

BACKGROUND: Anxiety disorders are common in later life, but little is known about the long-term benefits and risks of pharmacotherapy. METHOD: 30 patients aged 60 years and older, with a DSM-IV anxiety disorder, entered a 32-week trial of citalopram. Data gathered at baseline and follow-up included anxiety symptoms using Hamilton Rating Scale for Anxiety (HAM-A) scores, quality of life using the Medical Outcomes Study 36-item Short Form (SF-36), and sleep using the Pittsburgh Sleep Quality Index (PSQI). Data analysis consisted of mixed-effect repeated measures models of HAM-A scores and pre-post comparison of SF-36 and PSQI scores. RESULTS: 30 persons entered treatment; most (27/30) had a primary DSM-IV diagnosis of generalized anxiety disorder (2 had panic disorder; 1 had posttraumatic stress disorder). Three subjects discontinued study medication due to side effects, 5 were terminated because of nonresponse, and 5 dropped out of the study for other reasons; thus, 17 subjects (57%) completed 32 weeks of treatment. Subjects' HAM-A scores improved significantly, with continuing improvements up until about 20 weeks of treatment. On the basis of a criterion of reduction in HAM-A to < 10 during the trial, 60% (18/30) of subjects were responders. Those who completed the 32-week trial had significant improvements in sleep and quality of life-including social functioning, vitality, mental health, and role difficulties due to emotional problems. CONCLUSIONS: In this 32-week study of citalopram for elderly persons with anxiety disorders, 60% responded. Those who received a full course of treatment experience significant improvements in quality of life and sleep quality.

Davidson, J. R., A. Bose, et al. (2004). "Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study." Depress Anxiety **19**(4): 234-40.

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 > or = 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.

Davidson, J. R., A. Bose, et al. (2005). "Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder." J Clin Psychiatry **66**(11): 1441-6.

INTRODUCTION: Generalized anxiety disorder (GAD) is a chronic disorder that requires long-term treatment. Escitalopram has previously been shown to be effective and well tolerated in the acute treatment of GAD. METHOD: Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted of escitalopram in moderate-to-severe GAD (DSM-IV criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10-20 mg/day). Data were collected from September 20, 2000, to August 15, 2002. RESULTS: Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The mean Hamilton Rating Scale for Anxiety (HAM-A) score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continuing improvement on all anxiety and quality-of-life (QOL) scores. Of those completing 24 weeks of treatment, 92.0% were responders (Clinical Global Impressions-Improvement scale score < or = 2), and the mean HAM-A score in the completed analysis was 6.9; using the last observation carried forward (LOCF), 75.9% were responders, and the mean HAM-A score in the LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. No clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed. CONCLUSION: These results support the long-term tolerability and effectiveness of escitalopram in the treatment of GAD.

Goodman, W. K., A. Bose, et al. (2005). "Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials." J Affect Disord **87**(2-3): 161-7.

BACKGROUND: Escitalopram 10 mg/day is an effective and well-tolerated antidepressant. Three randomized controlled trials recently evaluated the safety and efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD). METHODS: The trial designs were virtually identical, allowing data to be pooled across studies. Male and female outpatients, ages 18-80 years, with DSM-IV-defined GAD were randomized to double-blind treatment with escitalopram or placebo for 8 weeks. Escitalopram dose was fixed at 10 mg/day for the first 4 weeks, after which increases to 20 mg/day were permitted. The primary efficacy variable was the mean change from baseline in total Hamilton

Anxiety Scale (HAMA) score. RESULTS: Approximately 850 patients were randomized to double-blind treatment. In each individual study, escitalopram was significantly superior to placebo ($p<0.05$) as measured by change from baseline in HAMA score. By-visit analyses of data pooled across studies revealed significantly greater improvement ($p<0.05$) in the escitalopram group beginning at week 1 or 2 and continuing through week 8 for all primary and secondary efficacy variables. The mean change in HAMA total score from baseline to endpoint also was significantly greater for patients maintained at escitalopram 10 mg/day than for those receiving placebo. Escitalopram was generally well tolerated. LIMITATIONS: The studies included in this analysis were of short-term duration and excluded patients with significant medical and psychiatric comorbidities, such as major depressive disorder. CONCLUSION: Results from the individual trials and the pooled analysis demonstrate that escitalopram is effective and well tolerated for the treatment of GAD.

Lenze, E. J., B. H. Mulsant, et al. (2005). "Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial." Am J Psychiatry **162**(1): 146-50.

OBJECTIVE: Anxiety disorders are highly prevalent in elderly persons. However, to date, the efficacy of selective serotonin reuptake inhibitors (SSRIs) for the treatment of anxiety disorders in this age group has not been established. METHOD: Thirty-four participants age 60 and older with a DSM-IV anxiety disorder (mainly generalized anxiety disorder) and a Hamilton Anxiety Rating Scale score of 17 or higher were randomly assigned under double-blind conditions to either citalopram or placebo. Response was defined as a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Improvement scale or a 50% reduction in the Hamilton anxiety scale score. Response and side effects with citalopram and placebo were compared by using chi-square tests and linear modeling. RESULTS: Eleven (65%) of the 17 citalopram-treated participants responded by 8 weeks, versus four (24%) of the 17 placebo-treated participants. The most common and problematic side effect in the citalopram group was sedation. CONCLUSIONS: The authors believe this to be the first prospective controlled study to test the efficacy of an SSRI in the management of anxiety disorders among the elderly. These results support the efficacy of citalopram in late-life anxiety disorders. They need to be replicated in a larger study group.

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." Am J Geriatr Pharmacother **4**(3): 201-9.

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 > or =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 > or =4 weeks and had a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of >22 and a Hamilton Rating Scale for Anxiety (HAM-A) score of > or =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 also found (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.

Stein, D. J., H. F. Andersen, et al. (2005). "Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes." Ann Clin Psychiatry **17**(2): 71-5.

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.

Varia, I. and F. Rauscher (2002). "Treatment of generalized anxiety disorder with citalopram." Int Clin Psychopharmacol **17**(3): 103-7.

Serotonin reuptake inhibitors (SSRI), such as venalafaxine and paroxetine, are used in the treatment of generalized anxiety disorder (GAD). Patients with GAD frequently have comorbid psychiatric disorders, such as depression. SSRIs are effective in the treatment of a variety of anxiety disorders and depression. Citalopram, a newer SSRI used in the treatment of depression, has not been studied for GAD. This is the first report of the use of citalopram, the most selective SSRI, for the treatment of GAD in a retrospective case observation study. Thirteen patients diagnosed with GAD were treated with citalopram at an academic outpatient clinic. The main outcome measures were the Hamilton Rating Scale for Anxiety (HAM-A), Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impressions of Severity (CGI-S; at baseline) and Improvement (CGI-I). The mean age of the patients was 38 years. The mean dose of citalopram at endpoint was 33 mg/day (range 10-60 mg/day). After 12 weeks of treatment with citalopram, all 13 patients experienced full or partial improvement in GAD and depressive symptoms leading to meaningful improvement in social and occupational functioning. Mean baseline HAM-A scores (mean+/-SEM) decreased from 22.2+/-1.3 to 6.2+/-0.9 after citalopram treatment. The mean CGI-I score was 1.8+/-0.2 with 11 of the 13 patients responding (CGI-I of 1 or 2). These data suggest that citalopram may be an effective treatment for GAD. Several patients who had failed previous treatment with other SSRIs responded to citalopram, suggesting that a second SSRI, such as citalopram, may be beneficial in this population. A larger placebo-controlled study of citalopram is warranted in GAD.

3 EBM Databases (Cochrane)

Allgulander C, F. I., Huusom AK (2006). "Prevention of relapse in generalized anxiety disorder by escitalopram treatment." The international journal of neuropsychopharmacology **9**(5): 495-505.

Escitalopram has demonstrated a robust and dose-dependent efficacy in the treatment of generalized anxiety disorder (GAD) for up to 3 months. In the present study, the efficacy and tolerability of escitalopram in the prevention of relapse in GAD was investigated. A total of 491 patients with a primary diagnosis of GAD and a Hamilton Anxiety (HAMA) total score>or=20 received 12 wk of open-label treatment with a fixed dose of escitalopram (20 mg/d). Of these, 375 patients responded (HAMA total score<or=10) and were randomized to double-blind treatment with 20 mg/d escitalopram (n=187) or placebo (n=188). Treatment was continued for 24-76 wk unless the patient relapsed or was withdrawn for other reasons. Relapse was defined as either an increase in HAMA total score to >or=15, or lack of efficacy, as judged by the investigator. The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, p<0.001). The risk of relapse was 4.04 times higher for placebo-treated patients than for escitalopram-treated patients; the proportion of patients who relapsed was statistically significantly higher in the placebo group (56%) than in the escitalopram group (19%) (p<0.001). Escitalopram was well tolerated and 7% of the escitalopram-treated patients withdrew due to adverse events, vs. 8% of the placebo patients. The incidence of discontinuation symptoms with escitalopram during tapered withdrawal was low; the symptoms primarily being dizziness (10-12%), nervousness (2-6%), and insomnia (2-6%). Escitalopram 20 mg/d significantly reduced the risk of relapse and was well tolerated in patients with GAD.

Bielski RJ, B. A., Chang CC (2005). "A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder." Annals of clinical psychiatry **17**(2): 65-69.

BACKGROUND: This study compared the efficacy and tolerability of escitalopram, a newer SSRI, with paroxetine in the treatment of generalized anxiety disorder (GAD). METHODS: Patients with DSM-IV-defined GAD were randomized to receive 24 weeks of double-blind flexible-dose treatment with either escitalopram (10-20 mg/day) or paroxetine (20-50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in Hamilton Anxiety Scale (HAMA) scores was the primary efficacy variable. RESULTS: Mean baseline HAMA scores for the escitalopram (N = 60) and paroxetine (N = 61) groups were 23.7 and 23.4, respectively. After 24 weeks of treatment, mean changes in HAMA scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p = 0.13). Significantly fewer patients withdrew from

escitalopram than paroxetine treatment due to adverse events (6.6% vs. 22.6%; p = 0.02). The frequency of treatment-emergent adverse events was higher with paroxetine vs. escitalopram: overall (88.7% vs. 77.0%), insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30.0% vs. 14.8%), anorgasmia (26.2% vs. 5.9%), and decreased libido (22.6% vs. 4.9%). Conversely, diarrhea and upper respiratory tract infection were reported more with escitalopram than paroxetine (21.3% vs. 8.1%, and 14.8% vs. 4.8%, respectively). CONCLUSIONS: These results support the use of escitalopram as a first-line treatment for GAD.

Davidson JR, B. A., Korotzer A, Zheng H (2004). "Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study." Depression and anxiety. **19**(4): 234-40.

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 > or = 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.

Goodman WK, B. A., Wang Q (2005). " Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials." Journal of affective disorders **87**(2-3): 161-7.

BACKGROUND: Escitalopram 10 mg/day is an effective and well-tolerated antidepressant. Three randomized controlled trials recently evaluated the safety and efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD). METHODS: The trial designs were virtually identical, allowing data to be pooled across studies. Male and

female outpatients, ages 18-80 years, with DSM-IV-defined GAD were randomized to double-blind treatment with escitalopram or placebo for 8 weeks. Escitalopram dose was fixed at 10 mg/day for the first 4 weeks, after which increases to 20 mg/day were permitted. The primary efficacy variable was the mean change from baseline in total Hamilton Anxiety Scale (HAMA) score. RESULTS: Approximately 850 patients were randomized to double-blind treatment. In each individual study, escitalopram was significantly superior to placebo ($p<0.05$) as measured by change from baseline in HAMA score. By-visit analyses of data pooled across studies revealed significantly greater improvement ($p<0.05$) in the escitalopram group beginning at week 1 or 2 and continuing through week 8 for all primary and secondary efficacy variables. The mean change in HAMA total score from baseline to endpoint also was significantly greater for patients maintained at escitalopram 10 mg/day than for those receiving placebo. Escitalopram was generally well tolerated. LIMITATIONS: The studies included in this analysis were of short-term duration and excluded patients with significant medical and psychiatric comorbidities, such as major depressive disorder. CONCLUSION: Results from the individual trials and the pooled analysis demonstrate that escitalopram is effective and well tolerated for the treatment of GAD.

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).

Stein DJ, A. H., Goodman WK (2005). " Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes." Annals of clinical psychiatry **17**(2): 71-5.

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.

4 Conference Papers Index

Davidson, J. Bose., A; Wang, Q (2005). "Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder." Journal of Clinical Psychiatry **66**(11): 1441-1446.

Introduction: Generalized anxiety disorder (GAD) is a chronic disorder that requires long-term treatment. Escitalopram has previously been shown to be effective and well tolerated in the acute treatment of GAD. Method: Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted of escitalopram in moderateto-severe GAD (DSM-IV criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10-20 mg/day). Data were collected from September 20, 2000, to August 15, 2002. Results: Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The mean Hamilton Rating Scale for Anxiety (HAM-A) score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continuing improvement on all anxiety and quality-of-life (QOL) scores. Of those completing 24 weeks of treatment, 92.0% were responders (Clinical Global impressions-Improvement scale score :5 2), and the mean HAM-A score in the completer analysis was 6.9; using the last observation carried forward (LOCF), 75.9% were responders, and the mean HAM-A score in the LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. No clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed. Conclusion: These results support the longterm tolerability and effectiveness of escitalopram in the treatment of GAD.

5 Clinical Trials

Bristol-Myers Squibb (2007). "Study of Pexacerfont (BMS-562086) in the Treatment of Outpatients With Generalized Anxiety Disorder."

Purpose

The purpose of this study is to learn about the safety and efficacy of pexacerfont in outpatients diagnosed with Generalized Anxiety Disorder

Forest Laboratories (2005). "Cognitive-Behavioral Therapy and Lexapro for GAD."

Purpose

The goals of this pilot study are as follows:

1) To disseminate and examine the effectiveness of a manualized, individual, cognitive-behavioral psychotherapy (CBT) for adults with Generalized Anxiety Disorder(GAD), 2) to test the effectiveness of augmentation (the addition of) antidepressant therapy in participants who do not fully respond to CBT, and 3) to examine individual and clinical predictors of non-response to CBT and predictors of response to augmentation antidepressant therapy. A related goal is to examine the maintenance of treatment gains obtained from CBT alone and CBT with augmentation antidepressant therapy, over a twenty-four month follow-up period. This study will serve as a pilot investigation in preparation for a larger federally funded study using this treatment approach. We hypothesize that CBT will result in remission (no longer having GAD) and/or high endstate functioning (clinically meaningful improvement) in approximately 40-50% of participants. Further, we hypothesize that augmentation antidepressant therapy in participants who do not fully respond to CBT will result in further clinically significant improvement.

National Institute of Mental Health (NIMH) (2006). "Drug Therapy for Generalized Anxiety Disorder Among the Elderly."

Purpose

This study will determine the effectiveness of escitalopram (Lexapro®), an anti-anxiety drug, for generalized anxiety disorder (GAD) and the ways genetics affect response to treatment for GAD in elderly individuals.

Sanofi-Aventis (2007). "An Eight-Week Study to Evaluate the Efficacy and Safety of Saredutant in Patients With Generalized Anxiety Disorder."

Purpose

The primary objective is to evaluate the efficacy of a 100 mg dose of saredutant compared to placebo in patients with generalized anxiety disorder. The secondary objectives are to evaluate the efficacy of

saredutant on disability and quality of life in patients with generalized anxiety disorder, and to evaluate blood levels of saredutant.

Appendix 3: Article Abstracts for Escitalopram and Benzodiazepines

HF, S. I. (2006). "Discontinuation of Antipsychotics and Antidepressants Among Patients With BPSD."

Purpose

The aim of this study is to discontinue antipsychotics and antidepressants, and to study its effect on Behavioural- and Psychological Symptoms in Dementia (BPSD).

Prasko, J., P. Houbova, et al. (2005). "Influence of personality disorder on the treatment of panic disorder - Comparison study." Neuroendocrinology Letters **26**(6): 667-674.

Most clinicians tend to believe that the occurrence of the anxiety disorder in comorbidity with a personality disorder often leads to longer treatment, worsens the prognosis, and thus increasing treatment costs. The study is designed to compare the short-term effectiveness of combination of cognitive behavioral therapy and pharmacotherapy in patient suffering with panic disorder with and without personality disorder. Method: We compare the efficacy of 6th week therapeutic progr am and 6th week follow up in patients suffering with panic disorder and/or agoraphobia and comorbid personality disorder (29 patients) and panic disorder and/or agoraphobia without comorbid personality disorder (31 patients). Diagnosis was done according to the ICD-10 research diagnostic criteria confirmed with MINI and support with psychological methods: IPDE, MCMI-III and TCI. Patients were treated with CBT and psychopharmacs. They were regularly assessed in week 0, 2, 4, 6 and 12 by an independent reviewer on the CGI (Clinical Global Improvement) for severity and change, PDSS (Panic Disorder Severity Scale), HAMA (Hamilton Anxiety Rating Scale), SDS (Sheehan Disability Scale), HDRS (Hamilton Depression Rating Scale), and in self-assessments BAI (Beck Anxiety Inventory) and BDI (Beck Depression Inventory). Results: A comb ination of CBT and pharmacotherapy proved to be the effective treatment of patients suffering with panic disorder and/or agoraphobia with or without comorbid personality disorder. The 12th week treatment efficacy in the patients with panic disorder without personality disorder had been showed significantly better compared with the group with panic disorder comorbid with personality disorder in CGI and specific inventory for panic disorder - PDSS. Also the scores in depression inventories HDRS and BDI showed significantly higher decrease during the treatment comparing with group without personality disorder. But the treatment effect between groups did not differ in objective anxiety scale HAMA, and subjective anxiety scale BAI. (copyright) Neuroendocrinology Letters.

Appendix 4: Full list of articles from Various Databases for Escitalopram and Benzodiazepines

1 Embase + Medline

Prasko, J., P. Houbova, et al. (2005). "Influence of personality disorder on the treatment of panic disorder - Comparison study." Neuroendocrinology Letters **26**(6): 667-674.

Most clinicians tend to believe that the occurrence of the anxiety disorder in comorbidity with a personality disorder often leads to longer treatment, worsens the prognosis, and thus increasing treatment costs. The study is designed to compare the short-term effectiveness of combination of cognitive behavioral therapy and pharmacotherapy in patient suffering with panic disorder with and without personality disorder. Method: We compare the efficacy of 6th week therapeutic progr am and 6th week follow up in patients suffering with panic disorder and/or agoraphobia and comorbid personality disorder (29 patients) and panic disorder and/or agoraphobia without comorbid personality disorder (31 patients). Diagnosis was done according to the ICD-10 research diagnostic criteria confirmed with MINI and support with psychological methods: IPDE, MCMI-III and TCI. Patients were treated with CBT and psychopharmacs. They were regularly assessed in week 0, 2, 4, 6 and 12 by an independent reviewer on the CGI (Clinical Global Improvement) for severity and change, PDSS (Panic Disorder Severity Scale), HAMA (Hamilton Anxiety Rating Scale), SDS (Sheehan Disability Scale), HDRS (Hamilton Depression Rating Scale), and in self-assessments BAI (Beck Anxiety Inventory) and BDI (Beck Depression Inventory). Results: A comb ination of CBT and pharmacotherapy proved to be the effective treatment of patients suffering with panic disorder and/or agoraphobia with or without comorbid personality disorder. The 12th week treatment efficacy in the patients with panic disorder without personality disorder had been showed significantly better compared with the group with panic disorder comorbid with personality disorder in CGI and specific inventory for panic disorder - PDSS. Also the scores in depression inventories HDRS and BDI showed significantly higher decrease during the treatment comparing with group without personality disorder. But the treatment effect between groups did not differ in objective anxiety scale HAMA, and subjective anxiety scale BAI. (copyright) Neuroendocrinology Letters.

2 Clinical Trials

Oxazepam and Escitalopram

HF, S. I. (2006). "Discontinuation of Antipsychotics and Antidepressants Among Patients With BPSD."

Purpose

The aim of this study is to discontinue antipsychotics and antidepressants, and to study its effect on Behavioural- and Psychological Symptoms in Dementia (BPSD).

Appendix 5: Article Abstracts for Benzodiazepines: DSM –IV

1. Andreatini, R., V. A. Sartori, et al. (2002). "Effect of valepotriates (valerian extract) in generalized anxiety disorder: A randomized placebo-controlled pilot study." Phytotherapy Research **16**(7): 650-654.

The aim of the present study was to carry out a controlled pilot study on the putative anxiolytic effect of valepotriates. Thirty-six outpatients with generalized anxiety disorder (DSM III-R), after a 2-week wash-out, were randomized to one of the following three treatments for 4 weeks (n = 12 per group): valepotriates (mean daily dose: 81.3 mg), diazepam (mean daily dose: 6.5 mg), or placebo. A parallel, double-blind, flexible-dose, placebo-controlled design was employed. No significant difference was observed among the three groups at baseline or in the change from baseline on the Hamilton anxiety scale (HAM-A) or in the trait part of the state-trait anxiety inventory (STAI-trait). Moreover, the three groups presented a significant reduction in the total HAM-A scores. On the other hand, only the diazepam and valepotriates groups showed a significant reduction in the psychic factor of HAM-A. The diazepam group also presented a significant reduction of the STAI-trait. Although the principal analysis (HAM-A between group comparison) found negative results (probably due to the small sample size in each group), the preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. However, since the number of subjects per group was very small, the present results must be viewed as preliminary. Thus, further studies addressing this issue are warranted. Copyright (copyright) 2002 John Wiley & Sons, Ltd.

2. Ansseau, M., J. P. Olie, et al. (1991). "Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder." Psychopharmacology (Berl) **104**(4): 439-43.

The anxiolytic activity and tolerance of four doses of suriclone (0.1, 0.2, 0.3 and 0.4 mg tid), diazepam (5 mg tid), and placebo were compared in six parallel groups of 54-59 outpatients with generalized anxiety disorder (DSM III-R). After a 1-week placebo run-in period, the patients were treated for 4 weeks, with assessments at baseline and after 1, 2, and 4 weeks by the Hamilton anxiety scale and the Clinical Global Impressions. Results showed better improvement with active drugs as compared to placebo, without significant differences among the four different doses of suriclone and diazepam. The number of adverse events, particularly drowsiness, was significantly higher with diazepam than with suriclone, particularly 0.1 and 0.2 mg tid which did not differ from placebo. These results demonstrate that suriclone at daily doses ranging from 0.1 to 0.4 mg tid is an effective anxiolytic, better tolerated than diazepam.

3. Ban, T. A. and M. M. Amin (1979). "Clobazam: uncontrolled and standard controlled clinical trials." Br J Clin Pharmacol **7 Suppl 1**: 135S-138S.

1 In an uncontrolled clinical trial, carried out in 11 psychiatric patients with the clinical diagnoses of anxiety neurosis and depressive neurosis, clobazam, a new benzodiazepine preparation, in the dosage range 10-60 mg daily produced statistically significant improvement in the total and both factor scores of the Hamilton Anxiety Scale (HAM-A). The lowest mean total HAM-A scores occurred with a mean clobazam dosage of 48 mg daily. 2 Results of the uncontrolled clinical trial were further substantiated in a standard-controlled clinical study in which no statistically significant difference between the therapeutic effectiveness of clobazam and diazepam could be revealed. The lowest mean total HAM-A scores occurred with a mean clobazam dosage of 49 mg daily. There was a lower incidence of adverse effects reported in patients receiving clobazam than in those taking the control drug (diazepam).

4. Basile, A. S., A. S. Lippa, et al. (2006). "GABAA receptor modulators as anxioselective anxiolytics." Drug Discovery Today: Therapeutic Strategies **3**(4): 475-481.

Benzodiazepines are effective anxiolytics whose use is limited by sedation, amnesia and myorelaxation, driving the search for novel, anxioselective GABAA receptor modulators. Preclinical data from 'knock-in' mice and (alpha)2,3-subunit selective GABAA receptor agonists suggest that these targets may yield anxioselective agents. In contrast, additional preclinical and clinical evidence suggests that a combination of mechanisms, including partial agonism and receptor subtype selectivity, will be required to achieve anxioselectivity in the clinic. (copyright) 2006 Elsevier Ltd. All rights reserved.

5. Bobon, D. P., J. Fanielle, et al. (1978). "Time-blind videotaped evaluation of injectable diazepam, lorazepam and placebo." Acta Psychiatr Belg **78**(4): 619-34.

Eighteen inpatients suffering from a severe anxiety received in double-blind and crossover conditions iv and im injections of 10 mg diazepam, 5 mg lorazepam or saline t.i.d. during 5 days. The morning injections was made iv in a CCTV studio. Before injection and 20 mn after it, the patient filled out a 100 mm Visual Analogue Scale; his doctor-in-charge proceeded to a standard interview and to physiological measurements (tremor of hand, patellar reflexes, blood pressure, pulse rate). The videotaped interviews were randomly, i.e. time-blind, rated by two independent observers on 3 scales: the VAS, the Hamilton Anxiety Scale and an ad hoc Verbal and Non-Verbal Anxiety Scale (VNVA). The statistical analysis was completed by a logical analysis according to Lewis Carroll. The results demonstrate the superiority of lorazepam over diazepam on psychic anxiety, somatic anxiety, sleep and blood pressure, the only significant side-effect being drowsiness.

6. Borison, R., Albrecht, JW, Diamond, BI. (1990). "Efficacy and safety of a putative anxyiolitic agent: Ipsapirone." Psychopharmacology Bulletin. **6**(26): 207-209.

7. Boyer, W., Feighner, JP. (1993). "A placebo-controlled double-blind multicenter trial of two doses of ipsapirone versus diazepam in generalized anxiety disorder." International Clinical Psychopharmacology **8**: 173-76.

8. Brawman-Mintzer, O., R. G. Knapp, et al. (2005). "Adjunctive risperidone in generalized anxiety disorder: A double-blind, placebo-controlled study." Journal of Clinical Psychiatry **66**(10): 1321-1325.

Objective: Although significant advances have been made in recent years in the treatment of generalized anxiety disorder (GAD), many patients remain symptomatic despite ongoing treatment, underscoring the need for adjunctive new treatments to help improve response. Method: Forty patients with a primary diagnosis of DSM-IV GAD, who continued to experience GAD symptoms despite current anxiolytic treatment of at least 4 weeks' duration, as evidenced by Hamilton Rating Scale for Anxiety (HAM-A) total score (greater-than or equal to) 18 and Clinical Global Impressions-Severity of Illness scale score of moderate or greater, completed a 1-week screening phase and were then randomly assigned to 5 weeks of double-blind adjunctive treatment with placebo or risperidone at flexible doses of 0.5 to 1.5 mg/day. Patients continued to take their anxiolytics throughout the study. The study was conducted from June 2001 through March 2003. Results: Adjunctive risperidone was associated with statistically significant improvements in core anxiety symptoms, as demonstrated by greater reductions in HAM-A total scores (p = .034) and HAM-A psychic anxiety factor scores (p = .047) compared with placebo. Although change scores on other outcome variables, including response rates, were higher in the risperidone group, differences did not achieve statistical significance. Conclusion: Study findings suggest that risperidone at low doses may represent a useful tool in the management of symptomatic GAD patients.

9. Casacalenda, N. e. a. (1998). "Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. ." Canadian Journal of Psychiatry. . **43**(7): 722.

10. Centre for Reviews and Dissemination (2007). " Long-term pharmacological treatment of generalized anxiety disorder (Structured abstract)." Database of Abstracts of Reviews **2**.

11. Centre for Reviews and Dissemination (2007). "A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder (Structured abstract)." Database of Abstracts of Reviews of Effects. **3**.

12. 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.

13. Coak, A. R., J; Morris, S. (2007). "Thioridazine for anxiety and depressive disorders. ." Cochrane Database of Systematic Reviews.(2).

14. Cohn, J., Rickels, K. (1989). "A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. ." Current Medical Research and Opinion **11**(5): 304-20.

15. Cooper, S. J., C. B. Kelly, et al. (1990). "Beta 2-adrenoceptor antagonism in anxiety." Eur Neuropsychopharmacol **1**(1): 75-7.

The relative role of beta 1- and beta 2-adrenoceptor antagonism in the management of anxiety symptoms is not clear. We studied the effect of ICI 118,551, a selective beta 2-antagonist, in 51 patients presenting with acute anxiety symptoms and fulfilling DSM-III criteria for anxiety disorder. All patients received placebo during the first week of treatment followed by thrice daily diazepam (2 mg) or ICI 118,551 (50 mg) or placebo for 4 weeks with double-blind, random allocation. Hamilton anxiety scale scores improved on all treatments but there was no significant difference between treatments. Beta 2-adrenoceptor antagonism does not appear to be effective in acute anxiety neurosis. Some earlier literature suggests that beta 1-antagonism may be more important.

16. Cutler, N. R., J. M. Hesselink, et al. (1994). "A phase II multicenter dose-finding, efficacy and safety trial of ipsapirone in outpatients with generalized anxiety disorder." Prog Neuropsychopharmacol Biol Psychiatry **18**(3): 447-63.

Benzodiazepines have been prescribed for the treatment of Generalized Anxiety Disorder (GAD) for nearly three decades due to their proven anxiolytic efficacy, despite a considerable side effect and abuse liability profile. A new class of compounds, the azapirones, have been developed as an alternative to benzodiazepine treatment. Ipsapirone is a novel anxiolytic azapirone which has high specificity for the 5-HT1A receptor and which has the potential for offering certain advantages over buspirone. The present 5-week study investigated three doses of ipsapirone (2.5mg, 5.0mg and 7.5mg tid) versus placebo in 267 GAD outpatients. Efficacy was evaluated using the Hamilton Anxiety Rating Scale (HAM-A), Zung Anxiety Scale (Zung-A), and Clinical Global Impression (CGI). The study design consisted of a 1-week placebo run-in, a 4-week double-blind treatment period, and a 1-

week placebo washout. The 5.0mg group demonstrated consistently superior improvement in all efficacy variables during the treatment period, with significant differences ($p < 0.05$) from placebo and, at times, the 2.5mg and 7.5mg groups. Incidence of adverse events, primarily dizziness, nausea, sedation, and asthenia, was found to be dose proportional, with significant increase in the 7.5mg group, which may account for the diminished effectiveness seen with this dose. Our results suggest that ipsapirone may represent a viable treatment for GAD.

17. DeMartinis, N., Runn, M, Rickels, K, Mandos, L. P. (2000). "Prior Benzodiazepine Use and Buspirone Response in the Treatment of Generalized Anxiety Disorder. ." The Journal of Clinical Psychiatry **61**(2): 91-94.

18. Downing, R. W. and K. Rickels (1985). "Early treatment response in anxious outpatients treated with diazepam." Acta Psychiatr Scand **72**(6): 522-8.

Two hundred and two moderately chronic psychiatric outpatients, all suffering from anxiety of at least moderate severity and all diagnosable as cases of Generalized Anxiety Disorder, participated in a single-blind 6-week trial of diazepam (15-40 mg/day). The trial was preceded by a 1 week placebo washout, and provided for evaluation visits after 1, 2, 4 and 6 weeks of diazepam treatment. Patients were divided into High, Medium and Low Initial Improvers using 1 week change in Hamilton Anxiety Scale total score to assign patients to three subgroups of equal size. These groups did not differ significantly on those demographic factors and attributes of illness history which were documented, nor on assessments of symptom and illness severity, and mode of intake. Examination of a number of patient and physician assessments of illness severity revealed that the High group had the greatest 6-week improvement, the Low group the least. During the first week, the High group attained 86%, the Medium group, 65%, and the Low group, 29% of its full 6-week drug response. Diazepam dose levels were lowest for the High group and highest for the Low group. Placebo response was least for the High group and greatest for the Low group. An attempt to find distinctive attributes of the three initial improvement groups was unsuccessful.

19. Ebadi, M. and Y. Hama (1988). "Dopamine, GABA, cholecystokinin and opioids in neuroleptic-induced tardive dyskinesia." Neuroscience and Biobehavioral Reviews **12**(3-4): 179-187.

20. Falissard, B. (2003). "Statistical considerations about the question of a selection of discriminating centres in the analysis of clinical trial. In response to the paper: "A method for controlling for a high response rate in a comparison of venlafaxine XR and diazepan in the short-term treatment of patients with generalised anxiety disorder"." Eur Psychiatry **18**(4): 188-9.

21. Fontaine, R., L. Annable, et al. (1983). "Bromazepam and diazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations." J Clin Psychopharmacol **3**(2): 80-7.

In a double-blind, placebo-controlled study, 48 anxious outpatients with a primary diagnosis of generalized anxiety disorder were randomly assigned to 4 weeks of treatment with bromazepam (18 mg/day), diazepam (15 mg/day), or placebo, after a 1-week washout period. From week 1 onward both active drugs were superior to placebo in relieving anxiety symptoms. Bromazepam was found to be significantly more effective than diazepam with respect to the somatic anxiety factor and the total score for the Hamilton Anxiety Rating Scale and the fear/anxiety factor of the Patient's Self-Rating Symptom Scale. Plasma concentrations of diazepam plus active metabolites were correlated significantly (r = 0.60, p less than 0.05) with the percentage reduction in self-rating anxiety scores. Bromazepam plasma concentration measurements showed greater variability than those of diazepam and were not found to be correlated significantly with clinical response. It is suggested that the use of strict diagnostic criteria (1978 draft of the third edition of Diagnostic and Statistical Manual of Mental Disorders), adequate sample sizes, and a 4-week study period gave increased sensitivity for the detection of significant differences between the two benzodiazepines.

22. Fontaine, R., P. Beaudry, et al. (1987). "Comparison of withdrawal of buspirone and diazepam: a placebo controlled study." Prog Neuropsychopharmacol Biol Psychiatry **11**(2-3): 189-97.

In a 8-week double-blind placebo controlled study, 48 outpatients with generalized anxiety disorder were randomized to diazepam, buspirone, a non-benzodiazepine anxiolytic, or placebo. During the treatment phase of 4 weeks duration diazepam was found to be significantly better than placebo and buspirone. Following abrupt withdrawal by placebo substitution the diazepam group showed a gradual relapse maximal after two weeks while the buspirone and the placebo groups did not differ. There were more cases of rebound anxiety with diazepam as compared to buspirone or placebo. In addition, there were three early terminations related to rebound anxiety in the diazepam group while there were none in the placebo and buspirone groups. There were significantly more new symptoms in the diazepam group than in the placebo or buspirone group.

23. Fontaine, R., G. Chouinard, et al. (1984). "Bromazepam and diazepam in generalized anxiety: a placebo-controlled study of efficacy and withdrawal." Psychopharmacol Bull **20**(1): 126-7.

24. Fontaine, R., G. Chouinard, et al. (1984). "Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment." Am J Psychiatry **141**(7): 848-52.

In this double-blind, placebo-controlled study of 4 weeks of benzodiazepine treatment followed by 3 weeks of abrupt or gradual drug withdrawal, 16 patients whose benzodiazepine was withdrawn

abruptly were worse (p less than .05) than 13 who had received placebo in terms of change in mean anxiety scores from the pretreatment level. The scores of seven patients (44%) whose benzodiazepine was withdrawn abruptly increased 10% or more on both the Hamilton Rating Scale for Anxiety and the Self Rating Symptom Scale. There were no cases of rebound anxiety in 14 patients whose benzodiazepine was withdrawn gradually; fewer cases of rebound anxiety were seen with a benzodiazepine that had a long half-life.

25. Forest Laboratories (2007). Initiating Acamprosate Within Versus Post-Detoxification in the Rehabilitative Treatment of Alcohol Dependence.

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Study Type: Interventional

Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Crossover Assignment

Further study details as provided by National Institute on Drug Abuse (NIDA):

Primary Outcome Measures:

The mean number of adverse events rated moderate to severe;

The week of detoxification treatment discontinuation;

The total amount of oxazepam given;

The rate of change in CIWA scores.

The mean number of adverse events rated moderate to severe;

The week of open-label treatment discontinuation;

Any reemergence of detoxification symptoms;

Percentage of pills taken over what was proposed to be prescribed (medication exposure);

Percentage days abstinent;

Percentage days heavy drinking. The number of drinks per day will be used to identify a heavy drinking day, defined as 5 or more drinks/day for males and 4 or more drinks/day for females.

Secondary Outcome Measures:

Changes in alcohol craving will be measured by Penn Alcohol Craving Scale (PACS; Flannery et al, 1999)

Changes in anxiety symptoms will be measured by the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Hamilton, 1969)

Changes in depressive symptoms will be measured by the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Hamilton 1967)

Changes in social functioning will be measured by several of the subscales of the Addiction Severity Index (ASI; McLellan et al, 1992); namely, medical, legal, psychiatric, and family/social.

Quality of Life, measured by the Short Form-36 Health Status Questionnaire (SF-36; Ware & Sherbourne, 1999)

Overall clinical impression of improvement will be measured by the Clinical Global Impression Scale (CGI)

26. Gao, K., D. Muzina, et al. (2006). "Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: A review." Journal of Clinical Psychiatry **67**(9): 1327-1340.

Objective: The efficacy of antipsychotics in the treatment of primary or comorbid anxiety disorders or anxiety symptoms in major depressive disorder or bipolar disorder was reviewed. Data Sources: English-language literature cited in MEDLINE from January 1, 1968, to December 31, 2005, was searched with the keywords anxiety disorder, anxiety symptoms, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, bipolar disorder, major depressive disorder, Hamilton Rating Scale for Anxiety, antipsychotics, typical antipsychotics, atypical antipsychotics, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, fluspirilene, penfluridol, pipothiazine, flupenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, amisulpride, and clinical trial. Randomized, double-blind, placebo-controlled trials and open-label studies with a minimum of 20 subjects with a DSM-III/IV or ICD-10 diagnosis of anxiety disorder and studies without a DSM-III/IV or ICD-10 diagnosis of anxiety disorder but with Hamilton Rating Scale for Anxiety (HAM-A) scores as an outcome were prioritized. Studies on bipolar disorder or major depressive disorder with the analysis of changes in anxiety symptoms were reviewed. Early studies on neurosis/anxiety or anxious depression without a HAM-A component were also reviewed. Data Synthesis: Six trials in primary generalized anxiety disorder (GAD), 15 in refractory obsessive-compulsive disorder (OCD), 8 in posttraumatic stress disorder (PTSD), 6 in neurosis with the HAM-A, 1 in social phobia, and 2 in anxiety symptoms in bipolar depression were identified. Low doses of trifluoperazine were superior to placebo in the treatment of GAD. Most of the less well-designed studies showed that other typical antipsychotics might be superior to placebo or as effective as benzodiazepines in the treatment of GAD and other anxiety conditions. In most studies, risperidone, olanzapine, and quetiapine augmentation to antidepressants was superior to placebo in treating refractory OCD and PTSD. Both olanzapine and quetiapine significantly reduced anxiety compared to placebo in studies of bipolar depression. Conclusion: Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

27. Goldberg, H. L. and R. Finnerty (1982). "Comparison of buspirone in two separate studies." J Clin Psychiatry **43**(12 Pt 2): 87-91.

Two double-blind studies are described in which buspirone was compared with placebo and diazepam (Study A) or clorazepate (Study B) in outpatients with moderate to severe anxiety. Results, assessed on the Hamilton Rating Scales for Depression and Anxiety, the SCL-56, the Profile of Mood States, and the Covi and Raskin scales, indicated

that buspirone consistently relieved both anxiety and associated depression. In Study B, trends in favor of buspirone were seen on several SCL-56 items and the Hamilton somatic factor; significant differences in this direction were found for several POMS items. Sedation was seen less often with buspirone than either diazepam or clorazepate.

28. Hackett, D., V. Haudiquet, et al. (2003). "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 **18**(4): 182-187.

This randomised, double-blind, placebo-controlled study compared the efficacy of venlafaxine XR (75 or 150 mg/d) with diazepam (15 mg/d) over an 8-week treatment period in 540 non-depressed outpatients with generalised anxiety disorder (GAD). At week 8, significant improvements from baseline were observed in the venlafaxine XR, diazepam and placebo groups. Although these improvements were higher in the first two groups than in the placebo group for each of the primary efficacy variables (Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A psychic anxiety factor, Hospital Anxiety and Depression Scale (HAD) anxiety sub-scale and Clinical Global Impression (CGI) improvement), there were no statistically significant differences between groups. These non-positive results were thought to be due to the very high placebo response observed in some centres. To understand the variability of the study, a secondary preplanned analysis was performed. This involved sub-dividing the study centres according to their ability to detect a two-point mean difference between diazepam and placebo at week 8 on the HAM-A total score. Centres able to show such a difference were termed verum-sensitive. Improvements from baseline to week 8 in venlafaxine XR-treated patients from verum-sensitive centres were significantly greater than in placebo on each of the primary efficacy measures (P (less-than or equal to) 0.05). This suggests that those centres able to detect an anxiolytic effect of diazepam were also able to detect an anxiolytic effect of venlafaxine XR. Significant differences in baseline demographics, rates of adverse event reporting and rates of patient discontinuations were noted between patients enrolled at verum-sensitive and verum-insensitive sites. These results reflect the importance of study centre selection in accurately determining efficacy in placebo-controlled trials. (copyright) 2003 Editions scientifiques et medicales Elsevier SAS. All rights reserved.

29. Heideman, J., van Rijswijk E, van Lin N, de Loos S, Laurant M, Wensing M, van de Lisdonk E, Grol R. (2005). "Interventions to improve management of anxiety disorders in general practice: a systematic review." British Journal of General Practice. **55**(520): 867-874.

30. Jacobson, A. F., R. A. Dominguez, et al. (1985). "Comparison of buspirone and diazepam in generalized anxiety disorder." Pharmacotherapy **5**(5): 290-6.

A total of 66 outpatients meeting Diagnostic and Statistical Manual (DSM-III) criteria for generalized anxiety disorder began treatment in a randomized double-blind study that compared the efficacy and safety of buspirone and diazepam. Thirty-nine outpatients completed the 4-week trial. Both drugs were administered in a 1:1 dosage ratio; the daily prescribed dose did not exceed 40 mg. The mean daily dose of buspirone prescribed throughout the study was significantly higher than that of diazepam. Diazepam had a significantly earlier onset of efficacy than buspirone, although both drugs were equivalent after 4 weeks of treatment. Adverse reactions were more frequent in the diazepam group. Total scores from the Hamilton anxiety scale and physician's global ratings show that diazepam was significantly superior to buspirone during the initial 2 weeks of treatment. These findings are further corroborated by the results of patients' self-rated scales.

31. Jesinger, D. K. and N. Gostick (1989). "Anxiety neurosis in general practice. A double-blind comparative study of diazepam and clovoxamine, a novel inhibitor of noradrenaline and serotonin reuptake." Int Clin Psychopharmacol **4**(4): 301-11.

This was a multicentre prospectively randomized double-blind parallel comparison of clovoxamine (n = 37) and diazepam (n = 35) in 72 patients suffering from anxiety neurosis, in general practice. Patients were seen weekly. Treatment was for 4 weeks (50 mg clovoxamine b.d. or 5 mg diazepam b.d.) rising according to response to a maximum of 300 mg clovoxamine or 30 mg diazepam daily. Drug was tapered off in week 5 and patients were seen again in week 6 after they had been off drug for at least a week. A treatment period of 4 weeks was selected in line with WHO guidelines for the testing of anxiolytic drugs. Although more patients dropped out due to intolerance on clovoxamine (24%) compared with diazepam (11%), analysis of completed patients showed that clovoxamine was equally effective with significant improvement in both groups at week 4 (p less than .001) compared with baseline Morbid Anxiety Inventory scores and Hamilton Anxiety Scale scores. Diazepam patients had a more rapid response which levelled off, whereas those on clovoxamine continued to improve after 2 weeks. At 6 weeks after taper off the improvement on clovoxamine was sustained whereas on diazepam there was evidence of deterioration after stopping the drug. Clovoxamine appears to have potential as an alternative treatment to diazepam for anxiety in general practice.

32. 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.

33. King Pharmaceuticals Research and Development (2007). A Study on the Effectiveness and Safety of Diazepam Injection (Vanquix™) for Patients With Epilepsy That Receive Antiepileptic Drugs, But Still Experience Acute Repetitive Seizures (Bouts or Clusters of Seizures) That Require Treatment. **Clinical Trials identifier: NCT00319501**.

Total Enrollment: 325

Study start: January 2006

In the United States, more than 2 million people have epilepsy. Most patients with epilepsy are able to control their seizures with drugs and/or surgery. However, many patients (400,000 to greater than 600,000) are considered refractory to antiepileptic drugs and still experience acute repetitive seizures (ARS). An ARS is an episode of multiple seizures that differs from the patient's usual seizure pattern and is often recognizable by the patient's family and caregivers. The ARS is usually described as a bout or cluster of seizures that occurs over a short period of time in which the patient regains consciousness in between seizures. Only one drug is currently available that persons other than health care professionals (e.g., patient's caregiver) may give to control ARS. This drug is called Diastat®. Diastat® is a diazepam rectal gel and, although it is effective, it may be difficult, inconvenient, or objectionable to use because of its rectal administration. Vanquix™ (diazepam autoinjector) also contains diazepam, but is administered by an automated injectable device into the leg muscle. Vanquix™ may be less difficult and more convenient to use by caregivers, however, its effectiveness and safety have not been studied in patients. This study will determine the effectiveness and safety of Vanquix™ compared to placebo for treating ARS.

34. Llorca, P. M., C. Spadone, et al. (2002). "Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: A 3-month double-blind study." Journal of Clinical Psychiatry **63**(11): 1020-1027.

Background: The prevalence of generalized anxiety disorder (GAD) represents an important public health issue. Hydroxyzine, an antagonist of histamine receptors, showed both efficacy and safety in previous short-term double-blind studies over placebo in this pathology. The aim of the current study was to confirm those positive results over a 3-month period in adult outpatients. Method: This multicenter, parallel (hydroxyzine [50 mg/day]; bromazepam [6 mg/day]), randomized, double-blind, placebo-controlled trial included 2 weeks of single-blind run-in placebo, 12 weeks of double-blind randomized treatment, and 4 weeks of single-blind run-out placebo. Three hundred thirty-four of 369 selected outpatients with a diagnosis of GAD according to DSM-IV criteria and a Hamilton Rating Scale for Anxiety (HAM-A) total score (greater-than or equal to) 20 were randomized before entering the double-blind period. The primary outcome criterion was the change in the HAM-A score from baseline to 12 weeks of double-blind treatment with hydroxyzine compared with placebo. Results: In the intent-to-treat analysis, the mean (plus or minus) SD change in HAM-A scores from

baseline to endpoint was -12.16 (plus or minus) 7.74 for hydroxyzine and -9.64 (plus or minus) 7.74 for placebo (p = .019). Results at endpoint for percentage of responders (p = .003) and remission rates (p = .028), Clinical Global Impressions-Severity scale score (p = .001), maintenance of efficacy (p = .022), and Hospital Anxiety and Depression scale score on day 84 (p = .008) also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam. Except for drowsiness, which was more frequent with bromazepam, safety results were comparable in the 3 groups. Conclusion: Hydroxyzine showed both efficacy and safety in the treatment of GAD and appears to be an effective alternative treatment to benzodiazepine prescription.

35. Mahe, V. e. a. (2000). "Long-term pharmacological treatment of generalized anxiety disorder. ." International Clinical psychopharmacology. **15**(2): 99-105.

36. Martin JL., S.-P. M. F. T. M.-S. E. S. T. G. C. (2007). "Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials." Journal of Psychopharmacology **21**(7): 774-82.

No systematic review or meta-analysis using a hard outcome has been conducted on the role of benzodiazepines for generalized anxiety disorder (GAD). The objective of this study was to assess the effectiveness and efficacy of benzodiazepines in the treatment of GAD based on trial drop-out rates. We used a systematic review of randomized controlled trials that compared any of the three best established benzodiazepines (diazepam, Lorazepam and aLprazolam) against placebo. Our primary outcome for effectiveness was withdrawal for any reason. Our secondary outcome tapping efficacy was withdrawal due to lack of efficacy, and that tapping side effects was withdrawals due to adverse events.We included 23 trials. Pooled analysis indicated less risk of treatment discontinuation due to lack of efficacy for benzodiazepines, compared to placebo, relative risk (RR) 0.29 (95% CI 0.18-0.45; p < 0.00001). Nevertheless, pooled analysis showed no conclusive results for risk of all-cause patient discontinuation, RR 0.78 (95% CI 0.62-1.00; p = 0.05). Meta-regression model showed that 74% of the variation in logRR across the studies was explained by year of publication (p <0.001).This systematic review did not find convincing evidence of the short-term effectiveness of the benzodiazepines in the treatment of GAD. On the other hand, for the outcome of efficacy, this review found robust evidence in favour of benzodiazepines. Due to the heterogeneity induced by year of publication, three hypotheses are plausibLe when it comes to being able to account for the differences between efficacy and effectiveness observed in the outcomes (publication bias, quality of the trial literature and a non-differential response to the placebo effect).

37. Meoni, P., D. Hackett, et al. (2004). "Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder." Depression and Anxiety **19**(2): 127-132.

We evaluated the relative efficacy of venlafaxine XR on the psychic versus somatic symptoms of anxiety in patients with generalized anxiety disorder as determined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Data were pooled and analyzed from 1,841 patients with generalized anxiety disorder who participated in five short-term (8-week) double-blind, multicenter, placebo-controlled studies, two of which had long-term (6-month) extensions. Somatic and psychic anxieties were studied using the Hamilton rating scale for anxiety (HAM-A) factor scores. We examined response rates ((greater-than or equal to) 50% improvement over baseline severity score) in the overall population and in patients with mainly somatic symptomatology at baseline (somatizers). Venlafaxine XR significantly reduced factor scores for both psychic and somatic HAM-A factors compared with placebo, from the first and second weeks of treatment, respectively. Patients treated with venlafaxine XR had significantly higher rates of response than patients receiving placebo on the psychic (58% vs. 38%, P < .001 at week 8; 66% vs. 35% at week 24, P < .001) and somatic (56% vs. 43%, P < .001 at week 8; 67% vs. 47% at week 24, P < .001) factors of the HAM-A. There was a Treatment x Factor interaction (P < .027) in response rates: Patients treated with venlafaxine showed similar somatic and psychic anxiety response rates, whereas placebo-treated patients showed higher somatic compared with psychic response rates. Somatizers showed similar rates of response to the total population for the somatic factor of the HAM-A in either treatment group. Patients with generalized anxiety disorder treated with venlafaxine XR showed similar absolute rates of response on somatic and psychic symptoms, but relative to patients treated with placebo, more improvement in psychic than somatic symptoms. (copyright) 2004 Wiley-Liss, Inc.

38. Mitte K, N. P., Steil R, Hautzinger M. (2005). "Ameta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. ." Journal of Clinical Psychopharmacology. **25**(2): 141-150.

39. 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.

40. Murphy, S. M., R. Owen, et al. (1989). "Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone." Br J Psychiatry **154**: 529-34.

Fifty-one out-patients presenting with generalised anxiety disorder were included in a double-blind trial, and treated with either buspirone (a new non-benzodiazepine antianxiety drug) or diazepam over 6 or 12 weeks, after which they were abruptly withdrawn and continued on placebo to 14 weeks. Ratings of anxiety and other symptoms were administered fortnightly and additional withdrawal symptoms noted. Forty patients completed the study; 8 of the 11 drop-outs were taking buspirone. Both drugs reduced anxiety, diazepam more rapidly, but with greater withdrawal symptoms, particularly after 6 weeks. Regular treatment with diazepam for 6 weeks leads to a significant risk of pharmacological dependence that is not present with buspirone.

41. Pecknold, J., Familamiri, P, Chang, H, Wilson, R, Alarcia, J, Mc-Clure, J. (1985). "Buspirone: Anxiolytic?. ." Progress in Neuro-psychopharmacol-ogy & Biological Psychiatry **9**: 638-642.

42. Pecknold, J. C., M. Matas, et al. (1989). "Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo." Can J Psychiatry **34**(8): 766-71.

Buspirone has previously been demonstrated to be efficacious in the treatment of anxiety. This four-week double-blind parallel study compared buspirone to diazepam and placebo in the treatment of 119 outpatients diagnosed as having generalized anxiety disorder. After a seven-day placebo washout period, eligible patients were randomized to one of three treatment groups. Buspirone (5 mg) and diazepam (5 mg) were administered BID and individually titrated to an optimal therapeutic dose by the end of week two. Buspirone and diazepam were equally effective in reducing Hamilton Anxiety (HAM-A) total and psychic factor scores from baseline values. Buspirone alone was significantly better than placebo in reducing the HAM-A somatic factor score. Sixty-seven percent of both active treatment groups who were classified as "ill" on the baseline global psychopathology rating scale achieved a "not ill" status by study end. There were no significant differences between treatment groups at endpoint on the 56-item Symptom Checklist self-rating scale. Buspirone was demonstrated to be as effective as diazepam in relieving anxiety in this outpatient sample.

43. Pomara, N., L. M. Willoughby, et al. (2005). "Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder." Psychopharmacology (Berl) **178**(1): 1-8.

OBJECTIVE: Acute diazepam administration has been shown to decrease plasma cortisol levels consistent with decreased activity of the hypothalamic-pituitary-adrenal axis, especially in individuals experiencing stress. However, the effects of chronic diazepam treatment on cortisol have been less studied, and the relationship to age, anxiety, duration of treatment, and dose are not well understood. METHOD: This double-blind placebo-controlled study examined acute and chronic effects of diazepam on plasma cortisol levels in young (19-35 years) and elderly (60-79 years) individuals with and without

generalized anxiety disorder (GAD). Subjects received single oral challenges of placebo or diazepam (2.5 mg or 10 mg) in a placebo-controlled cross-over design, followed by 3 weeks of chronic daily treatment with 2.5 mg or 10 mg diazepam or placebo taken at 10 p.m., and then by a final acute challenge with a single oral dose of the same study medication received during chronic treatment. RESULTS: The elderly experienced significant reductions in plasma cortisol levels compared to placebo both in the initial challenge and during chronic treatment, but the young did not. However, cortisol response to drug was comparable in both groups. Final challenge did not produce any significant cortisol effects in either group and the cortisol response in the elderly was significantly reduced compared to the initial challenge. GAD status was not a factor in plasma cortisol responses to diazepam. CONCLUSIONS: Diazepam reduced cortisol both acutely and during chronic treatment, but not during final challenge, consistent with some tolerance development. This effect was most apparent in the elderly compared with the young adults and was not modulated by GAD status or dosage, and was not related to drug effects on performance and on self-ratings of sedation and tension.

44. Pourmotabbed, T., D. R. McLeod, et al. (1996). "Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder." J Clin Psychopharmacol **16**(3): 202-7.

Twenty-one women with generalized anxiety disorder (GAD) participated in a 6-week, double-blind, placebo-controlled trial to assess the treatment and abrupt withdrawal effects of diazepam on psychic and somatic symptoms of anxiety. The results confirmed those of previous studies reporting that (1) clinical doses of diazepam are effective in attenuating the symptoms of generalized anxiety to a greater extent than placebo during the first 3 weeks of treatment; (2) somatic symptoms are more responsive to diazepam treatment than psychic symptoms; and (3) patients taking diazepam exhibit increased anxiety upon abrupt withdrawal of medication. This finding, combined with the fact that diazepam discontinuation did not produce withdrawal effects in non-anxious volunteers, suggests that diazepam discontinuation after 6 weeks results in rebound anxiety rather than a physical withdrawal syndrome. Diazepam did not improve psychomotor performance in GAD patients. Psychomotor impairment after 6 weeks of diazepam was similar to that seen in nonanxious volunteers.

45. Power, K. e. a. (1990). "A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo, alone and in combination, the the treatment fo generalized anxiety disorder. ." J. anxiety disorder. **4**(4): 267-292.

46. Rickels, K., N. DeMartinis, et al. (2000). "A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder." J Clin Psychopharmacol **20**(1): 12-8.

In a multicenter, double-blind trial, 310 patients who had received a diagnosis of generalized anxiety disorder were treated for 6 weeks with either abecarnil, diazepam, or placebo at mean daily doses of 12 mg of

abecarnil or 22 mg of diazepam administered three times daily. Patients who were improved at 6 weeks could volunteer to continue double-blind treatment for a total of 24 weeks. The maintenance treatment phase allowed the comparison of taper results for the three treatments at several study periods (0-6 weeks, 7-12 weeks, and more than 12 weeks). Slightly more diazepam (77%) and placebo (75%) patients completed the 6-week study than abecarnil patients (66%). At intake and baseline, after a 1-week placebo washout, the patient was required to have a Hamilton Rating Scale for Anxiety score of > or =20. Major adverse events for both abecarnil and diazepam were drowsiness, dizziness, fatigue, and coordination difficulties. Clinical improvement data showed that both abecarnil and diazepam produced statistically significantly more symptom relief than did placebo after 1 week of treatment. At 6 weeks treatment (using last observation carried forward analysis), however, only diazepam still differed significantly ($p < 0.01$) from placebo. High placebo response (56% moderate to marked global improvement) at 6 weeks, as well as a slightly lower nonsignificant improvement rate observed with abecarnil, a partial y-aminobutyric acid (GABA) agonist, when compared with diazepam, a full GABA agonist, most likely contributed to our findings. Finally, taper results showed that only diazepam and not abecarnil caused the presence of temporary discontinuation symptoms, but only in patients who had been treated for at least 12 weeks.

47. Rickels, K., R. Downing, et al. (1993). "Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam." Arch Gen Psychiatry **50**(11): 884-95.

OBJECTIVE: The current study examines whether antidepressants, contrary to current thinking, are safe and effective treatments for generalized anxiety disorder (GAD) not complicated by depression or panic disorder. DESIGN: Randomized, double-blind, placebo-controlled, flexible-dose, 8-week treatment study comparing imipramine hydrochloride (mean maximum daily dose, 143 mg), trazodone hydrochloride (255 mg), and diazepam (26 mg). PATIENTS: Two hundred thirty patients with a DSM-III diagnosis of GAD in whom major depression and panic disorder has been excluded, and who had a Hamilton Anxiety Scale total score of at least 18. SETTING: Seventy-five percent of patients were treated in family practice settings in the community, with the remainder treated in psychiatric practices, either academic or private. RESULTS: Patients treated with diazepam showed the most improvement in anxiety ratings during the first 2 weeks of treatment, with somatic symptoms being most responsive. From week 3 through week 8 trazodone achieved comparable, and imipramine somewhat better, anxiolytic efficacy when compared with diazepam, with psychic symptoms of tension, apprehension, and worry being more responsive to the antidepressants. Among completers, moderate to marked improvement was reported by 73% of patients treated with imipramine, 69% of patients treated with trazodone, 66% of patients treated with diazepam, but only 47% of patients treated with placebo. Overall, patients treated with antidepressants reported a

higher rate of adverse effects than diazepam-treated patients, but attention rates were the same across all treatments. CONCLUSIONS: The results of the study need replication, but suggest a potentially important role for antidepressants, particularly imipramine, in patients suffering from GAD.

48. Rickels, K., E. Schweizer, et al. (1997). "Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial." J Clin Psychopharmacol **17**(4): 272-7.

This randomized, double-blind clinical trial involving 198 generalized anxiety disorder (GAD) patients was conducted to more clearly define gepirone's role for the treatment of anxiety in daily dosages of 10 to 45 mg compared with diazepam and placebo. A secondary goal was to test for possible discontinuation symptoms after abrupt discontinuation of therapy. After a 1-week washout period, patients were treated for 8 weeks and then abruptly shifted under single-blind conditions for 2 weeks on placebo. The highest attrition rate occurred with patients on gepirone (58%) and the lowest on diazepam (34%). Medication intake for week 4 was 19.5 +/- 12.5 mg/day diazepam and 19.0 +/- 11.5 mg/day gepirone and was similar at week 8. The major adverse events were light-headedness, nausea, and insomnia for gepirone and drowsiness and fatigue for diazepam. Clinical improvement data showed gepirone's anxiolytic response to be delayed, being significant from placebo beginning at week 6, whereas diazepam caused significantly more relief than placebo from week 1 onward. Taper results showed that only diazepam, but not gepirone, caused a temporary worsening of anxiety symptoms or rebound.

49. Rickels, K., K. Weisman, et al. (1982). "Buspirone and diazepam in anxiety: a controlled study." J Clin Psychiatry **43**(12 Pt 2): 81-6.

The anxiolytic properties of buspirone were assessed in a 4-week double-blind study in 240 anxious patients, 81 of whom received buspirone, 81 diazepam, and 78 placebo. Patients were required to have scores greater than or equal to 9 on the Covi and greater than or equal to 18 on the Hamilton Rating Scale for Anxiety, and to endorse at least 5 items on a 17-item Anxiety Entry Checklist. Among 212 evaluable patients, those who improved most were married, well-educated females who had both a positive family adjustment and a low level of depression. Diazepam produced relatively equal improvement in females and males. Diazepam seems more effective in reducing somatic symptoms, while buspirone appears more effective in reducing symptoms associated with cognitive and interpersonal problems. Main differences between the drugs were seen in side effect profiles.

50. Rocca, P., V. Fonzo, et al. (1997). "Paroxetine efficacy in the treatment of generalized anxiety disorder." Acta Psychiatr Scand **95**(5): 444-50.

Recently, there has been a renewed interest in alternatives to the benzodiazepines for the treatment of generalized anxiety disorder (GAD). The aim of the present study was to compare the efficacy of paroxetine vs. imipramine and 2'-chlordesmethyldiazepam in 81

patients with a DSM-IV diagnosis of GAD. Approximately two-thirds of the patients who completed the study improved greatly or moderately on all three active drugs. During the first 2 weeks of treatment, 2'-chlordesmethyldiazepam treatment resulted in the greatest improvement in anxiety ratings. Both paroxetine and imipramine treatment resulted in more improvement than 2'-chlordesmethyldiazepam by the fourth week of treatment. Paroxetine and imipramine affect predominantly psychic symptoms, whereas 2'-chlordesmethyldiazepam affects predominantly somatic symptoms. Our results suggest that paroxetine is effective for the treatment of GAD.

51. Ross, C., Matas, M. (1987). "A Clinical Trial of Buspirone and Diazepam in the Treatment of Generalized Anxiety Disorder. ." Canandian Journal of Psychiatry **32**: 351-355.

52. Rynn, M., S. Khalid-Khan, et al. (2006). "Early response and 8-week treatment outcome in GAD." Depression and Anxiety **23**(8): 461-465.

Our objective was to compare the predictive value of early response to treatment outcome in patients with generalized anxiety disorder (GAD) treated with benzodiazepines, serotonin receptor (5HT-1A) partial agonists, or placebo. Data from two double-blind GAD studies were combined. Subjects were evaluated with the Hamilton Anxiety Scale (HAM-A) and the Clinical Global Impression of Improvement (CGI-I) scale over 8 weeks. Categories of response at weeks 1 and 2 were defined by the HAM-A total score. Analyses of covariance and Kaplan-Meier survival analyses were the primary analyses used to assess 8-week end point treatment outcomes as a function of early improvement. HAM-A change from baseline to weeks 1 and 2 significantly predicted last observation carried forward (LOCF) response at week 8 for both medications and for placebo (P<.001). Early improvement was a strong predictor for treatment outcome irrespective of whether active medication or placebo was the treatment agent.

53. Schwartz, T. L. and N. Nihalani (2006). "Tiagabine in anxiety disorders." Expert Opinion on Pharmacotherapy **7**(14): 1977-1987.

GABA has been implicated in both the aetiology and treatment of anxiety. Tiagabine is currently the only selective GABA reuptake inhibitor available in US markets; it exerts its action via GAT-1 transporter blockade presynaptically, facilitating GABA neurotransmission. Preclinical studies and current human studies suggest tiagabine possesses anxiolytic properties. The anxiolytic properties of tiagabine have also been suggested in a number of case series, open-label studies and placebo-controlled studies in patients with different anxiety disorders. Throughout these studies, tiagabine has been reasonably tolerated; the most commonly reported adverse events include dizziness, headache and nausea. Tiagabine may be a useful addition to currently available drugs for anxiety; however, the data from small open-label investigations remain to be confirmed in larger controlled studies. (copyright) 2006 Informa UK Ltd.

54. Shah, L. P., et al., (1990). "A controlled double blind clinical trial of buspirone and diazepam in generalised anxiety disorder. ." Indian Journal of Psychiatry. **32**(2): 166-169.

55. Strand, M., J. Hetta, et al. (1990). "A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam." J Clin Psychiatry **51 Suppl**: 40-5.

Two hundred thirty patients with generalized anxiety and Hamilton Rating Scale for Anxiety (HAM-A) scores greater than or equal to 18 were subdivided at random, according to a double-blind design, into one group treated with 5-10 mg of oral buspirone t.i.d. or one group treated with 10-20 mg of oral oxazepam t.i.d. for 6 weeks. No anxiolytic treatment was allowed 3 months prior to trial entry. Analysis of demographic variables revealed no significant imbalance between the two treatment groups. Twenty patients were excluded from efficacy analysis because of treatment withdrawal before the first efficacy evaluation on Day 7. Another 4 patients were excluded because they were taking concomitant psychotropic medication. The remaining 206 patients displayed a decrease in HAM-A scores (mean +/- SD) from 23.9 +/- 4.1 to 10.6 +/- 7.7 in the buspirone group and from 23.9 +/- 4.2 to 11.5 +/- 8.0 in the oxazepam group. The two treatment groups were also found to be virtually identical in an "intent to treat" analysis of all 230 patients as well as in other ratings (Hamilton Rating Scale for Depression, Raskin Depression Scale, Covi Anxiety Scale, Physicians Questionnaire, global ratings, and Hopkins Symptom Checklist [HSCL]-56). However, oxazepam was never superior to buspirone in any of the efficacy analyses. Of the 230 patients, 127 spontaneously reported adverse events, including drowsiness, dizziness, headache, nausea, and nervousness. Adverse events were relatively similar in the two groups. In conclusion, buspirone and oxazepam appear to be equally effective in the treatment of generalized anxiety encountered by general practitioners. This outcome, in addition to a previously documented absence of any dependency liability, makes buspirone a clinically important anxiolytic drug.

56. Tyrer, P. and R. Owen (1984). "Anxiety in primary care: is short-term drug treatment appropriate?" J Psychiatr Res **18**(1): 73-8.

Thirty-six patients with generalised anxiety disorder, panic disorder or agoraphobia with panic attacks, diagnosed by DSM-III criteria, were treated with a new non-benzodiazepine anti-anxiety drug, buspirone, and with diazepam and placebo, in a cross-over design. Each patient took buspirone, diazepam and placebo for one week each in flexible dosage and balanced order. Ratings of symptomatology using the Comprehensive Psychopathological Rating Scale were made after each week's treatment and a sub-scale used for measuring anxiety change alone was used separately. There was no overall difference in efficacy between the drugs, but when the scores for individual symptoms were analysed, diazepam was significantly superior to the other treatments for the symptom of muscle tension only. The results

suggest that the common practice of giving short-term therapy with tranquilising drugs for anxiety in primary care is pharmacologically suspect.

57. Tyrer, P., N. Seivewright, et al. (1993). "The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years." Br J Psychiatry **162**: 219-26.

Repeated assessments of psychopathology, together with personality status, were made over two years on 181 psychiatric out-patients with generalised anxiety disorder (59), panic disorder (66), or dysthymic disorder (56) diagnosed using an interview schedule for DSM-III. Patients were randomly allocated to drug treatment, cognitive and behaviour therapy, or a self-help treatment programme. Although there were no overall differences in compliance rate and efficacy between the three modes of treatment, the psychological treatment methods, particularly self-help, were more effective in patients without personality disorder, and those with personality disorder responded better to drug treatment, primarily antidepressants. The findings suggest that assessment of personality status could be a valuable aid to selection of treatment in neurotic disorders and that self-help approaches are particularly valuable once personality disorder has been excluded.

Tyrer, P., N. Seivewright, et al. (1988). "The Nottingham study of neurotic disorder: 58. comparison of drug and psychological treatments." Lancet **2**(8605): 235-40.

210 psychiatric outpatients with generalised anxiety disorder (71), or panic disorder (74), or dysthymic disorder (65) diagnosed by an interview schedule for DSM-III were allocated by constrained randomisation to one of five treatments: diazepam (28), dothiepin (28), placebo (28), cognitive and behaviour therapy (84), and a self-help treatment programme (42). All treatments were given for 6 weeks and then withdrawn by 10 weeks. Ratings of psychopathology were made by psychiatric assessors blind to both treatment and diagnosis before treatment and at 2, 4, 6, and 10 weeks after randomisation. 18 patients had insufficient data for analysis because of early drop-out. There were no important differences in treatment response between the diagnostic groups, but diazepam was less effective than dothiepin, cognitive and behaviour therapy, or self-help, these three treatments being of similar efficacy. Significantly more patients in the placebo group took additional psychotropic drugs in the 10 week period, and those allocated to dothiepin and cognitive and behaviour therapy took the least.

59. University of Utah, P. C. s. M. C. F. (2006). Intranasal Midazolam Versus Rectal Diazepam for Treatment of Seizures.

Purpose

We will conduct a randomized controlled trial comparing the use of nasal midazolam, using a Mucosal Atomization Devise, to rectal diazepam for the treatment of acute seizure activity in children under the age of 18

years with epilepsy in the community setting. Our primary hypothesis is that nasal midazolam will be more effective and have shorter seizure time compared to rectal diazepam in the community. Our secondary hypotheses are that patients treated with nasal midazolam will have less respiratory complications, Emergency Department visits and admissions.

Total Enrollment: 200
Study start: June 2006; Expected completion: June 2007

Study Design: This is a prospective randomized controlled study.

60. Wingerson, D. K., D. S. Cowley, et al. (1996). "Effect of benzodiazepines on plasma levels of homovanillic acid in anxious patients and control subjects." Psychiatry Res **65**(1): 53-9.

The effects of four logarithmically increasing doses of intravenous diazepam or placebo on plasma homovanillic acid (HVA) were determined in benzodiazepine-naive patients with panic disorder (PD) or generalized anxiety disorder (GAD), and in healthy controls. Plasma HVA was measured at baseline and 3 min after the first and fourth doses of diazepam/placebo. Mean baseline plasma HVA levels were significantly lower in PD patients compared with GAD patients and controls. Although plasma HVA levels decreased significantly with time in all groups, there was no diazepam effect. This study suggests that low dopaminergic activity may occur in a subset of anxious patients (PD), and that diazepam does not significantly affect dopaminergic activity as measured by plasma HVA in humans.

Appendix 6: Full list of articles from Various Databases for Benzodiazepines DSM-IV

1 EMBASE and MEDLINE

Andreatini, R., V. A. Sartori, et al. (2002). "Effect of valepotriates (valerian extract) in generalized anxiety disorder: A randomized placebo-controlled pilot study." Phytotherapy Research **16**(7): 650-654.

The aim of the present study was to carry out a controlled pilot study on the putative anxiolytic effect of valepotriates. Thirty-six outpatients with generalized anxiety disorder (DSM III-R), after a 2-week wash-out, were randomized to one of the following three treatments for 4 weeks (n = 12 per group): valepotriates (mean daily dose: 81.3 mg), diazepam (mean daily dose: 6.5 mg), or placebo. A parallel, double-blind, flexible-dose, placebo-controlled design was employed. No significant difference was observed among the three groups at baseline or in the change from baseline on the Hamilton anxiety scale (HAM-A) or in the trait part of the state-trait anxiety inventory (STAI-trait). Moreover, the three groups presented a significant reduction in the total HAM-A scores. On the other hand, only the diazepam and valepotriates groups showed a significant reduction in the psychic factor of HAM-A. The diazepam group also presented a significant reduction of the STAI-trait. Although the principal analysis (HAM-A between group comparison) found negative results (probably due to the small sample size in each group), the preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. However, since the number of subjects per group was very small, the present results must be viewed as preliminary. Thus, further studies addressing this issue are warranted. Copyright (copyright) 2002 John Wiley & Sons, Ltd.

Basile, A. S., A. S. Lippa, et al. (2006). "GABAA receptor modulators as anxioselective anxiolytics." Drug Discovery Today: Therapeutic Strategies **3**(4): 475-481.

Benzodiazepines are effective anxiolytics whose use is limited by sedation, amnesia and myorelaxation, driving the search for novel, anxioselective GABAA receptor modulators. Preclinical data from 'knock-in' mice and (alpha)2,3-subunit selective GABAA receptor agonists suggest that these targets may yield anxioselective agents. In contrast, additional preclinical and clinical evidence suggests that a

combination of mechanisms, including partial agonism and receptor subtype selectivity, will be required to achieve anxioselectivity in the clinic. (copyright) 2006 Elsevier Ltd. All rights reserved.

Brawman-Mintzer, O., R. G. Knapp, et al. (2005). "Adjunctive risperidone in generalized anxiety disorder: A double-blind, placebo-controlled study." Journal of Clinical Psychiatry **66**(10): 1321-1325.

Objective: Although significant advances have been made in recent years in the treatment of generalized anxiety disorder (GAD), many patients remain symptomatic despite ongoing treatment, underscoring the need for adjunctive new treatments to help improve response. Method: Forty patients with a primary diagnosis of DSM-IV GAD, who continued to experience GAD symptoms despite current anxiolytic treatment of at least 4 weeks' duration, as evidenced by Hamilton Rating Scale for Anxiety (HAM-A) total score (greater-than or equal to) 18 and Clinical Global Impressions-Severity of Illness scale score of moderate or greater, completed a 1-week screening phase and were then randomly assigned to 5 weeks of double-blind adjunctive treatment with placebo or risperidone at flexible doses of 0.5 to 1.5 mg/day. Patients continued to take their anxiolytics throughout the study. The study was conducted from June 2001 through March 2003. Results: Adjunctive risperidone was associated with statistically significant improvements in core anxiety symptoms, as demonstrated by greater reductions in HAM-A total scores (p = .034) and HAM-A psychic anxiety factor scores (p = .047) compared with placebo. Although change scores on other outcome variables, including response rates, were higher in the risperidone group, differences did not achieve statistical significance. Conclusion: Study findings suggest that risperidone at low doses may represent a useful tool in the management of symptomatic GAD patients.

Ebadi, M. and Y. Hama (1988). "Dopamine, GABA, cholecystokinin and opioids in neuroleptic-induced tardive dyskinesia." Neuroscience and Biobehavioral Reviews **12**(3-4): 179-187.

Gao, K., D. Muzina, et al. (2006). "Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: A review." Journal of Clinical Psychiatry **67**(9): 1327-1340.

Objective: The efficacy of antipsychotics in the treatment of primary or comorbid anxiety disorders or anxiety symptoms in major depressive disorder or bipolar disorder was reviewed. Data Sources: English-language literature cited in MEDLINE from January 1, 1968, to December 31, 2005, was searched with the keywords anxiety disorder, anxiety symptoms, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, bipolar disorder, major depressive disorder, Hamilton Rating Scale for Anxiety, antipsychotics, typical antipsychotics, atypical antipsychotics, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, fluspirilene, penfluridol, pipothiazine,

flupenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, amisulpride, and clinical trial. Randomized, double-blind, placebo-controlled trials and open-label studies with a minimum of 20 subjects with a DSM-III/IV or ICD-10 diagnosis of anxiety disorder and studies without a DSM-III/IV or ICD-10 diagnosis of anxiety disorder but with Hamilton Rating Scale for Anxiety (HAM-A) scores as an outcome were prioritized. Studies on bipolar disorder or major depressive disorder with the analysis of changes in anxiety symptoms were reviewed. Early studies on neurosis/anxiety or anxious depression without a HAM-A component were also reviewed. Data Synthesis: Six trials in primary generalized anxiety disorder (GAD), 15 in refractory obsessive-compulsive disorder (OCD), 8 in posttraumatic stress disorder (PTSD), 6 in neurosis with the HAM-A, 1 in social phobia, and 2 in anxiety symptoms in bipolar depression were identified. Low doses of trifluoperazine were superior to placebo in the treatment of GAD. Most of the less well-designed studies showed that other typical antipsychotics might be superior to placebo or as effective as benzodiazepines in the treatment of GAD and other anxiety conditions. In most studies, risperidone, olanzapine, and quetiapine augmentation to antidepressants was superior to placebo in treating refractory OCD and PTSD. Both olanzapine and quetiapine significantly reduced anxiety compared to placebo in studies of bipolar depression. Conclusion: Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

Hackett, D., V. Haudiquet, et al. (2003). "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 **18**(4): 182-187.

This randomised, double-blind, placebo-controlled study compared the efficacy of venlafaxine XR (75 or 150 mg/d) with diazepam (15 mg/d) over an 8-week treatment period in 540 non-depressed outpatients with generalised anxiety disorder (GAD). At week 8, significant improvements from baseline were observed in the venlafaxine XR, diazepam and placebo groups. Although these improvements were higher in the first two groups than in the placebo group for each of the primary efficacy variables (Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A psychic anxiety factor, Hospital Anxiety and Depression Scale (HAD) anxiety sub-scale and Clinical Global Impression (CGI) improvement), there were no statistically significant differences between groups. These non-positive results were thought to be due to the very high placebo response observed in some centres. To understand the variability of the study, a secondary preplanned analysis was performed. This involved sub-dividing the study centres according to their ability to detect a two-point mean difference between diazepam and placebo at week 8 on the HAM-A total score. Centres able to show such a difference were termed verum-sensitive.

Improvements from baseline to week 8 in venlafaxine XR-treated patients from verum-sensitive centres were significantly greater than in placebo on each of the primary efficacy measures (P (less-than or equal to) 0.05). This suggests that those centres able to detect an anxiolytic effect of diazepam were also able to detect an anxiolytic effect of venlafaxine XR. Significant differences in baseline demographics, rates of adverse event reporting and rates of patient discontinuations were noted between patients enrolled at verum-sensitive and verum-insensitive sites. These results reflect the importance of study centre selection in accurately determining efficacy in placebo-controlled trials. (copyright) 2003 Editions scientifiques et medicales Elsevier SAS. All rights reserved.

Llorca, P. M., C. Spadone, et al. (2002). "Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: A 3-month double-blind study." Journal of Clinical Psychiatry **63**(11): 1020-1027.

Background: The prevalence of generalized anxiety disorder (GAD) represents an important public health issue. Hydroxyzine, an antagonist of histamine receptors, showed both efficacy and safety in previous short-term double-blind studies over placebo in this pathology. The aim of the current study was to confirm those positive results over a 3-month period in adult outpatients. Method: This multicenter, parallel (hydroxyzine [50 mg/day]; bromazepam [6 mg/day]), randomized, double-blind, placebo-controlled trial included 2 weeks of single-blind run-in placebo, 12 weeks of double-blind randomized treatment, and 4 weeks of single-blind run-out placebo. Three hundred thirty-four of 369 selected outpatients with a diagnosis of GAD according to DSM-IV criteria and a Hamilton Rating Scale for Anxiety (HAM-A) total score (greater-than or equal to) 20 were randomized before entering the double-blind period. The primary outcome criterion was the change in the HAM-A score from baseline to 12 weeks of double-blind treatment with hydroxyzine compared with placebo. Results: In the intent-to-treat analysis, the mean (plus or minus) SD change in HAM-A scores from baseline to endpoint was -12.16 (plus or minus) 7.74 for hydroxyzine and -9.64 (plus or minus) 7.74 for placebo (p = .019). Results at endpoint for percentage of responders (p = .003) and remission rates (p = .028), Clinical Global Impressions-Severity scale score (p = .001), maintenance of efficacy (p = .022), and Hospital Anxiety and Depression scale score on day 84 (p = .008) also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam. Except for drowsiness, which was more frequent with bromazepam, safety results were comparable in the 3 groups. Conclusion: Hydroxyzine showed both efficacy and safety in the treatment of GAD and appears to be an effective alternative treatment to benzodiazepine prescription.

Meoni, P., D. Hackett, et al. (2004). "Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder." Depression and Anxiety **19**(2): 127-132.

We evaluated the relative efficacy of venlafaxine XR on the psychic versus somatic symptoms of anxiety in patients with generalized anxiety disorder as determined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Data were pooled and analyzed from 1,841 patients with generalized anxiety disorder who participated in five short-term (8-week) double-blind, multicenter, placebo-controlled studies, two of which had long-term (6-month) extensions. Somatic and psychic anxieties were studied using the Hamilton rating scale for anxiety (HAM-A) factor scores. We examined response rates ((greater-than or equal to) 50% improvement over baseline severity score) in the overall population and in patients with mainly somatic symptomatology at baseline (somatizers). Venlafaxine XR significantly reduced factor scores for both psychic and somatic HAM-A factors compared with placebo, from the first and second weeks of treatment, respectively. Patients treated with venlafaxine XR had significantly higher rates of response than patients receiving placebo on the psychic (58% vs. 38%, P < .001 at week 8; 66% vs. 35% at week 24, P < .001) and somatic (56% vs. 43%, P < .001 at week 8; 67% vs. 47% at week 24, P < .001) factors of the HAM-A. There was a Treatment x Factor interaction (P < .027) in response rates: Patients treated with venlafaxine showed similar somatic and psychic anxiety response rates, whereas placebo-treated patients showed higher somatic compared with psychic response rates. Somatizers showed similar rates of response to the total population for the somatic factor of the HAM-A in either treatment group. Patients with generalized anxiety disorder treated with venlafaxine XR showed similar absolute rates of response on somatic and psychic symptoms, but relative to patients treated with placebo, more improvement in psychic than somatic symptoms. (copyright) 2004 Wiley-Liss, Inc.

Rynn, M., S. Khalid-Khan, et al. (2006). "Early response and 8-week treatment outcome in GAD." Depression and Anxiety **23**(8): 461-465.

Our objective was to compare the predictive value of early response to treatment outcome in patients with generalized anxiety disorder (GAD) treated with benzodiazepines, serotonin receptor (5HT-1A) partial agonists, or placebo. Data from two double-blind GAD studies were combined. Subjects were evaluated with the Hamilton Anxiety Scale (HAM-A) and the Clinical Global Impression of Improvement (CGI-I) scale over 8 weeks. Categories of response at weeks 1 and 2 were defined by the HAM-A total score. Analyses of covariance and Kaplan-Meier survival analyses were the primary analyses used to assess 8-week end point treatment outcomes as a function of early improvement. HAM-A change from baseline to weeks 1 and 2 significantly predicted last observation carried forward (LOCF) response at week 8 for both medications and for placebo (P<.001). Early improvement was a strong predictor for treatment outcome irrespective of whether active medication or placebo was the treatment agent.

Schwartz, T. L. and N. Nihalani (2006). "Tiagabine in anxiety disorders." Expert Opinion on Pharmacotherapy **7**(14): 1977-1987.

GABA has been implicated in both the aetiology and treatment of anxiety. Tiagabine is currently the only selective GABA reuptake inhibitor available in US markets; it exerts its action via GAT-1 transporter blockade presynaptically, facilitating GABA neurotransmission. Preclinical studies and current human studies suggest tiagabine possesses anxiolytic properties. The anxiolytic properties of tiagabine have also been suggested in a number of case series, open-label studies and placebo-controlled studies in patients with different anxiety disorders. Throughout these studies, tiagabine has been reasonably tolerated; the most commonly reported adverse events include dizziness, headache and nausea. Tiagabine may be a useful addition to currently available drugs for anxiety; however, the data from small open-label investigations remain to be confirmed in larger controlled studies. (copyright) 2006 Informa UK Ltd.

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Andreatini, R., V. A. Sartori, et al. (2002). "Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study." Phytother Res **16**(7): 650-4.

The aim of the present study was to carry out a controlled pilot study on the putative anxiolytic effect of valepotriates. Thirty-six outpatients with generalized anxiety disorder (DSM III-R), after a 2-week wash-out, were randomized to one of the following three treatments for 4 weeks (n = 12 per group): valepotriates (mean daily dose: 81.3 mg), diazepam (mean daily dose: 6.5 mg), or placebo. A parallel, double-blind, flexible-dose, placebo-controlled design was employed. No significant difference was observed among the three groups at baseline or in the change from baseline on the Hamilton anxiety scale (HAM-A) or in the trait part of the state-trait anxiety inventory (STAI-trait). Moreover, the three groups presented a significant reduction in the total HAM-A scores. On the other hand, only the diazepam and valepotriates groups showed a significant reduction in the psychic factor of HAM-A. The diazepam group also presented a significant reduction of the STAI-trait. Although the principal analysis (HAM-A between group comparison) found negative results (probably due to the small sample size in each group), the preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. However, since the number of subjects per group was very small, the present results must be viewed as preliminary. Thus, further studies addressing this issue are warranted.

Ansseau, M., J. P. Olie, et al. (1991). "Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder." Psychopharmacology (Berl) **104**(4): 439-43.

The anxiolytic activity and tolerance of four doses of suriclone (0.1, 0.2, 0.3 and 0.4 mg tid), diazepam (5 mg tid), and placebo were compared in six parallel groups of 54-59 outpatients with generalized anxiety disorder (DSM III-R). After a 1-week placebo run-in period, the patients were treated for 4 weeks, with assessments at baseline and after 1, 2, and 4 weeks by the Hamilton anxiety scale and the Clinical Global Impressions. Results showed better improvement with active drugs as compared to placebo, without significant differences among the four different doses of suriclone and diazepam. The number of adverse events, particularly drowsiness, was significantly higher with diazepam than with suriclone, particularly 0.1 and 0.2 mg tid which did not differ from placebo. These results demonstrate that suriclone at daily doses ranging from 0.1 to 0.4 mg tid is an effective anxiolytic, better tolerated than diazepam.

Ban, T. A. and M. M. Amin (1979). "Clobazam: uncontrolled and standard controlled clinical trials." Br J Clin Pharmacol **7 Suppl 1**: 135S-138S.

1 In an uncontrolled clinical trial, carried out in 11 psychiatric patients with the clinical diagnoses of anxiety neurosis and depressive neurosis, clobazam, a new benzodiazepine preparation, in the dosage range 10-60 mg daily produced statistically significant improvement in the total and both factor scores of the Hamilton Anxiety Scale (HAM-A). The lowest mean total HAM-A scores occurred with a mean clobazam dosage of 48 mg daily. 2 Results of the uncontrolled clinical trial were further substantiated in a standard-controlled clinical study in which no statistically significant difference between the therapeutic effectiveness of clobazam and diazepam could be revealed. The lowest mean total HAM-A scores occurred with a mean clobazam dosage of 49 mg daily. There was a lower incidence of adverse effects reported in patients receiving clobazam than in those taking the control drug (diazepam).

Bobon, D. P., J. Fanielle, et al. (1978). "Time-blind videotaped evaluation of injectable diazepam, lorazepam and placebo." Acta Psychiatr Belg **78**(4): 619-34.

Eighteen inpatients suffering from a severe anxiety received in double-blind and crossover conditions iv and im injections of 10 mg diazepam, 5 mg lorazepam or saline t.i.d. during 5 days. The morning injections was made iv in a CCTV studio. Before injection and 20 mn after it, the patient filled out a 100 mm Visual Analogue Scale; his doctor-in-charge proceeded to a standard interview and to physiological measurements (tremor of hand, patellar reflexes, blood pressure, pulse rate). The videotaped interviews were randomly, i.e. time-blind, rated by two independent observers on 3 scales: the VAS, the Hamilton Anxiety Scale and an ad hoc Verbal and Non-Verbal Anxiety Scale (VNVA). The statistical analysis was completed by a logical analysis according to Lewis Carroll. The results demonstrate the superiority of lorazepam over diazepam on psychic anxiety, somatic anxiety, sleep and blood pressure, the only significant side-effect being drowsiness.

Cooper, S. J., C. B. Kelly, et al. (1990). "Beta 2-adrenoceptor antagonism in anxiety." Eur Neuropsychopharmacol **1**(1): 75-7.

The relative role of beta 1- and beta 2-adrenoceptor antagonism in the management of anxiety symptoms is not clear. We studied the effect of ICI 118,551, a selective beta 2-antagonist, in 51 patients presenting with acute anxiety symptoms and fulfilling DSM-III criteria for anxiety disorder. All patients received placebo during the first week of treatment followed by thrice daily diazepam (2 mg) or ICI 118,551 (50 mg) or placebo for 4 weeks with double-blind, random allocation. Hamilton anxiety scale scores improved on all treatments but there was no significant difference between treatments. Beta 2-adrenoceptor antagonism does not appear to be effective in acute anxiety neurosis. Some earlier literature suggests that beta 1-antagonism may be more important.

Cutler, N. R., J. M. Hesselink, et al. (1994). "A phase II multicenter dose-finding, efficacy and safety trial of ipsapirone in outpatients with generalized anxiety disorder." Prog Neuropsychopharmacol Biol Psychiatry **18**(3): 447-63.

Benzodiazepines have been prescribed for the treatment of Generalized Anxiety Disorder (GAD) for nearly three decades due to their proven anxiolytic efficacy, despite a considerable side effect and abuse liability profile. A new class of compounds, the azapirones, have been developed as an alternative to benzodiazepine treatment. Ipsapirone is a novel anxiolytic azapirone which has high specificity for the 5-HT1A receptor and which has the potential for offering certain advantages over buspirone. The present 5-week study investigated three doses of ipsapirone (2.5mg, 5.0mg and 7.5mg tid) versus placebo in 267 GAD outpatients. Efficacy was evaluated using the Hamilton Anxiety Rating Scale (HAM-A), Zung Anxiety Scale (Zung-A), and Clinical Global Impression (CGI). The study design consisted of a 1-week placebo run-in, a 4-week double-blind treatment period, and a 1-week placebo washout. The 5.0mg group demonstrated consistently superior improvement in all efficacy variables during the treatment period, with significant differences ($p < 0.05$) from placebo and, at times, the 2.5mg and 7.5mg groups. Incidence of adverse events, primarily dizziness, nausea, sedation, and asthenia, was found to be dose proportional, with significant increase in the 7.5mg group, which may account for the diminished effectiveness seen with this dose. Our results suggest that ipsapirone may represent a viable treatment for GAD.

Downing, R. W. and K. Rickels (1985). "Early treatment response in anxious outpatients treated with diazepam." Acta Psychiatr Scand **72**(6): 522-8.

Two hundred and two moderately chronic psychiatric outpatients, all suffering from anxiety of at least moderate severity and all diagnosable as cases of Generalized Anxiety Disorder, participated in a single-blind 6-week trial of diazepam (15-40 mg/day). The trial was preceded by a 1 week placebo washout, and provided for evaluation visits after 1, 2, 4 and 6 weeks of diazepam treatment. Patients were divided into High, Medium and Low Initial Improvers using 1 week change in Hamilton Anxiety Scale total score to assign patients to three subgroups of equal size. These groups did not differ significantly on those demographic factors and attributes of illness history which were documented, nor on assessments of symptom and illness severity, and mode of intake. Examination of a number of patient and physician assessments of illness severity revealed that the High group had the greatest 6-week improvement, the Low group the least. During the first week, the High group attained 86%, the Medium group, 65%, and the Low group, 29% of its full 6-week drug response. Diazepam dose levels were lowest for the High group and highest for the Low group. Placebo response was least for the High group and greatest for the Low group. An attempt to find distinctive attributes of the three initial improvement groups was unsuccessful.

Falissard, B. (2003). "Statistical considerations about the question of a selection of discriminating centres in the analysis of clinical trial. In response to the paper: "A method for controlling for a high response rate in a

comparison of venlafaxine XR and diazepan in the short-term treatment of patients with generalised anxiety disorder"." Eur Psychiatry **18**(4): 188-9.

Hackett, D., V. Haudiquet, et al. (2003). "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." Eur Psychiatry **18**(4): 182-7.

This randomised, double-blind, placebo-controlled study compared the efficacy of venlafaxine XR (75 or 150 mg/d) with diazepam (15 mg/d) over an 8-week treatment period in 540 non-depressed outpatients with generalised anxiety disorder (GAD). At week 8, significant improvements from baseline were observed in the venlafaxine XR, diazepam and placebo groups. Although these improvements were higher in the first two groups than in the placebo group for each of the primary efficacy variables (Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A psychic anxiety factor, Hospital Anxiety and Depression Scale (HAD) anxiety sub-scale and Clinical Global Impression (CGI) improvement), there were no statistically significant differences between groups. These non-positive results were thought to be due to the very high placebo response observed in some centres. To understand the variability of the study, a secondary preplanned analysis was performed. This involved sub-dividing the study centres according to their ability to detect a two-point mean difference between diazepam and placebo at week 8 on the HAM-A total score. Centres able to show such a difference were termed verum-sensitive. Improvements from baseline to week 8 in venlafaxine XR-treated patients from verum-sensitive centres were significantly greater than in placebo on each of the primary efficacy measures (P </= 0.05). This suggests that those centres able to detect an anxiolytic effect of diazepam were also able to detect an anxiolytic effect of venlafaxine XR. Significant differences in baseline demographics, rates of adverse event reporting and rates of patient discontinuations were noted between patients enrolled at verum-sensitive and verum-insensitive sites. These results reflect the importance of study centre selection in accurately determining efficacy in placebo-controlled trials.

Jacobson, A. F., R. A. Dominguez, et al. (1985). "Comparison of buspirone and diazepam in generalized anxiety disorder." Pharmacotherapy **5**(5): 290-6.

A total of 66 outpatients meeting Diagnostic and Statistical Manual (DSM-III) criteria for generalized anxiety disorder began treatment in a randomized double-blind study that compared the efficacy and safety of buspirone and diazepam. Thirty-nine outpatients completed the 4-week trial. Both drugs were administered in a 1:1 dosage ratio; the daily prescribed dose did not exceed 40 mg. The mean daily dose of buspirone prescribed throughout the study was significantly higher than that of diazepam. Diazepam had a significantly earlier onset of efficacy than buspirone, although both drugs were equivalent after 4 weeks of treatment. Adverse reactions were more frequent in the diazepam group. Total scores from the Hamilton anxiety scale and physician's global ratings show that diazepam was significantly superior to

buspirone during the initial 2 weeks of treatment. These findings are further corroborated by the results of patients' self-rated scales.

Jesinger, D. K. and N. Gostick (1989). "Anxiety neurosis in general practice. A double-blind comparative study of diazepam and clovoxamine, a novel inhibitor of noradrenaline and serotonin reuptake." Int Clin Psychopharmacol **4**(4): 301-11.

This was a multicentre prospectively randomized double-blind parallel comparison of clovoxamine (n = 37) and diazepam (n = 35) in 72 patients suffering from anxiety neurosis, in general practice. Patients were seen weekly. Treatment was for 4 weeks (50 mg clovoxamine b.d. or 5 mg diazepam b.d.) rising according to response to a maximum of 300 mg clovoxamine or 30 mg diazepam daily. Drug was tapered off in week 5 and patients were seen again in week 6 after they had been off drug for at least a week. A treatment period of 4 weeks was selected in line with WHO guidelines for the testing of anxiolytic drugs. Although more patients dropped out due to intolerance on clovoxamine (24%) compared with diazepam (11%), analysis of completed patients showed that clovoxamine was equally effective with significant improvement in both groups at week 4 (p less than .001) compared with baseline Morbid Anxiety Inventory scores and Hamilton Anxiety Scale scores. Diazepam patients had a more rapid response which levelled off, whereas those on clovoxamine continued to improve after 2 weeks. At 6 weeks after taper off the improvement on clovoxamine was sustained whereas on diazepam there was evidence of deterioration after stopping the drug. Clovoxamine appears to have potential as an alternative treatment to diazepam for anxiety in general practice.

Murphy, S. M., R. Owen, et al. (1989). "Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone." Br J Psychiatry **154**: 529-34.

Fifty-one out-patients presenting with generalised anxiety disorder were included in a double-blind trial, and treated with either buspirone (a new non-benzodiazepine antianxiety drug) or diazepam over 6 or 12 weeks, after which they were abruptly withdrawn and continued on placebo to 14 weeks. Ratings of anxiety and other symptoms were administered fortnightly and additional withdrawal symptoms noted. Forty patients completed the study; 8 of the 11 drop-outs were taking buspirone. Both drugs reduced anxiety, diazepam more rapidly, but with greater withdrawal symptoms, particularly after 6 weeks. Regular treatment with diazepam for 6 weeks leads to a significant risk of pharmacological dependence that is not present with buspirone.

Pecknold, J. C., M. Matas, et al. (1989). "Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo." Can J Psychiatry **34**(8): 766-71.

Buspirone has previously been demonstrated to be efficacious in the treatment of anxiety. This four-week double-blind parallel study compared buspirone to diazepam and placebo in the treatment of 119

outpatients diagnosed as having generalized anxiety disorder. After a seven-day placebo washout period, eligible patients were randomized to one of three treatment groups. Buspirone (5 mg) and diazepam (5 mg) were administered BID and individually titrated to an optimal therapeutic dose by the end of week two. Buspirone and diazepam were equally effective in reducing Hamilton Anxiety (HAM-A) total and psychic factor scores from baseline values. Buspirone alone was significantly better than placebo in reducing the HAM-A somatic factor score. Sixty-seven percent of both active treatment groups who were classified as "ill" on the baseline global psychopathology rating scale achieved a "not ill" status by study end. There were no significant differences between treatment groups at endpoint on the 56-item Symptom Checklist self-rating scale. Buspirone was demonstrated to be as effective as diazepam in relieving anxiety in this outpatient sample.

Pomara, N., L. M. Willoughby, et al. (2005). "Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder." Psychopharmacology (Berl) **178**(1): 1-8.

OBJECTIVE: Acute diazepam administration has been shown to decrease plasma cortisol levels consistent with decreased activity of the hypothalamic-pituitary-adrenal axis, especially in individuals experiencing stress. However, the effects of chronic diazepam treatment on cortisol have been less studied, and the relationship to age, anxiety, duration of treatment, and dose are not well understood. METHOD: This double-blind placebo-controlled study examined acute and chronic effects of diazepam on plasma cortisol levels in young (19-35 years) and elderly (60-79 years) individuals with and without generalized anxiety disorder (GAD). Subjects received single oral challenges of placebo or diazepam (2.5 mg or 10 mg) in a placebo-controlled cross-over design, followed by 3 weeks of chronic daily treatment with 2.5 mg or 10 mg diazepam or placebo taken at 10 p.m., and then by a final acute challenge with a single oral dose of the same study medication received during chronic treatment. RESULTS: The elderly experienced significant reductions in plasma cortisol levels compared to placebo both in the initial challenge and during chronic treatment, but the young did not. However, cortisol response to drug was comparable in both groups. Final challenge did not produce any significant cortisol effects in either group and the cortisol response in the elderly was significantly reduced compared to the initial challenge. GAD status was not a factor in plasma cortisol responses to diazepam. CONCLUSIONS: Diazepam reduced cortisol both acutely and during chronic treatment, but not during final challenge, consistent with some tolerance development. This effect was most apparent in the elderly compared with the young adults and was not modulated by GAD status or dosage, and was not related to drug effects on performance and on self-ratings of sedation and tension.

Pourmotabbed, T., D. R. McLeod, et al. (1996). "Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder." J Clin Psychopharmacol **16**(3): 202-7.

Twenty-one women with generalized anxiety disorder (GAD) participated in a 6-week, double-blind, placebo-controlled trial to assess the treatment and abrupt withdrawal effects of diazepam on psychic and somatic symptoms of anxiety. The results confirmed those of previous studies reporting that (1) clinical doses of diazepam are effective in attenuating the symptoms of generalized anxiety to a greater extent than placebo during the first 3 weeks of treatment; (2) somatic symptoms are more responsive to diazepam treatment than psychic symptoms; and (3) patients taking diazepam exhibit increased anxiety upon abrupt withdrawal of medication. This finding, combined with the fact that diazepam discontinuation did not produce withdrawal effects in non-anxious volunteers, suggests that diazepam discontinuation after 6 weeks results in rebound anxiety rather than a physical withdrawal syndrome. Diazepam did not improve psychomotor performance in GAD patients. Psychomotor impairment after 6 weeks of diazepam was similar to that seen in nonanxious volunteers.

Rickels, K., R. Downing, et al. (1993). "Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam." Arch Gen Psychiatry **50**(11): 884-95.

OBJECTIVE: The current study examines whether antidepressants, contrary to current thinking, are safe and effective treatments for generalized anxiety disorder (GAD) not complicated by depression or panic disorder. DESIGN: Randomized, double-blind, placebo-controlled, flexible-dose, 8-week treatment study comparing imipramine hydrochloride (mean maximum daily dose, 143 mg), trazodone hydrochloride (255 mg), and diazepam (26 mg). PATIENTS: Two hundred thirty patients with a DSM-III diagnosis of GAD in whom major depression and panic disorder has been excluded, and who had a Hamilton Anxiety Scale total score of at least 18. SETTING: Seventy-five percent of patients were treated in family practice settings in the community, with the remainder treated in psychiatric practices, either academic or private. RESULTS: Patients treated with diazepam showed the most improvement in anxiety ratings during the first 2 weeks of treatment, with somatic symptoms being most responsive. From week 3 through week 8 trazodone achieved comparable, and imipramine somewhat better, anxiolytic efficacy when compared with diazepam, with psychic symptoms of tension, apprehension, and worry being more responsive to the antidepressants. Among completers, moderate to marked improvement was reported by 73% of patients treated with imipramine, 69% of patients treated with trazodone, 66% of patients treated with diazepam, but only 47% of patients treated with placebo. Overall, patients treated with antidepressants reported a higher rate of adverse effects than diazepam-treated patients, but attention rates were the same across all treatments. CONCLUSIONS: The results of the study need replication, but suggest a potentially

important role for antidepressants, particularly imipramine, in patients suffering from GAD.

Rickels, K., E. Schweizer, et al. (1997). "Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial." J Clin Psychopharmacol **17**(4): 272-7.

This randomized, double-blind clinical trial involving 198 generalized anxiety disorder (GAD) patients was conducted to more clearly define gepirone's role for the treatment of anxiety in daily dosages of 10 to 45 mg compared with diazepam and placebo. A secondary goal was to test for possible discontinuation symptoms after abrupt discontinuation of therapy. After a 1-week washout period, patients were treated for 8 weeks and then abruptly shifted under single-blind conditions for 2 weeks on placebo. The highest attrition rate occurred with patients on gepirone (58%) and the lowest on diazepam (34%). Medication intake for week 4 was 19.5 +/- 12.5 mg/day diazepam and 19.0 +/- 11.5 mg/day gepirone and was similar at week 8. The major adverse events were light-headedness, nausea, and insomnia for gepirone and drowsiness and fatigue for diazepam. Clinical improvement data showed gepirone's anxiolytic response to be delayed, being significant from placebo beginning at week 6, whereas diazepam caused significantly more relief than placebo from week 1 onward. Taper results showed that only diazepam, but not gepirone, caused a temporary worsening of anxiety symptoms or rebound.

Rocca, P., V. Fonzo, et al. (1997). "Paroxetine efficacy in the treatment of generalized anxiety disorder." Acta Psychiatr Scand **95**(5): 444-50.

Recently, there has been a renewed interest in alternatives to the benzodiazepines for the treatment of generalized anxiety disorder (GAD). The aim of the present study was to compare the efficacy of paroxetine vs. imipramine and 2'-chlordesmethyldiazepam in 81 patients with a DSM-IV diagnosis of GAD. Approximately two-thirds of the patients who completed the study improved greatly or moderately on all three active drugs. During the first 2 weeks of treatment, 2'-chlordesmethyldiazepam treatment resulted in the greatest improvement in anxiety ratings. Both paroxetine and imipramine treatment resulted in more improvement than 2'-chlordesmethyldiazepam by the fourth week of treatment. Paroxetine and imipramine affect predominantly psychic symptoms, whereas 2'-chlordesmethyldiazepam affects predominantly somatic symptoms. Our results suggest that paroxetine is effective for the treatment of GAD.

Rynn, M., S. Khalid-Khan, et al. (2006). "Early response and 8-week treatment outcome in GAD." Depress Anxiety **23**(8): 461-5.

Our objective was to compare the predictive value of early response to treatment outcome in patients with generalized anxiety disorder (GAD) treated with benzodiazepines, serotonin receptor (5HT-1A) partial agonists, or placebo. Data from two double-blind GAD studies were combined. Subjects were evaluated with the Hamilton Anxiety Scale (HAM-A) and the Clinical Global Impression of Improvement (CGI-I)

scale over 8 weeks. Categories of response at weeks 1 and 2 were defined by the HAM-A total score. Analyses of covariance and Kaplan-Meier survival analyses were the primary analyses used to assess 8-week end point treatment outcomes as a function of early improvement. HAM-A change from baseline to weeks 1 and 2 significantly predicted last observation carried forward (LOCF) response at week 8 for both medications and for placebo (P<.001). Early improvement was a strong predictor for treatment outcome irrespective of whether active medication or placebo was the treatment agent.

Strand, M., J. Hetta, et al. (1990). "A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam." J Clin Psychiatry **51 Suppl**: 40-5.

Two hundred thirty patients with generalized anxiety and Hamilton Rating Scale for Anxiety (HAM-A) scores greater than or equal to 18 were subdivided at random, according to a double-blind design, into one group treated with 5-10 mg of oral buspirone t.i.d. or one group treated with 10-20 mg of oral oxazepam t.i.d. for 6 weeks. No anxiolytic treatment was allowed 3 months prior to trial entry. Analysis of demographic variables revealed no significant imbalance between the two treatment groups. Twenty patients were excluded from efficacy analysis because of treatment withdrawal before the first efficacy evaluation on Day 7. Another 4 patients were excluded because they were taking concomitant psychotropic medication. The remaining 206 patients displayed a decrease in HAM-A scores (mean +/- SD) from 23.9 +/- 4.1 to 10.6 +/- 7.7 in the buspirone group and from 23.9 +/- 4.2 to 11.5 +/- 8.0 in the oxazepam group. The two treatment groups were also found to be virtually identical in an "intent to treat" analysis of all 230 patients as well as in other ratings (Hamilton Rating Scale for Depression, Raskin Depression Scale, Covi Anxiety Scale, Physicians Questionnaire, global ratings, and Hopkins Symptom Checklist [HSCL]-56). However, oxazepam was never superior to buspirone in any of the efficacy analyses. Of the 230 patients, 127 spontaneously reported adverse events, including drowsiness, dizziness, headache, nausea, and nervousness. Adverse events were relatively similar in the two groups. In conclusion, buspirone and oxazepam appear to be equally effective in the treatment of generalized anxiety encountered by general practitioners. This outcome, in addition to a previously documented absence of any dependency liability, makes buspirone a clinically important anxiolytic drug.

Tyrer, P. and R. Owen (1984). "Anxiety in primary care: is short-term drug treatment appropriate?" J Psychiatr Res **18**(1): 73-8.

Thirty-six patients with generalised anxiety disorder, panic disorder or agoraphobia with panic attacks, diagnosed by DSM-III criteria, were treated with a new non-benzodiazepine anti-anxiety drug, buspirone, and with diazepam and placebo, in a cross-over design. Each patient took buspirone, diazepam and placebo for one week each in flexible dosage and balanced order. Ratings of symptomatology using the

Comprehensive Psychopathological Rating Scale were made after each week's treatment and a sub-scale used for measuring anxiety change alone was used separately. There was no overall difference in efficacy between the drugs, but when the scores for individual symptoms were analysed, diazepam was significantly superior to the other treatments for the symptom of muscle tension only. The results suggest that the common practice of giving short-term therapy with tranquilising drugs for anxiety in primary care is pharmacologically suspect.

Tyrer, P., N. Seivewright, et al. (1993). "The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years." Br J Psychiatry **162**: 219-26.

Repeated assessments of psychopathology, together with personality status, were made over two years on 181 psychiatric out-patients with generalised anxiety disorder (59), panic disorder (66), or dysthymic disorder (56) diagnosed using an interview schedule for DSM-III. Patients were randomly allocated to drug treatment, cognitive and behaviour therapy, or a self-help treatment programme. Although there were no overall differences in compliance rate and efficacy between the three modes of treatment, the psychological treatment methods, particularly self-help, were more effective in patients without personality disorder, and those with personality disorder responded better to drug treatment, primarily antidepressants. The findings suggest that assessment of personality status could be a valuable aid to selection of treatment in neurotic disorders and that self-help approaches are particularly valuable once personality disorder has been excluded.

Tyrer, P., N. Seivewright, et al. (1988). "The Nottingham study of neurotic disorder: comparison of drug and psychological treatments." Lancet **2**(8605): 235-40.

210 psychiatric outpatients with generalised anxiety disorder (71), or panic disorder (74), or dysthymic disorder (65) diagnosed by an interview schedule for DSM-III were allocated by constrained randomisation to one of five treatments: diazepam (28), dothiepin (28), placebo (28), cognitive and behaviour therapy (84), and a self-help treatment programme (42). All treatments were given for 6 weeks and then withdrawn by 10 weeks. Ratings of psychopathology were made by psychiatric assessors blind to both treatment and diagnosis before treatment and at 2, 4, 6, and 10 weeks after randomisation. 18 patients had insufficient data for analysis because of early drop-out. There were no important differences in treatment response between the diagnostic groups, but diazepam was less effective than dothiepin, cognitive and behaviour therapy, or self-help, these three treatments being of similar efficacy. Significantly more patients in the placebo group took additional psychotropic drugs in the 10 week period, and those allocated to dothiepin and cognitive and behaviour therapy took the least.

Wingerson, D. K., D. S. Cowley, et al. (1996). "Effect of benzodiazepines on plasma levels of homovanillic acid in anxious patients and control subjects." Psychiatry Res **65**(1): 53-9.

The effects of four logarithmically increasing doses of intravenous diazepam or placebo on plasma homovanillic acid (HVA) were determined in benzodiazepine-naive patients with panic disorder (PD) or generalized anxiety disorder (GAD), and in healthy controls. Plasma HVA was measured at baseline and 3 min after the first and fourth doses of diazepam/placebo. Mean baseline plasma HVA levels were significantly lower in PD patients compared with GAD patients and controls. Although plasma HVA levels decreased significantly with time in all groups, there was no diazepam effect. This study suggests that low dopaminergic activity may occur in a subset of anxious patients (PD), and that diazepam does not significantly affect dopaminergic activity as measured by plasma HVA in humans.

3 Medline in Process

Martin JL., S.-P. M. F. T. M.-S. E. S. T. G. C. (2007). "Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials." Journal of Psychopharmacology **21**(7): 774-82.

No systematic review or meta-analysis using a hard outcome has been conducted on the role of benzodiazepines for generalized anxiety disorder (GAD). The objective of this study was to assess the effectiveness and efficacy of benzodiazepines in the treatment of GAD based on trial drop-out rates. We used a systematic review of randomized controlled trials that compared any of the three best established benzodiazepines (diazepam, Lorazepam and aLprazolam) against placebo. Our primary outcome for effectiveness was withdrawal for any reason. Our secondary outcome tapping efficacy was withdrawal due to lack of efficacy, and that tapping side effects was withdrawals due to adverse events.We included 23 trials. Pooled analysis indicated less risk of treatment discontinuation due to lack of efficacy for benzodiazepines, compared to placebo, relative risk (RR) 0.29 (95% CI 0.18-0.45; p < 0.00001). Nevertheless, pooled analysis showed no conclusive results for risk of all-cause patient discontinuation, RR 0.78 (95% CI 0.62-1.00; p = 0.05). Meta-regression model showed that 74% of the variation in logRR across the studies was explained by year of publication (p <0.001).This systematic review did not find convincing evidence of the short-term effectiveness of the benzodiazepines in the treatment of GAD. On the other hand, for the outcome of efficacy, this review found robust evidence in favour of benzodiazepines. Due to the heterogeneity induced by year of publication, three hypotheses are plausibLe when it comes to being able to account for the differences between efficacy and effectiveness observed in the outcomes (publication bias, quality of the trial literature and a non-differential response to the placebo effect).

4 EBM Databases (Cochrane)

Centre for Reviews and Dissemination (2007). "A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder (Structured abstract)." Database of Abstracts of Reviews of Effects. **3**.

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.

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.

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.

Rickels K, D. R., Schweizer E, Hassman H (1993). "Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam." Archives of general psychiatry. **50**(11): 884-95.

OBJECTIVE: The current study examines whether antidepressants, contrary to current thinking, are safe and effective treatments for

generalized anxiety disorder (GAD) not complicated by depression or panic disorder. DESIGN: Randomized, double-blind, placebo-controlled, flexible-dose, 8-week treatment study comparing imipramine hydrochloride (mean maximum daily dose, 143 mg), trazodone hydrochloride (255 mg), and diazepam (26 mg). PATIENTS: Two hundred thirty patients with a DSM-III diagnosis of GAD in whom major depression and panic disorder has been excluded, and who had a Hamilton Anxiety Scale total score of at least 18. SETTING: Seventy-five percent of patients were treated in family practice settings in the community, with the remainder treated in psychiatric practices, either academic or private. RESULTS: Patients treated with diazepam showed the most improvement in anxiety ratings during the first 2 weeks of treatment, with somatic symptoms being most responsive. From week 3 through week 8 trazodone achieved comparable, and imipramine somewhat better, anxiolytic efficacy when compared with diazepam, with psychic symptoms of tension, apprehension, and worry being more responsive to the antidepressants. Among completers, moderate to marked improvement was reported by 73% of patients treated with imipramine, 69% of patients treated with trazodone, 66% of patients treated with diazepam, but only 47% of patients treated with placebo. Overall, patients treated with antidepressants reported a higher rate of adverse effects than diazepam-treated patients, but attention rates were the same across all treatments. CONCLUSIONS: The results of the study need replication, but suggest a potentially important role for antidepressants, particularly imipramine, in patients suffering from GAD.

5 Clinical Trials

Forest Laboratories (2007). Initiating Acamprosate Within Versus Post-Detoxification in the Rehabilitative Treatment of Alcohol Dependence.
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Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Crossover Assignment
Further study details as provided by National Institute on Drug Abuse (NIDA):
Primary Outcome Measures:
The mean number of adverse events rated moderate to severe;
The week of detoxification treatment discontinuation;
The total amount of oxazepam given;
The rate of change in CIWA scores.
The mean number of adverse events rated moderate to severe;
The week of open-label treatment discontinuation;
Any reemergence of detoxification symptoms;
Percentage of pills taken over what was proposed to be prescribed (medication exposure);
Percentage days abstinent;
Percentage days heavy drinking. The number of drinks per day will be used to identify a heavy drinking day, defined as 5 or more drinks/day for males and 4 or more drinks/day for females.

Secondary Outcome Measures:
Changes in alcohol craving will be measured by Penn Alcohol Craving Scale (PACS; Flannery et al, 1999)
Changes in anxiety symptoms will be measured by the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Hamilton, 1969)
Changes in depressive symptoms will be measured by the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Hamilton 1967)
Changes in social functioning will be measured by several of the subscales of the Addiction Severity Index (ASI; McLellan et al, 1992); namely, medical, legal, psychiatric, and family/social.
Quality of Life, measured by the Short Form-36 Health Status Questionnaire (SF-36; Ware & Sherbourne, 1999)
Overall clinical impression of improvement will be measured by the Clinical Global Impression Scale (CGI)

King Pharmaceuticals Research and Development (2007). A Study on the Effectiveness and Safety of Diazepam Injection (Vanquix™) for Patients With Epilepsy That Receive Antiepileptic Drugs, But Still Experience Acute Repetitive Seizures (Bouts or Clusters of Seizures) That Require Treatment. **Clinical Trials identifier: NCT00319501**.

Total Enrollment: 325
Study start: January 2006

In the United States, more than 2 million people have epilepsy. Most patients with epilepsy are able to control their seizures with drugs and/or surgery. However, many patients (400,000 to greater than 600,000) are considered refractory to antiepileptic drugs and still experience acute repetitive seizures (ARS). An ARS is an episode of multiple seizures that differs from the patient's usual seizure pattern and is often recognizable by the patient's family and caregivers. The ARS is usually described as a bout or cluster of seizures that occurs over a short period of time in which the patient regains consciousness in between seizures. Only one drug is currently available that persons other than health care professionals (e.g., patient's caregiver) may give to control ARS. This drug is called Diastat®. Diastat® is a diazepam rectal gel and, although it is effective, it may be difficult, inconvenient, or objectionable to use because of its rectal administration. Vanquix™ (diazepam autoinjector) also contains diazepam, but is administered by an automated injectable device into the leg muscle. Vanquix™ may be less difficult and more convenient to use by caregivers, however, its effectiveness and safety have not been studied in patients. This study will determine the effectiveness and safety of Vanquix™ compared to placebo for treating ARS.

University of Utah, P. C. s. M. C. F. (2006). Intranasal Midazolam Versus Rectal Diazepam for Treatment of Seizures.

Purpose

We will conduct a randomized controlled trial comparing the use of nasal midazolam, using a Mucosal Atomization Devise, to rectal diazepam for the treatment of acute seizure activity in children under the age of 18 years with epilepsy in the community setting. Our primary hypothesis is that nasal midazolam will be more effective and have shorter seizure time compared to rectal diazepam in the community. Our secondary hypotheses are that patients treated with nasal midazolam will have less respiratory complications, Emergency Department visits and admissions.

Total Enrollment: 200
Study start: June 2006; Expected completion: June 2007

Study Design: This is a prospective randomized controlled study.

6 Hand Searched References

Borison, R., Albrecht, JW, Diamond, BI. (1990). "Efficacy and safety of a putative anxyiolitic agent: Ipsapirone." Psychopharmacology Bulletin. **6**(26): 207-209.

Boyer, W., Feighner, JP. (1993). "A placebo-controlled double-blind multicenter trial of two doses of ipsapirone versus diazepam in generalized anxiety disorder." International Clinical Psychopharmacology **8**: 173-76.

Casacalenda, N. e. a. (1998). "Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. ." Canadian Journal of Psychiatry. . **43**(7): 722.

Centre for Reviews and Dissemination (2007). " Long-term pharmacological treatment of generalized anxiety disorder (Structured abstract)." Database of Abstracts of Reviews **2**.

Coak, A. R., J; Morris, S. (2007). "Thioridazine for anxiety and depressive disorders. ." Cochrane Database of Systematic Reviews.(2).

Cohn, J., Rickels, K. (1989). "A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. ." Current Medical Research and Opinion **11**(5): 304-20.

DeMartinis, N., Runn, M, Rickels, K, Mandos, L. P. (2000). "Prior Benzodiazepine Use and Buspirone Response in the Treatment of Generalized Anxiety Disorder. ." The Journal of Clinical Psychiatry **61**(2): 91-94.

Fontaine, R., L. Annable, et al. (1983). "Bromazepam and diazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations." J Clin Psychopharmacol **3**(2): 80-7.

In a double-blind, placebo-controlled study, 48 anxious outpatients with a primary diagnosis of generalized anxiety disorder were randomly assigned to 4 weeks of treatment with bromazepam (18 mg/day), diazepam (15 mg/day), or placebo, after a 1-week washout period. From week 1 onward both active drugs were superior to placebo in relieving anxiety symptoms. Bromazepam was found to be significantly more effective than diazepam with respect to the somatic anxiety factor and the total score for the Hamilton Anxiety Rating Scale and the fear/anxiety factor of the Patient's Self-Rating Symptom Scale. Plasma concentrations of diazepam plus active metabolites were correlated significantly (r = 0.60, p less than 0.05) with the percentage reduction in self-rating anxiety scores. Bromazepam plasma concentration measurements showed greater variability than those of diazepam and were not found to be correlated significantly with clinical response. It is suggested that the use of strict diagnostic criteria (1978 draft of the

third edition of Diagnostic and Statistical Manual of Mental Disorders), adequate sample sizes, and a 4-week study period gave increased sensitivity for the detection of significant differences between the two benzodiazepines.

Fontaine, R., P. Beaudry, et al. (1987). "Comparison of withdrawal of buspirone and diazepam: a placebo controlled study." Prog Neuropsychopharmacol Biol Psychiatry **11**(2-3): 189-97.

In a 8-week double-blind placebo controlled study, 48 outpatients with generalized anxiety disorder were randomized to diazepam, buspirone, a non-benzodiazepine anxiolytic, or placebo. During the treatment phase of 4 weeks duration diazepam was found to be significantly better than placebo and buspirone. Following abrupt withdrawal by placebo substitution the diazepam group showed a gradual relapse maximal after two weeks while the buspirone and the placebo groups did not differ. There were more cases of rebound anxiety with diazepam as compared to buspirone or placebo. In addition, there were three early terminations related to rebound anxiety in the diazepam group while there were none in the placebo and buspirone groups. There were significantly more new symptoms in the diazepam group than in the placebo or buspirone group.

Fontaine, R., G. Chouinard, et al. (1984). "Bromazepam and diazepam in generalized anxiety: a placebo-controlled study of efficacy and withdrawal." Psychopharmacol Bull **20**(1): 126-7.

Fontaine, R., G. Chouinard, et al. (1984). "Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment." Am J Psychiatry **141**(7): 848-52.

In this double-blind, placebo-controlled study of 4 weeks of benzodiazepine treatment followed by 3 weeks of abrupt or gradual drug withdrawal, 16 patients whose benzodiazepine was withdrawn abruptly were worse (p less than .05) than 13 who had received placebo in terms of change in mean anxiety scores from the pretreatment level. The scores of seven patients (44%) whose benzodiazepine was withdrawn abruptly increased 10% or more on both the Hamilton Rating Scale for Anxiety and the Self Rating Symptom Scale. There were no cases of rebound anxiety in 14 patients whose benzodiazepine was withdrawn gradually; fewer cases of rebound anxiety were seen with a benzodiazepine that had a long half-life.

Goldberg, H. L. and R. Finnerty (1982). "Comparison of buspirone in two separate studies." J Clin Psychiatry **43**(12 Pt 2): 87-91.

Two double-blind studies are described in which buspirone was compared with placebo and diazepam (Study A) or clorazepate (Study B) in outpatients with moderate to severe anxiety. Results, assessed on the Hamilton Rating Scales for Depression and Anxiety, the SCL-56, the Profile of Mood States, and the Covi and Raskin scales, indicated that buspirone consistently relieved both anxiety and associated

depression. In Study B, trends in favor of buspirone were seen on several SCL-56 items and the Hamilton somatic factor; significant differences in this direction were found for several POMS items. Sedation was seen less often with buspirone than either diazepam or clorazepate.

Heideman, J., van Rijswijk E, van Lin N, de Loos S, Laurant M, Wensing M, van de Lisdonk E, Grol R. (2005). "Interventions to improve management of anxiety disorders in general practice: a systematic review." British Journal of General Practice. **55**(520): 867-874.

Mahe, V. e. a. (2000). "Long-term pharmacological treatment of generalized anxiety disorder. ." International Clinical psychopharmacology. **15**(2): 99-105.

Mitte K, N. P., Steil R, Hautzinger M. (2005). "Ameta-analytic review of the efficacy of drug treatment in generalized anxiety disorder." Journal of Clinical Psychopharmacology. **25**(2): 141-150.

Pecknold, J., Familamiri, P, Chang, H, Wilson, R, Alarcia, J, Mc-Clure, J. (1985). "Buspirone: Anxiolytic?. ." Progress in Neuro-psychopharmacol-ogy & Biological Psychiatry **9**: 638-642.

Power, K. e. a. (1990). "A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo, alone and in combination, the the treatment fo generalized anxiety disorder. ." J. anxiety disorder. **4**(4): 267-292.

Rickels, K., N. DeMartinis, et al. (2000). "A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder." J Clin Psychopharmacol **20**(1): 12-8.

In a multicenter, double-blind trial, 310 patients who had received a diagnosis of generalized anxiety disorder were treated for 6 weeks with either abecarnil, diazepam, or placebo at mean daily doses of 12 mg of abecarnil or 22 mg of diazepam administered three times daily. Patients who were improved at 6 weeks could volunteer to continue double-blind treatment for a total of 24 weeks. The maintenance treatment phase allowed the comparison of taper results for the three treatments at several study periods (0-6 weeks, 7-12 weeks, and more than 12 weeks). Slightly more diazepam (77%) and placebo (75%) patients completed the 6-week study than abecarnil patients (66%). At intake and baseline, after a 1-week placebo washout, the patient was required to have a Hamilton Rating Scale for Anxiety score of > or =20. Major adverse events for both abecarnil and diazepam were drowsiness, dizziness, fatigue, and coordination difficulties. Clinical improvement data showed that both abecarnil and diazepam produced statistically significantly more symptom relief than did placebo after 1 week of treatment. At 6 weeks treatment (using last observation carried forward analysis), however, only diazepam still differed significantly ($p < 0.01$) from placebo. High placebo response (56% moderate to marked global improvement) at 6 weeks, as well as a slightly lower nonsignificant improvement rate observed with abecarnil, a partial y-

aminobutyric acid (GABA) agonist, when compared with diazepam, a full GABA agonist, most likely contributed to our findings. Finally, taper results showed that only diazepam and not abecarnil caused the presence of temporary discontinuation symptoms, but only in patients who had been treated for at least 12 weeks.

Rickels, K., K. Weisman, et al. (1982). "Buspirone and diazepam in anxiety: a controlled study." J Clin Psychiatry **43**(12 Pt 2): 81-6.

The anxiolytic properties of buspirone were assessed in a 4-week double-blind study in 240 anxious patients, 81 of whom received buspirone, 81 diazepam, and 78 placebo. Patients were required to have scores greater than or equal to 9 on the Covi and greater than or equal to 18 on the Hamilton Rating Scale for Anxiety, and to endorse at least 5 items on a 17-item Anxiety Entry Checklist. Among 212 evaluable patients, those who improved most were married, well-educated females who had both a positive family adjustment and a low level of depression. Diazepam produced relatively equal improvement in females and males. Diazepam seems more effective in reducing somatic symptoms, while buspirone appears more effective in reducing symptoms associated with cognitive and interpersonal problems. Main differences between the drugs were seen in side effect profiles.

Ross, C., Matas, M. (1987). "A Clinical Trial of Buspirone and Diazepam in the Treatment of Generalized Anxiety Disorder. ." Canandian Journal of Psychiatry **32**: 351-355.

Shah, L. P., et al., (1990). "A controlled double blind clinical trial of buspirone and diazepam in generalised anxiety disorder. ." Indian Journal of Psychiatry. **32**(2): 166-169.

Attachment 5

Detailed assessment of the measures taken by investigators to minimise bias in the randomised trials (addendum to Section B.3)

Information on randomisation, blinding and follow-up in the key randomised, controlled trials is provided in Table B.3.1 below. Further detail on each of these methodological topics is provided below the table.

Table B.3.1 Summary of the measures undertaken to minimise bias in the randomised, controlled trials

Trial ID	Concealment of randomisation[a]	Blinding			Basis of analysis[b]
		Participants	Investigators	Outcomes assessors	
Escitalopram versus placebo					
SCT-MD-05	B (p .29, 30)	Yes (p. 30)	Yes (p. 30)	Yes (p. 30)	E[c, d] (p. 42)
SCT-MD-06	B (p. 27, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	E[c, d] (p. 41)
SCT-MD-07	B (p. 27, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	E[c, d] (p. 41)
SCT-MD-31[1]					
99815	B (p. 28, 29)	Yes (p. 27-29)	Yes (p. 27-29)	Yes (p. 27-29)	E[d, e] (p. 39)
99769	B (p. 28, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)
Placebo versus benzodiazepine					
Hacket et al.	NR[f]	NR[f]	NR[f]	NR[f]	E[g] (p. 183)

a A = central telephone randomisation service; B = third-party randomisation service (eg pharmacy, pharmaceutical company);
C = sequentially labelled, fully opaque, sealed envelopes
b D = intention-to-treat (all randomised participants: specify how the analysis dealt with missing data); E = all treated participants (specify how the analysis dealt with missing data); F = per protocol participants; G = other (specified)
c The ITT population consisted of all randomised patients who received at least one dose of double-blind study medication with at least one post-baseline efficacy assessment on the HAMA.
d. Last Observation Carried Forward (LOCF) was used in the analysis to account for missing data (SCT-MD-05 p. 44, SCT-MD-06 p. 42, SCT-MD-07 p. 42, 99815 p. 42)
e. All efficacy analyses were conducted on the full-analysis-set (FAS), i.e. all randomised patients who took at least one dose of study medication and who had at least one valid post-baseline assessment of the primary efficacy variable. Safety analyses (except analyses of DESS) were based on the all-patients-treated set (APTS), i.e. all randomised patients who took at least one dose of study medication. DESS analyses were conducted on the all-patients-completed set (APCS), i.e. all patients in the FAS who completed 12 weeks of double-blind treatment
f. The study is reported as being double-blind and randomised. No details of blinding or randomisation are given.
g. The analysis population was "randomised patients who had received at least one dose of study medication and who had at least one evaluation on one of the primary efficacy parameters, either during therapy, or within 3 days of the last treatment".
BZD = benzodiazepine, DESS = Discontinuation Emergent Signs and Symptoms, HAMA = Hamilton Anxiety Scale

[1] t the stage the time the submission went in – there was no information available regarding 031.

Randomisation

SCT-MD-05, SCT-MD-06, SCT-MD-07

All patients were randomised into the two treatment groups (escitalopram 10mg/day, possibly increasing to 20mg/day or placebo) for the eight-week double-blind treatment period following a one-week single-blind placebo lead-in period. A list of patient randomisation numbers with corresponding assigned treatment was generated by Forest Laboratories Department of Biostatistics. Each study site was provided with drug supplies corresponding to this of sequence of patient numbers. The first patient to enter into the study was assigned the first number in the sequence, and each subsequent patient entered was assigned a sequential patient number

99815

This was a multinational, multicentre, randomised, double-blind, parallel-group, placebo-controlled, active-reference (paroxetine), fixed-dose study in outpatients with GAD. There was a one-week, single-blind placebo run-in period, after which patients were randomised to 12 weeks of double-blind treatment with escitalopram (fixed doses of 5, 10 or 20mg/day), paroxetine (20mg/day) or placebo, followed by a 2-week washout period. Details of the paroxetine treatment arm are not presented in the submission as paroxetine is not a relevant comparator. The randomisation code was generated by H.Lundbeck A/S. A total of 1121 randomisation numbers were prepared, with 224 numbers assigned to each treatment group. At each centre, the intention was to consecutively assign the lowest randomisation number available. Block randomisation ensured that equal numbers of patients entered each treatment group.

99769

This was a multinational, multicentre, fixed-dose study with a 12-week, open-label treatment period with escitalopram followed by a double-blind, parallel-group comparison of escitalopram and placebo in the prevention of relapse of GAD. Patients were in the double-blind period for a minimum of 24 weeks and a maximum of 76 weeks, depending on when in the accrual period they entered the study, as all patients were to complete the double-blind period simultaneously. Patients who completed the double-blind period entered a 2-week, double-blind, down-tapering period. During the first week of the open-label period, the patients received 10mg/day escitalopram. The dose was doubled to 20mg/day escitalopram from Week 2. No down-titration was allowed. Patients who had responded to treatment at the end of the 12-week, open-label period were eligible for randomisation to double-blind treatment with escitalopram or placebo. During the double-blind period, patients randomised to placebo received 10mg/day escitalopram for one week and then continued on placebo. Patients randomised to escitalopram continued on 20mg/day escitalopram.

Eligible patients were randomised to double-blind treatment with either placebo or escitalopram in a 1:1 ratio according to a randomisation code generated by H.Lundbeck A/S. Block randomisation (in blocks of four) ensured that equal numbers of patients entered each treatment group. At each centre the 4-digit randomisation code was to be assigned consecutively (according to the timing of Visit 7, i.e. the end of the 12-week open-label period), starting with the lowest number available.

Hackett et al.

It is stated in the publication that the study was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. No details of the randomisation method are provided.

Blinding

SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31

For the double-blind treatment period patients were supplied with identically appearing tablets containing either escitalopram or placebo. The randomisation code was to be broken only in an emergency. The randomisation code was not broken and no patient was unblinded during the studies.

99815

The study products were all identical brownish-red capsules for oral administration. All capsules contained a tablet (either escitalopram, placebo or paroxetine) and white powder and were indistinguishable from one another since they were identical in appearance, shape, taste and smell. The randomisation code was to be broken on in an emergency, however the code was not broken for any patients during the study.

99769

Escitalopram and placebo were supplied as film-coated tablets of identical appearance. The randomisation code was to be broken on in an emergency, however the code was not broken for any patients during the study.

Hackett et al.

It is stated that the study was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. No details of blinding are provided.

Basis of the analysis

SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31[2]

The following analysis sets were defined *a priori*:

- Randomised population - all patients randomised into the study
- Safety Population – all randomised patients who took at least one dose of double-blind study medication
- Intent-to-Treat (ITT) population consisted of all patients in the safety population with at least one post-baseline efficacy assessment on the Hamilton Anxiety Scale (HAMA).

All efficacy analyses were conducted on the ITT population. The analyses were performed using the Last Observation Carried Forward (LOCF) approach. All safety analyses were conducted on the Safety Population.

99815

The following analysis sets were defined *a priori*:

- All-patients-randomised set (APRS) – all patients randomised into the study
- All-patients treated set (APTS) – all randomised patients who took at least one dose of double-blind study product
- Full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the primary efficacy variable.
- All-patients-completed-set (APCS) – all patients in the FAS who completed 12 weeks of double-blind treatment
- Per-protocol set (PPS) – all patients in the FAS who received double-blind study product for at least 4 weeks, who had at least one valid assessment of the HAM-A total score at or after the Week 4 assessment, and who had no major protocol violations

All efficacy analyses were conducted on the FAS. The analyses were performed using the Last Observation Carried Forward (LOCF) approach. Safety analyses (except analyses of Discontinuation-Emergent Signs and Symptoms (DESS)) were conducted on the APTS.

[2] At the stage the time the submission went in – there was no information available regarding 031. However given the similarities of the trials, this is likely to be the case.

99769

The following analysis sets were defined *a prior* for the double-blind study period:

- All-patients-randomised set (APRS) – all patients who completed the open-label period and were randomised into double-blind study period.
- All-patients treated set (APTS II) – all randomised patients in the APRS who took at least one dose of study product in the double-blind period.
- Full-analysis set (FAS) – all patients in the APRS who took at least one dose of study product in the double-blind period.
- All-patients-completed-set (APCS) – all patients in the FAS who completed 12 weeks of double-blind treatment
- Per-protocol set (PPS) – all patients in the FAS who had no major protocol deviations. Patients could be completely or partly (only selected visits) excluded from the PPS.

To be consistent with the usual terminology used by the sponsor in the escitalopram GAD clinical trial program, both an APTS II and FAS were defined, even though the definition was the same for both.

All efficacy analyses in the double-blind period were conducted on the FAS. The analyses were performed using the Last Observation Carried Forward (LOCF) approach, where relevant. Safety analyses (in the double-blind period) were based on the APTS II.

Hackett et al.

Randomised patients who had received at least one dose of study medication and who had at least one evaluation on one of the primary efficacy parameters, either during therapy, or within 3 days of the last treatment, constituted the intent-to-treat population (ITT) for the evaluation of efficacy. The safety population was evaluated in the randomised population. The primary efficacy analysis was carried out using the LOCF method to impute missing data.

Adequacy of follow-up

Escitalopram versus placebo studies

The flow of participants through the individual randomised, controlled trials comparing escitalopram with placebo was well documented in the Study Reports. Data from the majority of patients randomised into the studies was analysed in the efficacy analyses (over 95%).

Placebo versus benzodiazepines study

The flow of participants in each treatment arm of the study by Hackett et al. was poorly documented, with only the number of patients discontinued and the number of patients analysed reported.

Table B.3.2 summarises the flow of participants through the key randomised, controlled trials.

Table B.3.2 Flow of participants through the randomised, controlled trials

Trial ID • Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Dis-continued	Analysed	Source of information
Escitalopram vs placebo						
SCT-MD-05						Study Report p. 52, Panel 8, 9.
• Escitalopram	129	3 (2.3%)	4 (3.1%)	29[a] (23%)	124[b] (96%)	
• Placebo	128	0 (0%)	8 (6.3%)	33 (26%)	128 (100%)	
SCT-MD-06						Study Report p. 50, Panel 8, 9.
• Escitalopram	149	4 (2.7%)	7 (4.7%)	27[a] (18%)	143[c] (96%)	
• Placebo	145	3 (2.1%)	10 (6.9%)	28[a] (19.%)	138[d] (95%)	
SCT-MD-07						Study Report p. 50, Panel 8, 9.
• Escitalopram	161	3 (1.9%)	12 (7.5%)	39[a] (24%)	154[d] (96%)	
• Placebo	159	2 (1.3 %)	12 (7.5%)	34[a] (21.%)	153[e] (96%)	
SCT-MD-31[f]						Study Report p. 29, 30
• Escitalopram	131	4 (3.0%)	4 (3.0%)	29 (22%)	125 (95%)	
• Placebo	140	4 (2.9 %)	4 (2.9%)	36 (26%)	135 (96%)	
99815						Study Report p. 45 Panel 7, p. 47 Panel 9.
• Escitalopram 5mg	134	0 (0%)	1 (0.7)	17 (13%)	134 (100%)	
• Escitalopram 10mg	136	0 (0%)	2 (1.5)	18 (13%)	134 (99%)	
• Escitalopram 20mg	133	0 (0%)	0 (0)	22 (17%)	132 (99%)	
• Placebo	139	0 (0%)	0 (0)	15 (11%)	138 (99%)	
99769						Study Report p. 47, Panel 8, p. 49 Panel 12.
• Escitalopram	187	1[g] (0.5%)	8 (4.3%)	71 (38%)	186 (99%)	
• Placebo	188	1[g] (0.5 %)	4 (2.1%)	136 (72%)	187 (99%)	
BZD vs placebo						
Hackett et al.						Hackett et al. p. 183, 184.
• Diazepam 15mg d	NR[h]	NR[h]	NR	14[i]	89	
• Placebo	NR[h]	NR[h]	NR	16[i]	97	

a. This figure does not include the patients who "Did not receive intervention".
b. 2 patients had no post-baseline primary efficacy (HAMA) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 3 patients who did not receive the intervention
c. 2 patients had no post-baseline primary efficacy (HAMA) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 4 patients who did not receive the intervention
d. 4 patients had no post-baseline primary efficacy (HAMA) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 3 patients who did not receive the intervention
e. 4 patients had no post-baseline primary efficacy (HAMA) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 2 patients who did not receive the intervention
f. Details of the venlafaxine XR treatment arm not detailed, as it is not a comparator
g. 1 patient was randomised into each treatment group even though they were not eligible for randomisation
h. The study consisted of 4 treatment arms – diazepam, placebo and two different doses of venlafaxine XR. Only the diazepam and placebo results are reported in the submission. In total 564 patients entered the study, 556 received at least one dose of study medication and were included in the randomised population. 16 patients failed to provide a primary efficacy evaluation on therapy. The remaining 540 patients constituted the defined ITT population. The patient numbers in the individual treatment arms are not provided.
i. Patients discontinued in the analysed population only are reported.