ATTACHMENT 4

DETAILS OF THE LITERATURE SEARCHES CONDUCTED FOR ESCITALOPRAM GAD SUBMISSION

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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.

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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.

2 PubMed

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.

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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.

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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.