Characteristics Table for The Clinical Question: In the treatment of generalised anxiety disorder does pharmacology improve outcome?

Comparisons Included in this Clinical Question

Anticonvulsants versus Placebo
FELTNER2003
KASPER2009
MONTGOMERY2006
MONTGOMERY2008
PANDE2003
PFIZER2005
POHL2005
RICKELS2005

Anticonvulsants vs Venlafaxine (SNRI) vs Placebo
KASPER2009
MONTGOMERY2006

Antihistamine vs Placebo
DARCIS1995
LADER1998
LLORCA2002

Benzodiazepines versus Anticonvulsants
FELTNER2003
PANDE2003
PFIZER2005
RICKELS2005

Benzodiazepines versus Azapirones
BOURIN1992

Benzodiazepines versus Placebo
ANDREATINI2002
ANSSEAU2001
CUTLER1993A
FELTNER2003
FRESQUET2000
HACKETT2003
LYDIARD1997
MCLEOD1992
MOLLER2001
PANDE2003
PFIZER2008
RICKELS2000B
RICKELS2005

Buspirone vs Placebo
DAVIDSON1999
LADER1998
MAJERCSIK2003
POLLACK1997
SRAMEK1996

Duloxetine (SNRI) vs. placebo
HARTFORD2007
KOPONEN2007
NICOLINI2009
RYNN2008

Duloxetine (SNRI) vs. Venlafaxine (SNRI)
HARTFORD2007
NICOLINI2009

Quetiapine versus Placebo
ASTRAZENECA2007A
ASTRAZENECA2007B
ASTRAZENECA2007C
ASTRAZENECA2008

SSRI vs Venlafaxine
BOSE2008

SSRIs versus Placebo
ALLGULANDER2004
ASTRAZENECA2007A
ASTRAZENECA2007B
BALDWIN2006
BOSE2008
BRAWMAN-MINTZER2006
DAVIDSON2004
GOODMAN2005
GSK2002
GSK2005
HEWETT2001
LENZE2005
LENZE2009
PFIZER2008
POLLACK2001
RICKELS2003

SSRIs versus SSRIs
BALDWIN2006
BALL2005
BIELSKI2005

TCA vs Placebo
MCLEOD1992

Venlafaxine (SNRI) versus Azapirones
DAVIDSON1999

Venlafaxine (SNRI) versus placebo
ALLGULANDER2001
BOSE2008
DAVIDSON1999
GELENBERG2000
HACKETT2003
HARTFORD2007
KASPER2009
LENOXSMITH2003
MONTGOMERY2006
NICOLINI2009
NIMATOUDIS2004
RICKELS2000A

Venlafaxine vs Benzo
HACKETT2003

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ALLGULANDER2001 Study Type: RCT Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication Type of Analysis: ITT/LOCF	n= 529 Age: Mean 45 Range 18-86 Sex: 201 males 328 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV	**Data Used** HAMA Leaving the study due to inefficacy Leaving the study due to adverse events Leaving the study early for any reason **Data Not Used**	**Group 1 N= 137** Venlafaxine (extended release). Mean dose 150mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily.	Funding: Wyeth-Ayerst Research. Quality assessed: +.

Blindness: Double blind

Duration (days): Mean 168

Setting: Belgium, Finland, France, Sweden, UK
Outpatient (14 centres)

Notes: RANOMISATION: not reported.
ALLOCATION CONCEALMENT: not addressed

Info on Screening Process: 541 randomised, 529 met ITT criteria for inclusion.

Exclusions: - DSM-IV diagnosis of GAD
- HAMA score < 20
- HAMA (anxious mood & tension items) < 2
- MDD or other psychiatric disorder
- Clinically important medical disease
- Non-pharmacological drugs with psychotropic effects

Notes: 74% had received prior treatment for anxiety (mostly benzodiazepines & antidepressants); 85% received non-anxiolytic concomitant therapy during the study (26 had beta-blocker, 52 on zolpidem or chloral hydrate)

Baseline: HAMA baseline depression score (approx): 26.48 (range 20 to 52). No significant differences between groups at baseline. Venlafaxine 37.5mg/d: 26.6 (range 20 to 44). Venlafaxine 75mg/d: 26.3 (range 20 to 43). Venlafaxine 150mg/d: 26.3 (17 to 38). Placebo: 26.7 (20 to 52).

Response (50% reduction in HAMA score) - not extractable

Notes: TAKEN AT: 1,2,3,4,6,8,10,12,16,20,24,25 weeks. Efficacy looked at 8 & 24 weeks. DROP OUTS: 36% CHANGE SCORES USED.

Group 2 N= 134

Venlafaxine (extended release). Mean dose 75mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily.

Group 3 N= 130

Placebo - No further information

Group 4 N= 138

Venlafaxine (extended release). Mean dose 37.85mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily.

ALLGULANDER2004

Study Type: RCT

Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication

Type of Analysis: ITT/LOCF

Blindness: Double blind

Duration (days): Mean 84

Setting: Australia, Canada, Denmark, Norway, Sweeden
Outpatient (21 centres)

Notes: RANDOMISATION: procedure not reported.
ALLOCATION CONCEALMENT: not addressed.

Info on Screening Process: 562 screened, 378 randomised, 5 did not receive study medication.

n= 373

Age: Mean 41

Sex: 167 males 206 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Less than 18 years of age
- No DSM-IV primary diagnosis of GAD
- HAMA score < 18
- HAMA (anxious mood & tension items) < 2
- No current use of medically accepted contraception in fertile women
- Other psychiatric diagnosis
- MADRS score > 15
- Concurrent psychotherapy for GAD
- Clinically significant acute/ unstable medical condition
- Treatment with any other psychotropic drug (other than infrequent use of chloral hydrate)
- Suicide risk
- Previous failure to respond to antidepressant drug treatment

Notes: 14% reported a previous diagnosis of depression. 30% reported previous treatment with a psychotropic medication.

Baseline: HAMA baseline depression score (approx): 24.80 (4.75). Sertraline: 24.6 (4.6). Placebo: 25.0 (4.9). No significant differences between groups at baseline.

Data Used

CGI-I

HAMA

Adverse events

Hospital Anxiety and Depression Scale (anxiety)

Leaving the study due to adverse events

Leaving the study early for any reason

Remission (less than 7 on HAMA)

QoL

Response (50% reduction in HAMA score)

Notes: TAKEN AT: 1, 2, 4, 6, 8, 12 weeks. DROP OUTS: 23%. CHANGE SCORES.

Group 1 N= 188

Placebo - No details given.

Group 2 N= 182

Sertraline - 1 week placebo lead-in period. 12 weeks treatment. Taper period. Flexible doses. Week 1: 25mg/d. Week 2,3,4: 50mg/d. Week 5,6 flexible doses in range of 50 - 150mg/g.

Funding: Pzifer, Inc. Quality assessed: +

ANDREATINI2002

Study Type: RCT

Study Description: ITT using LOCF included all those who completed at least 1 week of treatment

Type of Analysis: ITT

n= 36

Age: Mean 41

Sex: 17 males 19 females

Data Used

STAI-trait

HAMA

Leaving the study due to inefficacy

Leaving the study due to adverse events

Group 1 N= 12

Diazepam. Mean dose 6.5mg/day - Following a two week washout period, study drugs were administered in identical capsules containing 2.5mg. The capsules

Drug company funded: BYK Quimica e Farmaceutica Ltds (Brazil). Quality assessment score = +
The study included a number of participants with

Blindness: Double blind

Duration (days): Mean 28

Setting: Sao Paulo ,BRAZIL

Notes: RANDOMISATION: used a computer programme

Info on Screening Process: 132 people were interviewed of which 96 were excluded and 36 participated in the study. Participants were excluded due to the presence of another mental illness, refusal, marked reduction in HAMA prior to study, use of other medications.

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: - No DSM-III-R diagosis of GAD
- current or previous MDD, manic episode, panic disorder, OCD, drug dependence or any psychotic symptoms
- major medical disorders (e.g. CVD, renal disorders etc.)
- drug treatment apart from over the counter drugs
- receiving psychotherapy
- Patients under treatment with Benzodiazepines were excluded if:
1) they had a clinical response or no evidence of side effects to the curent drug
2) they did not undergo a gradual reduction of medication followed by a 2 week wash-out period
- Social phobia or simple phobia excluded if anxiety was secondary to these disorders
- females not using a medically accepted form of birth control

Notes: All participants were evaluated using the SCI-R

Baseline: HAMA - Placebo: 25.1(7.5), Diazepam: 25.2(4.5), Valepotriates: 22.8(7.6)

Notes: TAKEN AT: baseline, end of treatment (4 weeks)
DROPOUTS:Diazepam 1/12 (8.3%), Valepotriate 2/12 (16.6%), Placebo 2/12 (16.6%)

were adminstered three times a day with thelowest dose consisting of two placebo and one active capsules based on response. 4 week

Group 2 N= 12

Placebo - Following a two week washout period, study drugs were administered in identical capsules. The capsules were adminstered three times a day.

Group 3 N= 12

Valepotriates. Mean dose 81.3mg/day - Following a two week washout period, study drugs were administered in identical capsules containing 50mg. The capsules were adminstered three times a day with thelowest dose consisting of two placebo and one active capsules based on response.

current social phobia and simple phobias in addition to GAD

Results from this paper:

ANSSEAU2001

Study Type: RCT

Study Description: 6 parallel groups. 1 week placebo run-in period following by 4 weeks treatment.

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 28

Setting: Outpatients. France.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: 341 entered: 325 went on to DB treatment phase (16 excluded - 9 did not fit inclusion criteria and 7 improved more than 25% on HAMA scale during placebo week).

n= 325

Age: Mean 42

Sex: 133 males 208 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: Could not have a score >2 on item 6 of the Hamilton Anxiety Scale, and score could not be higher than 8 on the Raskin Depression Scale. Evidence of contraindication for an anxiolytic benzodiazepine or serious or uncontrolled medical illness.

Notes: Ppts scored >20 on HAMA and >9 on Covi Anxiety Scale.

Baseline: HAMA at baseline: Suriclone 0.1 29.0 (5.6), Suriclone 0.2 28.6 (5.0), Suriclone 0.3 30.1 (5.2), Suriclone 0.4 30.0 (5.7), Diazepam 29.9 (5.2) and Placebo 29.4 (5.7).

Data Used
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Notes: Assessments made at baseline and after 1, 2 and 4 weeks.

Group 1 N= 56

Suriclone. Mean dose 0.2mg/day - No details provided.

Group 2 N= 57

Suriclone. Mean dose 0.1mg/day - No details provided.

Group 3 N= 54

Diazepam. Mean dose 5mg/day - No details provided.

Group 4 N= 57

Placebo - No details provided.

Group 5 N= 58

Suriclone. Mean dose 0.3mg/day - No details provided.

Group 6 N= 59

Suriclone. Mean dose 0.4mg/day - No details provided.

Funding: no details provided. Quality assessed +.

ASTRAZENECA2007A

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

n= 873

Age: Mean 41

Sex: 306 males 567 females

Data Used
Discontinuation adverse events (DAEs)
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 218

Quetiapine. Mean dose 150mg

Group 2 N= 217

Placebo

Funding: Astra Zeneca

South Africa

Notes: Randomisation: no further details

Info on Screening Process: 1054 screened, 873 randomized

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - <18 years >65 years
- HAM-A <20, and items 1 and 2 <2
- CGI <4
- MADRS >16

Data Not Used
HAMA - no SD

Group 3 N= 217
Paroxetine. Mean dose 20mg

Group 4 N= 221
Quetiapine. Mean dose 50mg

ASTRAZENECA2007B

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: US

Notes: Randomisation: no further details

Info on Screening Process: 1344 screened, 854 randomized

n= 854

Age: Mean 38

Sex: no information

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - <18 years >65 years
- HAM-A <20, and items 1 and 2 <2
- CGI <4
- MADRS >16

Data Used
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Data Not Used
HAMA - no SD

Group 1 N= 213
Escitalopram. Mean dose 10mg

Group 2 N= 207
Quetiapine. Mean dose 300mg

Group 3 N= 219
Quetiapine. Mean dose 150mg

Group 4 N= 215
Placebo

Funding: Astra Zeneca

ASTRAZENECA2007C

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: US

Notes: Randomisation: no further details

Info on Screening Process: 1364 screened, 951 randomized

n= 951

Age: Mean 40

Sex: no information

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - <18 years >65 years
- HAM-A <20, and items 1 and 2 <2
- CGI <4
- MADRS >16

Data Used
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Data Not Used
HAMA - no SDs

Group 1 N= 235
Placebo

Group 2 N= 234
Quetiapine. Mean dose 50mg

Group 3 N= 241
Quetiapine. Mean dose 300mg

Group 4 N= 241
Quetiapine. Mean dose 150mg

Funding: Astra Zeneca

ASTRAZENECA2008

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 64

Setting: Estonia, Polland, Russia, Ukraine, United States

Notes: Randomisation: no further details

Info on Screening Process: 556 screened, 450

n= 556

Age: Mean 70 Range 65-87

Sex: 132 males 316 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - < 66 years of age
- HAM-A <20, and items 1 and 2 <2

Data Used
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Data Not Used
HAMA - no SDs

Group 1 N= 222
Quetiapine - Flexible dosing (50mg-300mg), periodic stepwise increases up to maximum of 300mg

Group 2 N= 216
Placebo

randomized

- CGI <4
- MADRS >16

Baseline: HAM-A: Quetiapine 25.2 (3.5) Placebo 25.1 (3.5)
MADRS: Quetiapine 12.4 (2.6) Placebo 12.3 (2.3)

BALDWIN2006

Study Type: RCT

Study Description: ITT: patients who took at least one dose of the study medication & at least one baseline efficacy assessment were included in analysis

Type of Analysis: LOCF/ITT

Blindness: Double blind

Duration (days): Mean 84

Setting: UK

Notes: RANDOMISATION: computer-generated randomisation list.
ALLOCATION CONCEALMENT: sealed opaque envelopes.

Info on Screening Process: Details not provided.

n= 682

Age: Mean 41

Sex: 244 males 438 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV-TR

Exclusions: - not primary diagnosis of GAD (DSM-IV-TR)
- not between 18 and 65
- HAMA score < 20
- HAMA (anxious mood & tension items) < 2
- MADRS >15
- Diagnosis of: MDD, panic disorder, social anxiety, PTSD, bipolar, OCD, body dysmorhpic disorder, substance abuse, personality disorder
- suicide risk
- receiving psychosocial interventions (i.e. CBT, ECT)
- physical health problems (i.e. vascular)
- concomittant medication (i.e. psychoactive substances, antidepressants, benzodiazepines, antipsychotics)

Baseline: HAMA scores at baseline (approx): 27.04 (4.46); No significant differences at baseline

Data Used
HAMA
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason
DESS (modified)
Response (50% reduction in HAMA score)

Data Not Used
Remission (less than 7 on HAMA) - not extractable

Notes: TAKEN AT: 1,2,4,6,8,10,12,13,14 weeks.DROP OUTS: 14% (98) MEAN CHANGE SCORES.

Group 1 N= 133
Escitalopram. Mean dose 20 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period.

Group 2 N= 134
Escitalopram. Mean dose 5 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period.

Group 3 N= 140
Paroxetine. Mean dose 20 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period.

Group 4 N= 136
Escitalopram. Mean dose 10 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period.

Group 5 N= 139
Placebo - Identical appearance, taste and smell. Oral administration.

Received support from Lundbeck and sponsored by GlaxoSmith Kline. Quality assessed: +.

Results from this paper:

BALL2005

Study Type: RCT

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

Setting: US outpatients

Notes: Randomisation: no further details

Info on Screening Process: 61 ppts; 6 failed for medical or diagnostic reasons.

n= 55

Age: Mean 39

Sex: 14 males 41 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - <18 years
- HAM-A <18
- GAD not primary diagnosis
- HAM-D >20
- history of psychotic or bipolar illness

Baseline: HAM-A: Paroxetine 20.8 (2.3) Sertraline 21.4 (3.4)

Data Used
HAMA
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 28
Sertraline - Starting dose 25mg could be increase up to maximum of 100mg

Group 2 N= 25
Paroxetine - starting dose 10mg and then could be increased up to 40mg

Funding: Pfizer. Quality assessed +.

BIELSKI2005

Study Type: RCT

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 168

Setting: US,outpatients

Notes: Randomisation: no further details

n= 121

Age: Mean 37

Sex: 76 males 45 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - not 18-65 years
- HAM-A <18
- HDRS >17
- Axis I psychiatric disorder
- Psychosis

Baseline: HAM-A: Escitalopram 23.7 (SE =0.5) Paroxetine 23.4 (SE = 0.4)

Data Used
CGI-I
HAMA
Leaving the study due to adverse events
Leaving the study early for any reason
QoL

Data Not Used
CGI (Response) - Not critical outcome

Notes: Response based on CGI score of 1 or 2.

Group 1 N= 61
Escitalopram - 10mg first four weeks, could then be increased to 20mg/day, then every 2 weeks could be increased by 10mg/day

Group 2 N= 60
Paroxetine - 20mg/day first 2 weeks, increased every 2 weeks by 10mg/day

Funding: Forest Laboratories. Quality assessed +.

BOSE2008

Study Type: RCT

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 56

Setting: Outpatients from 28 centres, US

Notes: RANDOMISATION: no further details

Info on Screening Process: 597 screened, 404 randomized, 7 dropped out before start of sudy

n= 404

Age: Mean 38

Sex: 152 males 252 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - HAM-A <20
- HAM-A items 1 and 2 <2
- HDRS >15
- pregnant
- Any other Axis I diagnosis
- Bipolar Disorder, schizophrenia, psychosis, OCD, personality disorder
- learning disabilities

Baseline: HAM-A: Placebo 23.7 (SE = 0.3) Escitalopram 24.2 (SE=0.4) Venlafaxine 23.8 (SE=0.3)

Data Used
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Notes: Side effects reported if incidence over 10%.

Group 1 N= 131
Escitalopram - starting dose of 10mg/day for first week, second week could be increased to 20mg/day

Group 2 N= 140
Placebo - No details given

Group 3 N= 133
Venlafaxine (extended release) - Starting dose of 75mg/day could be increased to maximum of 150mg/day on week 2, and up to 225mg/day in weeks 3-8.

Funded by Forest Laboratories. Quality assessed +.

BOURIN1992

Study Type: RCT

Study Description: Compared discontinuation following 8 weeks of treatment. Parallel groups.

Type of Analysis: Unclear

Blindness: Double blind

Duration (days): Mean 56

Setting: Outpatients. France: multicentre.

Notes: RANDOMISATION: allocation done before the study (30 ppts in each group).

Info on Screening Process: 60 ppts assessed before and after washout period.

n= 43

Age: Range 18-65

Sex: 14 males 29 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: Pregnant women or women not using adequate contraception, nursing mothers, use of digitalis or MAOIs and contra-indications to the use of benzodiazepines. No severe somatic illness. No use of psychotropic drugs or agents with anxiolytic activity during the 2 weeks preceding the study.

Data Used
HAMA
Adverse events
Visual Analog Scale (VAS)
Leaving the study early for any reason

Notes: Assessments performed at baseline, 2, 4, 6 and 8 weeks (active phase) and 9 and 10 weeks (withdrawal phase).

Group 1 N= 20
Lorazepam - 3 or 4mg/day. 1mg in 3-4 divided doses.

Group 2 N= 23
Buspirone - 15-20mg/day. 3-4 capsules of 5mg in 3-4 divided doses per day.

Funding: no details proivded. Quality assessed +.

Notes: Ppts had HAM-A score >=18.

Baseline: HAM-A at baseline. Lorazepam: 27.55 (1.84) and Buspirone: 26.74 (1.89)

BRAWMAN-MINTZER2006

Study Type: RCT

Study Description: ITT: all randomly assigned participants who had at least 1 postbaseline primary outcome measurement.

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 70

Setting: US
Outpatient (9 centres)

Notes: RANDOMISATION: computerized list
ALLOCATION CONCEALMENT: not addressed

Info on Screening Process: Patients registered 428; 338 randomly assigned.

n= 326

Age: Mean 40

Sex: 136 males 190 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Less than 18 years of age
- No DSM-IV primary diagnosis of GAD
- HAMA score > 20
- HAMA (anxious mood & tension items) < 2
- Lower scores on the Covi Anxiety scale than the Raskin Depression Scale
- MDD
- Other psychiatric diagnosis
- MADRS > 17
- Other psychotropic medication
- ECT
- Women lactating, pregnant or childbearing potential not using an acceptable form of contraception

Notes: 53.7% and 51.2% received prior psychotropic medication. 17% reported previous history with depression.

Baseline: HAMA scores at baseline (approx) total: 24.3 (3.00); sertraline: 24.5 (3.1); placebo; 24.1 (2.8). No significant differences at baseline.

Data Used
HAMA
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Notes: TAKEN AT: 1,2,3,4,6,8,10, 11 weeks.
DROP OUTS: 26% CHANGE SCORES USED.

Group 1 N= 165

Sertraline. Mean dose 149.1mg/d - Did not include a placebo run-in phase. 10 weeks of treatment. 1 week taper period. Flexible dose. Week 1: 35mg/d. Weeks: 2,3,4,7 could be increased by 50mg increments. Maximum dose 200mg/d. Dosage reduction permitted.

Group 2 N= 163

Placebo

Financial contributions from Eli Lilly. Quality assessed: +.

CUTLER1993A

Study Type: RCT

Study Description: ITT using LOCF only included participants who completed at least 2 out of the 4 weeks of the study and had a 2 week evaluation

Type of Analysis: ITT

Blindness:

Duration (days): Mean 28

Setting: Not reported: study reports single centre results of a multicentre trial

Notes: Study comprised of a 4 week acute phase followed by an optional 4 week continuation phase and 2 week placebo washout phase

Info on Screening Process: Not reported

n= 90

Age: Mean 31

Sex: 34 males 56 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III

Exclusions: - Does not meet DSM-III criteria for GAD and/or HAMD<18, Covi <8 and a depression scale <8
- experienced anxiety < 1 month
- <85% compliance during placebo washout phase or >20% improvement in anxiety scores during washout
- Females not using acceptable forms of birth control
- evidence of drug abuse
- clinically significant medical or psychiatic disorder or abnormalities.
- Phobic disorder, panic disorder, OCD, MDD Cyclothymic disorder, Bipolar disorder, Briquet's disorder, somatizatio disorder, schizophrenia or psychotic symptoms or any

Data Used
HAMA
Adverse events

Notes: TAKEN AT: baseline, end of treatment (acute phase)
DROP OUTS: Ipsapirone 4/30 (13%), Lorazepam 3/30 (10%), Placebo 6/30 (20%)

Group 1 N= 30

Ipsapirone - Following a one-week placebo wash-out phase participants received 4 weeks acute treatment. Dose ranged from 10-30 mg/day. Starting dose 5mg with titrated increments of 5mg

Group 2 N= 30

Lorazepam - Following a one-week placebo wash-out phase participants received 4 weeks acute treatment. Dose ranged from 2mg to 6 mg daily t.i.d Starting dose 1mg with titrated increments of 1mg

Group 3 N= 30

Placebo - Participants in the placebo group received identical capsules. Capsules were titrated one at a time.

No information about study funding. Quality assessment score = +

personality disorder

Baseline: Analysis only included 79/90 participant
HAM-A: Ip: 25.67(3.57) Loz: 25.11(4.00) Plc: 25.72(4.03)

DARCIS1995

Study Type: RCT

Study Description: Ppts were randomly allocated to either hydroxyzine or placebo for 4 weeks, followed by a treatment-free period of 1 week.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 28

Followup: 1 week

Setting: No details provided.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: 133 assessed but 9 were excluded. No details provided.

n= 124

Age: Mean 44

Sex: 55 males 69 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: No details provided.

Baseline: HAM-A at baseline. Hydroxyzine: 25.9 (4.2) and Placebo: 24.1 (3.9).

Data Used
Adverse events
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study due to adverse events

Notes: Ppts were assessed at the start of the study, after 1 and 4 weeks of treatment, and one week after stopping therapy.

Group 1 N= 60
Hydoxyzine. Mean dose 50mg/day - 12.5mg at breakfast and at lunchtime, and 25mg at bedtime.

Group 2 N= 64
Placebo. Mean dose 2 tablets/day - 3 doses a day. 1/2 tablet at breakfast and lunch and one tablet at bedtime.

Funding: no details provided. Quality assessed +.

DAVIDSON1999

Study Type: RCT

Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication

Type of Analysis: ITT/LOCF

Blindness: Double blind

Duration (days): Mean 56

Setting: US
Outpatient (17 centres)

Notes: RANDOMISATION: details not provided. ALLOCATION CONCEALMENT: not addressed.

Info on Screening Process: 405 patients completed placeb run-in period & received study drug, 36 had no primary efficacy evaluations & 4 randomised at one site were excluded for administrative reasons.

n= 365

Age: Mean 38

Sex: 224 males 141 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Not 18 years or older
- Primary diagnosis not GAD (DSM-IV)
- HAMA score < 18
- HAMA (anxious mood & tension items) < 2
- Raskin depression score > 9 or > Covi anxiety score or any item > 3
- Presence of clinically significant psychiatric disorder other than GAD
- use of other pharmacology except for chloral hydrate

Notes: No. of participants taking chloral hydrate: placebo (N=7), venlafaxine 75mg/d (N = 2), venlafaxine, 150mg/d, buspirone (N=2)

Baseline: HAMA scores at baseline (approx) total: 23.55 (4.23); venlafaxine 75mg/ day: 23.7 (4.1), 150 mg/d: 23.0 (4.0); buspirone: 23.8 (4.6); placebo; 23.7 (4.2). No significant differences at baseline.

Data Used
HAMA
Leaving the study due to adverse events
Compliance
Response (50% reduction in HAMA score)

Notes: TAKEN AT: 1, 2, 3, 4, 6, 8 weeks & 4 to 10 days after drug taper. DROP OUTS: 27%. MEAN CHANGE SCORES.

Group 1 N= 102
Venlafaxine (extended release). Mean dose 75mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed dose of 75mg/d.

Group 2 N= 104
Placebo - Matched placebo.

Group 3 N= 98
Buspirone. Mean dose 30 mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed doses. Daily 3 divided doses. Days 1 & 2: 15 mg/d. Days 3 & 4: 20 mg/d. Days 5-7: 25mg/d. Days 8-56: 30 mg/d.

Group 4 N= 101
Venlafaxine (extended release). Mean dose 150 mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed doses. Weel 1: 75mg/d. Week 2: 150 mg/d.

Funding: Wyeth-Ayerst Research. Quality assessed: +.

Results from this paper:

DAVIDSON2004

Study Type: RCT

Study Description: ITT: patients who took at least one dose of the study medication & at least one baseline efficacy assessment were included in analysis

Type of Analysis: LOCF

Blindness: Double blind

Duration (days): Mean 56

Followup: None

Setting: US
Outpatient

Notes: Randomisation procedure not reported. Allocation consealment not addressed.

Info on Screening Process: Details not provided.

n= 315

Age: Mean 40

Sex: 149 males 166 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - not between the ages of 18 and 80
- did not meet DSM-IV criteria for GAD
- abnormal physical/ laboratory examination
- Less than 18 on the HAMA
- At least 2 on the HAMA tension & anxiety items
- 17 + on the HAMD
- Lower scores on the Covi Anxiety scale than the Raskin Depression Scale
- Bipolar disorder, schizophrenia, any psychotic disorder, OCD, learning disability, any pervasive developmental disorder or cognitive disorder
- Axis I disorder other than GAD
- Use of psychoactive medications, neuroleptics 6 months prior to study entry
- Any neuroleptic, antidepressant, anxiolytic within 2 weeks (5 weeks for fluoxetine)
- Daily benzodiazepne therapy within 1 month
- Concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with any psychotripic component
- women who were pregnant/ breastfeeding/ childbearing potential/ not practising a reliable method of birth control

Notes: 34% (placebo), 40% (escitalopram) received prior GAD pharmacotherapy, majority were nonresponders or intolerant to prior treatment

Baseline: HAMA scores at baseline (approx): 23.40 (4.40); No significant differences at baseline.

Data Used
HAMA
CGI (Response)
Adverse events
CGI (Remission
Leaving the study due to adverse events
QoL

Notes: TAKEN AT: 1, 2, 4, 6 and 8 weeks. DROP OUTS: 4/158 (escitalopram),4/157 (placebo). CHANGE SCORES USED.

Group 1 N= 158

Escitalopram. Mean dose 12.3 mg - 1 week placebo lead-in phase, 8 weeks intervention. 1 tablet/ day. 10 mg first 4 weeks, increased to 20 mg at week 4 or 6 if therapeutic response not achieved. Patients could return to starting dose for tolerability reasons.

Group 2 N= 159

Placebo - Matching placebo

Funding: Forest Laboratories, Inc. Quality assessed: +.

FELTNER2003

Study Type: RCT

Study Description: ITT included all randomised participants who received at least one dose of study medication

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 28

Setting: Four study centres, USA
Outpatients

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: Not reported

n= 271

Age: Mean 38 Range 18-74

Sex: 128 males 143 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Did not meet DSM-IV criteria for GAD, or GAD not the primary diagnosis in the case of comorbidity and HAMA >20
- Aged <18 years
- Suffering from another other Axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder or a histpry pf MDD
- Current MDD
- Severe personality disorders, drug or alcohol abuse /

Data Used
Remission (less than 7 on HAMA)
CGI-I
HAMA
Adverse events
Serious Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Group 1 N= 68

Lorazepam. Mean dose 6MG - Fixed dose regimen with 2 mg TID. Study medication was tirated during days 1-6 of double-blind treatment.

Group 2 N= 70

Pregabalin. Mean dose 150mg - Fixed dose regimen with 50 mg TID. Study medication was tirated during days 1-6 of double-blind treatment.

Group 3 N= 66

Pregabalin. Mean dose 600mg - Fixed dose regimen with 200 mg TID. Study medication was tirated during days 1-6 of double-blind treatment.

The ITT population was 271, this included all randomised participants who received at least one dose of study medication. No details given on the original number randomised to each condition. Funding: no details. Quality assessment score = +

dependence (active within 6 months of study)
- Suicide risk
- Covi anxiety scale <9
Raskin depression > 7

Notes: Participants with a dual comorbid psychiatric disorders were required to have GAD as a primary disorder as judged by the psychiatrist, considering relative severity and time of onset

Baseline: HAMA: Pregabalin (50mg) 24.9(3.9), Pregabalin (200mg) 25.4(4.6), Lorazepam 24.7(3.7), Placebo 24.8(4.1)

Notes: TAKEN AT: Baseline and end of active treatment (4 weeks)
DROPOUTS: total drop outs not reported

Group 4 N= 67

Placebo

FRESQUET2000

Study Type: RCT

Study Description: Phase II study. 1 week placebo lead-in. Received placebo, lesopitron or lorazepam twice daily for 6 weeks followed by 1 week taper period.

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 42

Setting: Outpatients. Single centre (outpatient clinic).

Notes: RANDOMISATION: no details provided.

Info on Screening Process: No details provided.

n= 161

Age: Mean 37 Range 20-58

Sex: 33 males 35 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Ppts whose HAM-A score decreased by >=20% between screening and baseline, other Axis I psychiatric diagnosis, substance abuse disorder within the last 6 months, two or more discrete panic attacks within 4 weeks, clinically significant hematopoeitic, cardiovascular, or autoimmune disease, clinically significant 12-lead electrocardiogram abnormality at screening and baseline, presence or history of clinically significant gastrointestinal, hepatic, renal, endocrine, cerebrovascular or seizure disorders, malignancy within 5 years of baseline or positive urine drug test.

Notes: 68 ppts with documented history of GAD or anxiety NOS were included in subgroup. Ppts scored >=18 on HAM-A, >=2 on anxious mood item, <16 on HAM-D and Covi > Raskin. Many ppts used medication before study.

Baseline: HAM-A at baseline. Placebo: 20.3 (1.7), Lesopitron: 21.7 (3.0) and Lorazepam: 21.5 (3.2).

Data Used
CGI-I
HAMA
Adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Data Not Used
Leaving the study due to adverse events - not extractable

Notes: Assessments conducted weekly.

Group 1 N= 18

Other active treatments. Mean dose 63.3mg/day - Lesopitron. Week 1: 40mg/day. Week 2: 60mg/day. Week 4: 80mg/day. These represent maximum titrations allowed. Twice daily.

Group 2 N= 30

Lorazepam. Mean dose 3.4mg/day - Titrated from 2-3mg/day to a maximum of 4mg/day. Titration was allowed during first three weeks according to tolerance but dosage could not be altered in weeks 4-6. Twice daily.

Group 3 N= 20

Placebo - Twice daily.

Funding: Laboratorios Dr. Esteve, S.A., Barcelona, Spain. Quality assessed: +.

GELENBERG2000

Study Type:

Study Description: ITT: patients who took at least one dose of the study medication & at least one baseline efficacy assessment were included in analysis

Type of Analysis: LOCF/ITT

Blindness: Double blind

Duration (days): Mean 196

Setting: US
Outpatients (14 centres)

Notes: RANDOMISATION: table of random

n= 238

Age: Mean 40

Sex: 98 males 140 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - less than 18 years
- MDD
- primary diagnosis not GAD (DSM-IV)
- HAMA score < 18
- HAMA (anxious mood & tension items) < 2

Data Used
HAMA
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason

Data Not Used
Response (40% reduction in HAMA score) - does not meet criteria

Group 1 N= 127

Placebo - Identical appearing capsules.

Group 2 N= 124

Venlafaxine (extended release) - 6 months of treatment. Flexible dose schedule; week 1: 75 mg/d, week 2 to 3 up to 150mg/d, week 3+ 225 mg/d. Minimum dose: 75mg/d.

Funding: likely to be pharma. Quality assessed: +.

numbers.
ALLOCATION CONCEALMENT: not addressed

Info on Screening Process: 261 patients enrolled; 251 randomized, 10 LTFU, 127 placebo, 124 venlafaxine; 4 placebo, 9 venlafaxine no primary outcome measure (not included in ITT); 44 placebo, 60 venlafaxine completed trial

- Reduction of at least 20% in the HAMA total score between screening visit & baseline
- Lower scores on the Covi Anxiety scale than the Raskin Depression Scale
- Raskin Depression Scale score greater than 3 on any item
- History of previous psychotic illness, bipolar disorder, ASPD or severe Axis II disorder
- Previous treatment with venlafaxine
- Concomittant medication (i.e. antipsychotic drugs, antidepressant, benzodiazepine) or ECT
- Women lactating, pregnant or childbearing potential not using an acceptable form of contraception

Baseline: HAMA scores at baseline (approx): 25.00 (5.00); No significant differences at baseline

Notes: TAKEN AT: 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 28 weeks. DROP OUTS: 61% but adequately taken account of in ITT (LOCF). CHANGE SCORES - NEED TO CALCULATE SDs

Results from this paper:

GOODMAN2005

Study Type: RCT

Study Description: Pooled analysis from 3 RCTs. Single-blind placebo lead-in for 1 week followed by 8 weeks of double-blind treatment with escitalopram or placebo.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

Setting: Multicentre: US.

Notes: RANDOMISATION: no details given.

Info on Screening Process: No details given.

n= 856

Age: Mean 39

Sex: 377 males 479 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Score of >=17 on the HAMD or a lower score on the Covi Anxiety Scale than the Raskin Depression Scale. Patients with a principal diagnosis of any Axis I disorder other than GAD (including MDD) or who met DSM-IV criteria for bipolar disorder, schizophrenia or any psychotic disorder, obsessive compulsive disorder, mental retardation, or any pervasive developmental disorder or cognitive disorder. A history of psychotic features or disorder, or substance abuse or dependence within the past 6 months. Use of any of the following psychoactive medications prior to study entry: depot neuroleptics within 6 months, any neuroleptic, antidepressants or anxiolytic within 2 weeks (5 weeks for fluoxetine), or daily benzodiazepine therapy within 1 month. Use of concomitant treatment with any psychotropic drug (except zolpidem as needed for sleep). Women who were pregnant or breastfeeding, or of child-bearing potential and not practicing a medically reliable method of birth control.

Notes: ONLY USING STUDY 1 & 2 (as study 3 is reported already in Davidson 2004)

Baseline: HAMA baseline scores: Placebo 22 (0.2) and Escitalopram 23.0 (0.2). Baseline scores are based on the ITT population.

Data Used
HAMA

Data Not Used
Adverse events - not extractable for individual studies

Leaving the study due to adverse events - not extractable for individual studies

Leaving the study early for any reason - not extractable for individual studies

Remission (less than 7 on HAMA) - Not extractable for individual studies

Response (50% reduction in HAMA score) - not extractable for individual studies

Notes: TAKEN AT: Baseline and endpoint DROP OUT:13% across both groups.

Group 1 N= 267

Escitalopram - During the first 4 weeks, patients received a fixed dose of 10mg/day. If the therapeutic response was judged by the investigator to be insufficient at the week4 or 6 visit, the dose could be doubled to 20mg/day. Otherwise went back to 10mg/day.

Group 2 N= 266

Placebo - No details given.

Funding: Forest Laboratories Inc. Quality assessed +.

GSK2002

Study Type: RCT

Study Description: Parallel-group study. 1 week single-blind placebo run-in phase. Randomised to either paroxetine or placebo.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

Setting: Multicentre (32 centres): USA.

Notes: RANDOMISATION: no details given.

Info on Screening Process: No details given.

n= 335

Age: Mean 39

Sex: 119 males 208 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Diagnosis of any current Axis I disorder or within the 6 months prior to screening, posed a current suicidal or homicidal risk in the investigator's judgement, had a score of =>18 on the MADRS at screening or at baseline, showed greater than a 20% reduction in the HAM-A total score from screening to baseline, had taken other psychotropic drugs that had not been discontinued within the minimum discontinuation period prior to screening, had received formal psychotherapy either concurrently or in the 12 weeks prior to screening.

Notes: Ppts received medication for a maximum of 10 weeks, including a one-week placebo run-in phase followed by an eight-week treatment phase and a double-blind taper phase of up to 1 week.

Baseline: HAM-A: Paroxetine 24.43 (3.71) and Placebo 24.83 (3.64).

Data Used
CGI-I
HAMA
CGI (Response)
Adverse events
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)

Notes: Response was defined as CGI 1 or 2.

Group 1 N= 168

Paroxetine - Dose range 12.5-37.5mg/day. Weeks 1-2: 12.5mg/day. Dose increases of 12.5mg/day no more frequently than every 7 days were allowed at the discretion of the investigator according to response and tolerability. Max dose was 37.5mg/day.

Group 2 N= 167

Placebo - Received medication identical in appearance to that received by ppts assigned to the active medication.

Funding: GlaxoSmithKline. Quality assessed +.

GSK2005

Study Type: RCT

Study Description: Placebo run-in medication for one week followed by randomisation to paroxetine (20mg/day) or placebo.

Type of Analysis: LOCF method used.

Blindness: Double blind

Duration (days): Mean 56

Setting: Multicentre (58 centres): Japan.

Notes: RANDOMISATION: procedure not known.

Info on Screening Process: Not known.

n= 361

Age: Mean 40

Sex: 144 males 214 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Subjects with suspected history of psychiatric disorder other than GAD or with history or complications of such diseases, subjects who had taken MAOIs within1 week prior to week 1 and subjects with history of complications thatn might affect the subjects' safety.

Notes: Subjects classed as non-responders at week 8 continued to receive paroxetine or placebo orally for a further 4 weeks in a flexible dosing schedule.

Baseline: Baseline statistics not provided.

Data Used
CGI-I
HAMA
Adverse events
Sheehan Disability Scale (SDS)
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Notes: Response was defined as either a CGI score of 1 or 2 or a HAMA score of <=10.

Group 1 N= 182

Placebo - No details given.

Group 2 N= 179

Paroxetine - Began with 10mg for 1 weeks, followed by forced titration to 20mg/day for 7 weeks.

Funding: GlaxoSmithKline. Quality assessed +.

HACKETT2003

Study Type: RCT

Study Description: Randomised, double-blind, placebo-controlled, parallel-group study. Followed by long-term phase study that is reported separately.

Type of Analysis: ITT (LOCF method)

n= 540

Age: Mean 44

Sex: 175 males 365 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Data Used
CGI-I
HAMA
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Group 1 N= 179

Venlafaxine (extended release). Mean dose 150mg - 150mg/day.

Group 2 N= 191

Venlafaxine (extended release). Mean dose 75mg - 75mg/day.

Funded by Wyeth. Quality assessed +.

Blindness: Double blind

Duration (days): Mean 56

Setting: Outpatients. Multicentre: France.

Notes: RANDOMISATION: no further details

Info on Screening Process: 564 entered study, 16 did not receive any medication before dropping out

Exclusions: - <18 years of age
- HAM-A <20
- HAMA <2 for items 1 and 2
- MDD
- more than 2 panic attacks in last month

Baseline: HAM-A: Placebo =27.6 Venlafaxine 75mg = 27.9 Venlafaxine 150mg = 27.9 Diazepam = 28.4. Doesn't report SDs or SEs.

Notes: Rating scales were administered at baseline, and again after 7, 14, 21, 28, 42 and 56 days.

Group 3 N= 97

Placebo - No details given.

Group 4 N= 89

Diazepam. Mean dose 15mg/d - 15 mg/day.

HARTFORD2007

Study Type: RCT

Study Description: ITT analysis included all randomised participants with >=1 postbaseline analysis. Safety analysis included all randomised participants

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 70

Setting: Outpatients. Multicentre 42 sites in the USA

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: 707 people were evaluated of which 220 failed to meet the inclusion criteria.

n= 487

Age: Mean 41

Sex: 182 males 305 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: <18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covia Anxiety score <9 or not greater and then Raskin depression total score.
Raskin depression scale item rated >3
- Medical illness that would contraindicate use of duloxetine
- Women of childbearing age not using adequate contraception
- recent diagnosis of depression or substance abuse/depence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of psychotic, bipolar, OCD or psychosis
- lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments
- psychotherapy iniated 6 weeks prior to study enrollment
- Benzodiazepine use in the 2 weeks before visit 2
- Judged clinically to be a serious suicide risk
- Previous duloxetine treatment

Baseline: HAMA: Dulox 25.6(5.8) Venl 24.9(5.4) Placebo 25.0(5.8)

Data Used

Q-LES-Q-SF
Response (50% reduction in HAMA score)
Remission (less than 7 on HAMA)
Leaving the study early for any reason
PGI-I
Leaving the study due to adverse events
Significant improvement (30% reduction)
EQ-5D
CGI-I
Leaving the study due to inefficacy
Serious Adverse events
Hospital Anxiety and Depression Scale (anxiety)
Sheehan Disability Scale (SDS)
Adverse events
HAMA
Discontinuation adverse events (DAEs)

Notes: TAKEN AT: Baseline and enpoint
DROPOUT: Duloxetine: 67/162 (45.7%), Venlafaxine 62/164 (37.8%), Placebo 62/161 (38.5%)

Group 1 N= 164

Venlafaxine (extended release). Mean dose 183.82mg/d - Started at 37.5mg/d for week 1, increased to 75mg/d week 2 onwards. Dose could be increased to 150mg/d for at least 1 week and then to 225mg/d based on efficacy and tolerability.

Group 2 N= 161

Placebo

Group 3 N= 162

Duloxetine. Mean dose 107.73mg/d - Started at 30mg/d for week 1, increased to 60mg/d week 2 onwards. After titration to 60mg, flexible dosing was allowed in weekly increments of 30mg/d up to a max of 120mg/d. Dose increases were based on efficacy and tolerability

Drug company funded - Eli Lilly trial 7107 NCT00122850. Quality assessment score = +/++ All participants underwent a single-blind placebo lead-in week, 10 week acute phase and a 2 week discontinuation tapering phase.

HEWETT2001

Study Type: RCT

Study Description: Parallel group study. 1 week single-blind placebo run-in phase. Ppts randomised to receive either paroxetine or placebo.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

n= 372

Age: Mean 46

Sex: 110 males 262 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Following conditions currently or within 6 months

Data Used

CGI-I
CGI (Response)
Adverse events
Sheehan Disability Scale (SDS)
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study due to inefficacy
Leaving the study due to adverse events

Group 1 N= 188

Paroxetine - Weeks 1-2: 20mg/day. Dose could then be uptirated in 10mg/day increments at intervals no more frequently than every 7 days at the discretion of the investigator, according to response and tolerability. Range 20-50mg/day.

Group 2 N= 186

Placebo - No details given.

Funding: GlaxoSmithKline. Quality assessed +.

Setting: Multicentre (50 centres): France, UK, Germany, Ireland, Austria and Italy.

Notes: RANDOMISATION: no details given.

Info on Screening Process: No details given.

prior to screening visit: MDD, panic disorder, social phobia, agoraphobia, PTSD, OCD, and eating disorders. Current diagnosis of dysthymia or within the previous 6 months as a predominant psychiatric condition relative to GAD. Current psychotic disorder or history of psychotic disorder. Current bipolar disorder or history of bipolar disorder, or had a current history of cyclothymic disorder. Posed a current suicidal or homicidal risk. A score of >=18 on the MADRS at either screening or baseline. Had shown a greater than 20% reduction in HAM-A total score from screening to baseline. Had taken other psychotropic drugs which had not been discontinued within the minimum discontinuation periods prior to screening. Had ECT in the 3 months prior to screening. Had received formal psychotherapy, either concurrently or in the 12 weeks prior to screening.

Notes: Ppts requiring more than one dose reduction were withdrawn from the study. Gradual reduction of study medication during double-blind taper phase of up to 3 weeks for ppts who completed treatment or withdrew prematurely at dose of 30mg/day or higher.

Baseline: HAM-A: Paroxetine 26.0 (0.4) and Placebo 25.9 (0.4).

Leaving the study early for any reason

Remission (less than 7 on HAMA)

Notes: Response was CGI score of 1 or 2. Remission was <=10 on HAM-A.

KASPER2009

Study Type: RCT

Study Description: 1 week open-label lead-in period, then randomised to 8 weeks of double-blind, parallel-group treatment.

Blindness: Double blind

Duration (days): Mean 56

Setting: 47 sites in Belgium, Canada, France, Ireland, Italy, Netherlands, Spain, Sweden

Notes: RANDOMISATION: computer generated randomisation list.

Info on Screening Process: 466 screened, 374 met eligibility criteria

n= 374

Age: Mean 41

Sex: 146 males 228 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: <18 years or >65 years
- HAM-A <20
- HAM-A psychic and somatic factors <10
- bipolar disorder, schizophrenia, psychosis
- MDD, dysthymia, OCD, PTSD, eating disorder, substance abuse or dependence
- pregnant

Baseline: HAM-A: Placebo 26.8 (SE=0.8) Venlafaxine 27.4 (SE=0.4) Pregabalin 27.6 (SE=0.4)

Data Used

CGI-I

HAMA

Adverse events

Sheehan Disability Scale (SDS)

Hospital Anxiety and Depression Scale (anxiety)

EQ-5D

Leaving the study due to adverse events

Leaving the study early for any reason

Response (50% reduction in HAMA score)

Group 1 N= 121

Pregabalin - Starting dose of 150mg/day for first week, thereafter flexible from 300-600mg/day

Group 2 N= 125

Venlafaxine (extended release) - starting dose of 75mg/day for first week then flexible thereafter between 75-225 mg/day

Group 3 N= 128

Placebo - No details given.

Funded by Pfizer. Quality assessed +.

KOPONEN2007

Study Type: RCT

Study Description: ITT analysis included all randomised participants with >=1 postbaseline analysis. Safety analysis included all randomised participants

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 63

n= 513

Age: Mean 44

Sex: 165 males 348 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: -<18 years

Data Used

Q-LES-Q-SF

Response (50% reduction in HAMA score)

Remission (less than 7 on HAMA)

Leaving the study early for any reason

PGI-I

Leaving the study due to adverse events

Significant improvement (30% reduction)

Group 1 N= 175

Placebo

Group 2 N= 168

Duloxetine. Mean dose 60mg/d - Participants were started with 60mg/d, if there were tolerability concerns this was lowered to 30mg/d with all participants gradually increased to their randomised dose within the first 2 study weeks.

Drug company funded - Eli Lilly studyF1J-MC-HMBR (NCT00122824) - trial report collected
All participants underwent a single-blind placebo lead-in week, 9 week acute phase and a 2 week discontinuation tapering phase. Quality assessment

Setting: outpatient clinics.
Multicentre - 7 countries

Notes: RANDOMISATION: procedure not reported. Participants were stratified by baseline HAM-A score.

Info on Screening Process: 639 participants were screened for the study with 126 failing to meet the inclusion criteria.

- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covia Anxiety score <9 or not greater and then Raskin depression total score.
Raskin depression scale item rated >3
- Medical illness that would contraindicate use of duloxetine
- Women of childbearing age not using adequate contraception
- recent diagnosis of depression or substance abuse/depence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of psychotic, bipolar, OCD or psychosis
- lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments
- psychotherapy iniated 6 weeks prior to study enrollment

Baseline: HAMA (total) Dulox (60mg) 25.0(7.1); Dulox (120mg) 25.2(7.3); Placebo 25.8(7.6)

EQ-5D
CGI-I
Symptom Questionnaire-Somatic subscale (SQ-SS)
Leaving the study due to inefficacy
Serious Adverse events
Sheehan Disability Scale (SDS)
Visual Analog Scale (VAS)
HAMA
Discontinuation adverse events (DAEs)

Notes: TAKEN AT: baseline and endpoint
DROP OUT: Dul 60 33/168 (19.6%); Dul 120 46/170 (27.1%); Placebo 45/175 (25.7%)

Group 3 N= 170

Duloxetine. Mean dose 120mg/d - Participants were started with 60mg/d, if there were tolerability concerns this was lowered to 30mg/d with all participants gradually increased to their randomised dose within the first 2 study weeks.

score = + / ++

LADER1998

Study Type: RCT

Study Description: 1-week single-blind placebo run-in then 4-week DB treatment with either hydroxyzine, buspirone or placebo followed by 1 week placebo administration.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 28

Setting: Multicentre (62 centres): France (48 centres) and UK (14 centres). Patients seen by primary care doctors.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: Excluded anyone who responded in placebo period of showed positive for benzodiazepines at entry. 266 recruited: 20 failed to meet inclusion criteria.

n= 244

Age: Mean 41 Range 30-42

Sex: 73 males 171 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Depressive disorders according to DSM-IV criteria. Pregnancy or inadequate contraceptive precautions, major depressive disorder, alcohol abuse, organic or psychotic disorders, undergoing long-term psychotherapy or intake of psychotropic medication during the previous 4 weeks.

Notes: Ppts had HRSA score >20. Low levels of depressive symptoms allowed.

Baseline: HARS at baseline: Hydroxyzine: 26.6 (4.3), Buspirone: 26.7 (4.1) and Placebo: 26.2 (4.2).

Data Used
CGI-I
HAMA
Adverse events
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Notes: Assessments carried out weekly.

Group 1 N= 81

Hydoxyzine. Mean dose 50mg/day - 12.5mg morning and midday, 25mg evening.

Group 2 N= 81

Placebo. Mean dose 3 capsules/day - 3 capsules throughout the day.

Group 3 N= 82

Buspirone. Mean dose 20mg/day - 5mg morning and midday, 10mg evening.

Funding: UCB, S.A. Quality assessed +.

LENOXSMITH2003

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 168

Setting: 31 Primary care centres, UK

Notes: RANDOMISATION: no further details

n= 244

Age: Mean 47

Sex: 100 males 144 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - HAM-A <20
- <18 years of age
- psychosis

Data Used
HAMA
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 122

Placebo

Group 2 N= 122

Venlafaxine (extended release) - Starting dose 75mg, could be increased to 150mg after 2 weeks. At end of 24 weeks patients on 150mg were reduced to 75mg and then the second week all patients received placebo.

Funded by Wyeth. Quality assessed: -.

- substance abuse or dependence
- PTSD
- pregnant
- MADRS >23

Baseline: HAM-A: Venlafaxine 28 Placebo 28

LENZE2005

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: Recruited from adverts and in a primary care centre, US

Notes: RANDOMISATION: method not reported

Info on Screening Process: 791 screened, 47 consented to participate. Of these 10 refused randomization, 1 spontaneous improvement, 1 did not meet diagnostic criteria, 1 had MDD

n= 34

Age: Mean 69

Sex: 13 males 21 females

Diagnosis:
90% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - current MDD
- dementia
- psychosis
- unstable medical illness
- substance abuse

Notes: 2 people in each group did not have GAD. 8 people in Citalopram group and 4 people in placebo group received lorazepam.

Baseline: HAMA: Citalopram 21.4(4.6) Placebo 23.1(3.8) HDRS: Citalopram 11.3 (2.1) Placebo 12.4 (3.8)

Data Used
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 17
Citalopram - 10mg /day at first dose, increased after week to 20mg/day, a further increase to 30mg/day after 4 weeks if no response

Group 2 N= 17
Placebo - No details given.

Funded by Forest Pharmaceuticals. Quality assessed +.

LENZE2009

Study Type: RCT

Study Description: ITT: all participants who dropped out or were considered non responders were included except for 2 participants who did not receive medication

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 84

Setting: USA

Notes: Randomisation: permuted block, 1:1 randomised list generated by study stastistician

Info on Screening Process: 550 screened, 293 excluded, 257 consented to further assessment, 179 randomised, 2 did not receive medication

n= 177

Age: Mean 72

Sex: 58 males 119 females

Diagnosis:
14% Major depressive disorder by DSM-IV

100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Less than 60 years of age
- Without a principal diagnosis of GAD
- Less than 17 on the HAMA
- Bipolar disorder, dementia
- Increased suicide risk
- Medical instability
- Ongoing psychotherapy
- Current antidepressant or anxiolytic use (except for benzodiazepines up to 2 mg/ day equivalent of lorazepam)

Notes: 17.1% (escitalopram), 13.2% (placebo) were on benzodiazepines. 12.1% of escitalopram and 15.2% of placebo had MDD diagnosis.

Baseline: HAMA baseline depression score (approx): 23.00 (2.30). No significant differences between groups at

Data Used
HAMA
CGI (Response)
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
QoL

Notes: TAKEN AT: 1, 2, 3, 4, 6, 8, 10, 12 weeks. DROP OUTS: SMDs REPORTED. DROP OUTS 18.5% (escitalopram), 18.4% (placebo)

Group 1 N= 85
Escitalopram - 12 weeks. 10 mg of escitalopram, 1 pill/ day, 2 pills/ day after 4 weeks for non-responders, as tolerated.

Group 2 N= 92
Placebo

Funded by National Institute of Health grant, drugs provided by Forest Laboratories. Quality assessed +.

baseline.

Results from this paper:

LLORCA2002

Study Type: RCT

Study Description: Parallel-group. 2 weeks SB run-in placebo, 12 weeks DB treatment and 4 weeks SB run-out placebo.

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 84

Setting: Multicentre: France. Outpatients. Conducted by French GPs under supervision of psychiatrists.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: 369 entered recruitment period. 334 entered DB treatment.

n= 334

Age: Mean 43

Sex: 106 males 228 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Pregnant, breast-feeding, absence of a contraception method for women, known alcohol or drug dependence, major depressive episode wtihin the preceding 6 months or >=7 on Raskin Severity of Depression and Mania scale, psychotic or delusional disorders within the preceding 3 years, concomitant chronic diseases, closed-angle glaucoma or prostatic adenoma, intolerance or allergy to hydroxyzine, bromazepam, lactose or cellulose, inability to use self-assessment scales, treatment with antidepressants, neuroleptics, mood regulators, morphine or derivatives, hydroxyzine or bromazepam within the preceding 4 weeks, treatment with benzodiazepines >2 days per week during the previous 30 days or benzodiazepine intake during the previous 2 weeks, CNS active treatment within the last week preceding inclusion, need for psychotherapy.

Notes: GPs were trained to diagnose GAD. Ppts not diagnosed by psychiatrists. Ppts scored >=20 on HAM-A.

Baseline: HAM-A at baseline. Placebo: 25.73 (4.14). Hydroxyzine: 25.49 (3.61). Bromazepam: 25.32 (3.44).

Data Used
CGI-I
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 116
Bromazepam. Mean dose 6mg/day - 1.5mg in the morning and at noon and 3mg in the evening.

Group 2 N= 113
Placebo - Oral capsules divided into 3 daily doses.

Group 3 N= 105
Hydoxyzine. Mean dose 50mg/day - 50mg/day. 12.5mg in the morning and at noon and 25mg in th evening.

Funding: UCB-Pharma.
Quality assessed: +.

LYDIARD1997

Study Type: RCT

Study Description: 4 weeks treatment with either abecarnil, alprazolam or placebo followed by 1-2 week taper.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 28

Setting: Multicenter: outpatients. USA.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: No details provided.

n= 192

Age: Mean 42

Sex: 89 males 103 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: No psychotherapeutic medication for at least 1 week and for at least 1 month for therapeutic doses of neuroleptics or antidepressants. History of pytschosis, mania, current major depression, substance abuse, or other Axis I disorders likely to interfere with objectives of study. Any investigational drug taken within 30 days preceding study admission. Women of childbearing potential who were not using medically accepted birth-control methods or who were planning on becoming pregnant. Pregnant women.

Notes: Flexible dosage schedules used. Patients who discontinued for reasons unrelated to medication before

Data Used
CGI-I
HAMA
Adverse events
Leaving the study early for any reason

Notes: Assessed weekly.

Group 1 N= 67
Abercarnil - 3.0-9.0mg/day. Capsules contained 1.0mg. Dosages were titrated to 1 capsule t.i.d. by day 4, 2 capsules t.i.d. by day 8 and 3 capsules t.i.d. by day 15. Based dosage on clinical judgement. All ppts had to take at least 1 capsule b.i.d. to stay in study.

Group 2 N= 63
Alprazolam - 1.5mg-4.5mg/day. Capsules contained 0.5mg. Dosages were titrated to 1 capsule t.i.d. by day 4, 2 capsules t.i.d. by day 8 and 3 capsules t.i.d. by day 15. Based dosage on clinical judgement. All ppts had to take at least 1 capsule b.i.d. to stay in study.

Funding: no details provided. Likely to be pharma funded. Quality assessed: -.

	completing 2 weeks of treatment were replaced. Ppts had HAM-A score >=18 and Covi>Raskin score. Baseline: HAM-A at baseline. Abecarnil: 24.3, Alprazolam: 24.1 and Placebo: 24.8.		**Group 3 N= 62** Placebo - Dosages were titrated to 1 capsule t.i.d. by day 4, 2 capsules t.i.d. by day 8 and 3 capsules t.i.d. by day 15. Based dosage on clinical judgement. All ppts had to take at least 1 capsule b.i.d. to stay in study.	
MAJERCSIK2003				
Study Type: RCT Blindness: Double blind Duration (days): Mean 42 Setting: Hungary Notes: randomisation: no further details	n= 52 Age: Mean 81 Sex: all males Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - HAM-A <15 - anxiolytic medication in previous 6 months Baseline: HAM-A Buspirone 19.45 (SE=0.46) Placebo 21.48 (SE=0.47)	**Data Used** HAMA	**Group 1 N= 33** Buspirone - 30mg/day for 6 weeka **Group 2 N= 19** Placebo - 3 tablets a day	
MCLEOD1992				
Study Type: RCT Blindness: Double blind Duration (days): Mean 42 Setting: US volunteers recruited through adverts in local newspapers. Notes: RANDOMISATION: no further details. Assignments were made so that the groups were matched according to gender.	n= 42 Age: Mean 41 Sex: 15 males 27 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - history of panic attacks, psychosis or substance abuse and could not have taken any medications that affect the autonomic or central nervous systems for at least 2 weeks prior to entry into the study Notes: Ppts were seen weekly for medication pick-up and supportive therapy, in which they discussed how they were coming along and received a sympathetic and understanding response from a therapist. Baseline: HAM-A: Placebo 25.1 (2.0) Imipramine 25.3 (4.0) Alprazolam 28.1 (4.3)	**Data Used** HAMA Blood pressure	**Group 1 N= 14** Imipramine. Mean dose 92.6mg - Starting dose 25mg but could be adjusted according to clinical need. Range 1-12 capsules. **Group 2 N= 14** Alprazolam. Mean dose 2.3mg - Starting dose of 0.5mg but could be adjusted according to clinical need. **Group 3 N= 14** Placebo - Took 1 capsule three times a day unless they developed excessive side effects.	Funded by NIH grant. Quality assessed -.
MOLLER2001				
Study Type: RCT Study Description: ITT using LOCF. 307/313 participants were included in the ITT analysis Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28	n= 313 Age: Mean 48 Sex: 104 males 209 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by ICD-10	**Data Used** Plasma concentrations HAMA Adverse events **Data Not Used** Leaving the study due to adverse events - not extractable	**Group 1 N= 107** Placebo - 4 capsules were given, two in the morning and two in the evening	No details reported regarding funding. Quality assessed: -. The study included a 7 day placebo washout period, followed by 4 weeks of active treatment. Active treatment was followed by

Setting: Multicentre, GERMANY. Outpatients

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: No details reported

Exclusions: - No ICD-10 diagnosis of GAD
- HAM-A <17 and HAMD >20
- Ages <18 or >65 years
- Significant other psychiatric disorders such as panic disorder, MDD
- Known substance abuse
- Relevant comcomitant other diseases such as epilepsy, severe renal or hepatic impairment, cancer
- Placebo responders (defined as those showing a decrease >6 points during the washout period)

Notes: ~66% of participants had concomitant diseases

Baseline: No relevant differences at baseline
HAMA: Opipramol 27.7(7.4), Alprazolam: 29.7(7.6), Placebo: 29.3(7.0)

Leaving the study early for any reason - data not extractable

Notes: TAKEN AT: baseline and end of treatment (end of active treatment)
DROPOUTS: Opipramol 8/101 (8%), Alprazolam 13/105 (12%), Placebo 18/107 (17%)

Group 2 N= 105

Alprazolam. Mean dose 2mg/day - Medication was prepared in identical capsules containing 0.5mg. Day 0 1 of the 2 evening capsules was active, day 1, 2 of the evening capsules active, day 2 morning capsules were also active. By Day 3 the final dose of 2mg was given.

Group 3 N= 101

Opipramol. Mean dose 200mg/day - Medication was prepared in identical capsules containing 50mg. Day 0 1 of the 2 evening capsules was active, day 1, 2 of the evening capsules active, day 2 morning capsules were also active. By Day 3 the final dose of 200mg was given.

tapering with placebo.

MONTGOMERY2006

Study Type: RCT

Study Description: ITT: all randomized patients who received at least 1 dose of study drug. LOCF used on all primary and secondary outcome measures.

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 42

Followup: None

Setting: Multicentre (76): Austria, Belgium, Germany, the Netherlands and the United Kingdom. Outpatients attending primary care or psychiatric practices.

Notes: Randomisation procedure not reported. Parallel-group design.

Info on Screening Process: 543 ppts entered baseline phase; 421 were randomised and received study medication. Reasons for exclusion: did not meet entry criteria, lost to follow-up, withdrew consent, other/administrative and randomised but did not take study medication.

n= 421

Age: Mean 44

Sex: 160 males 261 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Diagnosis of any other current Axis 1 disorders except depression not otherwise specificied, dysthymia, simple phobia or somatisation disorder. Additional exclusion criteria: clinically relevant hematologic, autoimmune, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or neurologic disorders; a history of seizure disorder; borderline, avoidant or antisocial personality disorder; alcohol or substance use disorder within the past 6 months; and patients considered at risk of suicide. Women who were pregnant or lactating, and women of childbearing potential who were not using a reliable method of contraception. Use of gabapentin or a benzodiazepine within 1 week of first baseline visit, the use of other psychotropic medications within 2 weeks prior to study entry, or ongoing psychodynamic or cognitive-behavioural psychotherapy for GAD. Use of corticosteroids (except topical or inhaled corticosteroids < 1000mg/day), antihypertensive agents, captopril, beta-blockers and psychotropic medication was not permitted during the study. Patients were allowed to take zolpidem for insomnia but not for more than 2 nights per week or the night before clinic visits.

Notes: Ppts were diagnosed using the Mini-International Neuropsychiatric Interview (MINI).

Baseline: Pregabalin 400mg/day (N=97, 23%), Pregabalin 600mg/day (N=110, 26%), Venlafaxine (N=113, 27%) and Placebo (N=101, 24%). HAM-A baseline: Pregabalin 400mg/day 26.3 (4.4), Pregabalin 600mg/day 26.5 (4.6), Venlafaxine 26.0 (4.6) and Placebo 27.4 (5.5). TOTAL: 26.6

Data Used
Remission (less than 7 on HAMA)
CGI-I
HAMA
Adverse events
Serious Adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Data Not Used
Leaving the study due to adverse events - not extractable
Significant improvement (30% reduction) - not required

Notes: HAM-D outcome scores also reported.
TAKEN AT: baseline, 1 week and endpoint.
DROP OUTS: Pregabalin 400mg/day 16/97, Pregabalin 800mg/day 29/110, Venlafaxine 34/113 and Placebo 20/101.

Group 1 N= 97

Pregabalin. Mean dose 400mg/day - 100mg/day for 2 days then 200mg/day for 2 days, before receiving the full dosage of 400mg/day on day 5. All administered twice-per-day (b.i.d.).

Group 2 N= 113

Venlafaxine (extended release). Mean dose 37.5mg/day - Began treatment at full 37.5mg/day (b.i.d.) dosage.

Group 3 N= 101

Placebo - No details given.

Group 4 N= 110

Pregabalin. Mean dose 600mg/day - 150mg/day for 2 days, 300mg/day for 2 days and 450mg/day for 2 days before receiving the full dosage of 600mg/day after day 7. All administered twice-per-day (b.i.d.).

Funded by pharma (Pfizer Inc, New York). This study involved a 1 week screening period. 6 weeks of double-blind treatment were followed up by a 1-week, double-blind taper and follow-up phase. Quality assessment score = +

(4.8). HAM-D baseline: Pregabalin 400mg/day 12.2 (3.6), Pregabalin 600mg/day 12.2 (4.0), Venlafaxine 12.0 (3.4) and Placebo 12.8 (4.9). TOTAL: 12.3 (4.0).

MONTGOMERY2008

Study Type: RCT

Study Description: Parallel group study. 1 week drug-free period then 8 week double-blind study, followed by a 1-5 day taper with a final follow-up visit at 1 week.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

Setting: Outpatients. Multicentre study: 13 in the US and 69 in Europe.

Notes: RANDOMISATION: were randomised 2:1 pregabalin: placebo.

Info on Screening Process: 366 people screened. 68 did not meet entry criteria, 16 withdrew consent and 11 did not enter for other reasons.

n= 273

Age: Mean 72

Sex: 63 males 210 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Current or past DSM-IV diagnosis of schizophrenia, schizoaffective, psychotic or bipolar disorder, current DSM-IV diagnosis of MDD, social anxiety disorder, panic disorder, OCD, PTSD, acute stress disorder, borderline or antisocial personality disorder, eating disorder, delirium, dementia, amnestic disorder, alcohol or substance dependence and/or misuse in the past 6 months, positive urine drug screen, any clinically significant acute or unstable medical condition or clinically significant ECG or laboratory abnormalities, alanine/aspartate aminotransferase levels >3 times the upper limit of normal or creatine clearance rates, concurrent psychotherapy for generalised anxiety disorder unless in stable treatment >3 months, concomitant treatment with psychotropic medication during the study and for at least 2 weeks prior to the screening visit, current suicide risk based on the clinical judgement of the investigator, depressive symptoms predominating over anxiety symptoms.

Notes: Diagnosis based on MINI interview, HRSA score >=20 and MMSE score >=24. Monitored adherence by counts of returned medication and ppts were counselled if they were found to be non-adherent.

Baseline: HRSA at baseline. Pregabalin: 27 (4.8) and Placebo: 26 (4.1).

Data Used
CGI-I
HAMA
Adverse events
SCL anxiety factor
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 177
Pregabalin - Initiated at 50mg/day, followed by an increase to 100mg/day on day 3 and 150mg/day on day 5. Dosing was flexible from weeks 1-6 in the range of 150-600mg/day administered either two or three times daily. Maintained on the same dose from weeks 6-8.

Group 2 N= 96
Placebo - No details provided.

Funding: Pfizer, Inc. Quality assessed: +.

NICOLINI2009

Study Type: RCT

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 70

Setting: Australia, Argentina, Belgium, Canada, Mexico, Russia, Taiwan, UK
Outpatients

Notes: RANDOMISATION: computer-generated ALLOCATION CONCEALMENT: interactive voice response system

Info on Screening Process: Patients entered (N=771); did not meet criteria/concent (N=190)patients randomised (N=581); patients

n= 581

Age: Mean 43

Sex: 43 males 57 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: -<18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covia Anxiety score <9 or not greater and then Raskin depression total score.
Raskin depression scale item rated >3

Data Used
CGI-I
HAMA
Sheehan Disability Scale (SDS)
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study due to inefficacy
Leaving the study due to adverse events
PGI-I
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 169
Venlafaxine (extended release). Mean dose 151.3mg/day - 75 - 225 mg/day; flexible dosing of an increase of 75mg/day. Dose increase required if CGI-I score > 4 after 3 weeks. Dosed could be decreased no more than twice. Dose stabilised after 6 weeks.

Group 2 N= 84
Duloxetine 20mg. Mean dose 20mg/day - Once daily fixed dose of 20mg. Those who required dose increase received additional placebo capsules.

FUNDED BY ELI LILLY: Trial report collected (#7106). Quality assessed: +

completed trial (N=396)

- Medical illness that would contraindicate use of duloxetine
- Women of childbearing age not using adequate contraception
- recent diagnosis of depression or substance abuse/depence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of psychotic, bipolar, OCD or psychosis
- lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments
- psychotherapy iniated 6 weeks prior to study enrollment

Notes: Duration of GAD M(S.D.) = 4.37 (8.19) years

Baseline: BASELINE HAMA scores = 27.4 (total); 27.33 (7.33) (placebo); 27.65 (7.99) - dul 20mg; 27.74 (7.32) - dul 60-120mg); 27.36 (7.57) - ven 75-125mg)

Notes: DROP OUTS: 21/84 (25%) - DULOX 20mg; 49/158 (31%) - DULOX 60-120 mg; 47/122 (39%) - VENLAFAXINE; 68/170 (40%) - PLACEBO.

Group 3 N= 170

Placebo

Group 4 N= 158

Duloxetine. Mean dose 90mg/day - 60-120 mg/day flexible dosing of an increase of 30mg/day. Dose increase required if CGI-I score > 4 after 3 weeks. Dosed could be decreased no more than twice. Dose stabilised after 6 weeks.

Results from this paper:

NIMATOUDIS2004

Study Type: RCT

Study Description: Venlafaxine vs. Placebo for 8 weeks. 1week placebo run-in phase.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

Followup: 4-10 days

Setting: Multicentre: outpatients. Greece.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: Removed anyone with a 20%+ decrease in HAM-A score during pre-study period.

n= 46

Age: Mean 43

Sex: 15 males 31 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: Major depressive disorder within 6 months of study day 1, total Raskin depression score >6, if the secondary depressive symptoms item scores on the Raskin Depression scale was >3 or if their total score on the HAM-D >12. Recent history or current diagnosis of drug or alcohol dependence, current suicidal ideation and/or a history of suicide attempt, evidence or an organic mental disorder, presence of uncontrolled congestive heart failure, myocardial infarction within 6 months of screening visit, history or presence of medical disease that might compromise the study, use of any investigational drug or procedure, any antipsychotic drug withint 30 days of study day 1 and presence of any other Axis I disorder or antisocial personality disorder. Women who were pregnant or lactating or women of childbearing potential who were not using a medically acceptable form of contraception. Concomitant use of psychotropic drugs as well as the introduction or change in intensity of psychotherapeutic interventions.

Notes: Ppts had HAM-A baseline score >=18 and Covi Anxiety score >=8.

Baseline: HAM-A at baseline. Venlafaxine: 27.1 (4.8) and Placebo: 28.5 (6.4)

Data Used

CGI-I

HAMA

Adverse events

Leaving the study early for any reason

Remission (less than 7 on HAMA)

Response (50% reduction in HAMA score)

Notes: Seen at baseline, days 8, 15, 22, 29, 43 and 57.

Group 1 N= 24

Venlafaxine (extended release). Mean dose 75mg/day - Ppts with a less than 30% decrease in their HAM-A total score at the end of 2 weeks compared to the end of the pre-study period doubled their dose for the rest of the treatment period (150mg/day).

Group 2 N= 22

Placebo - No details provided.

Funding: possibly Wyeth.
Quality assessed: -.

PANDE2003

Study Type: RCT

Study Description: 1 week placebo lead-in followed by 4 weeks of treatment and then a 1-week dose taper.

Type of Analysis: ITT (LOCF method)

Blindness: Double blind

Duration (days): Mean 28

Setting: Outpatients. Multicentre: USA (Seattle, Portland, Lansing, Los Angeles and Durham).

Notes: RANDOMISATION: no details provided.

Info on Screening Process: Recruited via clinic referrals or from advertisements. 361 screened; 84 excluded because didn't meet inclusion criteria (N=31), experienced an adverse event (N=1) or because of other administrative reasons (N=52).

n= 276

Age: Mean 36

Sex: 112 males 164 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Any axis I disorder except dysthymia, simple phobia, social phobia, somatisation disorder, or a history of MDD. Patients at suicide risk. No psychotropic medications for 2 weeks before enrollment. Score >=2 on HAM-D item 3.

Notes: Administered Mini International Neuropsychiatric Interview. Divergent findings between clinical interview and MINI were resolved by judgement of principal investigator. Had to have Covi Anxiety Scale >=9 and Raskin Depression Scale score <=7. HAMA >20.

Baseline: HAMA at baseline. Placebo: 22.90 (3.88), Pregabalin 150: 22.35 (2.68), Pregabalin 600: 23.16 (2.73) and Lorazepam: 23.85 (3.24). Slightly more females in placebo and lorazepam groups at baseline.

Data Used
CGI-I
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 69
Placebo - Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.

Group 2 N= 70
Pregabalin. Mean dose 600mg/day - 200mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.

Group 3 N= 69
Pregabalin. Mean dose 150mg/day - 50mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.

Group 4 N= 68
Lorazepam. Mean dose 6mg/day - 2mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.

Funding: no details provided. Pfizer Global Research are involved. Quality assessed: +.

PFIZER2005

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 28

Followup: No Info

Setting: No Info

Notes: No Info

Info on Screening Process: No Info

n= 266

Age:

Sex: no information

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: No information provided

Baseline: HAMA Placebo 23.9, Pregablin 150mg 25.5, Pregablin 600mg 24.4, Lorazepam 6mg 24.3

Data Used
HAMA
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Data Not Used
Discontinuation adverse events (DAEs) - not extractable

Group 1 N= 67
Placebo

Group 2 N= 64
Lorazepam. Mean dose 6mg

Group 3 N= 69
Pregabalin. Mean dose 600mg

Group 4 N= 66
Pregabalin. Mean dose 150mg

Funding: Pfizer

PFIZER2008

Study Type: RCT

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 28

Setting: No Info

Info on Screening Process: 237 screened. 169 randomized. 167 ITT. 115 Completed. 104 Not completed.

n= 169

Age: Mean 36 Range 18-64

Sex: 71 males 98 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Pregnant and lactating females. No primary diagnosis of GAD. HAMA <20. Covi Anxiety Scale total score <9. Raskin Depression Scale total score >7.Subjects who had past or current DSM-IV Axis I diagnosis or receiving daily benzodiazepines 3 months prior screening.

Baseline: HAMA Placebo 21.9 (4.9) Paroxetine 20.5 (3.9)

Data Used
HAMA total score

Group 1 N= 56
Paroxetine. Mean dose 20mg - Capsules for oral administration. 20mg daily for 28 days

Group 2 N= 56
Lorazepam. Mean dose 4.5mg - Capsules for oral administration. 3mg daily for 3 days increasing to 4.5mg dailty from day 4 to day 28.

Group 3 N= 57
Placebo - Double-blind placebo treatment for 28 days.

Funding: Pfizer

Lorazepam 24.2 (3.6)

POHL2005

Study Type: RCT

Study Description: Comparison of the efficacy and tolerability of BID versus TID dosing of pregabalin. 1-week drug-free screening phase followed by 6 weeks DB treatment.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 42

Setting: 19 centres: USA. Ppts recruited via clinic referrals and adverts in the local media.

Notes: RANDOMISATION: randomised in a 1:1:1:1 fashion.

Info on Screening Process: 605 screened: 174 did not meet entry criteria, 22 were lost to follow-up, 36 withdrew consent, 3 were randomised but did not take study medication and 29 were lost for other or administrative reasons.

n= 344

Age:

Sex:

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Other current Axis I disorders except dysthymia or simple phobia, patients at suicide risk, patients with any clinically significant, serious or unstable hematologic, autoimmune, endocrine, vardiovascular, renal, hepatic, gastrointestinal, or neurological disorder and patients with prior exposure to pregabalin.

Notes: Ppts scored >=20 on the HAM-A, >=9 on Covi Anxiety Scale and >=7 on the Raskin Depression Scale. Diagnosis made via MINI.

Baseline: No details provided.

Data Used
Remission (less than 7 on HAMA)
CGI-I
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAMA score)

Notes: Ppts were assessed at baseline and study weeks 1, 2, 3, 4 and 6.

Group 1 N= 89
Pregabalin. Mean dose 400mg/day - Treatment was initiated at 200mg/day and were titrated to 400mg/day on day 4.

Group 2 N= 86
Placebo

Group 3 N= 88
Pregabalin. Mean dose 450mg/day - Treatment was initiated at 300mg/day and titrated to 450mg/day on day 4.

Group 4 N= 78
Pregabalin. Mean dose 200mg/day - Treatment was initiated at 200mg/day and ppts were maintained on this dosage.

Funding: Pfizer, Inc. Quality assessed: +.

POLLACK1997

Study Type: RCT

Study Description: 1 week placebo run-in. 6 week DB treatment followed by a 18 week maintenance period for treatment responders.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 42

Setting: Outpatients. USA.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: No details provided.

n= 464

Age: Mean 39

Sex: 181 males 277 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: Current diagnosis of or a history of bipolar illness, organic mental syndromes, schizophrenia or other psychotic disorders, or seizure disorders.

Notes: Ppts scored >=20 on HAM-A, and a score >=2 on anxious mood item. Had to score Raskin Depression score <= Covi Anxiety score. HRSD score had to be <20.

Baseline: HAM-A at baseline. Abecarnil (high): 25.2. Abecarnil (low): 25.4. Buspirone: 24.4. Placebo: 25.1.

Data Used
HAMA
CGI (Response)
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason

Notes: Assessed after 1 week of washout and then weekly during DB treatment. Then assessed at weeks 8, 10, 12, 16, 20 and 24.

Group 1 N= 115
Buspirone - Started at 15-45mg/day. Increased in first 2 weeks up to 15mg three times a day by day 15. Kept fixed thereafter.

Group 2 N= 116
Abercarnil - Started at 3-9mg/day. Increased during first 2 weeks up to 3mg three times a day by day 15. Kept fixed after day 15.

Group 3 N= 112
Placebo - No details.

Group 4 N= 115
Abercarnil - Started at 7.5-22.5mg/day. Increased during first 2 weeks to be given maximum of 7.5mg three times a day by day 15. Kept fixed after day 15.

Funding: Sandoz and Schering, Berlin. Quality assessed: +.

POLLACK2001

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: outpatient clinics, US and Canada

Notes: Randomisation: no further details

n= 324

Age: Mean 40

Sex: 118 males 206 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Data Used
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 163
Placebo

Funding: GSK. Quality assessed +.

Info on Screening Process: 331 received baseline assessment, 7 withdrew before start of treatment

Exclusions: - < 18 years of age
- HAM-A <20
- HAM-A items 1 and 2 <2
- diagnosis of any other Axis I disorder
- MADRS >17
- substance abuse or dependence
- women of child bearing potential not using reliable contraception

Baseline: HAM-A: Placebo 24.1(0.30) Paroxetine 24.2(0.30)

Notes: Response was based on CGI score 1 or 2

Group 2 N= 161

Paroxetine - 10mg/day first week, 20mg/day second week, those who could not tolerate the medication during first two weeks were withdrawn. After 2 weeks could be increased every week by 10mg/day up to 50mg/day.

RICKELS2000A

Study Type: RCT

Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication

Type of Analysis: ITT/LOCF

Blindness: Double blind

Duration (days): Mean 56

Setting: US
Outpatient (15 centres)

Notes: RANDOMISATION: not reported. ALLOCATION CONCEALMENT: not addressed

Info on Screening Process: 370 completed placebo run-in period & received study drug, 21 of these were excluded as they had no primary outcome.

n= 349

Age: Mean 41 Range 20-75

Sex: 154 males 195 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - Less than 18 years of age
- DSM-IV criteria for GAD
- No MDD
- HAMA score < 18
- HAMA (anxious mood & tension items) < 2
- Reduction of at least 20% in the HAMA total score between screening visit & baseline
- Lower scores on the Covi Anxiety scale than the Raskin Depression Scale
- Raskin Depression Scale score greater than 3 on any item
- Use of other pharmacology (i.e. benzodiazepine, antipsychotic, antidepressants; patients were allowed to take chloral hydrate)
- Other clinically significant psychiatric disorder

Notes: 6.9% had a history of MDD; 0.5% had a history of dysthymia

Baseline: HAMA baseline depression score (approx): 24.23 (4.10). No significant differences between groups at baseline. Venlafaxine 75mg/d: 24.7 (4.4). Venlafaxine 150mg/d: 24.5 (4.1). Venlafaxine 225mg/d: 23.6 (3.7). Placebo: 24.1 (4.2).

Data Used
HAMA
Leaving the study due to inefficacy
Leaving the study due to adverse events
Compliance
Leaving the study early for any reason

Notes: TAKEN AT: week 1, 2, 3, 4, 6, 8 weeks 4-10 days after drug tapered. DROP OUTS: 29% CHANGE SCORES USED.

Group 1 N= 92

Venlafaxine (extended release). Mean dose 75mg/d - 8-week intervention. Fixed doses. Week 1 to 8: 75mg/d. One pill in the morning.

Group 2 N= 90

Venlafaxine (extended release). Mean dose 225mg/d - 8-week intervention. Fixed doses. Week 1: 75mg/d. Week 2: 150mg/d. Week 3 to 8: 225mg/d.

Group 3 N= 91

Venlafaxine (extended release). Mean dose 150mg/d - 8-week intervention. Fixed doses. Week 1: 75mg/d. Week 2 to 8: 150mg/d.

Group 4 N= 97

Placebo - No informtaion given.

Funding: Wyeth-Ayerst Laboratories. Quality assessed: -.

Results from this paper:
+

RICKELS2000B

Study Type: RCT

Study Description: ITT using LOCF for all participants who were randomised and received at least one dose of study medication before evaluation.

Type of Analysis: ITT

n= 310

Age: Mean 39

Sex: 118 males 192 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by

Data Used
CGI-I
HAMA
Adverse events
Leaving the study due to inefficacy

Group 1 N= 104

Placebo - All medication was supplied in encapsulated tablets. Week 1, fixed dosage escalation of up to 1 capsules three times daily. Week 2, dosage could increase depending on response within

Quality assessment score = +
Drug company sponsored: Schering AG, Berlin and

Blindness: Double blind

Duration (days): Mean 42

Setting: Outpatients, 12 sites in US

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: Not reported

DSM-III-R

Exclusions: -Aged <18 or >65
- no diagnosis of GAD according to DSM-III-R criteria
- HAMA <20 after 1 week placebo screenign period or HAMA anxious mood <2
- Raskin Depression score higher than a score on the covi anxiety scale
-HAMD >20
- Concomitant medical or psychiatric conditions, a history of seizures
- Pregnancy
- Participants receiving specified medication in the previous week or receiving neuroleptics, TCAs, MAOIs in previous month prior to study

Notes: Study consisted of 6 weeks double-blind treatment followed by an optional maintenace period for a total of 24 weeks. During the maintenance period, participants continued to receive double-blind treatment.

Baseline: HAMA: Abecarnil: 24.2, Diazepam: 24.0, Placebo: 24.9

Leaving the study due to adverse events

Leaving the study early for any reason

Response (50% reduction in HAMA score)

Notes: TAKEN AT: baseline and end of active treatment (6 weeks)
DROPOUTS: Abercarnil: 32/102 (34%), Diazepam: 24/104 (23%), Placebo: 29/104 (28%)

range of 3-7 capsules per day.

Group 2 N= 102

Abercarnil. Mean dose 12mg/day - All medication was supplied in encapsulated tablets. Active capsules contained 2.5mg. Week 1, fixed dosage escalation of up to 1 capsules three times daily. Week 2, dosage could increase depending on response within range of 3-7 capsules per day.

Group 3 N= 104

Diazepam. Mean dose 22mg - All medication was supplied in encapsulated tablets. Active capsules contained 5.0 mg. Week 1, fixed dosage escalation of up to 1 capsules three times daily. Week 2, dosage could increase depending on response within range of 3-7 capsules per day.

RICKELS2003

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: Outpatients, 50 sites in US and Canada

Notes: RANDOMISATION: no further details

Info on Screening Process: 661 eligible, 35 lost to follow up, 10 adverse events, 6 protocol violations, 44 for other reasons

n= 566

Age: Mean 40

Sex: 253 males 313 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: - <18 years
- HAM-A <20
- HAM-A items 1 and 2 <2
- another other psychiatric condition including MDD
- using other psychoactive drugs

Baseline: HAM-A: Placebo 24.4 (3.7) 20mg Parox 24.1 (3.6) 40mg Parox 23.8 (3.4)

Data Used
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)

Data Not Used
Response (50% reduction in HAMA score) - not extractable

Notes: Response based on CGI score of 1 or 2.

Group 1 N= 180

Placebo - No details given.

Group 2 N= 197

Paroxetine. Mean dose 40mg - Starting dose 10mg/day, increased 10mg/day each week until reach 40mg

Group 3 N= 188

Paroxetine. Mean dose 20mg - Starting dose 10mg, followed by 20mg at week 2

Funding: GSK. Quality assessed -.

RICKELS2005

Study Type: RCT

Study Description: 1 week drug-free screening period before 4 weeks of double-blind treatment. This was followed by a 1 week taper period and then 1 week drug-free.

Type of Analysis: ITT (LOCF method)

Blindness: Double blind

Duration (days): Mean 28

Setting: Recruited via clinic referrals and from advertisements in the local media. Outpatients.

n= 454

Age: Mean 39

Sex: 165 males 289 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: Raskin Depression Scale score >7, being a fertile woman having a positive pregnancy test result, not using a medically accepted contraceptive or currently nursing, a current or past history of bipolar, schizophrenic,

Data Used
CGI-I
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAMA)
Response (50% reduction in HAMA score)

Group 1 N= 91

Placebo - Three treatments a day.

Group 2 N= 91

Pregabalin. Mean dose 300mg/day - Pregabalin was initiated at 300mg/day and kept constant throughout the study. Three treatments a day.

Funding: Pfizer, Inc. Quality assessed: +.

Multicentre: USA.

Notes: RANDOMISATION: ppts were randomised in blocks of 10. No further details.

Info on Screening Process: 696 screened: 454 randomised (242 excluded). Reasons for exclusion not provided.

schizoaffective, psychotic or factitious disorder and dementia, current but not lifetime MDD, social anxiety disorder, panic disorder with or without agoraphobia, OCD, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse, positive urine drug screen result, any clinically significant acute or unstable medical condition or clinically significant ECG result or laboratory abnormalities, concurrent psychotherapy for GAD, unless undergoing stable treatment for longer than 3 months, concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit, current or past history of a seizure disorder or requiring anticonvulsant therapy for any indication, or suicide risk either currently or based on history.

Notes: Diagnosis was based on structured Mini-International Neuropsychiatric Interview. Had HAMA scores >9 and Covi Anxiety Scale scores >9.

Baseline: HAMA at baseline: Pregabalin 300: 25.0 (SE 0.4), Pregabalin 450: 24.6 (SE 0.4), Pregabalin 600: 25.2 (SE 0.4), Alprazolam: 24.9 (SE 0.4) and Placebo: 24.6 (SE 0.4).

Notes: Assessments were performed at screening, baseline and at study weeks 1, 2, 3 and 4.

Group 3 N= 89

Pregabalin. Mean dose 600mg/day - Pregabalin was initiated at 300mg/day and titrated to 450mg/day on day 4. Dosage was titrated to 600mg/day on day 7. Three treatments a day.

Group 4 N= 90

Pregabalin. Mean dose 450mg/day - Pregabalin was initiated at 300mg/day and then titrated to 450mg/day on day 4. Three treatments a day.

Group 5 N= 93

Alprazolam. Mean dose 1.5mg/day - Initiated at 0.5mg/day and increased to 1.0mg/day on day 4 and 1.5mg/day on day 7. Three treatments a day.

RYNN2008

Study Type: RCT

Study Description: ITT included all randomised participants with at least one postbaseline evaluation. Safety analysis included all randomised participants.

Type of Analysis: Double Blind

Blindness: ITT

Duration (days): Mean 70

Setting: Outpatients, Multicentre trail across USA

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: 515 patients were evaluated, 188 failed to meet the inclusion criteria

n= 327

Age: Mean 42

Sex: 125 males 202 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-IV

Exclusions: <18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covia Anxiety score <9 or not greater and then Raskin depression total score.
Raskin depression scale item rated >3
- Medical illness that would contraindicate use of duloxetine
- Women of childbearing age not using adequate contraception
- recent diagnosis of depression or substance abuse/depence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of psychotic, bipolar, OCD or psychosis
- lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments
- psychotherapy iniated 6 weeks prior to study enrollment

Baseline: HAMA: Duloxetine 22.6(7.4) Placebo 23.5(7.9)

Data Used

Q-LES-Q-SF
Response (50% reduction in HAMA score)
Remission (less than 7 on HAMA)
Leaving the study early for any reason
PGI-I
Leaving the study due to adverse events
Significant improvement (30% reduction)
EQ-5D
CGI-I
Leaving the study due to inefficacy
Serious Adverse events
Sheehan Disability Scale (SDS)
Visual Analog Scale (VAS)
Adverse events
HAMA
Discontinuation adverse events (DAEs)

Notes: TAKEN AT: Baseline and endpoint
DROP OUT: Duolxetine: 75/168 (44.6%), Placebo 50/159 (31.4%)

Group 1 N= 168

Duloxetine. Mean dose 101.94mg/d - Participants were started with 60mg/d, if there were tolerability concerns this was lowered to 30mg/d. Bt week 2 all patients were required to take a minimum of 60mg/d. Patient doses were progressively titrated if the CGI rating was >=3 up to max of 120mg

Group 2 N= 159

Placebo

Drug compnay funded. Eli Lilly trial 6089.
NCT00475969 - trial report collected
All participants underwent a single-blind placebo lead-in week, 10 week acute phase and a 2 week discontinuation tapering phase.. Quality Assessment Score = + / ++

Results from this paper:

SRAMEK1996

Study Type: RCT

Study Description: Placebo for 7-10 days. Randomised to receive either buspirone or placebo for 6 weeks.

Type of Analysis: LOCF method (completed >2 weeks treatment)

Blindness: Double blind

Duration (days): Mean 42

Setting: Multicentre: USA.

Notes: RANDOMISATION: no details provided.

Info on Screening Process: 222 patients entered study: 60 dropped out. 34 didn't meet study inclusion criteria.

n= 162

Age: Mean 38

Sex: 72 males 90 females

Diagnosis:
100% Generalised Anxiety Disorder (GAD) by DSM-III-R

Exclusions: Pregnant or lactating, DSM-III-R diagnosis of MDD, a concurrent DSM-III-R Axis I disorder, a history of two or more panic attacks within 4 weeks of the beginning of screening, score of 3 or more on the suicide item of the HAM-D scale, used benzodiazepines for 14 days or more in the last 2 months or an investigational drug within the past month, received ECT within the last 3 months or treatment with other psychotropics in the previous month. Clinically significant and/or uncontrolled medical conditions, positive urine drug screen, current or recent history of drug or alcohol abuse.

Notes: HAM-A score >=18, score of 2 or 3 on the 'depressed mood' item of the HAM-A scale, scored of >=2 on the 'anxious mood' and 'tension' items on the HAM-A. HAM-D score between 12 and 15. Covi > Raskin.

Baseline: HAM-A at baseline. Buspirone: 24.9 (4.2) and Placebo: 25.6 (4.4).

Data Used
CGI-I
HAMA
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason

Notes: Assessed weekly.

Group 1 N= 82

Placebo - No details.

Group 2 N= 80

Buspirone - Titrated from an initial dosage of 5mg t.i.d. to 10 mg t.i.d. over first week. Dosage increased by 5mg/day every 2-3 days. After 2 weeks of maintenance at 10mg t.i.d., those who didn't show an improvement were titrated to 15mg t.i.d. over next 7 days.

Funding: Bristol-Myers Squibb Pharmaceutical Research Institute. Quality assessed: +.

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
	no extractable data
ANSSEAU1984	pre-DSM-III-R diagnosis
ANSSEAU1985	pre DSM-III-R diagnosis
BJERRUM1992	DSM-III diagnosis
BLANK2006	no comparator
BOND2002	Combination treatment
BORAL1986	DSM-III diagnosis
BORISON1990	N<10 in each treatment arm
BOYER1993	DSM-III diagnosis
BRAMANTI1990	not double blind
BRESOLIN1988	pre DSM-III-R diagnosis
BRESSA1987	DSM-III diagnosis
BUCHSBAUM1985	DSM-III diagnosis
BUCHSBAUM1987	DSM-III diagnosis

BYSTRITSKY1991	N<10
CASTILLO1988	DSM-III diagnosis
CEPHALON2006A	open label study
CEULEMANS1985	DSM-III diagnosis
COHN1986B	Diagnosis pre-DSM-III-R
CUTLER1993A	Pre DSM-III-R diagnosis
CUTLER1994	DSM-III
ENKELMANN1991	DSM-III diagnosis
FEIGHNER1982	DSM-III diagnosis
FONTAINE1983	pre DSM-III-R diagnosis
FONTAINE1984	DSM-III diagnosis
FONTAINE1986	DSM-III diagnosis
FONTAINE1987	DSM-III diagnosis
FONTAINE1990	DSM-III diagnosis
FONTAINE1993	DSM-III diagnosis
GINSBERG1929	no comparator
HOEHNSARIC1988	DSM-III diagnosis
HOGE2008	open label
JACOBSON1985	DSM-III diagnosis
KIM2006c	Design: open label
KINRYS2002	N <10
KRAGHSORENSEN1990	DSM-III diagnosis
LAPIERRE1982A	DSM-III diagnosis
LAPIERRE1983A	DSM-III diagnosis
LINDSAY1987	pre DSM-III-R diagnosis
MANDOS1995	DSM-III diagnosis
MATHEW2005	open label study
MATHEW2008	open label study
MENDELS1986	DSM-III diagnosis
MENZA2007	open label trial
MOKHBER2010	not double blind
MORTON1992A	DSM-III diagnosis
MURPHY1989	DSM-III diagnosis
NAUKKARINEN2005	not relevant intervention
PANGALILARATU1988	DSM-III diagnosis
PEET1986	DSM-III diagnosis
PETRACCA1990	DSM-III diagnosis
POMARA2005	DSM-III diagnosis

POURMOTABBED1996	one group n<10
POWER1985	pre DSM-III-R diagnosis
POWER1989	pre DSM-III-R diagnosis
POWER1990	DSM-III diagnosis
POWER1990A	DSM-III diagnosis
RAMCHANDRAN1990	DSM-III diagnosis
RAPAPORT2006	open label study
REALINI1990	DSM-III diagnosis
RICKELS1972	pre DSM-III-R diagnosis
RICKELS1993	DSM-III diagnosis
RICKELS1997	DSM-III diagnosis
ROCCA1997	open label study
ROLLAND2002	n < 10 per treatment group
ROSENTHAL2003	open label study
SACCHETTI1994	DSM-III diagnosis
SHAH1990	DSM-III diagnosis
SHAH1991	DSM-III diagnosis
SIMON2006A	no comparator
SPENARD1988	DSM-III diagnosis
SPRATLIN2003	not an RCT
SRAMEK1996A	n <10 per arm
STRAND1990	pre DSM-III-R
TSUKAMOTO2004	open label study
WILCOX1994	one group n<10
WINGERSON1992	not RCT
WURTHMAN2006	not RCT
WURTHMANN2006	no comparator

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ALLGULANDER2001 (Published Data Only)

Allgulander, C., Hackett, D. & Salinas, E. (2001) Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder. British Journal of Psychiatry, 179, 15-22.

ALLGULANDER2004 (Published Data Only)

Allgulander, C., Dahl A.A., & Austin, C. (2004) Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. American Journal of Psychiatry, 161, 1642-1649.

Dahl, A.A., Ravindran, A., Allgulander, C., Kutcher, S.P., Austin, C., & Burt, T. (2005) Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. Acta Psychiatrica Scandinavica, 111, 429-435.

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ANDREATINI2002 (Published Data Only)

Andreatini, R., Sartori, V.A., Seabra, M.L.V. & Leite, J.R. (2002) Effect of Valepotriates (Valerian Extract) in generalized anxiety disorder: a randomized placebo-controlled study. Phytotherapy Research, 16, 650-654.

ANSSEAU2001 (Published Data Only)

Ansseau, M., Olie, J-P., von Frenckell, R., Jourdain, G., Stehle, B., & Guillet, P. (2001) Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder. Psychopharmacology, 104, 439-443.

ASTRAZENECA2007A (Published Data Only)

AstraZeneca (2007) An international, multi-center, randomized, double-blind, parallel-group, placebo-controlled, active-controlled study of the efficacy and safety of sustained-release quetiapine fumarate (Seroquel SR) in the treatment of Generalized Anxiety Disorder (SILVER Study).

ASTRAZENECA2007B (Published Data Only)

AstraZeneca (2007b) A multicenter, randomized, double-blind, parallel-group, placebo-controlled, active-controlled study of the efficacy and safety of sustained-release quetiapine fumarate (Seroquel) compared with placebo in the treatment of generalized anxiety disorder (Gold Study).

ASTRAZENECA2007C (Published Data Only)

AstraZeneca (2007c) A multi-center, randomized, double-blind, parallel-group, placebo-controlled, study of the efficacy and safety of sustained-release quetiapine fumarate (Seroquel) compared with placebo in the treatment of generalized anxiety disorder (Titanium Study)

ASTRAZENECA2008 (Published Data Only)

Astra Zeneca (2008) A multi-center, double-blind, randomized, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate extended-release (Seroquel XR) as monotherapy in the treatment of elderly patients with generalized anxiety disorder (CHROMIUM STUDY)

BALDWIN2006 (Published Data Only)

Baldwin, D.S., Huusom, A.K.T. & Maehlum, E. (2006) Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, doube-blind study. British Journal of Psychiatry, 189, 264-272.

BALL2005 (Published Data Only)

Ball, S.G., Kuhn, A., Wall, D. et al. (2005) Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. Journal of Clinical Psychiatry, 66, 94-99.

BIELSKI2005 (Published Data Only)

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

BOSE2008 (Published Data Only)

Bose, A., Korotzer, A., Gommoll, C., & Li, D. (2008) Randomized placebo-controlled trial of escitalopram and venlafaxine xr in the treatment of generalized anxiety disorder. Depression and Anxiety, 25, 854-861.

BOURIN1992 (Published Data Only)

Bourin, M., & Malinge, M. (1995) Controlled comparison of the effects and abrupt discontinuation of buspirone and lorazepam. Progres in Neuro-Psychopharmacology & Biological Psychiatry, 19, 567-575.

BRAWMAN-MINTZER2006 (Published Data Only)

Brawman-Mintzer, O., Knapp, R.G., Rynn, M. et al. (2006) Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry, 67, 874-881.

CUTLER1993A (Published Data Only)

Cutler, N.R. Sramek, J.J., Wardle, T.S., Keppel Hesslink, J.M. & Roeschen, J.K. (1993) The saefty and efficacy of Ipsapirone vs. Lorazepam in outpatients with generalized anxiety disorder (GAD): Single site findings from a multicenter trial. Psychopharmacology Bulletin, 29, 2 303-308

DARCIS1995 (Published Data Only)

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Characteristics Table for The Clinical Question: In the treatment of generalised anxiety disorder what treatment dose improves outcome?

Comparisons Included in this Clinical Question

Anticonvulsants versus Anticonvulsants
FELTNER2003
MONTGOMERY2006
PANDE2003
POHL2005
RICKELS2005

Duloxetine (SNRI) vs Duloxetine (SNRI)
KOPONEN2007
NICOLINI2009

SSRIs versus SSRIs
BALDWIN2006
RICKELS2003

Venlafaxine (SNRI) vs Venlafaxine (SNRI)
ALLGULANDER2001
DAVIDSON1999
HACKETT2003
RICKELS2000A

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ALLGULANDER2001 Study Type: RCT Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication Type of Analysis: ITT/LOCF Blindness: Double blind Duration (days): Mean 168 Setting: Belgium, Finland, France, Sweden, UK Outpatient (14 centres) Notes: RANOMISATION: not reported. ALLOCATION CONCEALMENT: not addressed Info on Screening Process: 541 randomised, 529 met ITT criteria for inclusion.	n= 529 Age: Mean 45 Range 18-86 Sex: 201 males 328 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - DSM-IV diagnosis of GAD - HAMA score < 20 - HAMA (anxious mood & tension items) < 2 - MDD or other psychiatric disorder - Clinically important medical disease - Non-pharmacological drugs with psychotropic effects Notes: 74% had received prior treatment for anxiety (mostly benzodiazepines & antidepressants); 85% received non-anxiolytic concomitant therapy during the study (26 had beta-blocker, 52 on zolpidem or chloral hydrate) Baseline: HAMA baseline depression score (approx): 26.48 (range 20 to 52). No significant differences between groups at baseline. Venlafaxine 37.5mg/d: 26.6 (range 20 to 44). Venlafaxine 75mg/d: 26.3 (range 20 to 43). Venlafaxine 150mg/d: 26.3 (17 to 38). Placebo: 26.7 (20 to 52).	**Data Used** HAMA Leaving the study due to inefficacy Leaving the study due to adverse events Leaving the study early for any reason **Data Not Used** Response (50% reduction in HAMA score) - not extractable Notes: TAKEN AT: 1,2,3,4,6,8,10,12,16,20,24,25 weeks. Efficacy looked at 8 & 24 weeks. DROP OUTS: 36% CHANGE SCORES USED.	**Group 1 N= 137** Venlafaxine (extended release). Mean dose 150mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily. **Group 2 N= 134** Venlafaxine (extended release). Mean dose 75mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily. **Group 3 N= 130** Placebo - No further information **Group 4 N= 138** Venlafaxine (extended release). Mean dose 37.85mg/d - Single blind wash-out period & discontinuation period. 24 week treatment. Fixed doses. Once daily.	Funding: Wyeth-Ayerst Research. Quality assessed: +.
BALDWIN2006 Study Type: RCT Study Description: ITT: patients who took at least one dose of the study medication & at least one baseline efficacy assessment were included in analysis Type of Analysis: LOCF/ITT	n= 682 Age: Mean 41 Sex: 244 males 438 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV-TR	**Data Used** HAMA Leaving the study due to inefficacy Leaving the study due to adverse events Leaving the study early for any reason DESS (modified) Response (50% reduction in HAMA score)	**Group 1 N= 133** Escitalopram. Mean dose 20 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period.	Received support from Lundbeck and sponsored by GlaxoSmith Kline. Quality assessed: +.

Blindness: Double blind Duration (days): Mean 84 Setting: UK Notes: RANDOMISATION: computer-generated randomisation list. ALLOCATION CONCEALMENT: sealed opaque envelopes. Info on Screening Process: Details not provided.	Exclusions: - not primary diagnosis of GAD (DSM-IV-TR) - not between 18 and 65 - HAMA score < 20 - HAMA (anxious mood & tension items) < 2 - MADRS >15 - Diagnosis of: MDD, panic disorder, social anxiety, PTSD, bipolar, OCD, body dysmorhpic disorder, substance abuse, personality disorder - suicide risk - receiving psychosocial interventions (i.e. CBT, ECT) - physical health problems (i.e. vascular) - concomittant medication (i.e. psychoactive substances, antidepressants, benzodiazepines, antipsychotics) Baseline: HAMA scores at baseline (approx): 27.04 (4.46); No significant differences at baseline	**Data Not Used** Remission (less than 7 on HAMA) - not extractable Notes: TAKEN AT: 1,2,4,6,8,10,12,13,14 weeks.DROP OUTS: 14% (98) MEAN CHANGE SCORES.	**Group 2 N= 134** Escitalopram. Mean dose 5 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period. **Group 3 N= 140** Paroxetine. Mean dose 20 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period. **Group 4 N= 136** Escitalopram. Mean dose 10 mg/ day - 1 week, single blind placebo lead-in period, 12 weeks of treatment with fixed doses. 2 week placebo wash-out period. **Group 5 N= 139** Placebo - Identical appearance, taste and smell. Oral administration.	
DAVIDSON1999 Study Type: RCT Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication Type of Analysis: ITT/LOCF Blindness: Double blind Duration (days): Mean 56 Setting: US Outpatient (17 centres) Notes: RANDOMISATION: details not provided. ALLOCATION CONCEALMENT: not addressed. Info on Screening Process: 405 patients completed placeb run-in period & received study drug, 36 had no primary efficacy evaluations & 4 randomised at one site were excluded for administrative reasons.	n= 365 Age: Mean 38 Sex: 224 males 141 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - Not 18 years or older - Primary diagnosis not GAD (DSM-IV) - HAMA score < 18 - HAMA (anxious mood & tension items) < 2 - Raskin depression score > 9 or > Covi anxiety score or any item > 3 - Presence of clinically significant psychiatric disorder other than GAD - use of other pharmacology except for chloral hydrate Notes: No. of participants taking chloral hydrate: placebo (N=7), venlafaxine 75mg/d (N = 2), venlafaxine, 150mg/d, buspirone (N=2) Baseline: HAMA scores at baseline (approx) total: 23.55 (4.23); venlafaxine 75mg/ day: 23.7 (4.1), 150 mg/d: 23.0 (4.0); buspirone: 23.8 (4.6); placebo; 23.7 (4.2). No significant differences at baseline.	**Data Used** HAMA Leaving the study due to adverse events Compliance Response (50% reduction in HAMA score) Notes: TAKEN AT: 1, 2, 3, 4, 6, 8 weeks & 4 to 10 days after drug taper. DROP OUTS: 27%. MEAN CHANGE SCORES.	**Group 1 N= 102** Venlafaxine (extended release). Mean dose 75mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed dose of 75mg/d. **Group 2 N= 104** Placebo - Matched placebo. **Group 3 N= 98** Buspirone. Mean dose 30 mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed doses. Daily 3 divided doses. Days 1 & 2: 15 mg/d. Days 3 & 4: 20 mg/d. Days 5-7: 25mg/d. Days 8-56: 30 mg/d. **Group 4 N= 101** Venlafaxine (extended release). Mean dose 150 mg/ day - 1 week placebo run-in phase; 8 weeks of treatment. Fixed doses. Weel 1: 75mg/d. Week 2: 150 mg/d.	Funding: Wyeth-Ayerst Research. Quality assessed: +.
FELTNER2003 Study Type: RCT Study Description: ITT included all randomised participants who received at least one dose of study medication	n= 271 Age: Mean 38 Range 18-74 Sex: 128 males 143 females	**Data Used** Remission (less than 7 on HAMA) CGI-I HAMA	**Group 1 N= 68** Lorazepam. Mean dose 6MG - Fixed dose regimen with 2 mg TID. Study medication was tirated during days 1-6 of double-blind treatment	The ITT population was 271, this included all randomised participants who received at least one dose of study medication. No details given

Blindness: Double blind Duration (days): Mean 28 Setting: Four study centres, USA Outpatients Notes: RANDOMISATION: procedure not reported Info on Screening Process: Not reported	Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - Did not meet DSM-IV criteria for GAD, or GAD not the primary diagnosis in the case of comorbidity and HAMA >20 - Aged <18 years - Suffering from another other Axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder or a histpry pf MDD - Current MDD - Severe personality disorders, drug or alcohol abuse / dependence (active within 6 months of study) - Suicide risk - Covi anxiety scale <9 Raskin depression > 7 Notes: Participants with a dual comorbid psychiatric disorders were required to have GAD as a primary disorder as judged by the psychiatrist, considering relative severity and time of onset Baseline: HAMA: Pregabalin (50mg) 24.9(3.9), Pregabalin (200mg) 25.4(4.6), Lorazepam 24.7(3.7), Placebo 24.8(4.1)	Adverse events Serious Adverse events Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAMA score) Notes: TAKEN AT: Baseline and end of active treatment (4 weeks) DROPOUTS: total drop outs not reported	**Group 2 N= 70** Pregabalin. Mean dose 150mg - Fixed dose regimen with 50 mg TID. Study medication was tirated during days 1-6 of double-blind treatment. **Group 3 N= 66** Pregabalin. Mean dose 600mg - Fixed dose regimen with 200 mg TID. Study medication was tirated during days 1-6 of double-blind treatment. **Group 4 N= 67** Placebo	on the original number randomised to each condition. Funding: no details. Quality assessment score = +
Results from this paper:				
HACKETT2003 Study Type: RCT Study Description: Randomised, double-blind, placebo-controlled, parallel-group study. Followed by long-term phase study that is reported separately. Type of Analysis: ITT (LOCF method) Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients. Multicentre: France. Notes: RANDOMISATION: no further details Info on Screening Process: 564 entered study, 16 did not receive any medication before dropping out	n= 540 Age: Mean 44 Sex: 175 males 365 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - <18 years of age - HAM-A <20 - HAMA <2 for items 1 and 2 - MDD - more than 2 panic attacks in last month Baseline: HAM-A: Placebo =27.6 Venlafaxine 75mg = 27.9 Venlafaxine 150mg = 27.9 Diazepam = 28.4. Doesn't report SDs or SEs.	**Data Used** CGI-I HAMA Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAMA score) Notes: Rating scales were administered at baseline, and again after 7, 14, 21, 28, 42 and 56 days.	**Group 1 N= 179** Venlafaxine (extended release). Mean dose 150mg - 150mg/day. **Group 2 N= 191** Venlafaxine (extended release). Mean dose 75mg - 75mg/day. **Group 3 N= 97** Placebo - No details given. **Group 4 N= 89** Diazepam. Mean dose 15mg/d - 15 mg/day.	Funded by Wyeth. Quality assessed +.
KOPONEN2007 Study Type: RCT Study Description: ITT analysis included all randomised participants with >=1 postbaseline analysis. Safety analysis included all randomised participants Type of Analysis: ITT	n= 513 Age: Mean 44 Sex: 165 males 348 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by	**Data Used** Q-LES-Q-SF Response (50% reduction in HAMA score) Remission (less than 7 on HAMA) Leaving the study early for any reason PGI-I	**Group 1 N= 175** Placebo	Drug company funded - Eli Lilly studyF1J-MC-HMBR (NCT00122824) - trial report collected All participants underwent a single-blind placebo lead-in week, 9 week acute phase

Blindness: Double blind Duration (days): Mean 63 Setting: outpatient clinics. Multicentre - 7 countries Notes: RANDOMISATION: procedure not reported. Participants were stratified by baseline HAM-A score. Info on Screening Process: 639 participants were screened for the study with 126 failing to meet the inclusion criteria.	DSM-IV Exclusions: -<18 years - No primary DSM-IV diagnosis of GAD - CGI-S <4 - HADS anxiety subscale <10 - Covia Anxiety score <9 or not greater and then Raskin depression total score. Raskin depression scale item rated >3 - Medical illness that would contraindicate use of duloxetine - Women of childbearing age not using adequate contraception - recent diagnosis of depression or substance abuse/depence - past year history of panic disorder, PTSD or eating disorder - lifetime history of psychotic, bipolar, OCD or psychosis - lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments - psychotherapy iniated 6 weeks prior to study enrollment Baseline: HAMA (total) Dulox (60mg) 25.0(7.1); Dulox (120mg) 25.2(7.3); Placebo 25.8(7.6)	Leaving the study due to adverse events Significant improvement (30% reduction) EQ-5D CGI-I Symptom Questionnaire-Somatic subscale (SQ-SS) Leaving the study due to inefficacy Serious Adverse events Sheehan Disability Scale (SDS) Visual Analog Scale (VAS) HAMA Discontinuation adverse events (DAEs) Notes: TAKEN AT: baseline and endpoint DROP OUT: Dul 60 33/168 (19.6%); Dul 120 46/170 (27.1%); Placebo 45/175 (25.7%)	**Group 2 N= 168** Duloxetine. Mean dose 60mg/d - Participants were started with 60mg/d, if there were tolerability concerns this was lowered to 30mg/d with all participants gradually increased to their randomised dose within the first 2 study weeks. **Group 3 N= 170** Duloxetine. Mean dose 120mg/d - Participants were started with 60mg/d, if there were tolerability concerns this was lowered to 30mg/d with all participants gradually increased to their randomised dose within the first 2 study weeks.	and a 2 week discontinuation tapering phase. Quality assessment score = + / ++
MONTGOMERY2006 Study Type: RCT Study Description: ITT: all randomized patients who received at least 1 dose of study drug. LOCF used on all primary and secondary outcome measures. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Followup: None Setting: Multicentre (76): Austria, Belgium, Germany, the Netherlands and the United Kingdom. Outpatients attending primary care or psychiatric practices. Notes: Randomisation procedure not reported. Parallel-group design. Info on Screening Process: 543 ppts entered baseline phase; 421 were randomised and received study medication. Reasons for exclusion: did not meet entry criteria, lost to follow-up, withdrew consent, other/administrative and randomised but did not take study medication.	n= 421 Age: Mean 44 Sex: 160 males 261 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Diagnosis of any other current Axis 1 disorders except depression not otherwise specificied, dysthymia, simple phobia or somatisation disorder. Additional exclusion criteria: clinically relevant hematologic, autoimmune, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or neurologic disorders; a history of seizure disorder; borderline, avoidant or antisocial personality disorder; alcohol or substance use disorder within the past 6 months; and patients considered at risk of suicide. Women who were pregnant or lactating, and women of childbearing potential who were not using a reliable method of contraception. Use of gabapentin or a benzodiazepine within 1 week of first baseline visit, the use of other psychotropic medications within 2 weeks prior to study entry, or ongoing psychodynamic or cognitive-behavioural psychotherapy for GAD. Use of corticosteroids (except topical or inhaled corticosteroids < 1000mg/day), antihypertensive agents, captopril, beta-blockers and psychotropic medication was not permitted during the study. Patients were allowed to take zolpidem for insomnia but not for more than 2 nights per week or the night before clinic visits. Notes: Ppts were diagnosed using the Mini-International	**Data Used** Remission (less than 7 on HAMA) CGI-I HAMA Adverse events Serious Adverse events Leaving the study early for any reason Response (50% reduction in HAMA score) **Data Not Used** Leaving the study due to adverse events - not extractable Significant improvement (30% reduction) - not required Notes: HAM-D outcome scores also reported. TAKEN AT: baseline, 1 week and endpoint. DROP OUTS: Pregabalin 400mg/day 16/97, Pregabalin 800mg/day 29/110, Venlafaxine 34/113 and Placebo 20/101.	**Group 1 N= 97** Pregabalin. Mean dose 400mg/day - 100mg/day for 2 days then 200mg/day for 2 days, before receiving the full dosage of 400mg/day on day 5. All administered twice-per-day (b.i.d.). **Group 2 N= 113** Venlafaxine (extended release). Mean dose 37.5mg/day - Began treatment at full 37.5mg/day (b.i.d.) dosage. **Group 3 N= 101** Placebo - No details given. **Group 4 N= 110** Pregabalin. Mean dose 600mg/day - 150mg/day for 2 days, 300mg/day for 2 days and 450mg/day for 2 days before receiving the full dosage of 600mg/day after day 7. All administered twice-per-day (b.i.d.).	Funded by pharma (Pfizer Inc, New York). This study involved a 1 week screening period. 6 weeks of double-blind treatment were followed up by a 1-week, double-blind taper and follow-up phase. Quality assessment score = +

	Neuropsychiatric Interview (MINI). Baseline: Pregabalin 400mg/day (N=97, 23%), Pregabalin 600mg/day (N=110, 26%), Venlafaxine (N=113, 27%) and Placebo (N=101, 24%). HAM-A baseline: Pregabalin 400mg/day 26.3 (4.4), Pregabalin 600mg/day 26.5 (4.6), Venlafaxine 26.0 (4.6) and Placebo 27.4 (5.5). TOTAL: 26.6 (4.8). HAM-D baseline: Pregabalin 400mg/day 12.2 (3.6), Pregabalin 600mg/day 12.2 (4.0), Venlafaxine 12.0 (3.4) and Placebo 12.8 (4.9). TOTAL: 12.3 (4.0).			
Results from this paper:				
NICOLINI2009 Study Type: RCT Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 70 Setting: Australia, Argentina, Belgium, Canada, Mexico, Russia, Taiwan, UK Outpatients Notes: RANDOMISATION: computer-generated ALLOCATION CONCEALMENT: interactive voice response system Info on Screening Process: Patients entered (N=771); did not meet criteria/concent (N=190)patients randomised (N=581); patients completed trial (N=396)	n= 581 Age: Mean 43 Sex: 43 males 57 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: -<18 years - No primary DSM-IV diagnosis of GAD - CGI-S <4 - HADS anxiety subscale <10 - Covia Anxiety score <9 or not greater and then Raskin depression total score. Raskin depression scale item rated >3 - Medical illness that would contraindicate use of duloxetine - Women of childbearing age not using adequate contraception - recent diagnosis of depression or substance abuse/depence - past year history of panic disorder, PTSD or eating disorder - lifetime history of psychotic, bipolar, OCD or psychosis - lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments - psychotherapy iniated 6 weeks prior to study enrollment Notes: Duration of GAD M(S.D.) = 4.37 (8.19) years Baseline: BASELINE HAMA scores = 27.4 (total); 27.33 (7.33) (placebo); 27.65 (7.99) - dul 20mg; 27.74 (7.32) - dul 60-120mg); 27.36 (7.57) - ven 75-125mg)	**Data Used** CGI-I HAMA Sheehan Disability Scale (SDS) Hospital Anxiety and Depression Scale (anxiety) Leaving the study due to inefficacy Leaving the study due to adverse events PGI-I Leaving the study early for any reason Remission (less than 7 on HAMA) Response (50% reduction in HAMA score) Notes: DROP OUTS: 21/84 (25%) - DULOX 20mg; 49/158 (31%) - DULOX 60-120 mg; 47/122 (39%) - VENLAFAXINE; 68/170 (40%) - PLACEBO.	**Group 1 N= 169** Venlafaxine (extended release). Mean dose 151.3mg/day - 75 - 225 mg/day; flexible dosing of an increase of 75mg/day. Dose increase required if CGI-I score > 4 after 3 weeks. Dosed could be decreased no more than twice. Dose stabilised after 6 weeks. **Group 2 N= 84** Duloxetine 20mg. Mean dose 20mg/day - Once daily fixed dose of 20mg. Those who required dose increase received additional placebo capsules. **Group 3 N= 170** Placebo **Group 4 N= 158** Duloxetine. Mean dose 90mg/day - 60-120 mg/day flexible dosing of an increase of 30mg/day. Dose increase required if CGI-I score > 4 after 3 weeks. Dosed could be decreased no more than twice. Dose stabilised after 6 weeks.	FUNDED BY ELI LILLY: Trial report collected (#7106). Quality assessed: +
PANDE2003 Study Type: RCT Study Description: 1 week placebo lead-in followed by 4 weeks of treatment and then a 1-week dose taper. Type of Analysis: ITT (LOCF method)	n= 276 Age: Mean 36 Sex: 112 males 164 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV	**Data Used** CGI-I HAMA Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAMA)	**Group 1 N= 69** Placebo - Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.	Funding: no details provided. Pfizer Global Research are involved. Quality assessed: +.

Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients. Multicentre: USA (Seattle, Portland, Lansing, Los Angeles and Durham). Notes: RANDOMISATION: no details provided. Info on Screening Process: Recruited via clinic referrals or from advertisements. 361 screened; 84 excluded because didn't meet inclusion criteria (N=31), experienced an adverse event (N=1) or because of other administrative reasons (N=52).	Exclusions: Any axis I disorder except dysthymia, simple phobia, social phobia, somatisation disorder, or a history of MDD. Patients at suicide risk. No psychotropic medications for 2 weeks before enrollment. Score >=2 on HAM-D item 3. Notes: Administered Mini International Neuropsychiatric Interview. Divergent findings between clinical interview and MINI were resolved by judgement of principal investigator. Had to have Covi Anxiety Scale >=9 and Raskin Depression Scale score <=7. HAMA >20. Baseline: HAMA at baseline. Placebo: 22.90 (3.88), Pregabalin 150: 22.35 (2.68), Pregabalin 600: 23.16 (2.73) and Lorazepam: 23.85 (3.24). Slightly more females in placebo and lorazepam groups at baseline.	Response (50% reduction in HAMA score)	**Group 2 N= 70** Pregabalin. Mean dose 600mg/day - 200mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached. **Group 3 N= 69** Pregabalin. Mean dose 150mg/day - 50mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached. **Group 4 N= 68** Lorazepam. Mean dose 6mg/day - 2mg three times a day. Day 1 received 1/6 of dose, which was increased daily until targeted dose was reached.	
PFIZER2005 Study Type: RCT Blindness: Double blind Duration (days): Mean 28 Followup: No Info Setting: No Info Notes: No Info Info on Screening Process: No Info	n= 266 Age: Sex: no information Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: No information provided Baseline: HAMA Placebo 23.9, Pregablin 150mg 25.5, Pregablin 600mg 24.4, Lorazepam 6mg 24.3	**Data Used** HAMA Leaving the study early for any reason Remission (less than 7 on HAMA) Response (50% reduction in HAMA score) **Data Not Used** Discontinuation adverse events (DAEs) - not extractable	**Group 1 N= 67** Placebo **Group 2 N= 64** Lorazepam. Mean dose 6mg **Group 3 N= 69** Pregabalin. Mean dose 600mg **Group 4 N= 66** Pregabalin. Mean dose 150mg	Funding: Pfizer
POHL2005 Study Type: RCT Study Description: Comparison of the efficacy and tolerability of BID versus TID dosing of pregabalin. 1-week drug-free screening phase followed by 6 weeks DB treatment. Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 42 Setting: 19 centres: USA. Ppts recruited via clinic referrals and adverts in the local media. Notes: RANDOMISATION: randomised in a 1:1:1:1 fashion. Info on Screening Process: 605 screened: 174 did not meet entry criteria, 22 were lost to follow-up, 36 withdrew consent, 3 were randomised but did not take study medication and 29 were	n= 344 Age: Sex: Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Other current Axis I disorders except dysthymia or simple phobia, patients at suicide risk, patients with any clinically significant, serious or unstable hematologic, autoimmune, endocrine, vardiovascular, renal, hepatic, gastrointestinal, or neurological disorder and patients with prior exposure to pregabalin. Notes: Ppts scored >=20 on the HAM-A, >=9 on Covi Anxiety Scale and >=7 on the Raskin Depression Scale. Diagnosis made via MINI. Baseline: No details provided.	**Data Used** Remission (less than 7 on HAMA) CGI-I Adverse events Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAMA score) Notes: Ppts were assessed at baseline and study weeks 1, 2, 3, 4 and 6.	**Group 1 N= 89** Pregabalin. Mean dose 400mg/day - Treatment was initiated at 200mg/day and were titrated to 400mg/day on day 4. **Group 2 N= 86** Placebo **Group 3 N= 88** Pregabalin. Mean dose 450mg/day - Treatment was initiated at 300mg/day and titrated to 450mg/day on day 4. **Group 4 N= 78** Pregabalin. Mean dose 200mg/day - Treatment was initiated at 200mg/day and ppts were maintained on this dosage.	Funding: Pfizer, Inc. Quality assessed: +.

lost for other or administrative reasons.				
RICKELS2000A Study Type: RCT Study Description: ITT: all eligible participants with at least one efficacy evaluation made whilst receiving study medication Type of Analysis: ITT/LOCF Blindness: Double blind Duration (days): Mean 56 Setting: US Outpatient (15 centres) Notes: RANDOMISATION: not reported. ALLOCATION CONCEALMENT: not addressed Info on Screening Process: 370 completed placebo run-in period & received study drug, 21 of these were excluded as they had no primary outcome.	n= 349 Age: Mean 41 Range 20-75 Sex: 154 males 195 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - Less than 18 years of age - DSM-IV criteria for GAD - No MDD - HAMA score < 18 - HAMA (anxious mood & tension items) < 2 - Reduction of at least 20% in the HAMA total score between screening visit & baseline - Lower scores on the Covi Anxiety scale than the Raskin Depression Scale - Raskin Depression Scale score greater than 3 on any item - Use of other pharmacology (i.e. benzodiazepine, antipsychotic, antidepressants; patients were allowed to take chloral hydrate) - Other clinically significant psychiatric disorder Notes: 6.9% had a history of MDD; 0.5% had a history of dysthymia Baseline: HAMA baseline depression score (approx): 24.23 (4.10). No significant differences between groups at baseline. Venlafaxine 75mg/d: 24.7 (4.4). Venlafaxine 150mg/d: 24.5 (4.1). Venlafaxine 225mg/d: 23.6 (3.7). Placebo: 24.1 (4.2).	**Data Used** HAMA Leaving the study due to inefficacy Leaving the study due to adverse events Compliance Leaving the study early for any reason Notes: TAKEN AT: week 1, 2, 3, 4, 6, 8 weeks 4-10 days after drug tapered. DROP OUTS: 29% CHANGE SCORES USED.	**Group 1 N= 92** Venlafaxine (extended release). Mean dose 75mg/d - 8-week intervention. Fixed doses. Week 1 to 8: 75mg/d. One pill in the morning. **Group 2 N= 90** Venlafaxine (extended release). Mean dose 225mg/d - 8-week intervention. Fixed doses. Week 1: 75mg/d. Week 2: 150mg/d. Week 3 to 8: 225mg/d. **Group 3 N= 91** Venlafaxine (extended release). Mean dose 150mg/d - 8-week intervention. Fixed doses. Week 1: 75mg/d. Week 2 to 8: 150mg/d. **Group 4 N= 97** Placebo - No informtaion given.	Funding: Wyeth-Ayerst Laboratories. Quality assessed: -.
Results from this paper: +				
RICKELS2003 Study Type: RCT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients, 50 sites in US and Canada Notes: RANDOMISATION: no further details Info on Screening Process: 661 eligible, 35 lost to follow up, 10 adverse events, 6 protocol violations, 44 for other reasons	n= 566 Age: Mean 40 Sex: 253 males 313 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - <18 years - HAM-A <20 - HAM-A items 1 and 2 <2 - another other psychiatric condition including MDD - using other psychoactive drugs Baseline: HAM-A: Placebo 24.4 (3.7) 20mg Parox 24.1	**Data Used** HAMA Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAMA) **Data Not Used** Response (50% reduction in HAMA score) - not extractable	**Group 1 N= 180** Placebo - No details given. **Group 2 N= 197** Paroxetine. Mean dose 40mg - Starting dose 10mg/day, increased 10mg/day each week until reach 40mg **Group 3 N= 188** Paroxetine. Mean dose 20mg - Starting dose 10mg, followed by 20mg at week 2	Funding: GSK. Quality assessed -.

	(3.6) 40mg Parox 23.8 (3.4)	Notes: Response based on CGI score of 1 or 2.		
RICKELS2005 Study Type: RCT Study Description: 1 week drug-free screening period before 4 weeks of double-blind treatment. This was followed by a 1 week taper period and then 1 week drug-free. Type of Analysis: ITT (LOCF method) Blindness: Double blind Duration (days): Mean 28 Setting: Recruited via clinic referrals and from advertisements in the local media. Outpatients. Multicentre: USA. Notes: RANDOMISATION: ppts were randomised in blocks of 10. No further details. Info on Screening Process: 696 screened: 454 randomised (242 excluded). Reasons for exclusion not provided.	n= 454 Age: Mean 39 Sex: 165 males 289 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Raskin Depression Scale score >7, being a fertile woman having a positive pregnancy test result, not using a medically accepted contraceptive or currently nursing, a current or past history of bipolar, schizophrenic, schizoaffective, psychotic or factitious disorder and dementia, current but not lifetime MDD, social anxiety disorder, panic disorder with or without agoraphobia, OCD, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse, positive urine drug screen result, any clinically significant acute or unstable medical condition or clinically significant ECG result or laboratory abnormalities, concurrent psychotherapy for GAD, unless undergoing stable treatment for longer than 3 months, concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit, current or past history of a seizure disorder or requiring anticonvulsant therapy for any indication, or suicide risk either currently or based on history. Notes: Diagnosis was based on structured Mini-International Neuropsychiatric Interview. Had HAMA scores >9 and Covi Anxiety Scale scores >9. Baseline: HAMA at baseline: Pregabalin 300: 25.0 (SE 0.4), Pregabalin 450: 24.6 (SE 0.4), Pregabalin 600: 25.2 (SE 0.4), Alprazolam: 24.9 (SE 0.4) and Placebo: 24.6 (SE 0.4).	**Data Used** CGI-I HAMA Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAMA) Response (50% reduction in HAMA score) Notes: Assessments were performed at screening, baseline and at study weeks 1, 2, 3 and 4.	**Group 1 N= 91** Placebo - Three treatments a day. **Group 2 N= 91** Pregabalin. Mean dose 300mg/day - Pregabalin was initiated at 300mg/day and kept constant throughout the study. Three treatments a day. **Group 3 N= 89** Pregabalin. Mean dose 600mg/day - Pregabalin was initiated at 300mg/day and titrated to 450mg/day on day 4. Dosage was titrated to 600mg/day on day 7. Three treatments a day. **Group 4 N= 90** Pregabalin. Mean dose 450mg/day - Pregabalin was initiated at 300mg/day and then titrated to 450mg/day on day 4. Three treatments a day. **Group 5 N= 93** Alprazolam. Mean dose 1.5mg/day - Initiated at 0.5mg/day and increased to 1.0mg/day on day 4 and 1.5mg/day on day 7. Three treatments a day.	Funding: Pfizer, Inc. Quality assessed: +.

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BORISON1990	N<10 in each treatment arm

References of Included Studies

ALLGULANDER2001 (Published Data Only)

Allgulander, C., Hackett, D. & Salinas, E. (2001) Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder. British Journal of Psychiatry, 179, 15-22.

BALDWIN2006 (Published Data Only)

Baldwin, D.S., Huusom, A.K.T. & Maehlum, E. (2006) Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, doube-blind study. British Journal of Psychiatry, 189, 264-272.

DAVIDSON1999 (Published Data Only)

Davidson, J.R.T., DuPont, R.L., Hedges, D. et al. (1999) Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. Journal of Clinical Psychiatry, 60, 528-535.

FELTNER2003 (Published Data Only)

Feltner, D.E., Crockatt, J.G., Dubovsky, S.J. et al. 2003 A randomized, double0blind, placebo-controlled, fixed-dose, multicentre study of Pregabalin in patients with geralized anxiety disorder. Journal of Clinical Psychopharmacology, 23, 240-249

HACKETT2003 (Published Data Only)

Hackett, D., Haudiquet, V., Salinas, E. (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, 182-187.

KOPONEN2007 (Published Data Only)

Koponen, H., Allgulanderm C., Erickson, J., et al. (2007) Efficacy of Duloxetine for the treatment of generalized anxiety disorder: Implications for primary care physicians. Primary Care Companion yo the Journal of Clinical Psychiatry, 9, 100-107.

MONTGOMERY2006 (Published Data Only)

Montgomery, S.A, Tobias, K., Zornberg, G.L., Kasper, S. & Pande, A.C. (2006) Efficacy and safety of Pregabalin in the treatment of Generalized Anxiety Disorder: A 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of Pregabalin and Venlafaxine. Journal of Clinical Psychiatry, 67, 771-782.

NICOLINI2009 (Published Data Only)

Nicolini, H., Bakish, D., Duenas, H. et al. (2009) Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. Psychological Medicine, 39, 267-276

PANDE2003 (Published Data Only)

Pande, A.C., Crockatt, J.G., Feltner, D.E., Janney, C.A., Smith, W.T., Weisler, R., Londborg, P.D., Bielski, R.J., Zimbroff, D.L., Davidson, J.R.T., & Liu--Dumaw, M. (2003) Pregabalin in generalized anxiety disorder: a placebo-controlled trial. American Journal of Psychiatry, 160, 533-540.

PFIZER2005 (Unpublished Data Only)

EMEA 2006, European assessment report: LYRICA. London: EMEA.

POHL2005 (Published Data Only)

Pohl, R.B., Feltner, D.E., Fieve, R.R. & Pande, A.C. (2005) Efficacy of pregabalin in the treatment of generalized anxiety disorder. Double-blind, placebo-controlled comparison of BID versus TID dosing. Journal of Clinical Psychopharmacology, 25, 151-158.

RICKELS2000A (Published Data Only)

*Rickels, K., Pollack, M.H., Sheehan, D.V. et al. (2000) Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. American Journal of Psychiatry, 157, 968-974.

Sontheimer, D., & Ables, A. (2000) Is imipramine or buspirone treatment effective in patients wishing to discontinue long-term benzodiazepine use? The Journal of Family Practice, 50, INCOMPLETE.

RICKELS2003 (Published Data Only)

Rickels, K., Zaninelli, R., McCafferty, J. et al. (2003) Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. American Journal of Psychiatry, 160, 749-756.

RICKELS2005 (Published Data Only)

Rickels, K., Pollack, M.H., Feltner, D.E., Lydiard, B., Zimbroff, D.L., Bielski, R.J., Tobias, K., Brock, J.D., Zornberg, G.L., & Pande, A.C. (2005) Pregabalin for treatment of generalized anxiety disorder. A 4-week, multi-center, double-blind, placebo-controlled trial of pregabalin and alprazolam. Archives of General Psychiatry, 62, 1022-1030.

References of Excluded Studies

BORISON1990 (Published Data Only)

Borison, R.L., Albrecht, J.W. & Diamond, B.I. (1990) Efficacy and safety of a putative anxiolytic agent: Ipsapirone. Psychopharmacologuy Bulletin, 26, 2, 207-210

Characteristics Table for The Clinical Question: In the treatment of GAD, for people who are receiving a pharmacological intervention without adequate response, does augmentation improve outcome?

Comparisons Included in this Clinical Question

Anxiolytic & Risperidone vs Anxiolytic & Placebo
BRAWMAN-MINTZER2005

Fluoxetine & Olanzapine vs Fluoxetine & Placebo
POLLACK2006

Paroxetine & Quetiapine vs Paroxetne & Placebo
SIMON2008

Risperidone augmentation vs Placebo augmentation
Pandina2007

Ziprasidone augmentation vs Placebo augmentation
LOHOFF2010

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BRAWMAN-MINTZER2005 Study Type: RCT Study Description: Ppts who continued to experience GAD despite anxiolytic treatment of at least 4 weeks given placebo or risperidone at doses of 0.5 to 1.5mg/day. Type of Analysis: ITT (LOCF method) Blindness: Double blind Duration (days): Mean 35 Setting: Outpatients: US. Notes: RANDOMISATION: no details given. Info on Screening Process: No details provided.	n= 40 Age: Mean 50 Sex: 7 males 33 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Diagnosis of MDD within 1 month of study entry and subjects with substance use disorders wtihin 6 months of study entry. Subjects with current or past history of bipolar or any psychotic disorder. Notes: Ppts had HAM-A score >=18, score >=2 on items 1 and 2, moderate score on CGI-S and Covi Anxiety Scale total higher than Raskin Severity of Depression Scale score. Flexible dosage. Baseline: HAM-A at baseline: 22.1 (3.8) in the risperidone group and 20.4 (1.7) in the placebo group.	**Data Used** CGI-I HAMA Adverse events Hospital Anxiety and Depression Scale (anxiety) Leaving the study due to adverse events Leaving the study early for any reason	**Group 1 N= 20** Placebo - No details provided. **Group 2 N= 19** Other active treatments - Risperidone. Increased weekly from 0.5mg/day to 1.5mg/day according to tolerability and clinical response.	Funding: Janssen Pharmaceutica, Inc. Quality assessed +.
LOHOFF2010 Study Type: RCT Study Description: Assesses the efficacy, safety and tolerability of ziprasidone in adults with treatment resistant GAD Type of Analysis: LOCF Blindness: Double blind Duration (days): Mean 56 Setting: Subjects recruited from the University of Pennsylvania Mood and Anxiety Disorders Section.	n= 62 Age: Sex: Diagnosis: Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: <16 on HAM-A, <4 on CGI-S. History of mania, bipolar disorder, schizophrenia or other psychotic disorder or diagnosis that may affect clinical assessment. Clinically significant abnormailies on physical examination or unstable medical conditions. Females whoa are pregnant, breast	**Data Used** Discontinuation adverse events (DAEs) HAD CGI-S CGI-I HAMA	**Group 1 N= 41** Ziprasidone. Mean dose 20mg - Flexible dose strategy. Daily dose increased in weekly increments by 20mg/d up to 80mg/d. **Group 2 N= 21** Placebo - Identical placebo capsules	

Info on Screening Process: 73 subjects with GAD were recruited. 62 randomized. Inclusion criteria: subjects had to be 18yrs+ and meet DSM-IV criteria for GAD, treatment failure of 1 trial of an SSRI, SNRI, BZ or combination.	feeding. Baseline: Not reported			
Pandina2007 Study Type: RCT Study Description: Adjunctive risperidone in the treatment of GAD Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Notes: Randomization: An independent statistician provided randomization codes administered by telephone interactive voice response system. Info on Screening Process: 453 screened. 417 randomized, 390 in ITT population	n= 390 Age: Mean 44 Range 18-65 Sex: 114 males 276 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Females with known or suspected pregnancy, serious suicide risk or serious medical/neurological illness, active substance use disorders, history of clozapine treatment or currently taking over-the-counter and/or dietary psychotropic treatments to manage anxiety. Any Axis I diagnosis other than GAD, or no access to a touch-tone telephone. Notes: Subjects continued their standard anxiolytic/antidepressent regimen and dosage and were assigned to adjunctive risperidone or placebo augmentation using tablets of matching appearance, taste and smell. Baseline: HAMA: Risperidone 24.1 (6.8) Placebo 23.9 (6.4) Q-LES-Q Total Score: Risperidone 56.2 (12.4) Placebo 55.6 (11.9)	**Data Used** Q-LES-Q Remission (less than 7 on HAMA) Response (50% reduction in HAMA score) HAMA	**Group 1 N= 196** Risperidone. Mean dose 1mg - 0.25mg day 1-3. 0.5mg day 4-15. 1.0 mg day 16-28. On day 29 of the 6 week study, dose could increase to 2mg per day for patients considered to have insufficient response, (reduced to 1mg per day if intolerant). **Group 2 N= 194** Placebo - Placebo augmentation used tablets of matching appearance, taste and smell.	Funding: Not reported
POLLACK2006 Study Type: RCT Study Description: Ppts remaining symptomatic after 6 weeks treatment with fluoxetine (20mg/day) were randomised to 6 weeks of olanzapine or placebo augmentation. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 84 Setting: Outpatients. USA. Notes: RANDOMISATION: no details provided. Info on Screening Process: 46 ppts were in open-label fluoxetine treatment.	n= 24 Age: Mean 44 Sex: 11 males 13 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Bipolar disorder, psychotic disorders, alcohol or substance abuse in last 6 months, those receiving concurrent psychotherapies directed at GAD. Notes: Co-morbid depression or dysthymia and other anxiety disorders were permitted if clinician considered GAD to be primary. Baseline: HAM-A at baseline. Olanzapine: 17.4 (6.5) and Placebo: 22.6 (5.2).	**Data Used** CGI-I HAMA Adverse events Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAMA score)	**Group 1 N= 12** Placebo **Group 2 N= 12** Other active treatments - Olanzapine. Week 1: 2.5mg/day, week 2: 5mg/day and then flexible titration in 5mg/day increments per week according to clinical response and tolerability up to a maximum of 20mg/day.	Funding: Eli Lilly. Quality assessed: +.
SIMON2008				

Study Type: RCT Study Description: 2 phase 18 week prospective treatment trial. Phase 1 was open label 10 week parox trial. Phase 2 was trial open to those who did not remit in phase 1. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients recruited from academic centers via advertisement and clinical referral. Notes: RANDOMISATION: 1:1 ratio. Info on Screening Process: 101 recruited: 54 entered phase 1 of the trial and 22 entered phase 2. Most exclusions were due to not meeting entry criteria.	n= 22 Age: Mean 42 Sex: Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Pregnant or lactating women, women of childbearing potential not using acceptable means of birth control, a primary diagnosis of major depression, dysthymia, panic disorder, or social phobia, a lifetime history of bipolar disorder, schizophrenia, or other psychotic conditions, posttraumatic stress disorder, obsessive-compulsive disorder, alcohol or substance abuse or dependence within the last 6 months, significant unstable medical illness, cataracts, severe personality disorders, ongoing psychotherapy directed towards GAD, prior hypersensitivity to paroxetine CR, paroxetine or quietiapine, and concurrent use of psychotropic medications within 2 weeks of study entry, including herbs and dietary supplements with known psychotropic properties. Notes: Ppts had a HAM-A score >=18, MADRS score <=20 and MADRS item 10 score <3. Baseline: HAM-A at baseline. Quetiapine 16.27 (5.04) and Placebo 15.82 (4.77).	**Data Used** CGI-I HAMA Adverse events Q-LES-Q-SF Leaving the study due to adverse events Leaving the study early for any reason	**Group 1 N= 11** Placebo - No details provided. **Group 2 N= 11** Other active treatments. Mean dose 120.5mg/day - Quetiapine augmentation.	Funding: GlaxoSmithKline. Quality assessed: +.

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
FAVA2009	primary outcome insomnia not anxiety

References of Included Studies

BRAWMAN-MINTZER2005 (Published Data Only)

Brawman-Mintzer, O., Knapp, R.G., & Nietert, P.J. (2005) Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. Journal of Clinical Psychiatry, 66, 1321-1325.

LOHOFF2010 (Published Data Only)

Lohoff, F.W., Etemad, B., Mandos, L.A. et al. (2010) Ziprasidone treatment of refractory generalized anxiety disorder. Journal of Clinical Psychopharmacology, 30, 185-189.

Pandina2007 (Unpublished Data Only)

Pandina, G. J., Canuso, C., Turkoz, et al. (2007) Adjunctive rispiridone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. Psychopharmacology Bulletin, 40, 41-57.

POLLACK2006 (Published Data Only)

Pollack, M.H., Simon, N.M., Zalta, A.K., Worthington, J.J., Hoge, E.A., Mick, E., Kinrys, G., & Oppenheimer, J. (2006) Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: A placebo-controlled study. Biological Psychiatry, 59, 211-215.

SIMON2008 (Published Data Only)

Simon, N.M., Connor, K.M., LeBeau, R.T., Hoge, E.A., Worthington III., J.J., Zhang, W., Davidson, J.R.T., & Pollack, M.H. (2008) Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. Psychopharmacology, 197, 675-681.

References of Excluded Studies

FAVA2009 (Published Data Only)

Fava, M., Asnis, G.M., Shrivastava, R., et al. (2009) Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. Journal of clinical psychopharmacology, 29, 222-230.

Characteristics Table for The Clinical Question: In the treatment of GAD what pharmacological strategies are effective in preventing relapse (including maintenance treatment)?

Comparisons Included in this Clinical Question

Duloxetine (SNRI) vs. placebo
DAVIDSON2008

Duloxetine (SNRI) vs. Venlafaxine (SNRI)
DAVIDSON2008

Escitalopram vs Placebo
ALLGULANDER2006

Pregabalin vs Placebo
FELTNER2008

Quetiapine vs Placebo
ASTRAZENECA2008B

SSRI vs Placebo
STOCCHI2003

Venlafaxine (SNRI) vs. placebo
DAVIDSON2008

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ALLGULANDER2006 Study Type: RCT Study Description: 491 ppts received open-label escitalopram for 12 wk. 375 responded (HAMA score <=10) and were randomized to DB treatment with escitalopram or placebo. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 532 Setting: Multicentre (59 centres): multiple countries. Recruited by GPs, psychiatrists, and media advertisements. Outpatients. Notes: RANDOMISATION: randomised in a 1:1 fashion using computer generated randomisation list. Info on Screening Process: 424 completed open-label phase. 49 dropped out before DB phase: 8 due to AEs, 28 due to lack of efficacy, 3 withdrew consent, 5 did not comply and 5 for other reasons.	n= 375 Age: Mean 41 Range 18-65 Sex: 255 males 120 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV-TR Exclusions: Major depressive disorder, panic disorder, social anxiety disorder, PTSD, bipolar disorder, OCD, eating disorders, substance use disorder and any current or past psychotic disorder. Body dysmorphic disorder or any personality disorder. At risk of suicide or had made a suicide attempt within the past year. Unstable serious somatic illness and/or serious sequeale of liver or renal insufficiency were excluded. Pregnant or breastfeeding women. Notes: Treatment continued for 24-76 weeks until the patient relapsed or was withdrawn for other reasons. Relapse was defined as HAMA total score >=15. Was a 1 week screening period before open-label phase. Baseline: HAM-A at baseline. Escitalopram: 5.7 (3.9) and Placebo: 5.0 (3.1).	**Data Used** CGI-I HAMA Adverse events Sheehan Disability Scale (SDS) Hospital Anxiety and Depression Scale (anxiety) Leaving the study due to adverse events Leaving the study early for any reason Notes: Assessed at 1, 2 and 4 weeks and then every 4 weeks until last dose of DB treatment.	**Group 1 N= 187** Placebo - No details provided. **Group 2 N= 186** Escitalopram. Mean dose 20mg/day - 20mg/day.	Ppts who completed DB phase entered a 2 week taper period where escitalopram group received escitalopram 10mg/day for a week and placebo for 2nd week. Placebo ppts continued on placebo. Quality assessed: +. Funding: H. Lundbeck A/S.
ASTRAZENECA2008B Study Type: RCT Study Description: Efficacy of quetiapine SR in the maintenance treatment of patients with GAD Blindness: Double blind Duration (days): Mean 364 Setting: Asia, Europe, North America and Australia	n= 432 Age: Range 18-65 Sex: 151 males 281 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) Exclusions: HAM-A score >12, CGI-S score >3, MADRS score >16	**Data Used** SDS total score PSQI global score CGI-S Q-LES-Q 16 Q-LES-Q 15 Q-LES-Q maximum total score HAMA somatic anxiety cluster score	**Group 1 N= 216** Quetiapine - Flexible dosing (50mg-300mg), periodic stepwise increases up to maximum of 300mg **Group 2 N= 216** Placebo	

Info on Screening Process: 1811 screened, 433 randomized	Baseline: Not reported	HAMA psychic anxiety cluster score HAMA total score		
DAVIDSON2008 Study Type: RCT Study Description: Relapse prevention trial with a 26-week open ladel, felxible dose therapy followed by 26 week double-blind, placebo controlled contunuation therapy Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 182 Setting: Not reported Notes: RANDOMISATION: not reported ALLOCATION CONCEALMENT: interactive voice recognition system Info on Screening Process: Patients enrolled in open-label (N=887); 51.5% discontinued; 429 randomised in double-blind phase; 49/216 (23%) - duloxetine & 97/213 (46%) - placebo dropped out.	n= 429 Age: Sex: Diagnosis: Exclusions: - Patients who did not complete open label & met response criteria Exclusion criteria for open label trial: -<18 years - No primary DSM-IV diagnosis of GAD - CGI-S <4 - HADS anxiety subscale <10 - Covia Anxiety score <9 or not greater and then Raskin depression total score. Raskin depression scale item rated >3 - Medical illness that would contraindicate use of duloxetine - Women of childbearing age not using adequate contraception - recent diagnosis of depression or substance abuse/depence - past year history of panic disorder, PTSD or eating disorder - lifetime history of psychotic, bipolar, OCD or psychosis - lack of response of GAD to 2 prior adequate trails of antidepressants or benzodiazepine treatments - psychotherapy iniated 6 weeks prior to study enrollment Baseline: No differences at baseline.	**Data Used** Beck scale for suicide ideation HAMA Relapse Sheehan Disability Scale (SDS) Hospital Anxiety and Depression Scale (anxiety) Q-LES-Q-SF EQ-5D Leaving the study due to adverse events Notes: Relapse = (a) increase in CGI-S 2+ points to score 4+ while meeting criteria for GAD (MINI) or (b) discontinuation due to lack of efficacy. DROP OUTS: 49/216 (23%) - duloxetine; 97/213 (46%) - placebo	**Group 1 N= 213** Placebo - 2 week taper period. All patients received 4 capsules daily. **Group 2 N= 216** Duloxetine. Mean dose 60-120mg/day - Duloxetine continued at same doseas their open label phase treatment (between 60-120 mg/day). The paper does not report mean dose.	FUNDED BY ELI LILLY: Trial report collected (#7108). Quality assessed: +
Results from this paper:				
FELTNER2008 Study Type: RCT Study Description: 1 week screening phase followed by 8 weeks open label acute treatment phase, 24 week DB relapse prevention phase and 2 week discontinuation. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 245 Setting: Multicentre: USA (17 sites). Recrutied via advertisements in the local media.	n= 339 Age: Mean 39 Sex: 145 males 193 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: Current diagnosis of seizure disorder or a lifetime history of bipolar disorder, schizophrenia, psychotic disorder or factitious disorder. History within the past 6 months of any clinically significant Axis I disorder, including	**Data Used** CGI-I HAMA Adverse events Sheehan Disability Scale (SDS) Leaving the study due to adverse events Leaving the study early for any reason	**Group 1 N= 168** Pregabalin. Mean dose 450mg/day - 150mg thrice daily. Received DB treatment for up to 6 months or until relapsed or discontinued treatment. **Group 2 N= 170** Placebo - Received pregabalin at 300mg/day for 3 days before complete placebo substitution. Received DB treatment for up to 6 months or until relapsed or discontinued treatment.	Funding: Pfizer, Inc. Quality assessed: +.

Notes: RANDOMISATION: no details provided. Info on Screening Process: 859 ppts screened: 624 enrolled in acute phase. 339 randomised to DB treatment. 285 discontinued before DB phase: 89 AEs, 19 lack of efficacy, 62 lost to follow-up, 48 withdrew consent, 32 didn't meet inc. criteria, 9 did not comply and 26 for other.	panic disorder and social anxiety disorder. Use of psychotropic medication within 2 weeks of visit 1. Patients at risk of suicide. Women who were pregnant or lactating. Currently undergoing psychotherapy. Notes: Ppts had GAD >1 year. Diagnosis based on MINI. Ppts scored >=20 on HAM-A, >=9 on Covi and <=7 on Raskin. Allowed ppts with dysthymia, depession NOS, or specific phobia. Baseline: HAM-A at baseline (for DB phase). Pregabalin: 5.9 (3.2) and Placebo: 5.5 (3.4).	Notes: Assessed at 1 week screening phase and at weeks 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 28, 32, 33 and 34.		
STOCCHI2003 Study Type: RCT Study Description: Single blind paroxetine for 8 weeks, followed by double blind RCT placebo or paroxetine for 24 weeks Blindness: Double blind Duration (days): Mean 240 Setting: Outpatients from 47 centres including Finland, Norway, Denmark, Hungary, Greece, Italy, Czech Republic Notes: RANDOMISATION: no further details Info on Screening Process: 652 entered single blind phase, 566 entered double blind phase, 4 dropped out of the paroxetine group and 1 from placebo group	n= 561 Age: Mean 43 Sex: 203 males 358 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: - HAM-A <20 - HAM-A items 1 and 2 <2 - MADRS > 17 - <20% improvement in HAM-A during single blind phase	**Data Used** HAMA Relapse Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAMA)	**Group 1 N= 287** Placebo - Single blind phase as paroxetine group. Double blind phase: underwent a 3-week taper and received placebo at week 4 of continuation phase. **Group 2 N= 274** Paroxetine. Mean dose 28.1mg - Single blind phase: 20mg/day for 2 weeks then increase 10mg/day each week if needed up to 50mg/day. Double blind phase: continued treatment	Funding: GSK. Quality assessed: -.

Characteristics of Excluded Studies

References of Included Studies

ALLGULANDER2006 (Published Data Only)

Allgulander, C., Florea, I., & Huusom, A.K.T. (2006) Prevention of relapse in generalized anxiety disorder by escitalopram treatment. International Journal of Neuropsychopharmacology, 9, 495-505.

ASTRAZENECA2008B (Published Data Only)

Astra Zeneca (2008) A multi-center, double-blind, randomized-withdrawal, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate sustained release (Seroquel SR) as monotherapy in the maintenance treatment of patients with generalized anxiety disorder following an open-label stabilization period (PLATINUM STUDY)

DAVIDSON2008 (Published Data Only)

Davidson, J.R.T., Wittchen, H.-U., Llorca, P.M. et al.(2008) Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. European Neuropsychopharmacology, 18, 673-681

FELTNER2008 (Published Data Only)

Feltner, D., Wittchen, H-U., Kavoussi, R., Brock, J., Baldinetti, F., & Pande, A.C. (2008) Long-term efficacy of pregabalin in generalized anxiety disorder. International Clinical Psychopharmacology, 23, 18-28.

STOCCHI2003 (Published Data Only)

Stocchi, F., Nordera, G., Jokinen, R.H. et al. (2003) Efficacy and tolerability of paroxetine for the long term treatment of generalize anxiety disorder. Journal of Clinical Psychiatry, 64, 250-258.

References of Excluded Studies

Characteristics Table for The Clinical Question: In the treatment of GAD, what are the risks and benefits associated with different complimentary therapies?

Comparisons Included in this Clinical Question

Acupuncture and chinese medication vs Doxepin RUAN2003	**Acupuncture vs Behavioural desensitization** GUIZHEN1998	**Acupuncture vs Behavioural desensitization + acupuncture** GUIZHEN1998	**Acupuncture vs Doxepin** ZHANG2003
Acupuncture vs Fluoxetine/Paroextine YUAN2007	**Acupuncture vs Flupentixol vs combined** Zhou 2003	**Acupuncture vs Lorazepam & plant extract Propranolol** ZHILING2006	**Acupuncture vs medication + acupuncture** Zhou 2003
Chamomile vs Placebo AMSTERDAM2009	**Chinese Taoist Psychotherapy vs Benzodiazepine** ZHANG2002	**Galphimia glauca vs lorazepam** HERRERA2007	**Ginkgo biloba vs Placebo** WOELK2007
Hypnotherapy vs Alprazolam ZHAO2005	**Passionflower vs oxazepam** AKHONDZADEH2001A	**Silexan vs Lorazepam** WOELK2010	**Study drug vs Placebo** HANUS2004
Valerian extract vs Diazepam ANDREATINI2002	**Valerian extract vs Placebo** ANDREATINI2002		

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
AKHONDZADEH2001A Study Type: RCT Study Description: 4 week double-blind study comparing passion flower extract and oxazepam. Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients: Iran. Notes: RANDOMISATION: no details provided. Info on Screening Process: No details provided.	n= 36 Age: Range 19-47 Sex: 16 males 20 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: History of serious suicide attempt or current acute suicidal ideation, an unexpected recent panic attack or full DSM-IV panic disorder within the previous 6 months, a life-time diagnosis of DSM-IV mania, psychosis, paranoia or dementia, concurrent or recent diagnosis of substance abuse, drug psychosis, OCD, hypomania, or major depression. Pregnant and lactating women. Notes: Ppts had a HAM-A score >=14. Ppts were free from all psychotopic medication for a minimum of 7 days before	**Data Used** Adverse events **Data Not Used** HAMA - no data Notes: Assessed by a psychiatrist at baseline and 4, 7, 14, 21 and 28 days after the medication started.	**Group 1 N= 18** Oxazepam. Mean dose 30mg/day - 30mg/day plus placebo drops. **Group 2 N= 18** Other active treatments. Mean dose 45 drops/day - Passionflower 'passiflora' extract. 45 drops per day plus placebo tablet.	Funding: no details provided. Quality assessed: - . To date, the only published clinical trial looking at effects of passionflower on treatment of anxiety.

	starting study. Baseline: No data provided.			
AMSTERDAM2009 Study Type: RCT Study Description: Efficacy and tolerability trial of chamomile extract therapy in patients with GAD. Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 56 Setting: Department of Family Medicine and Community Health outpatient clinic. Notes: Blocked randomization with varying block sizes. Info on Screening Process: 61 screened. 4 failed (1 for non comliance and 3 for no consent) 57 randomized.	n= 57 Age: Mean 46 Sex: no information Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: HAMA <9. Another primary DSM-IV Axis I disorder. Current diagnosis of MDD, BD, PD, phobic disorder, OCD, PTSD, acute stress disorder, substance induced anxiety disorder, psychosis, dementia, or substanceabuse or dependence within the preceding 3 months. Unstable medical condition, hepatic/renal insufficiency, malignancy, abnormal serum thyrotropin level of 5 KIU/mL or more, or known sensitivity to chamomile, plants of the Asteraceae family, mugwort, or birch pollen. Concurrent use of anxiolytics, antidepressants, mood stabilizers, sedatives, or CAM remedies (eg, St John's wort) or other chamomile preparations. Negative pregnancy test and medically proven contraception for women. Baseline: HAMA: Chamomile 15.4 (4.2) Placebo 14.3 (2.8) BAI: Chamomile 9.5 (5.6) Placebo 12.0 (602) PGWB: 62.0 (14.7) Placeno 58.9 (14.1)	**Data Used** Response (50% reduction in HAMA score) Psychological General Well Being Index Beck Anxiety Inventory HAMA Notes: Capsules made identitcal in appearance and aroma. Outcome measures obtained at baseline, 2,4,6,8 weeks of treatment. 8 dropouts: 2 had adverse events, 3 withdrew consent, 2 lost to follow up and 1 non compliance.	**Group 1 N= 28** Chamomile extract therapy. Mean dose 220mg - Capsules containing pharmaceutical grade German chamomile extract standardized to a content of 1.2% apigenin. 1-5 capsules per day depending on tolerability. **Group 2 N= 29** Placebo - Capsule containing lactose monohydrate National Formulary. 1 per day one week. 2 per day in second week. 1-5 capsules per day depending on tolerability.	Quality assessment Funded by the National Institutes of Health/National Center for Complementary and Alternative Medicine grant
ANDREATINI2002 Study Type: RCT Study Description: ITT using LOCF included all those who completed at least 1 week of treatment Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Sao Paulo ,BRAZIL Notes: RANDOMISATION: used a computer programme Info on Screening Process: 132 people were interviewed of which 96 were excluded and 36 participated in the study. Participants were excluded due to the presence of another mental illness, refusal, marked reduction in HAMA prior to study, use of other medications.	n= 36 Age: Mean 41 Sex: 17 males 19 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-III-R Exclusions: - No DSM-III-R diagosis of GAD - current or previous MDD, manic episode, panic disorder, OCD, drug dependence or any psychotic symptoms - major medical disorders (e.g. CVD, renal disorders etc.) - drug treatment apart from over the counter drugs - receiving psychotherapy - Patients under treatment with Benzodiazepines were excluded if: 1) they had a clinical response or no evidence of side effects to the curent drug 2) they did not undergo a gradual reduction of medication followed by a 2 week wash-out period - Social phobia or simple phobia excluded if anxiety was secondary to these disorders - females not using a medically accepted form of birth control	**Data Used** STAI-trait HAMA Leaving the study due to inefficacy Leaving the study due to adverse events Notes: TAKEN AT: baseline, end of treatment (4 weeks) DROPOUTS:Diazepam 1/12 (8.3%), Valepotriate 2/12 (16.6%), Placebo 2/12 (16.6%)	**Group 1 N= 12** Diazepam. Mean dose 6.5mg/day - Following a two week washout period, study drugs were administered in identical capsules containing 2.5mg. The capsules were adminstered three times a day with thelowest dose consisting of two placebo and one active capsules based on response. 4 week **Group 2 N= 12** Placebo - Following a two week washout period, study drugs were administered in identical capsules. The capsules were adminstered three times a day.	Drug company funded: BYK Quimica e Farmaceutica Ltds (Brazil). Quality assessment score = + The study included a number of participants with current social phobia and simple phobias in addition to GAD

	Notes: All participants were evaluated using the SCI-R Baseline: HAMA - Placebo: 25.1(7.5), Diazepam: 25.2(4.5), Valepotriates: 22.8(7.6)		**Group 3 N= 12** Valepotriates. Mean dose 81.3mg/day - Following a two week washout period, study drugs were administered in identical capsules containing 50mg. The capsules were adminstered three times a day with thelowest dose consisting of two placebo and one active capsules based on response.	
Results from this paper:				
GUIZHEN1998 Study Type: RCT Study Description: Comparative study on acupuncture combined with behavioural desentisization for treatment of anxiety neurosis on 240 patients Type of Analysis: ITT Blindness: No mention Duration (days): Setting: China Notes: RANDOMISATION: Unclear Info on Screening Process: Unclear	n= 240 Age: Range 16-73 Sex: 109 males 131 females Diagnosis: 100% Anxiety Neurosis Exclusions: Those with underlying medical disorders or scores of <50 on the Zung self assessment score (SAS) Notes: Diagnosis tool unclear. Zhung self assessment scores (SAS) were greater than 50 (i.e moderate to severe anxiety) Baseline: Duration of disease: Acupuncture = one month to 16 years, Behavioural desentization = 6 months to 12 years, Combined = 2 weaks to 16 years	**Data Used** Remission (clinical symptoms gone & SAS <45) Response (symptoms improved & SAS reduced sign) Notes: Subjects were evaluated immediately after the last therapy in all three groups. Evaluation included physical examination and SAS score evaluation. Response: SAS reduced by 20 or more points. No drop outs.	**Group 1 N= 80** Acupuncture. Mean dose 10-30 sessions - A detailed history and physical exam was performed & stainless stel filofrom needles were inserted into 3-6 selected body points during each session & manipulated with uniform reinforcing reducing. Treatment was performed once every other day. **Group 2 N= 80** Behavioural desensitization. Mean dose 10 sessions (twice per week for 30 min) - Treatment consisted of self-relaxation techniques, psychotherapy, & a program of behavioural desensitization. Received instruction in muscle relaxation techniques to be practiced daily. Psychotherapy incorporated desensitization techniques. **Group 3 N= 80** Behavioural desensitization + acupuncture. Mean dose 10-40 sessions - Underwent the above program of behavioural desensitization followed by acupuncture treatments on the same day, as described for the acupuncture group. Received 1-4 courses of treatment with an interval of 3-7 days between courses.	FUNDING: No mention, Quality assessed = moderate quality
HANUS2004 Study Type: RCT Study Description: Clinical efficacy of fixed quantities of two plant extracts and magnesium vs placebo in anxiety disorders with functional disturbances. Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 90	n= 264 Age: Mean 45 Range 18- Sex: 50 males 214 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-III-R Exclusions: <18 years. No consent. No GAD according to DSM-III-R criteria. Patients with suicide risk. Use of	**Data Used** Response (50% reduction in HAMA score) Visual Analog Scale (VAS) HAMA **Data Not Used** CGI - no data	**Group 1 N= 130** Study drug. Mean dose 375mg - 2 plant extracts (Crataegus oxyacantha and eschscholtzia californica) and magnesium. Drug name: Sympathyl. Tablet form. 75mg Crataegus oxyyacantha, 20mg Eschscholtzia californica, 75mg elemental magnesium. 2 tablets per day for 3 months.	Quality assessment: low risk of bias. Funded by Laboratoires Innothera, France

Notes: Randomized box design used for randomization. Info on Screening Process: Not mentioned	psychotropic drugs or drugs with psychotropic properties or magnesium salts within one month. Notes: Total Hamilton Anxiety score between 16 and 28 Baseline: HAMA: Study group 22.7 Placebo 22.4	Notes: Efficacy assessment before at baseline and 7, 14, 30, 60 and 90 days after treatment. 31 drop outs due to inefficacy.	**Group 2 N= 134** Placebo - Tablets made from same ingredients as study drug except for active ingredients. Indistinguishable.	
HERRERA2007 Study Type: RCT Study Description: 4 week double-blind study of galphimia glauca vs. placebo in outpatients with GAD. Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients: Mexico. Notes: RANDOMISATION: no details provided. Info on Screening Process: No details provided.	n= 152 Age: Mean 38 Sex: 35 males 117 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: No pharmacological intervention for GAD within past 4 weeks, no drug or alcohol abuse for at least 6 months prior to study initiation, no suicidal behaviour or psychiatric co-morbidity of higher clinical importance than GAD. Notes: Ppts scored >=19 on HAM-A. 7% of ppts had had a drug/alcohol addiction. Baseline: None provided.	**Data Used** CGI-I HAMA Leaving the study due to adverse events Leaving the study early for any reason	**Group 1 N= 80** Lorazepam. Mean dose 2mg/day - 1mg twice daily. **Group 2 N= 72** Other active treatments. Mean dose 620mg/day - Galphimia glauca. Contained 310mg of dired aqueous G.G. extract twice a day.	Funding: unknown. Quality assessed: -.
HERRERA-ARELLANO2007 Study Type: RCT Blindness: Duration (days):				
RUAN2003 Study Type: RCT Study Description: compare efficacy of combined treatment (acupuncture and chinese medicine) versus Doxepin for treatment of anxiety neurosis Type of Analysis: unknown Blindness: No mention Duration (days): Mean 30 Setting: unknown. Probably inpatients Info on Screening Process: not reported	n= 169 Age: Range 14-62 Sex: 63 males 106 females Diagnosis: Anxiety Neurosis by CCMD-2-R Exclusions: Excluded those who score below 50 on CCMD-2 and SAS-CR Baseline: Did not report if both groups are comparable at baseline. Baseline score (SAS-CR) for acupuncutre group is 78.56(17.64) and Doxepin group is 77.68(18.23). Duration of diagnosis range from1 month to 8 years	**Data Used** SAS-CR	**Group 1 N= 86** Acupuncture. Mean dose 30days - Accupunture combined with chinese medicine. Participants took the chinese medicine twice a day for 30 days. They also receive acupunture once per day for 30-60min each session. **Group 2 N= 83** Doxepin. Mean dose 30days - average daily intake is 150mg	Quality assessed: all selection, performance, attrition, detection bias are unclear
Results from this paper: Both treatments are similarly effective.				

WOELK2007 Study Type: RCT Study Description: Anxiolytic-effects of ginkgo biloba in patients suffering from GAD and adjustment disorder. Dosage EGb 761: 480mg, 240mg. Type of Analysis: ITT with LOCF Blindness: Double blind Duration (days): Mean 28 Range 18-70 Setting: Private practices of specialists in neurology/ psychiatry, internal medicine, GPs and outpatient clinic of a psychiatric university hospital Notes: Validatd computer program randomly assigned numbers to 3 treatment groups. Randomisation code sealed and stored safely. Info on Screening Process: 109 screened. 2 excluded. 1 responded to placebo treatment and 1 withdrew consent.	n= 107 Age: Mean 47 Range 18-70 Sex: 41 males 66 females Diagnosis: Generalised Anxiety Disorder (GAD) by DSM-III-R Adjustment disorder with anxious mood by DSM-III-R Exclusions: Perceived risk of suicide, severely ill, other anxiety disorders, anxiety related to other psychiatric disorders, OCD, suspected dementia or severe somatic disorders. Substance abuselack of cooperation, inability to complete self-rating questionnaires or treatment with psyvhoactive drugs. Baseline: HAMA. No significant differences in baseline scores.	**Data Used** HAMA Notes: Assessment took place at baseline and on days 4, 8, 15, and 29.	**Group 1 N= 34** Ginkgo biloba. Mean dose 480mg - Patients took 2 film-coated tablets t.i.d (80mg). Active drug and placebo were of same appearance. **Group 2 N= 36** Ginkgo biloba. Mean dose 240mg - Patients took 2 film-coated tablets t.i.d (40mg). Active drug and placebo were of same appearance. **Group 3 N= 37** Ginkgo biloba. Mean dose n/a - Patients took 2 film-coated tablets t.i.d (no active drug). Active drug and placebo were of same appearance.	Funding unknown. Quality assessed. Low risk of bias.
WOELK2010 Study Type: RCT Study Description: To investigate the therapeutic efficacy and tolerability of silexan compared to lorazepam in treatment of patients with GAD. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Followup: 2 week discontinuation phase Setting: Multi outpatient centers in Germany. Notes: Randomization by validated computer program Info on Screening Process: One-week screening. Patients received placebo. Patients with decrease of 25% or more of HAMA during this phase were excluded.	n= 77 Age: Mean 43 Range 21-65 Sex: 18 males 59 females Diagnosis: Generalised Anxiety Disorder (GAD) by DSM-IV Exclusions: HAMA <18 and Item 1 'anxious mood' <2 and Item 2 'tension' <2. Baseline: HAMA: Silexan 25 Placebo 25, PSWQ: Silexan 61.4 Placebo 62.2, SAS: Silexan 61.4 Placebo 61.5, SF-36 mental health: Silexan 39.9 Placebo 36.5, SF-36 physical health: Silexan 59.5 Placebo 58.6.	**Data Used** Remission (less than 10 on HAMA) Response (50% reduction in HAMA score) CGI SF-36 Penn State Worry Questionnaire Self-rating Anxiety Scale (SAS) HAMA **Data Not Used** Sleep diary Notes: Assessment at baseline, 1, 2, 4, 6 and 8 weeks. 11 drop outs/incomplete assessment.	**Group 1 N= 40** Silexan. Mean dose 80mg - Patients received one capsule of silexan and 1 capsule lorazepam placebo. Silexan is an oil prodiced fro lavender. **Group 2 N= 37** Lorazepam. Mean dose 0.5mg - Patients received 1 capsule lorazepam and 1 capsule silexan placebo.	Quality assessment: Attrition bias: Unclear
YUAN2007 Study Type: Quasi-randomised Study Description: To observe the therapeutic efficacy of Jin-3-neeling (NL) therapy on GAD through clinical global impression scale (CGI). Type of Analysis: Completor	n= 86 Age: Range 18-65 Sex: 30 males 56 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by CCMD-3-R	**Data Used** Efficacy Index General Index Severity Index	**Group 1 N= 29** Western medicine - 1. Fluoxetine or paroxetine (20mg) 2. Alprazolam (0.4-1.6mg) per day. One or two of the above drugs were chosen with the former as the dominant grug and alprazolam was used in addition according to patients condition. 6 weeks course.	Quality assessment: Selection, performance and detection bias unknown/unclear. Attrition: low risk of bias.

Blindness: No mention Duration (days): Mean 36 Setting: The first affiliated hospital of Guangzhou traditional chinese medical university, Guangzhou municipal hospital of the brain. Notes: Assigned to treatment groups according to the sequence of their visiting between Oct 04 - Dec 05. Info on Screening Process: 86 enrolled upon meeting the inclusion criteria.	Exclusions: HAMA <15. Received any anianxietic agent or psychoactive drug. Patients with severe mental disorder, organic diseases of the brain, addiction to alcohol or drugs, severe somatopathy of the liver, kidney or heart, or women in pregnancy or lactation period were excluded. Notes: Diagnostic standard for GAD in the chinese classification scheme and diagnostic standard for psychotic diseases (CCMD-3-R) Baseline: HAMA: WM 26.74 (3.51) NL 27.65 (2.86) CT 27.33 (3.71. Severity Index: WM 5.12 (1.04) NL 5.36 (0.93) CT 5.71 (1.35). No significant difference.	Notes: Clinical Global Impression (CGI) scale scored before and after 6 week treatment with 3 scales. SI, GI and EI. 7 dropouts. 3- worsening condition 2-intolerability to side-effects 1-economic uptightness 1-emigration.	**Group 2 N= 29** Jin-3-Needling therapy - Needles inserted from four sites to produce a tightening or heavy sensation on the patient's scalp. Needles retained for 45min and run every 15min, once everyday, 6 times per week for 6 weeks. **Group 3 N= 28** Western medicine + Jin-3-Needling therapy - Combination of method for western medicine and J3N therapy. Doasage and manipulation as used in other 2 groups were applied simultaneously to these patients.	
ZHANG2002 Study Type: RCT Study Description: Combines elements of cognitive therapy and Taoist philosophy. Looks at efficacy of CTCP, BDZ and combined treatment in people with GAD. Type of Analysis: ITT (no mention of drop out analysis) Blindness: No mention Duration (days): Mean 168 Setting: 4 mental health centres in China Notes: Patients were randomly assigned to treatment groups. Procedure not mentioned. Info on Screening Process: 143 patients with GAD included. Exclusions not mentioned. Study lasted 6 months with two phases. One month of weekly sessions and 5 months of twice monthly sessions.	n= 143 Age: Mean 35 Sex: 80 males 53 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by CCMD-2-R Exclusions: Patients in psychiatric treatment prior to study. No consent given. Notes: CCMD-2-R criteria for GAD is the same as ICD-10 and DSM-IV except that condition has duration of 3 rather than 6 months. Baseline: SCL-90: CTCP 90.7, Drug 113.8 Combined 107.0 No significant difference in baseline characteristics	**Data Used** EPQ Coping Style Questionnaire Type A Personality Scale SCL-90 Chinese version Notes: Phase I-one month weekly sessions. Phase II-5 months of twice monthly sessions. 13 drop outs. Reason not mentioned.	**Group 1 N= 46** Chinese Taoist Cognitive Psychotherapy - Each session lasted 1hour. Carried out by first author and experienced psychiatrists trained for method. **Group 2 N= 48** BZD - Each session lasted 10 minutes. Drug dosage unaltered after phase I. Variable doses of oral BDZ (diazepam or alprazolam) administered according to patient condition. 10-20mg diazepam equivalent. **Group 3 N= 49** CTCP v BZD - Same as before	Quality assessment: Selection, performance and detection bias unknown/unclear. Attrition: low risk of bias.
ZHANG2003 Study Type: RCT Study Description: Examined the effectiveness of acupuncture treatment against doxepin in the treatment of anxiety neurosis. Type of Analysis: ITT Blindness: No mention Duration (days): Mean 30 Setting: In and out-patients, China Notes: RANDOMISATION: no mention Info on Screening Process: No mention	n= 296 Age: Range 16-60 Sex: 130 males 166 females Diagnosis: 100% Anxiety Neurosis by CCMD-2-R Exclusions: Did not achieve a score of greater than 50 on the SAS-CR. Notes: Duration of illness ranged from one month to 6 years Baseline: no data	**Data Used** SAS-CR Response (symptoms relieved, occas emotional fluc) Remission (symptoms disappeared & stable emotions) Notes: No drop outs	**Group 1 N= 157** Acupuncture. Mean dose 30 sessions - The treatment was given once a day, with a one day interval every 6 consecutive treatments. Treatment followed four different methods which are described in detail in the paper. **Group 2 N= 139** Doxepin. Mean dose 25 mg + - The dose for each session in the first week was 25mg & it could be modified properly based on the therapeutic effects and the adverse effect of the drug.	FUNDING: no mention, Quality assessed: low quality
ZHAO2005				

Study Type: RCT Study Description: compared the clinical efficacy of hypnotherapy and Alprazolam in the treatment of GAD. Type of Analysis: Completors (no drop outs) Blindness: No mention Duration (days): Mean 14 Followup: 4 wks Setting: Outpatients, China Notes: RANDOMISATION: according to patient number & date entered into trial. Info on Screening Process: no mention	n= 62 Age: Mean 38 Range 20-45 Sex: 23 males 39 females Diagnosis: 100% Generalised Anxiety Disorder (GAD) by CCMD-3 Exclusions: No diagnosis of GAD, not between age range of 20-45, scored under 14 in HAMA scale, unwilling to participate, had other serious cardio diseases Notes: In experimental group, the duration of diagnosis ranges from 1-11 years, with an average of 4 (+/-3) years. In control group, duration of diagnosis is 1-10 years, average 4 (+/-2) years. Baseline: HAMA (total) 28.8 (3.9) Psychological anxiety (subscale) 16.6 (2.3) Sensation (subscale) 12.2 (3.3) SAS 60.9 (4.9) There were no stat sig difference between the 2 groups (chi square= 0.005, P>0.05)	**Data Used** HAMA Hospital Anxiety and Depression Scale (anxiety) Body Sensations Questionnaire Social Adjustment Scale Notes: Assessments (HAMA and self report SAS) were given to both groups at pre-treatment (2 weeks before treatment) and follow up (4 weeks). Clinical significance is defined as reduction > 50% on HAMA scale. No drop outs	**Group 1 N= 32** Hypnotherapy. Mean dose 2 - Use different technique of hypnotherapy (catered to each individual's need) to reduce the patient's anxiety. Each session takes 30-40minutes **Group 2 N= 30** Alprazolam. Mean dose 2 - visits clinic twice a week, each session takes at least 30 minutes, the GP prescribe 0.8mg dose (taken twice a day).	Quality assessed: low-high risk of bias
Results from this paper: No difference found between groups				
ZHILING2006 Study Type: RCT Study Description: Treatment of GAD by acupuncture Type of Analysis: Completors (no dropouts) Blindness: No mention Duration (days): Mean 30 Setting: Out and in patients Notes: Randomization method not reported Info on Screening Process: Not mentioned	n= 65 Age: Sex: no information Diagnosis: 100% Generalised Anxiety Disorder (GAD) by CCMD-3 Exclusions: Severe organic psychosis Notes: SAS score >50 Baseline: Comparible in terms of sex, age and disease course. SAS: Treatment 79.88 (6.32) Control 78.96 (5.98)	**Data Used** Self-rating Anxiety Scale (SAS) Remission Notes: Remission criteria: disappearance of symptoms with stable emotions.	**Group 1 N= 35** Acupuncture - Acupuncture points modified according to individual patient conditions. Needles retained for 30 min. 30 days treatment. **Group 2 N= 30** Medication - Control group. 0.5-2 mg loracepam (bid or tid) with additional 20mg oryzanol (tid) or 10-20mg propranolol (tid) oraly administered for 30 days.	Quality assessment: Unclear/unknown risk.
Zhou 2003 Study Type: RCT Study Description: compare effectiveness of combined treatment of acupuncture with medication versus medication alone for anxiety neurosis Type of Analysis: unknown Blindness: No mention Duration (days): Mean 40 Setting: Unknown. Maybe conducted in The	n= 100 Age: Mean 52 Range 23-72 Sex: 32 males 68 females Diagnosis: Anxiety Neurosis by CCMD-2-R Exclusions: Not reported Baseline: No statistical difference between 2 groups on age, gender or chronicity. Patients in treatment group had	**Data Used** Remission **Data Not Used** Reliable & clinically significant change	**Group 1 N= 50** Acupuncture - given treatment once a day, 10 days as one treatment wave. There are 5 days of rest after each treatment wave. Participants received 3 treatment waves. **Group 2 N= 50** Study drug - 20mg of flupentixol 3 times per day. Taken 40 days continuously	Quality assessed: Selection bias-unclear; performance bias-unclear;attrition bias-unclear; detection bias-unclear

First Hospital of Yuhang District in Zhejiang, China Info on Screening Process: Did not report	average 2.5 years of diagnosis. Patients in comparison group average was 2.3 years of diagnosis.	Notes: Remission defined as no symptoms, can lead normal daily worktask; Response (normal functioning) defined as majority of symptom measures are lowered, can lead normal daily worktask; Response (unstable functioning) as unstable emotions, impaired daily life		
Results from this paper: Combined treatment was more effective than medication alone				

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BHATTACHARYYA2008	Not RCT
BONNE2003	Not a complementary intervention
Bonne2003a	Not considered a complimentary therapy
BYTRITSKY2008	Not RCT
SMITH2007	Not GAD
WANG2001	Not GAD

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