Appendix 15d: Study characteristics – pharmacological and physical interventions

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 versus venlafaxine (SNRI) versus placebo
KASPER2009
MONTGOMERY2006

Antihistamine versus placebo
DARCIS1995
LADER1998
LLORCA2002

Benzodiazepines versus anticonvulsants
FELTNER2003
PANDE2003
PFIZER2005
RICKELS2005

Benzodiazepines versus azapirones
BOURIN1995

Benzodiazepines versus placebo
ANDREATINI2002
ANSSEAU1991
FELTNER2003
FRESQUET2000
HACKETT2003
LYDIARD1997
MCLEOD1992
MOLLER2001
PANDE2003
PFIZER2008
RICKELS2000B
RICKELS2005

Buspirone versus placebo
DAVIDSON1999
LADER1998
MAJERCSIK2003
POLLACK1997
SRAMEK1996

Duloxetine (SNRI) versus placebo
HARTFORD2007
KOPONEN2007
NICOLINI2009
RYNN2008

Duloxetine (SNRI) versus venlafaxine (SNRI)
HARTFORD2007
NICOLINI2009

Quetiapine versus placebo
ASTRAZENECA2007A
ASTRAZENECA2007B
ASTRAZENECA2007C
ASTRAZENECA2008

SSRI versus 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 versus placebo
MCLEOD1992

Venlafaxine (SNRI) versus azapirones
DAVIDSON1999

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

Venlafaxine versus benzodiazepine
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 Blindness: Double blind Duration (days): Mean 168 Setting: Belgium, Finland, France, Sweden, UK Outpatient (14 centres) Notes: RANDOMISATION: 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% GAD by DSM-IV Exclusions: - DSM-IV diagnosis of GAD - HAM-A score < 20 - HAM-A (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 on beta-blockers, 52 zolpidem or chloral hydrate) Baseline: HAM-A baseline depression score (approximate): 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** HAM-A 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 HAM-A 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: +.
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, Sweden	n= 373 Age: Mean 41 Sex: 167 males 206 females Diagnosis: 100% GAD by DSM-IV Exclusions: - Less than 18 years of age - No DSM-IV primary diagnosis of GAD - HAM-A score < 18 - HAM-A (anxious mood & tension items) < 2	**Data Used** CGI-I HAM-A 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 HAM-A) QoL	**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: +

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.

- 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 psychotropic medication.

Baseline: HAM-A baseline depression score (approximately): 24.80 (4.75). Sertraline: 24.6 (4.6). Placebo: 25.0 (4.9). No significant differences between groups at baseline.

Response (50% reduction in HAM-A score)

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

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 whom 96 were excluded and 36 participated in the study. Participants were excluded due to the presence of another mental illness, refusal, marked reduction in HAM-A prior to study, use of other medications.

n= 36

Age: Mean 41

Sex: 17 males 19 females

Diagnosis:
100% GAD by DSM-III-R

Exclusions: - No DSM-III-R diagnosis 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 current 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 SCID-R

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

Data Used
STAI-trait
HAM-A
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 2-week washout period, study drugs were administered in identical capsules containing 2.5mg. The capsules were administered three times a day with the lowest dose consisting of two placebo and one active capsules based on response. 4 weeks.

Group 2 N= 12

Placebo - Following a 2-week washout period, study drugs were administered in identical capsules. The capsules were administered three times a day.

Group 3 N= 12

Valepotriates. Mean dose 81.3mg/day - Following a 2-week washout period, study drugs were administered in identical capsules containing 50mg. The capsules were administered three times a day with the lowest dose consisting of two placebo and one active capsules based on response.

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

ANSSEAU1991

Study Type: RCT

Study Description: 6 parallel groups. 1 week placebo run-in period following by 4 weeks of 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 HAM-A scale during placebo week).

n= 325

Age: Mean 42

Sex: 133 males 208 females

Diagnosis:
100% GAD by DSM-III-R

Exclusions: Could not have a score >2 on item 6 of the HAM-A, 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: Participants scored >20 on HAM-A and >9 on Covi Anxiety Scale.

Baseline: HAM-A at baseline: Suriclone 0.1 29.0 (5.6), Suriclone 0.2 28.6 (5.0), Suriclone 0.3 30.1 (5.2), Suriclone

Data Used
HAM-A
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAM-A 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.

Funding: no details provided. Quality assessed +.

0.4 30.0 (5.7), Diazepam 29.9 (5.2) and Placebo 29.4 (5.7).

Group 6 N= 59
Suriclone. Mean dose 0.4mg/day - No details provided.

ASTRAZENECA2007A

Study Type: RCT

Blindness: Double blind

Duration (days): Mean 56

Setting: Europe, Argentina, Canada, Mexico, South Africa

Notes: Randomisation: no further details

Info on Screening Process: 1054 screened, 873 randomised

n= 873

Age: Mean 41

Sex: 306 males 567 females

Diagnosis:
100% GAD by DSM-IV

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

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

Data Not Used
HAM-A - no SD

Group 1 N= 218
Quetiapine. Mean dose 150mg

Group 2 N= 217
Placebo

Group 3 N= 217
Paroxetine. Mean dose 20mg

Group 4 N= 221
Quetiapine. Mean dose 50mg

Funding: Astra Zeneca

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 randomised

n= 854

Age: Mean 38

Sex: no information

Diagnosis:
100% 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 HAM-A)
Response (50% reduction in HAM-A score)

Data Not Used
HAM-A - 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 randomised

n= 951

Age: Mean 40

Sex: no information

Diagnosis:
100% 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 HAM-A)
Response (50% reduction in HAM-A score)

Data Not Used
HAM-A - 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, Poland, Russia, Ukraine, United States

Notes: Randomisation: no further details

Info on Screening Process: 556 screened, 450 randomised

n= 556

Age: Mean 70 Range 65-87

Sex: 132 males 316 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: - < 66 years of age
- 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 HAM-A)
Response (50% reduction in HAM-A score)

Data Not Used
HAM-A - no SDs

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

Group 2 N= 216
Placebo

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 the 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% GAD by DSM-IV-TR

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

Baseline: HAM-A scores at baseline (approximate): 27.04 (4.46); No significant differences at baseline

Data Used
HAM-A
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 HAM-A score)

Data Not Used
Remission (less than 7 on HAM-A) - 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: +.

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 participants; 6 failed study entry for medical or diagnostic reasons.

n= 55

Age: Mean 39

Sex: 14 males 41 females

Diagnosis:
100% GAD by DSM-IV

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

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

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

Group 1 N= 28
Sertraline - Starting dose 25mg could be increased 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% 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
HAM-A
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 4 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 randomised, 7 dropped out before start of study

n= 404

Age: Mean 38

Sex: 152 males 252 females

Diagnosis:
100% 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
HAM-A
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAM-A)
Response (50% reduction in HAM-A 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 +.

BOURIN1995

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 participants assessed before and after washout period.

n= 43

Age: Range 18-65

Sex: 14 males 29 females

Diagnosis:
100% 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.

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

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

Data Used
HAM-A
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 +.

BRAWMAN-MINTZER2006

Study Type: RCT

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

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 70

Setting: US
Outpatient (9 centres)

Notes: RANDOMISATION: computerised 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% GAD by DSM-IV

Exclusions: - Less than 18 years of age
- No DSM-IV primary diagnosis of GAD
- HAM-A score > 20
- HAM-A (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 of childbearing potential not using an acceptable form of contraception

Notes: 53.7% (sertraline group) and 51.2% (placebo group) received prior psychotropic medication. 17% reported previous history of depression.

Data Used
HAM-A
Leaving the study due to inefficacy
Leaving the study due to adverse events
Leaving the study early for any reason
Response (50% reduction in HAM-A 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: +.

Baseline: HAM-A scores at baseline (approximately) total: 24.3 (3.00); sertraline: 24.5 (3.1); placebo; 24.1 (2.8). No significant differences at baseline.

DARCIS1995

Study Type: RCT

Study Description: Participants 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% 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
Hydroxyzine. 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 placebo 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% GAD by DSM-IV

Exclusions: - Not 18 years or older
- Primary diagnosis not GAD (DSM-IV)
- HAM-A score < 18
- HAM-A (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: HAM-A scores at baseline (approximate) 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
HAM-A
Leaving the study due to adverse events
Compliance
Response (50% reduction in HAM-A 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: +.

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.

n= 315

Age: Mean 40

Sex: 149 males 166 females

Diagnosis:
100% 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 HAM-A
- At least 2 on the HAM-A tension & anxiety items
- 17 + on the HAMD
- Lower scores on the Covi Anxiety scale than the Raskin

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

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: +.

Allocation concealment not addressed.

Info on Screening Process: Details not provided.

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 6 months prior to study entry
- Any neuroleptic, antidepressant, anxiolytic within 2 weeks (5 weeks for fluoxetine)
- Daily benzodiazepine therapy within 1 month
- Concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with any psychotropic component
- women who were pregnant/ of 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: HAM-A scores at baseline (approximate): 23.40 (4.40); No significant differences at baseline.

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

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% 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 HAM-A >20
- Aged <18 years
- Had another other Axis I disorder except dysthymia, simple phobia, social phobia, somatisation disorder or a history of MDD
- Current MDD
- Severe personality disorder, drug or alcohol misuse / dependence (active within 6 months of study)
- Suicide risk
- Covi anxiety scale <9
Raskin depression > 7

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

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

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

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

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 titrated 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 titrated during days 1-6 of double-blind treatment.

Group 4 N= 67
Placebo

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 = +

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.

n= 161

Age: Mean 37 Range 20-58

Sex: 33 males 35 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: Participants whose HAM-A score decreased by >=20% between screening and baseline, other Axis I psychiatric diagnosis, substance misuse disorder within the last 6 months, two or more discrete panic attacks within 4 weeks, clinically significant hematopoietic, cardiovascular, or autoimmune disease, clinically significant 12-lead

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

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

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 3 weeks according to tolerance but dosage could not be altered in weeks 4-6. Twice daily.

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

Info on Screening Process: No details provided.

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 participants with documented history of GAD or anxiety NOS were included in subgroup. Participants scored >=18 on HAM-A, >=2 on anxious mood item, <16 on HRSD and Covi > Raskin. Many participants 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).

Notes: Assessments conducted weekly.

Group 3 N= 20

Placebo - Twice daily.

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 numbers.
ALLOCATION CONCEALMENT: not addressed

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

n= 238

Age: Mean 40

Sex: 98 males 140 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: - less than 18 years
- MDD
- primary diagnosis not GAD (DSM-IV)
- HAM-A score < 18
- HAM-A (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
- History of previous psychotic illness, bipolar disorder, ASPD or severe Axis II disorder
- Previous treatment with venlafaxine
- Concomitant medication (i.e. antipsychotic drug, antidepressant, benzodiazepine) or ECT
- Women lactating, pregnant or of childbearing potential not using an acceptable form of contraception

Baseline: HAM-A scores at baseline (approximate): 25.00 (5.00); No significant differences at baseline

Data Used

HAM-A

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 HAM-A score) - does not meet criteria

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).

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 pharmaceutical industry. Quality assessed: +.

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% 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, OCD, mental retardation, or any pervasive developmental disorder or cognitive disorder. A history of psychotic features or disorder, or substance misuse 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

Data Used

HAM-A

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 HAM-A) - Not extractable for individual studies

Response (50% reduction in HAM-A 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 week 4 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 +.

sleep). Women who were pregnant or breastfeeding, or of child-bearing potential and not practising a medically reliable method of birth control.

Notes: ONLY USING STUDY 1 & 2 (as study 3 is reported already in DAVIDSON2004)

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

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% 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: Participants received medication for a maximum of 10 weeks, including a 1-week placebo run-in phase followed by an 8-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
HAM-A
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 HAM-A)

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 participants assigned to the active medication.

Funding: GlaxoSmithKline. Quality assessed +.

GSK2005

Study Type: RCT

Study Description: Placebo run-in medication for 1 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% 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 within 1 week prior to week 1 and subjects with history of complications that 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
HAM-A
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 HAM-A score)

Notes: Response was defined as either a CGI score of 1 or 2 or a HAM-A 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% GAD by DSM-IV
Exclusions: - <18 years of age

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

- HAM-A <20
- HAM-A <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 post-baseline 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 whom 220 failed to meet the inclusion criteria.

n= 487

Age: Mean 41

Sex: 182 males 305 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: <18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covi 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 misuse/dependence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of bipolar disorder, OCD or psychosis
- lack of response of GAD to 2 prior adequate trialss of antidepressants or benzodiazepine treatments
- psychotherapy initiated 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: HAM-A: 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 HAM-A score)
Remission (less than 7 on HAM-A)
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
HAM-A
Discontinuation adverse events (DAEs)

Notes: TAKEN AT: Baseline and endpoint 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 maximum 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. Participants randomised to receive either paroxetine or placebo.

Type of Analysis: ITT (LOCF)

Blindness: Double blind

Duration (days): Mean 56

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

Notes: RANDOMISATION: no details given.

Info on Screening Process: No details given.

n= 372

Age: Mean 46

Sex: 110 males 262 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: Following conditions currently or within 6 months 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

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
Leaving the study early for any reason
Remission (less than 7 on HAM-A)

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

Group 1 N= 188

Paroxetine - Weeks 1-2: 20mg/day. Dose could then be uptitrated in 10mg/day increments at intervals no more frequent 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 +.

concurrently or in the 12 weeks prior to screening.

Notes: Participan requiring more than one dose reduction were withdrawn from the study. Gradual reduction of medication during double-blind taper phase of >3 weeks for participants 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).

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% 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 misuse 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

HAM-A

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 HAM-A 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 post-baseline analysis. Safety analysis included all randomised participants

Type of Analysis: ITT

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.

n= 513

Age: Mean 44

Sex: 165 males 348 females

Diagnosis:
100% GAD by DSM-IV

Exclusions: -<18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covi Anxiety score <9 or not greater.
- 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 misuse/dependence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of bipolar disorder, OCD or psychosis
- lack of response of GAD to 2 prior adequate trials of antidepressants or benzodiazepine treatments
- psychotherapy iniated 6 weeks prior to study enrollment

Baseline: HAM-A (total) DUL (60mg) 25.0(7.1); DUL (120mg) 25.2(7.3); Placebo 25.8(7.6)

Data Used

Q-LES-Q-SF

Response (50% reduction in HAM-A score)

Remission (less than 7 on HAM-A)

Leaving the study early for any reason

PGI-I

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)

HAM-A

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 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 having their doses 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 having their doses gradually increased to their randomised dose within the first 2 study weeks.

Drug company funded - Eli Lilly study F1J-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 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 or 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% GAD by DSM-IV

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

Notes: Participants had HAM-A score >20. Low levels of depressive symptoms allowed.

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

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

Notes: Assessments carried out weekly.

Group 1 N= 81
Hydroxyzine. 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% GAD by DSM-IV

Exclusions: - HAM-A <20
- <18 years of age
- psychosis
- substance misuse or dependence
- PTSD
- pregnant
- MADRS >23

Baseline: HAM-A: Venlafaxine 28 Placebo 28

Data Used
HAM-A
Hospital Anxiety and Depression Scale (anxiety)
Leaving the study early for any reason
Remission (less than 7 on HAM-A)
Response (50% reduction in HAM-A 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: -.

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 randomisation, 1 spontaneous improvement, 1 did not meet diagnostic criteria, 1 had MDD

n= 34

Age: Mean 69

Sex: 13 males 21 females

Diagnosis:
90% GAD by DSM-IV

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

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

Baseline: HAM-A: 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 HAM-A)
Response (50% reduction in HAM-A 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

n= 177

Age: Mean 72

Sex: 58 males 119 females

Data Used
HAM-A
CGI (Response)
Adverse events

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.

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

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 statistician

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

Diagnosis:
14% Major depressive disorder by DSM-IV

100% GAD by DSM-IV

Exclusions: - Less than 60 years of age
- Without a principal diagnosis of GAD
- Less than 17 on the HAM-A
- 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 groups had MDD diagnosis.

Baseline: HAM-A baseline depression score (approximate): 23.00 (2.30). No significant differences between groups at baseline.

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 2 N= 92

Placebo

assessed +.

LLORCA2002

Study Type: RCT

Study Description: Parallel-group. 2 weeks single-blind 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% GAD by DSM-IV

Exclusions: Pregnant, breastfeeding, absence of a contraception method for women, known alcohol or drug dependence, major depressive episode within 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. Participants 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

HAM-A

Adverse events

Leaving the study due to adverse events

Leaving the study early for any reason

Remission (less than 7 on HAM-A)

Response (50% reduction in HAM-A 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

Hydroxyzine. 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% 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 psychosis, mania, current major depression, substance misuse, or other Axis I disorders likely to interfere with objectives of study. Any

Data Used

CGI-I

HAM-A

Adverse events

Leaving the study early for any reason

Notes: Assessed weekly.

Group 1 N= 67

Abecarnil - 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. Participants took at least 1 capsule b.i.d. to stay in study.

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

	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 completing 2 weeks of treatment were replaced. Participants 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 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. Participants took at least 1 capsule b.i.d. to stay in study. **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. Participants took 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% 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** HAM-A	**Group 1 N= 33** Buspirone - 30mg/day for 6 weeks **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% GAD by DSM-IV Exclusions: - history of panic attacks, psychosis or substance misuse 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: Participants 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** HAM-A 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 Setting: Multicentre, GERMANY. Outpatients Notes: RANDOMISATION: procedure not	n= 313 Age: Mean 48 Sex: 104 males 209 females Diagnosis: 100% GAD by ICD-10 Exclusions: - No ICD-10 diagnosis of GAD - HAM-A <17 and HRSD >20 - Ages <18 or >65 years - Significant other psychiatric disorders such as panic	**Data Used** Plasma concentrations HAM-A Adverse events **Data Not Used** Leaving the study due to adverse events - not extractable Leaving the study early for any reason - data not extractable	**Group 1 N= 107** Placebo - 4 capsules were given, two in the morning and two in the evening **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.	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 tapering with placebo.

reported

Info on Screening Process: No details reported

disorder, MDD
- Known substance misuse
- Relevant concomitant 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
HAM-A: Opipramol 27.7(7.4), Alprazolam: 29.7(7.6), Placebo: 29.3(7.0)

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 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.

MONTGOMERY2006

Study Type: RCT

Study Description: ITT: all randomised 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 participants 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% 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: Participants 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 (4.8). HRSD 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).

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

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

Notes: HRSD 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 the pharmaceutical industry (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 = +

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

n= 273

Age: Mean 72

Sex: 63 males 210 females

Diagnosis:
100% 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,

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

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.

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, HAM-A 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: HAM-A at baseline. Pregabalin: 27 (4.8) and Placebo: 26 (4.1).

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% GAD by DSM-IV

Exclusions: -<18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covi 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 misuse/dependence
- past year history of panic disorder, PTSD or eating disorder
- lifetime history of bipolar disorder, OCD or psychosis
- lack of response of GAD to 2 prior adequate trials of antidepressants or benzodiazepine treatments
- psychotherapy initiated 6 weeks prior to study enrollment

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

Baseline: BASELINE HAM-A 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
HAM-A
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 HAM-A)
Response (50% reduction in HAM-A score)

Notes: DROP OUTS: 21/84 (25%) - DUL 20mg; 49/158 (31%) - DUL 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. Dose 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. Dose could be decreased no more than twice. Dose stabilised after 6 weeks.

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

NIMATOUDIS2004

Study Type: RCT

Study Description: Venlafaxine vs. Placebo for 8 weeks. 1-week 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

n= 46

Age: Mean 43

Sex: 15 males 31 females

Diagnosis:
100% 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

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

Group 1 N= 24

Venlafaxine (extended release). Mean dose 75mg/day - Participants with a less than 30% decrease in their HAM-A total score at the end of 2 weeks compared with 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: -.

with a 20%+ decrease in HAM-A score during pre-study period.

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 within 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)

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

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% 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 HRSD 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. HAM-A >20.

Baseline: HAM-A 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
HAM-A
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAM-A)
Response (50% reduction in HAM-A 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 were 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% GAD by DSM-IV

Exclusions: No information provided

Baseline: HAM-A Placebo 23.9, Pregabalin 150mg 25.5, Pregabalin 600mg 24.4, Lorazepam 6mg 24.3

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

n= 169

Age: Mean 36 Range 18-64

Sex: 71 males 98 females

Diagnosis:
100% GAD by DSM-IV

Data Used
HAM-A total score

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

Funding: Pfizer

Setting: No Info

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

Exclusions: Pregnant and lactating females. No primary diagnosis of GAD. HAM-A <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 to screening.

Baseline: HAMA Placebo 24.0 (4.9) Paroxetine 23.5 (3.3) Lorazepam 24.2 (3.6)

Group 2 N= 56

Lorazepam. Mean dose 4.5mg - Capsules for oral administration. 3mg daily for 3 days increasing to 4.5mg daily from day 4 to day 28.

Group 3 N= 57

Placebo - Double-blind placebo treatment for 28 days.

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. Participants 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% 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, cardiovascular, renal, hepatic, gastrointestinal, or neurological disorder and patients with prior exposure to pregabalin.

Notes: Participants 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
CGI-I
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAM-A)
Response (50% reduction in HAM-A score)

Notes: Participants 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 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 participants 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% 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: Participants 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
HAM-A
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

Abecarnil - 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

Abecarnil - 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

Info on Screening Process: 331 received

n= 324

Age: Mean 40

Sex: 118 males 206 females

Diagnosis:
100% GAD by DSM-IV

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

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

Group 1 N= 163

Placebo

Funding: GSK. Quality assessed +.

baseline assessment, 7 withdrew before start of treatment

- HAM-A items 1 and 2 <2
- diagnosis of any other Axis I disorder
- MADRS >17
- substance misuse 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 2 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% GAD by DSM-IV

Exclusions: - Less than 18 years of age
- DSM-IV criteria for GAD
- No MDD
- HAM-A score < 18
- HAM-A (anxious mood & tension items) < 2
- Reduction of at least 20% in the HAM-A 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: HAM-A baseline depression score (approximate): 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
HAM-A
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 information given.

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

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

Blindness: Double blind

Duration (days): Mean 42

Setting: Outpatients, 12 sites in US

Notes: RANDOMISATION: procedure not reported

Info on Screening Process: Not reported

n= 310

Age: Mean 39

Sex: 118 males 192 females

Diagnosis:
100% GAD by DSM-III-R

Exclusions: -Aged <18 or >65
- no diagnosis of GAD according to DSM-III-R criteria
- HAM-A <20 after 1 week placebo screening period or HAM-A anxious mood <2
- Raskin Depression score higher than a score on the Covi anxiety scale
-HRSD >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 maintenance period for a total of 24

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

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

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 range of 3-7 capsules per day.

Group 2 N= 102

Abecarnil. 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.

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

weeks. During the maintenance period, participants continued to receive double-blind treatment.

Baseline: HAM-A: Abecarnil: 24.2, Diazepam: 24.0, Placebo: 24.9

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% 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
HAM-A
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAM-A)

Data Not Used
Response (50% reduction in HAM-A 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. Multicentre: USA.

Notes: RANDOMISATION: participants 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% 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, post-traumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or misuse, 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 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 HAM-A scores >9 and Covi Anxiety Scale scores >9.

Baseline: HAM-A 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
HAM-A
Adverse events
Leaving the study due to adverse events
Leaving the study early for any reason
Remission (less than 7 on HAM-A)
Response (50% reduction in HAM-A 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: +.

RYNN2008

Study Type: RCT

Study Description: ITT included all randomised participants with at least one post-baseline 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% GAD by DSM-IV

Exclusions: <18 years
- No primary DSM-IV diagnosis of GAD
- CGI-S <4
- HADS anxiety subscale <10
- Covi 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 misuse/dependence
- 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 trials of antidepressants or benzodiazepine treatments
- psychotherapy initiated 6 weeks prior to study enrollment

Baseline: HAM-A: Duloxetine 22.6(7.4) Placebo 23.5(7.9)

Data Used
Q-LES-Q-SF
Response (50% reduction in HAM-A score)
Remission (less than 7 on HAM-A)
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
HAM-A
Discontinuation adverse events (DAEs)

Notes: TAKEN AT: Baseline and endpoint
DROP OUT: Duloxetine: 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. By 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 company 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 = + / ++

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% 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 HRSD 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 misuse.

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. HRSD 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
HAM-A
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
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
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
GINSBERG2005	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

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.

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., et al. (2005) Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. Acta Psychiatrica Scandinavica, 111, 429-435.

Steiner, M., Allgulander, C., Ravindran, A., et al. (2005) Gender differences in clinical presentation and response to sertraline treatment of generalised anxiety disorder. Human Psychopharmacology, 20, 3-13.

ANDREATINI2002 (Published Data Only)

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ANSSEAU1991 (Published Data Only)
Ansseau, M., Olie, J-P., von Frenckell, R., et al. (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 (Unpublished 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 (Unpublished 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 (Unpublished 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 (Unpublished 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, double-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.

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

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DARCIS1995 (Published Data Only)
Darcis, T., Ferreri, M., Natens, J., et al. (1995) A multicentre double-blind placebo-controlled study investigating the anxiolytic efficacy of hydroxyzine in patients with generalized anxiety. Human Psychopharmacology, 10, 181-187.

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.

DAVIDSON2004 (Published Data Only)
Davidson, J.R.T., Bose, A., Korotzer, A., et al. (2004) Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled flexible-dose study. Depression and Anxiety, 19, 234-240.

FELTNER2003 (Published Data Only)
Feltner, D.E., Crockatt, J.G., Dubovsky, S.J., et al. (2003) A randomized, double-blind, placebo-controlled, fixed-dose, multicentre study of pregabalin in patients with generalized anxiety disorder. Journal of Clinical Psychopharmacology, 23, 240-249

FRESQUET2000 (Published Data Only)
Fresquet, A., Sust, M., Lloret, A., et al. (2000) Efficacy and safety of lesopitron in outpatients with generalized anxiety disorder. The Annals of Pharmacotherapy, 34, 147-153.

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Gelenberg, A.J., Lydiard, B., Rudolph, R.L., et al. (2000) Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. JAMA - Journal of the American Medical Association, 283, 3082-3088.

GOODMAN2005 (Published Data Only)
Goodman, W.K., Bose, A. & Wang, Q. (2005) Treatment of generalized anxiety disorder with escitalopram: Pooled results from double-blind, placebo-controlled trials. Journal of Affective Disorders, 87, 161-167.

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GSK (2002) A randomized, double-blind, placebo-controlled, flexible dosage trial to evaluate the efficacy and tolerability of paroxetine CR in patients with generalised anxiety disorder (GAD). Unpublished.

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GSK (2005) Clinical evaluation of BRL29060A (paroxetine hydrocholoride hydrate) in generalized anxiety disorder (GAD): A double-blind, placebo-controlled, comparative study. Unpublished.

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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: RANDOMISATION: 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% GAD by DSM-IV Exclusions: - DSM-IV diagnosis of GAD - HAM-A score < 20 - HAM-A (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 on beta-blockers, 52 zolpidem or chloral hydrate) Baseline: HAM-A baseline depression score (approximate): 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** HAM-A 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 HAM-A 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 the 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% GAD by DSM-IV-TR Exclusions: - not primary diagnosis of GAD (DSM-IV-TR) - not between 18 and 65 - HAM-A score < 20 - HAM-A (anxious mood & tension items) < 2 - MADRS >15 - Diagnosis of: MDD, panic disorder, social anxiety, PTSD, bipolar, OCD, body dysmorphic disorder, substance misuse, personality disorder - suicide risk - receiving psychosocial interventions (i.e. CBT, ECT) - physical health problems (i.e. vascular) - concomitant medication (i.e. psychoactive substances, antidepressants, benzodiazepines, antipsychotics)	**Data Used** HAM-A 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 HAM-A score) **Data Not Used** Remission (less than 7 on HAM-A) - 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.	Received support from Lundbeck and sponsored by GlaxoSmith Kline. Quality assessed: +.

	Baseline: HAM-A scores at baseline (approximate): 27.04 (4.46); No significant differences at baseline		**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 placebo 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% GAD by DSM-IV Exclusions: - Not 18 years or older - Primary diagnosis not GAD (DSM-IV) - HAM-A score < 18 - HAM-A (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: HAM-A scores at baseline (approximate) 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** HAM-A Leaving the study due to adverse events Compliance Response (50% reduction in HAM-A 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 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% 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 HAM-A >20 - Aged <18 years - Had another other Axis I disorder except dysthymia, simple phobia, social phobia, somatisation disorder or a history of MDD - Current MDD - Severe personality disorder, drug or alcohol misuse / dependence (active within 6 months of study) - Suicide risk - Covi anxiety scale <9 Raskin depression > 7 Notes: Participants with a dual comorbid psychiatric disorder were required to have GAD as a primary disorder as judged by the psychiatrist, considering relative severity and time of onset Baseline: HAM-A: Pregabalin (50mg) 24.9(3.9), Pregabalin (200mg) 25.4(4.6), Lorazepam 24.7(3.7), Placebo 24.8(4.1)	**Data Used** CGI-I HAM-A Adverse events Serious adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A score) Notes: TAKEN AT: Baseline and end of active treatment (4 weeks) DROPOUTS: total drop outs not reported	**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 titrated 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 titrated during days 1-6 of double-blind treatment. **Group 4 N= 67** Placebo	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 = +

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% GAD by DSM-IV Exclusions: - <18 years of age - HAM-A <20 - HAM-A <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 HAM-A Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAM-A 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 post-baseline analysis. Safety analysis included all randomised participants Type of Analysis: ITT 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.	n= 513 Age: Mean 44 Sex: 165 males 348 females Diagnosis: 100% GAD by DSM-IV Exclusions: -<18 years - No primary DSM-IV diagnosis of GAD - CGI-S <4 - HADS anxiety subscale <10 - Covi Anxiety score <9 or not greater. - 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 misuse/dependence - past year history of panic disorder, PTSD or eating disorder - lifetime history of bipolar disorder, OCD or psychosis - lack of response of GAD to 2 prior adequate trials of antidepressants or benzodiazepine treatments - psychotherapy iniated 6 weeks prior to study enrollment Baseline: HAM-A (total) DUL (60mg) 25.0(7.1); DUL (120mg) 25.2(7.3); Placebo 25.8(7.6)	**Data Used** Q-LES-Q-SF Response (50% reduction in HAM-A score) Remission (less than 7 on HAM-A) Leaving the study early for any reason PGI-I 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) HAM-A 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 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 having their doses 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 having their doses gradually increased to their randomised dose within the first 2 study weeks.	Drug company funded - Eli Lilly study F1J-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 score = + / ++
MONTGOMERY2006 Study Type: RCT Study Description: ITT: all randomised 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	n= 421 Age: Mean 44 Sex: 160 males 261 females Diagnosis: 100% 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;	**Data Used** CGI-I HAM-A Adverse events Serious adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A score) **Data Not Used** Leaving the study due to adverse events - not extractable	**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.	Funded by the pharmaceutical industry (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 = +

Kingdom. Outpatients attending primary care or psychiatric practices. Notes: Randomisation procedure not reported. Parallel-group design. Info on Screening Process: 543 participants 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.	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: Participants 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 (4.8). HRSD 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).	Significant improvement (30% reduction) - not required Notes: HRSD 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 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.).	
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% GAD by DSM-IV Exclusions: -<18 years - No primary DSM-IV diagnosis of GAD - CGI-S <4 - HADS anxiety subscale <10 - Covi 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 misuse/dependence - past year history of panic disorder, PTSD or eating disorder - lifetime history of bipolar disorder, OCD or psychosis - lack of response of GAD to 2 prior adequate trials of antidepressants or benzodiazepine treatments - psychotherapy initiated 6 weeks prior to study enrollment Notes: Duration of GAD M (S.D.) = 4.37 (8.19) years Baseline: BASELINE HAM-A 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 HAM-A 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 HAM-A) Response (50% reduction in HAM-A score) Notes: DROP OUTS: 21/84 (25%) - DUL 20mg; 49/158 (31%) - DUL 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. Dose 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. Dose 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% GAD by DSM-IV	**Data Used** CGI-I HAM-A Adverse events Leaving the study due to adverse events Leaving the study early for any reason	**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 were 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 HRSD 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. HAM-A >20. Baseline: HAM-A 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.	Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A 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% GAD by DSM-IV Exclusions: No information provided Baseline: HAM-A Placebo 23.9, Pregabalin 150mg 25.5, Pregabalin 600mg 24.4, Lorazepam 6mg 24.3	**Data Used** HAM-A Leaving the study early for any reason Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A 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 of DB treatment. Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 42 Setting: 19 centres: USA. Participants 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% 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, cardiovascular, renal, hepatic, gastrointestinal, or neurological disorder and patients with prior exposure to pregabalin. Notes: Participants 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** CGI-I Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A score) Notes: Participants 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 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 participants were maintained on this dosage.	Funding: Pfizer, Inc. Quality assessed: +.
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	n= 349 Age: Mean 41 Range 20-75 Sex: 154 males 195 females Diagnosis: 100% GAD by DSM-IV	**Data Used** HAM-A Leaving the study due to inefficacy Leaving the study due to adverse events Compliance Leaving the study early for any reason	**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.	Funding: Wyeth-Ayerst Laboratories. Quality assessed: -.

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.	Exclusions: - Less than 18 years of age - DSM-IV criteria for GAD - No MDD - HAM-A score < 18 - HAM-A (anxious mood & tension items) < 2 - Reduction of at least 20% in the HAM-A 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: HAM-A baseline depression score (approximate): 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).	Notes: TAKEN AT: week 1, 2, 3, 4, 6, 8 weeks 4-10 days after drug tapered. DROP OUTS: 29% CHANGE SCORES USED.	**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 information given.	
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% 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** HAM-A Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A) **Data Not Used** Response (50% reduction in HAM-A 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. Multicentre: USA. Notes: RANDOMISATION: participants 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% 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, post-traumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or misuse, 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 psychotropic medication during the study and for at least 2 weeks before the screening visit, current or	**Data Used** CGI-I HAM-A Adverse events Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A 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.	Funding: Pfizer, Inc. Quality assessed: +.

	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 HAM-A scores >9 and Covi Anxiety Scale scores >9. Baseline: HAM-A 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).		**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.	

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, double-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, double-blind, placebo-controlled, fixed-dose, multicentre study of pregabalin in patients with generalized 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., Allgulander, C., Erickson, J., et al. (2007) Efficacy of duloxetine for the treatment of generalized anxiety disorder: Implications for primary care physicians. Primary Care Companion to the Journal of Clinical Psychiatry, 9, 100-107.

MONTGOMERY2006 (Published Data Only)

Montgomery, S.A, Tobias, K., Zornberg, G.L., et al. (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., et al. (2003) Pregabalin in generalized anxiety disorder: a placebo-controlled trial. American Journal of Psychiatry, 160, 533-540.

PFIZER2005 (Unpublished Data Only)

Pfizer (2005) European Assessment Report: LYRICA. London: EMEA.

POHL2005 (Published Data Only)

Pohl, R.B., Feltner, D.E., Fieve, R.R., et al (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)

Sontheimer, D., & Ables, A. (2001) Is imipramine or buspirone treatment effective in patients wishing to discontinue long-term benzodiazepine use? The Journal of Family Practice, 50, 203.

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.

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., et al. (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. Psychopharmacology 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	Fluoxetine & olanzapine vs fluoxetine & placebo	Risperidone augmentation vs placebo augmentation	Ziprasidone augmentation vs placebo augmentation
BRAWMAN-MINTZER2005	POLLACK2006	PANDINA2007	LOHOFF2010

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BRAWMAN-MINTZER2005 Study Type: RCT Study Description: Participants who continued to experience GAD despite anxiolytic treatment 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% GAD by DSM-IV Exclusions: Diagnosis of MDD within 1 month of study entry and subjects with substance-use disorders within 6 months of study entry. Subjects with current or past history of bipolar or any psychotic disorder. Notes: Participants 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 HAM-A 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. Info on Screening Process: 73 subjects with GAD were recruited. 62 randomized. Inclusion criteria: subjects had to be 18 years+ and meet DSM-IV criteria for GAD, treatment failure of 1 trial of an SSRI, SNRI, BZ or combination.	n= 62 Age: Sex: Diagnosis: 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 abnormalities on physical examination or unstable medical conditions. Females who are pregnant, breast feeding. Baseline: Not reported	**Data Used** CGI-I HAM-A HAD Discontinuation adverse events (DAEs) CGI-S	**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	
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: Randomisation: An independent	n= 390 Age: Mean 44 Range 18-65 Sex: 114 males 276 females Diagnosis: 100% GAD by DSM-IV Exclusions: Females with known or suspected pregnancy, serious suicide risk or serious medical/neurological illness,	**Data Used** Q-LES-Q HAM-A Remission (less than 7 on HAM-A) Response (50% reduction in HAM-A score)	**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).	Funding: Not reported

statistician provided randomisation codes administered by telephone interactive voice response system. Info on Screening Process: 453 screened. 417 randomised, 390 in ITT population	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/antidepressant regimen and dosage and were assigned to adjunctive risperidone or placebo augmentation using tablets of matching appearance, taste and smell. Baseline: HAM-A: 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)		**Group 2 N= 194** Placebo - Placebo augmentation used tablets of matching appearance, taste and smell.	
POLLACK2006 Study Type: RCT Study Description: Participans 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 participants were in open-label fluoxetine treatment.	n= 24 Age: Mean 44 Sex: 11 males 13 females Diagnosis: 100% GAD by DSM-IV Exclusions: Bipolar disorder, psychotic disorders, alcohol or substance misuse in last 6 months, those receiving concurrent psychotherapies directed at GAD. Notes: Comorbid 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 HAM-A Adverse events Leaving the study due to adverse events Leaving the study early for any reason Response (50% reduction in HAM-A 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: +.

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
FAVA2009	Primary outcome insomnia not anxiety
SIMON2008	Outside scope of guideline

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, I., et al. (2007) Adjunctive risperidone 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., et al. (2006) Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: A placebo-controlled study. Biological Psychiatry, 59, 211-215.

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.

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.

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

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 participants received open-label escitalopram for 12 weeks. 375 responded 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 adverse events, 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% 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 sequelae of liver or renal insufficiency. 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 HAM-A 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 HAM-A 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.	Participants who completed DB phase entered a 2-week taper period where the escitalopram group received escitalopram 10mg/day for a week and placebo for 2nd week. Placebo participants continued on placebo. Quality assessed: +. Funding: H. Lundbeck A/S.
DAVIDSON2008 Study Type: RCT Study Description: Relapse prevention trial with a 26-week open label, flexible dose therapy followed by 26-week double-blind, placebo controlled continuation 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 - Covi 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 misuse/dependence	**Data Used** Beck scale for suicide ideation HAM-A 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 dose as 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: +

	- past year history of panic disorder, PTSD or eating disorder - lifetime history of bipolar, OCD or psychosis - lack of response of GAD to 2 prior adequate trials of antidepressants or benzodiazepine treatments - psychotherapy initiated 6 weeks prior to study enrollment Baseline: No differences at baseline.			
FELTNER2008 Study Type: RCT Study Description: 1-week screening phase followed by 8-week 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). Recruited via advertisements in the local media. Notes: RANDOMISATION: no details provided. Info on Screening Process: 859 participants screened: 624 enrolled. 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 inclusion criteria, 9 did not comply and 26 for other.	n= 339 Age: Mean 39 Sex: 145 males 193 females Diagnosis: 100% 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 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: Participants had GAD >1 year. Diagnosis based on MINI. Participants scored >=20 on HAM-A, >=9 on Covi and <=7 on Raskin. Allowed participants with dysthymia, depession NOS, or specific phobia. Baseline: HAM-A at baseline (for double-blind phase). Pregabalin: 5.9 (3.2) and Placebo: 5.5 (3.4).	**Data Used** CGI-I HAM-A Adverse events Sheehan Disability Scale (SDS) Leaving the study due to adverse events Leaving the study early for any reason 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.	**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: +.
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% 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** HAM-A Relapse Leaving the study due to adverse events Leaving the study early for any reason Remission (less than 7 on HAM-A)	**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.

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., et al. (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 generalized 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 complementary therapies?

Comparisons Included in this Clinical Question

Acupuncture and Chinese medication vs doxepin	Acupuncture vs behavioural desensitisation + acupuncture	Acupuncture vs behavioural desensitization	Acupuncture vs Doxepin
RUAN2003	GUIZHEN1998	GUIZHEN1998	ZHANG2003

Acupuncture vs fluoxetine/Paroxetine	Acupuncture vs flupentixol vs combined	Acupuncture vs lorazepam & plant extract propranolol	Acupuncture vs medication + acupuncture
YUAN2007	ZHOU2003	ZHILING2006	ZHOU2003

Chamomile vs placebo	Chinese Taoist psychotherapy vs benzodiazepine	Galphimia glauca vs lorazepam	Ginkgo biloba vs placebo
AMSTERDAM2009	ZHANG2002	HERRERA-ARELLANO2007	WOELK2007

Hypnotherapy vs alprazolam	Passionflower vs oxazepam	Silexan vs lorazepam	Study drug vs placebo
ZHAO2005	AKHONDZADEH2001A	WOELK2010	HANUS2004

Valerian extract vs diazepam	Valerian extract vs placebo
ANDREATINI2002	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% 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 misuse, drug psychosis, OCD, hypomania, or major depression. Pregnant and lactating women. Notes: Participants had a HAM-A score >=14. Participants were free from all psychotopic medication for a minimum of 7 days before starting study. Baseline: No data provided.	**Data Used** Adverse events **Data Not Used** HAM-A - 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.
AMSTERDAM2009 Study Type: RCT Study Description: Efficacy and tolerability trial of chamomile extract therapy in patients with GAD. Type of Analysis: ITT (LOCF)	n= 57 Age: Mean 46 Sex: no information Diagnosis: 100% GAD by DSM-IV	**Data Used** HAM-A Beck Anxiety Inventory Psychological General Well Being Index Response (50% reduction in HAM-A score)	**Group 1 N= 28** Chamomile extract therapy. Mean dose 220mg - Capsules containing pharmaceutical grade German chamomile extract standardised to a content of 1.2% apigenin. 1-5 capsules	Quality assessment Funded by the National Institutes of Health/National Center for Complementary and Alternative Medicine grant

Blindness: Double blind Duration (days): Mean 56 Setting: Department of Family Medicine and Community Health outpatient clinic. Notes: Blocked randomisation with varying block sizes. Info on Screening Process: 61 screened. 4 failed (1 for non compliance and 3 for no consent) 57 randomised.	Exclusions: HAM-A <9. Another primary DSM-IV Axis I disorder. Current diagnosis of MDD, bipolar disorder, PD, phobic disorder, OCD, PTSD, acute stress disorder, substance induced anxiety disorder, psychosis, dementia, or substance misuse 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 stabilisers, sedatives, or complementary and alternative medication remedies (eg, St John's wort) or other chamomile preparations. Baseline: HAM-A: 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) Placebo 58.9 (14.1)	Notes: Capsules made identical 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.	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.	
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 whom 96 were excluded and 36 participated in the study. Participants were excluded due to the presence of another mental illness, refusal, marked reduction in HAM-A prior to study, use of other medications.	n= 36 Age: Mean 41 Sex: 17 males 19 females Diagnosis: 100% GAD by DSM-III-R Exclusions: - No DSM-III-R diagnosis 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 current 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 SCID-R Baseline: HAM-A - Placebo: 25.1(7.5), Diazepam: 25.2(4.5), Valepotriates: 22.8(7.6)	**Data Used** STAI-trait HAM-A 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 2-week washout period, study drugs were administered in identical capsules containing 2.5mg. The capsules were administered three times a day with the lowest dose consisting of two placebo and one active capsules based on response. 4 weeks. **Group 2 N= 12** Placebo - Following a 2-week washout period, study drugs were administered in identical capsules. The capsules were administered three times a day. **Group 3 N= 12** Valepotriates. Mean dose 81.3mg/day - Following a 2-week washout period, study drugs were administered in identical capsules containing 50mg. The capsules were administered three times a day with the lowest dose consisting of two placebo and one active capsules based on response.	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
GUIZHEN1998 Study Type: RCT Study Description: Comparative study on acupuncture combined with behavioural desensitisation 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 = 1 month to 16 years, Behavioural desentisation = 6 months to 12 years, Combined = 2 weeks to 16 years	**Data Used** Response (symptoms improved & SAS reduced sign) Remission (clinical symptoms gone & SAS <45) 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 steel filiform needles were inserted into 3-6 selected body points during each session & manipulated with uniform reinforcing reducing. Treatment was performed once every other day.	FUNDING: No mention, Quality assessed = moderate quality

			Group 2 N= 80 Behavioural desensitisation. Mean dose 10 sessions (twice per week for 30 minutes) - Treatment consisted of self-relaxation techniques, psychotherapy, & a program of behavioural desensitisation. Received instruction in muscle relaxation techniques to be practiced daily. Psychotherapy incorporated desensitisation techniques. **Group 3 N= 80** Behavioural desensitisation + acupuncture. Mean dose 10-40 sessions - Underwent the above programme of behavioural desensitisation 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.	
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 Setting: Multi outpatient centers in Paris. Notes: Randomised box design used for randomisation. Info on Screening Process: Not mentioned	n= 264 Age: Mean 45 Range 18- Sex: 50 males 214 females Diagnosis: 100% GAD by DSM-III-R Exclusions: <18 years. No consent. No GAD according to DSM-III-R criteria. Patients with suicide risk. Use of psychotropic drugs or drugs with psychotropic properties or magnesium salts within 1 month. Notes: Total HAM-A score between 16 and 28 Baseline: HAM-A: Study group 22.7 Placebo 22.4	**Data Used** HAM-A Visual Analog Scale (VAS) Response (50% reduction in HAM-A score) **Data Not Used** CGI - no data Notes: Efficacy assessment before at baseline and 7, 14, 30, 60 and 90 days after treatment. 31 drop outs due to inefficacy.	**Group 1 N= 134** Placebo - Tablets made from same ingredients as study drug except for active ingredients. Indistinguishable. **Group 2 N= 130** Study drug. Mean dose 375mg - 2 plant extracts (Crataegus oxyacantha and eschscholzia californica) and magnesium. Drug name: Sympathyl. Tablet form. 75mg Crataegus oxyacantha, 20mg Eschscholzia californica, 75mg elemental magnesium. 2 tablets per day for 3 months.	Quality assessment: low risk of bias. Funded by Laboratoires Innothera, France
HERRERA-ARELLANO2007 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% GAD by DSM-IV Exclusions: No pharmacological intervention for GAD within past 4 weeks, no drug or alcohol misuse for at least 6 months prior to study initiation, no suicidal behaviour or psychiatric comorbidity of higher clinical importance than GAD. Notes: Participants scored >=19 on HAM-A. 7% of participants had had a drug/alcohol addiction. Baseline: None provided.	**Data Used** CGI-I HAM-A 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 dried aqueous G.G. extract twice a day.	Funding: unknown. Quality assessed: -.
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	n= 169 Age: Range 14-62 Sex: 63 males 106 females Diagnosis: Anxiety neurosis by CCMD-2-R	**Data Used** SAS-CR	**Group 1 N= 83** Doxepin. Mean dose 30 days - average daily intake is 150mg	Quality assessed: all selection, performance, attrition, detection bias are unclear

Blindness: No mention Duration (days): Mean 30 Setting: unknown. Probably inpatients Info on Screening Process: not reported	Exclusions: Excluded those who scored below 50 on CCMD-2 and SAS-CR Baseline: Did not report if both groups are comparable at baseline. Baseline score (SAS-CR) for acupuncture group is 78.56(17.64) and Doxepin group is 77.68(18.23). Duration of diagnosis ranges from1 month to 8 years		**Group 2 N= 86** Acupuncture. Mean dose 30days - Acupuncture combined with Chinese medicine. Participants took the Chinese medicine twice a day for 30 days. They also receive acupuncture once per day for 30-60min each session.	
WOELK2007 Study Type: RCT Study Description: Anxiolytic-effects of ginkgo biloba in patients with 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: Validated 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: Adjustment disorder with anxious mood by DSM-III-R GAD 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 abuse, lack of cooperation, inability to complete self-rating questionnaires or treatment with psychoactive drugs. Baseline: HAM-A. No significant differences in baseline scores.	**Data Used** HAM-A Notes: Assessment took place at baseline and on days 4, 8, 15, and 29.	**Group 1 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. **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= 34** Ginkgo biloba. Mean dose 480mg - Patients took 2 film-coated tablets t.i.d (80mg). 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 the treatment of GAD. Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Followup: 2-week discontinuation phase Setting: Multi outpatient centers in Germany. Notes: Randomisation by validated computer program Info on Screening Process: 1-week screening. Patients received placebo. Patients with decrease of 25% or more of HAM-A during this phase were excluded.	n= 77 Age: Mean 43 Range 21-65 Sex: 18 males 59 females Diagnosis: GAD by DSM-IV Exclusions: HAM-A <18 and Item 1 'anxious mood' <2 and Item 2 'tension' <2. Baseline: HAM-A: 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** HAM-A Self-rating Anxiety Scale (SAS) SF-36 Penn State Worry Questionnaire CGI Remission (less than 10 on HAMA) Response (50% reduction in HAM-A score) **Data Not Used** Sleep diary Notes: Assessment at baseline, 1, 2, 4, 6 and 8 weeks. 11 drop outs/incomplete assessment.	**Group 1 N= 37** Lorazepam. Mean dose 0.5mg - Patients received 1 capsule lorazepam and 1 capsule silexan placebo. **Group 2 N= 40** Silexan. Mean dose 80mg - Patients received one capsule of silexan and 1 capsule lorazepam placebo. Silexan is an oil produced from lavender.	Quality assessment: Attrition bias: Unclear
YUAN2007 Study Type: Quasi-randomised Study Description: To observe the therapeutic efficacy of Jin-3-needling (NL) therapy on GAD through Clinical Global Impression scale (CGI). Type of Analysis: Completer Blindness: No mention Duration (days): Mean 36 Setting: The first affiliated hospital of Guangzhou Traditional Chinese Medical	n= 86 Age: Range 18-65 Sex: 30 males 56 females Diagnosis: 100% GAD by CCMD-3-R Exclusions: HAM-A <15. Received any anxiolytic 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	**Data Used** Severity Index General Index Efficacy Index	**Group 1 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 45 minutes and run every 15 minutes, once everyday, 6 times per week for 6 weeks.	Quality assessment: Selection, performance and detection bias unknown/unclear. Attrition: low risk of bias.

University, Guangzhou Municipal Hospital of the Brain. Notes: Assigned to treatment groups according to the sequence of their visiting between Oct 2004 - Dec 2005. Info on Screening Process: 86 enrolled upon meeting the inclusion criteria.	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: HAM-A: 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** 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 drug and alprazolam was used in addition according to the patient's condition. 6-week course. **Group 3 N= 28** Western medicine + Jin-3-Needling therapy - Combination of method for western medicine and J3N therapy. Dosage 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% 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 SCL-90 Chinese version Coping Style Questionnaire Type A Personality Scale Notes: Phase I-1-month weekly sessions. Phase II-5 months of twice monthly sessions. 13 drop outs. Reason not mentioned.	**Group 1 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 2 N= 46** Chinese Taoist Cognitive Psychotherapy - Each session lasted 1hour. Carried out by first author and experienced psychiatrists trained for method. **Group 3 N= 49** CTCP v BZD - Same as above	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 outpatients, 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 1-month to 6 years Baseline: no data	**Data Used** Remission (symptoms disappeared & stable emotions) Response (symptoms relieved, some fluctuations) SAS-CR Notes: No drop outs	**Group 1 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. **Group 2 N= 157** Acupuncture. Mean dose 30 sessions - The treatment was given once a day, with a 1 day interval every 6 consecutive treatments. Treatment followed four different methods which are described in detail in the paper.	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: Completers (no drop outs) Blindness: No mention Duration (days): Mean 14	n= 62 Age: Mean 38 Range 20-45 Sex: 23 males 39 females Diagnosis: 100% GAD by CCMD-3 Exclusions: No diagnosis of GAD, not between age range of	**Data Used** HAM-A Hospital Anxiety and Depression Scale (anxiety) Body Sensations Questionnaire Social Adjustment Scale	**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 30-40 minutes	Quality assessed: low-high risk of bias

Setting: Outpatients, China Notes: RANDOMISATION: according to patient number & date entered into trial. Info on Screening Process: no mention	20-45, scored under 14 on HAM-A scale, unwilling to participate, had other serious cardiovascular 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: HAM-A (total) 28.8 (3.9) Psychological anxiety (subscale) 16.6 (2.3) Sensation (subscale) 12.2 (3.3) SAS 60.9 (4.9) There was no statistically significant difference between the 2 groups (chi square= 0.005, P>0.05)	Notes: Assessments (HAM-A 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 HAM-A scale. No drop outs	**Group 2 N= 30** Alprazolam. Mean dose 2 - visits clinic twice a week, each session takes at least 30 minutes, the GP prescribes 0.8mg dose (taken twice a day).	
ZHILING2006 Study Type: RCT Study Description: Treatment of GAD by acupuncture Type of Analysis: Completers (no dropouts) Blindness: No mention Duration (days): Mean 30 Setting: Out and inpatients Notes: Randomisation method not reported Info on Screening Process: Not mentioned	n= 65 Age: Sex: no information Diagnosis: 100% GAD by CCMD-3 Exclusions: Severe organic psychosis Notes: SAS score >50 Baseline: Comparable 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= 30** Medication - Control group. 0.5-2 mg lorazepam (bid or tid) with additional 20mg oryzanol (tid) or 10-20mg propranolol (tid) orally administered for 30 days. **Group 2 N= 35** Acupuncture - Acupuncture points modified according to individual patient conditions. Needles retained for 30 min. 30' days treatment.	Quality assessment: Unclear/unknown risk.
ZHOU2003 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 First Hospital of Yuhang District in Zhejiang, China Info on Screening Process: Did not report	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 average 2.5 years of diagnosis. Patients in comparison group average was 2.3 years of diagnosis.	**Data Used** Remission **Data Not Used** Reliable & clinically significant change Notes: Remission defined as no symptoms, can lead normal daily work task; 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	**Group 1 N= 50** Study drug - 20mg of flupentixol 3 times per day. Taken 40 days continuously **Group 2 N= 50** Acupuncture - given treatment once a day, 10 days as one treatment wave. There were 5 days of rest after each treatment wave. Participants received 3 treatment waves.	Quality assessed: Selection bias-unclear; performance bias-unclear; attrition bias-unclear; detection bias-unclear

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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