

National Institute for Health and Care Excellence

Consultation draft

Depression in adults: treatment and management

Appendix U2.9: Text from CG90 Appendix 17c that has
been deleted

NICE Guideline

Appendices

May 2018

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Appendix 17c: clinical studies characteristics tables – pharmacological and physical interventions

Contents

SSRIs versus placebo – studies in previous guideline.....	4
TCA versus placebo – new studies in the guideline update.....	16
Amitriptyline – studies in previous guideline.....	93
SSRIs versus antidepressants – studies in previous guideline.....	109
Escitalopram – studies in previous guideline.....	132
Acute phase escitalopram – new studies in the guideline update.....	135
Moclobemide – studies in previous guideline.....	151
Phenelzine – studies in previous guideline.....	157
Acute-phase duloxetine – new studies in the guideline update.....	160
Mirtazapine – studies in previous guideline	171
Reboxetine – studies in previous guideline	175
Venlafaxine – studies in previous guideline	177
Gender effects on antidepressant efficacy – studies in previous guideline.....	188
Psychotic depression – studies in previous guideline.....	189

Non-light therapy interventions for depression with a seasonal pattern/SAD – relapse prevention	
New studies in the guideline update.....	210
Low-dose tricyclics – studies in previous guideline.....	212
Switching strategies – studies in previous guideline.....	215
Treatment-resistant depression – studies in previous guideline.....	215
Augmentation with a second antidepressant – studies in previous guideline.....	218
Augmentation with antipsychotics – studies in previous guideline.....	220
Augmentation with benzodiazepines – studies in previous guideline.....	221
Augmentation with buspirone & lithium – studies in previous guideline.....	222
Augmentation with pindolol – studies in previous guideline.....	225
Augmentation with triiodothyronine (T3) – studies in previous guideline.....	227
Next-step treatments – new studies in the guideline update.....	228
Relapse prevention – older trials not listed elsewhere.....	241
Relapse prevention – studies in previous guideline.....	243
Relapse prevention – new studies in the guideline update.....	250

Please note that references for studies from the previous guideline are in Appendix 18.

Explanation of abbreviations and terms used in the tables from the previous guideline

Study IDs of studies in the pharmacology reviews in the previous guideline had a suffix made up of up to four letters, as follows:

First letter: age group

- (Y)oung (mean age <65 years)
- (E)lderly (at least 80% >65 years)

Second letter: setting:

- (I)npatients
- (O)utpatients
- (M)ixed inpatients and outpatients
- (P)rimary care
- ? = not clear

Third letter: analysis method of continuous data:

- C or E = mean scores at end of treatment or follow-up are for completers only
- I = intention-to-treat analysis using last observation carried forward for those leaving treatment early

Additional letters used in specific reviews as follows:

Augmentation with lithium:

- AN = Acute-phase non-responders
- TR = patients with treatment resistant depression

Treatment-resistant depression: A number indicating how many courses of antidepressants participants have failed.

SSRIs v placebo: Hnn refers to the version of the HRSD used in the efficacy analysis i.e. H21 = HRSD-21

St John's wort:

- A = SJW vs. antidepressant
- A/L = SJW vs. antidepressant at below therapeutic dose
- P = SJW vs. placebo

Venlafaxine:

- IR = venlafaxine immediate release
- XR = venlafaxine extended release

“Methods” describes the design of the trial including details of randomisation and blinding, the duration of the trial and whether analysis of continuous data was carried out on an intention-to-treat or completer sample. In some cases intention-to-treat may not refer to the number of patients originally randomised to each treatment group since many studies defined their own criteria, commonly that patients included in the intention-to-treat sample must have received at least one dose of study drug, and undergone at least one assessment.

“Participants” details of the patients who entered trials and the criteria for their inclusion in the study, patient setting, number of patients randomised, age range or mean age, number of female participants, diagnostic inclusion criteria and baseline depression scale scores, country in which the trial took place. This information refers to the total number of patients randomised in a study; where there were more than two treatment groups it may not relate to the patients entered into the review.

“Interventions” lists all the treatment groups that patients could be assigned to; in pharmacological trials the dose range or mean dose administered to patients is given. In trials with more than two treatment arms a note is made of which groups were used in the review.

Doses of pharmacological treatments are indicated as follows:

nnmg->*nnmg* indicates that all patients started on *nnmg* and increased to *nnmg*

nnmg up to *nnmg* means that all patients initially received *nnmg* and this was increased to a maximum of *nnmg* for some patients (usually those who didn't respond the lower dose or those could tolerate an increase)

nn-nnmg means that patients received between *nnmg* and *nnmg*

“Outcomes” lists the outcomes which have been extracted including how ‘response’ and ‘remission’ have been defined by individual studies where appropriate.

“Notes” contains additional information, for example, where the study was carried out and by whom, and mean baseline depression scale scores.

“Allocation concealment” grades studies from A-D according to how well treatment group assignment was concealed from investigators and patients. ‘A’ indicates concealment was adequate, ‘B’ unclear, ‘C’ inadequate, ‘D’ allocation concealment was not used as a criterion to assess validity.

The following abbreviations are used and further abbreviations are explained in the guideline update:

AD = antidepressant	GDS = Geriatric Depression Scale	RDC = Research Diagnostic Criteria
BDI = Beck Depression Inventory	GHQ = General Health Questionnaire	RDS = Raskin Depression Scale
CES-D = Centre for Epidemiological Studies - Depression scale	HRSD = Hamilton Rating Scale for Depression	SADS(-L) = Schedule for Affective Disorders and Schizophrenia (- Lifetime Version)
CGI-I = Clinical Global Impressions - Improvement scale	ICD = International Classification of Diseases	SCID = Structured Clinical Interview for DSM-III-R
CGI-S = Clinical Global Impressions - Severity scale	ITT = intention-to-treat	SCL-R = Depression Symptom Check List
CIS = Clinical Interview Schedule	LOCF = last observation carried forward	SD = standard deviation
CM = clinical management	MDD = major depressive disorder	SDS = Zung Self-Rating Depression Scale
CMHT: Community mental health team	MDE = major depressive episode	SE = standard error
CPN = community psychiatric nurse	MMPI = Minnesota Multi-phasic Inventory	TAU = treatment as usual
DPDS = Diagnostic Depression subscale of the Short- CARE inventory	OT = occupational therapist.	WHO-CIDI = World Health Organisation Composite International Diagnostic Interview
DSM = Diagnostic Statistical Manual	PRIME-MD = Primary Care Evaluation of Mental Disorders	WLC = wait list control
	Pts = patients	

SSRIs versus placebo - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Andreoli2002 Y M I	Allocation: Random (no details) Duration: 8 weeks (+4-28 day washout) Analysis: ITT	Inpatients and outpatients. N=381, aged: 18-65. Diagnosis: DSM-III-R major depression without psychotic features, HRSD≥22	1. Reboxetine (8mg up to 10mg after 4 weeks) 2. Fluoxetine (20mg up to 40mg after 4 weeks) 3. Placebo	1. Non-responders (Patients not achieving ≥50% decrease in HRSD) 2. Non-remitters (Patients not achieving HRSD≤10) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted in 33 centres in 6 countries.	B
Burke02 C Y O I H24	Allocation: Random no details. Duration 8 weeks (+ 1 week placebo washout) Analysis: LOCF	Outpatients. N=491. Aged 18-65. Diagnosis: DSM-IV major depressive disorder, MADRS ≥22 Baseline scores: Escitalopram 10mg - MADRS=28.0±4.9, HRSD-24=24.3±6.2. Escitalopram 20mg - MADRS=28.9±4.6, HRSD-24=25.8±5.7 Citalopram - MADRS=29.2±4.5, HRSD-24=25.9±5.9. Placebo - MADRS=29.5±5.0, HRSD-24=25.8±5.9	1. Escitalopram (10mg) 2. Escitalopram (20mg) 3. Citalopram (40mg) 4. Placebo (1 and 2 not extracted)	1. HRSD-24 mean change scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted at 35 centres in the US.	B
Byerley88 Y O C H21	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression of at least 1 month 20+ HRSD (21) Age: mean age 39. N=97, HRSD analysis: N=60	Fluoxetine versus imipramine (75mg -> 150mg by day 15) versus placebo	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects		B

		Country: US Setting: Outpatients				
Claghorn1996 Y O C	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression Age: 39 (+-10.9) years; N=150, HRSD analysis: N=61 Country: America Setting: Outpatient	1. Fluvoxamine (mean dose during 4th week 128.5 mg) 2. Imipramine (mean dose during 4th week 186.8 mg) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B
Claghorn92A Y O C H21	Double-blind RCT Concealment of Allocation: unclear Analysis: not clear, but irrelevant as efficacy data not extractable Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 18+ on HRSD-21; mean baseline HRSD: Paroxetine group 25 (+-0.59); Placebo group 24.6 (+-0.65) Mean age: approximately 35 years (18-65). N=72 (71 in efficacy sample), 23 women Country: US Setting: Outpatient	Paroxetine (mean 28.3 mg) versus placebo	1. HRSD mean endpoint scores * 2. Non-responders (patients not achieving ≥50% reduction in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects	* from Claghorn1992	B
Cohn1985 Y O I	Allocation: Random (no details) Duration: 6 weeks (+1 week washout) Analysis: ITT	N=166. 98 female. Age: 20-64. Diagnosis: DSM-III major depression, HRSD≥20. Setting: Outpatient.	1. Fluoxetine (20-80mg) 2. Placebo 3. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects	Same protocol as Stark 1985 but different patients.	B
Coleman01 Y O I	Allocation: Random (no details) Duration: 8 weeks (+1 week washout) Analysis: ITT (≥1 assessment post-baseline)	Outpatients. N=456 (HRSD analysis: N=427). Age: 18-76, mean=36.6-37.1. Diagnosis: DSM-IV moderate-severe recurrent major depression, HRSD-21≥20. Mean baseline HRSD: Placebo - 24.4, fluoxetine - 24.5 (ITT sample).	1. Fluoxetine (20-60mg, mean=26mg) 2. Placebo 3. Bupropion SR	1. Leaving the study early 2. Leaving the study early due to side effects	Extracted data for 1 and 2 only.	B

Coleman1999 Y M I	Double-blind RCT Concealment of Allocation: unclear Analysis: ITT (≥ 1 dose of medication and ≥ 1 post- baseline assessment Active treatment: 8 weeks	Inclusion Criteria: DSM-IV recurrent moderate to severe depression, 18+ on HRSD-31; mean baseline HRSD: 34; all in stable relationship (sexual function was focus of study) Age: 18-74; mean 38 years. N=242 (without bupropion group) Country: US Setting: Classified as 'mixed' as not clear	Sertraline versus placebo (versus bupropion - not extracted) (sertraline: mean 106 mg/ day)	1. Non-responders (patients not achieving $\geq 50\%$ reduction in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects	Undertaken in 11 centres.	B
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Conti1988 Y I	Allocation: Random (no details) Duration: 4 weeks (+3-7 day washout)	Inpatients. N=45, all female. Age: 18+, mean=53. Diagnosis: DSM-III major depressive episode, HRSD \geq 16	1. Fluvoxamine (50-300mg, mean=273mg) 2. Placebo	1. Leaving the study early 1. Leaving the study early due to side effects	Originally part of Amin 1984 multi-centre trial, but not included in that data and published separately.	B
Croft1999 Y M I	Double-blind RCT Concealment of Allocation: unclear Analysis: ITT (\geq 1 dose of medication and \geq 1 post-baseline assessment) Active treatment: 8 weeks	Inclusion Criteria: DSM IV moderate to severe depression, 18+ on HRSD-31; mean baseline HRSD: 32.78; all in stable relationship (sexual function was focus of study) Age: 19-30. N=360, HRSD analysis: N=348 Country: US Setting: Classified as 'mixed' as not clear	Sertraline versus placebo (versus bupropion - not extracted) (sertraline: mean 121 mg/day)	1. Non-responders (patients not achieving \geq 50% reduction in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects	Undertaken in 8 centres.	B
Dominguez85 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active treatment: 4 weeks	Inclusion Criteria: DSM-III major depression Age: 21-64 years; N=101 Country: America Setting: Outpatient	1. Fluvoxamine (100-300mg) 2. Imipramine 3. Placebo	1. Leaving the study early	Leaving study early due to side effects and mean endpoint data included in Kasper 1995.	B
Dunlop1990 Y O I	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=372. 58% female. Age: 19-70, mean=39.3. DSM-III major depressive disorder, HRSD \geq 14 and \leq 19. Raskin > Covi anxiety score	1. Fluoxetine (20mg) 2. Fluoxetine (40mg) 3. Fluoxetine (60mg) 4. Placebo	1. HRSD mean change scores (20mg only) 2. Non-responders (patients not achieving \geq 50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects	Dichotomous data is combined for 20, 40 and 60mg groups.	B
Edwards93 Y O I H17	Allocation: Random (no details). Duration: 6 weeks. Analysis: ITT	Outpatients. N=41. 23 female. Age: 18-65, mean=44. Diagnosis: DSM-III major depression (all but 3 patients met the criteria) or Feighner criteria definite depression (all but 3 met this criteria), HRSD-17 \geq 18.	1. Paroxetine (30mg) 2. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B

Fabre 1996 Y O I	Allocation: Random (no details). Duration: 6 weeks (+ 7-14 day placebo washout). Analysis: ITT (≥ 1 dose & ≥ 1 post-	Outpatients. N=150. Age: 18-65. Diagnosis: DSM-III major depressive disorder, HRSD-21 \geq 20, Raskin depression \geq 8 and > Covi anxiety score	1. Fluvoxamine (mean at week 6 =117mg) 2. Placebo 3. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects		B
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	baseline assessment)					
Fabre95 Y M I H17	Double-blind RCT Concealment of Allocation: unclear Analysis: ITT (≥ 1 dose of medication and ≥ 1 post-baseline assessment) Active treatment: 6 weeks	Inclusion Criteria: DSM-III for major depressive episode (2% bipolar), 22+ on HRSD-17; mean baseline HRSD: 24.8 to 25.7 Age: mean 37; 149 women. N=277, HRSD analysis: N=258 Country: US Setting: Classified as 'mixed' as not clear	Sertraline (3 groups) versus placebo Group 1: mean 50mg (not extracted); Group 2: mean 98mg; Group 3: mean 190 mg* Dichotomous outcomes: Groups 2 and 3 added; Continuous outcomes: Group 2 only	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	* overall mean dose for 100mg + 200mg groups is 144mg	B
Feighner1989 Y I I	Allocation: Random (no details). Duration: 6 weeks (+3 day placebo washout). Analysis: ITT	Inpatients. N=86, 85% female. Age: 18-71, mean=41. Diagnosis: DSM-III major depression	1. Fluvoxamine (150-300mg, mean=145mg) 2. Placebo 3. Imipramine	1. Leaving the study early due to side effects		B
Feighner99 C Y O I	Allocation: Random no details. Duration 6 weeks (+ 1 week placebo washout) Analysis: LOCF	N=650. Aged 18-65. Diagnosis: DSM-III-R major depression, HRSD-21 \geq 20. Baseline scores: All Citalopram - MADRS=27.5, HRSD-21=24.6 Placebo - MADRS=27.1, HRSD-21=24.6. Setting: Outpatients.	1. Citalopram (10mg) 2. Citalopram (20mg) 3. Citalopram (40mg) 4. Citalopram (60mg) 5. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B
Feighner89a Y O E H21	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥ 2 weeks treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 20+ HRSD (21), 8+ Raskin scale, and greater than Covi Age: 18-70. N=179, HRSD analysis: N=145 Country: US Setting: Outpatients	Fluoxetine versus imipramine (72% achieved >150mg) versus placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B
Feighner92 Y O I H21	Random (no details). Duration: 6 weeks. Analysis: ITT (> 1 post baseline efficacy)	Outpatients. N=726. Age: 18-65, mean=40. Diagnosis: DSM-III major depressive episode, HRSD-17 \geq 18. Raskin depression > Covi anxiety score. Mean Baseline HRSD: Paroxetine - 26.4, placebo - 26.6	1. Paroxetine (10-20mg, mean = 28.7-45.5mg) 2. Placebo 3. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects		B
Hackett96 Y O I H21	Double-blind RCT Concealment of	Inclusion Criteria: DSM-III-R major depression, HRSD-21 \geq 20	Paroxetine versus venlafaxine (150mg)	1. HRSD-21 mean endpoint scores		B

	Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Age: 18+ Country: Europe Setting: Outpatients. Mean baseline HRSD=26.6				
Itil 1983 Y O E H16	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: RDC major affective disorder Age: 21-68. N=69, HRSD analysis: N=37 Country: US Setting: Outpatients	Fluvoxamine versus imipramine (50mg -> 150mg on day 3, up to 300mg on day 8, mean=127mg +/- 46mg) versus placebo	1. Leaving the study early 1. Leaving the study early due to side effects	4% patients diagnosed with bipolar disorder.	B
Kasper95 Y M I H16	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active treatment: 4 weeks	Inclusion Criteria: DSM-III major depression or DSM-III bipolar disorder (14%) Age: 42.3 years; N=338, HRSD analysis: N=313 Country: Canada and America Setting: Mixed	3-7 day washout; inpatients received study medication for at least 2 weeks in hospital; after gradually increasing dose during first 3 days, dose range 50-300mg/day t.i.d. 1. Fluvoxamine: Mean dose 158.5 mg 2. Imipramine: Mean dose 151 mg (data not extracted) 3. Placebo	1. HRSD-16 mean endpoint scores (17 item scale, but 'loss of weight' item not included because of difficulties in interpreting changes in body weight, so only 16 items used) 2. Leaving the study early due to side effects	Paper reports on 5 N. American centres in Amin1984 (no extractable data) which include Dominguez 1985 and Lapierre1987. Therefore the data here includes patients from those studies along with the remaining 3 centres.	B
Lapierre1987 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 15+ HRSD Age: 20-69. N=63, HRSD analysis: N=10 Country: Canada Setting: Inpatients	1. Fluvoxamine (50-300mg, mean=180.3mg) 2. Imipramine 3. Placebo	1. Leaving the study early	Leaving study early due to side effects and mean endpoint data included in Kasper 1995.	B
Lydiard1989 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 22+ HRSD Age: 18+. N=54, HRSD analysis: N=52. Country: US Setting: Outpatients	1. Fluvoxamine (100-300mg, mode=240+-60mg) 2. Imipramine 3. Placebo	1. Non-responders (patients not achieving ≥50% decrease in HRSD and at least 'much improved' on CGI) 2. Leaving the study early due to side effects		B

McGrath00 Y M I H17	Allocation: Random (no details) Duration: 10	Setting unclear. N=154. Age: 18-65, mean=41.6 yrs. Diagnosis: DSM-IV	Fluoxetine(mean=51.4+ -14.6mg) versus	HRSD-17 mean endpoint scores		B
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	weeks. Analysis: ITT-LOCF	major depressive episode and Columbia criteria for atypical depression	Imipramine (50mg->300mg, mean=204.9+-90.7mg) versus placebo			
Mendels 1999 C Y O I	Allocation: Random no details. Duration 4 weeks (+ 1 week placebo washout) Analysis: LOCF	Outpatients. N=180. Mean age = 43. Diagnosis: DSM-III melancholia plus DSM-III major depression or bipolar, depressed‡. HRSD-24≥25. Baseline scores: Citalopram - HRSD-17=23.9+-3.2. Placebo - HRSD-17=24.1+-3.5	1. Citalopram (20mg up to 80mg) 2. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	‡ only 9/180 (5%) patients were diagnosed bipolar (depressed). Conducted at 3 centres in the US.	B
Miller1989 Y O ?	Double-blind RCT Concealment of Allocation: unclear Analysis: not clear, but irrelevant as efficacy data not extractable Active treatment: 4 weeks	Inclusion Criteria: Feighner criteria for depression, 18+ on HRSD-21; mean baseline HRSD: Paroxetine group 22.7; Placebo group 24.2 Mean age: 42 years. N=47, 32 women Country: UK Setting: Outpatient	Paroxetine (mean 30 mg) versus placebo	1. Leaving the study early 1. Leaving the study early due to side effects		B
Mont'mery01C Y P I	Allocation: Random no details. Duration 8 weeks (+ 1 week placebo washout) Analysis: LOCF	Primary care patients. N=471. Mean age 43 +- 11. Diagnosis: DSM-IV major depressive disorder, MADRS ≥22 & ≤40. Baseline scores: Escitalopram - MADRS=29. Citalopram - MADRS=29.2 Placebo - MADRS=28.7	1. Escitalopram (10mg up to 20mg) 2. Citalopram (20mg up to 40mg) 3. Placebo (1 not extracted)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	Conducted at 69 primary care centres in Europe.	B
Mont'mery92A C Y M I	Allocation: Random no details. Duration 6 weeks (+ 1 week placebo washout) Analysis: LOCF	Inpatients and outpatients. N=199, 138 female. Aged 19-72, mean age 44. Diagnosis: DSM-III-R major depression, MADRS≥22	1. Citalopram (20mg) 2. Citalopram (40mg) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	Conducted in the UK.	B

Norton1984 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 4 weeks	Inclusion Criteria: RDC for major depressive disorder (probable or definite), 15+ HRSD Age: 18-65. N=91, HRSD analysis: N=88 Country: UK Setting: Outpatients	Fluvoxamine versus imipramine (50mg -> 100mg on day 5, up to ? on day 8, mean in week 4=153.3) versus placebo	1. Leaving the study early due to side effects 2. Leaving the study early	This study is included in Amin1984 (data not extractable) but is not one of the centres included in Kasper95.	B
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O'Flynn1991 Y O I	Allocation: Random (no details) Duration: 4 weeks Analysis: ITT	Outpatients. N=12. 50% female. Age: 34-56. Diagnosis: DSM-III-R major depression - unipolar, nonpsychotic, HRSD \geq 17	Fluoxetine (20mg) placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD \leq 7) 3. HRSD mean endpoint scores	All patients underwent a desipramine/ growth hormone stimulation test prior to treatment.	B
Ravindram 1995 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (\geq 11 days treatment) Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depression (mild to moderate severity), 15+ on HRSD Age: 18-65. N=103, HRSD analysis: N=86 Country: Canada Setting: Outpatients	Sertraline versus desipramine (50-225mg, mean after week 4=163.75mg) versus placebo	1. Leaving the study early 2. Leaving the study due to side effects 3. Patients reporting side effects		B
Reimherr90 Y O I H17	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 18+ HRSD (18) without 25% reduction during washout, higher score on Raskin than Covi Age: 18-65. N=448, HRSD analysis: N= 376. Country: US Setting: Outpatients	Sertraline (50-200mg, mean=145mg) versus amitriptyline (50mg, up to 150mg by day 21, mean = 111mg) versus placebo	1. HRSD mean change scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving \geq 50% decrease in HRSD)	*extracted data for the 'all patients' group.	B
Rickels1986 Y M ?	Allocation: Random (no details) Duration: 5 weeks Analysis:	N=42. 79% female. Age: 21-70, mean=47.2+-13. Diagnosis: DSM-III unipolar major depressive disorder, HRSD \geq 20, Raskin \geq 8.	1. Fluoxetine (20-80mg) 2. Placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Leaving the study early 3. Patients reporting side effects		B
Rickels1989 Y O I	Double-blind RCT Concealment of Allocation: unclear Analysis: ITT. Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 18+ on HRSD-17; mean baseline HRSD: 26 (+-5) Mean age: 44 years. N=111, 62% female Country: US Setting: Outpatient	Paroxetine (mean 40 (+-10)) versus placebo (Allowed chloral hydrate for insomnia in first 2 weeks)	1. Non-responders (patients not achieving \geq 50% reduction in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B

Rickels1992 Y O C	Double-blind RCT Concealment of Allocation: unclear Analysis: Completer Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 18+ on HRSD-17; mean baseline HRSD: paroxetine 26.8 (SE+ 0.77), placebo 25.9 (SE+0.73); Mean age: Paroxetine: 43.4 years; Placebo: 46 years. N=111, 53 female Country: US	Paroxetine (mean 31.5 (SE+1.25) versus placebo (Allowed chloral hydrate for insomnia in first 2 weeks)	1. Non-responders (patients not achieving ≥50% reduction in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects (efficacy sample only - data not available for large number of participants due to concomitant		B
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		Setting: Outpatient		medication)		
Roth90 Y O E H17	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥3 weeks treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 22+ HRSD Age: 18+. N=90, HRSD analysis: N=80. Country: USA Setting: Outpatients	Fluvoxamine versus desipramine (50mg -> 100mg by day 14, 100- 300mg thereafter, mean at week 3 =195.8mg, mean at week 6 =224.6) versus placebo	1. HRSD mean endpoint scores 2. Leaving the study early		B
Rudolph99 Y O I H21	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion Criteria: DSM-IV major depressive disorder, HRSD-21 ≥ 20 Age: 18-40, mean=40 Country: US Setting: outpatient	Fluoxetine (20-60mg, mean = 47mg) versus venlafaxine XR (75- 225mg, mean = 175mg)	1. HRSD-21 mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Non-remitters 4. Leaving the study early 5. Leaving the study early due to side effects		B
Sil'stne99 Y O I H21	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 12 weeks	Inclusion Criteria: DSM-IV major depressive disorder, HRSD-17 ≥ 20 Age: 18-71. Country: Setting: Outpatients	Fluoxetine versus venlafaxine SR (mean = 111.2mg in week 4)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Non-responders (patients not achieving ≥50% decrease in HRSD) 4. Leaving the study early due to side effects 5. Patients reporting side effects		B
Smith1992 Y M I	Double-blind RCT Concealment of Allocation: unclear Analysis: ITT Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 18+ on HRSD-17; mean baseline HRSD: paroxetine 28.6 (SE+ 0.77), placebo 28.9 (SE+0.77); Age: mean 44 years. N=77, Female: paroxetine 44%, placebo 55% Country: US Setting: Classified as 'mixed' as not clear	Paroxetine (mean 33.8 mg/day) versus placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B
Sramek 95 Y M ? H24	Allocation: Random (no details) Duration: 9 weeks (+1 week washout)	Age: 18-65. N=216. Diagnosis: DSM- III-R major depressive disorder, HRSD-24≥21	1. Fluoxetine (20mg) 2. Placebo 3. ABT-200	1. HRSD mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects		B
Stahl00 Y M I H21	Allocation: Random no details. Duration 24 weeks (+ 1	Inpatients and outpatients. N=323, aged 18-60. Diagnosis: DSM-IV major depressive	1. Citalopram (20mg up to 60mg) 2. Sertraline	1. Leaving the study early 2. Leaving the study early due to side effects	Conducted at 8 centres in the US.	B 5

	week placebo washout) Analysis: LOCF	disorder, HRSD-17≥22. Baseline scores: Citalopram - MADRS=32.4, HRSD-21=26.5. Placebo - MADRS=31.1, HRSD-21=26.4	3. Placebo	3. Patients reporting side effects		
Stark85 Y O I H21	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥ 1 post baseline assessment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III unipolar major depressive disorder for 4 weeks, 20+ HRSD (21), less than 20% reduction in HRSD during wash out period, 8+ on Raskin Scale, and greater than Covi scale. Age: 18-70. N=540, HRSD analysis: N=539. Country: US Setting: Outpatients	Fluoxetine versus imipramine (125mg at day 4, up to 300mg thereafter) versus placebo	1. Leaving the study early 2. Leaving the study early due to side effects		B
Thakore1995 Y O I	Allocation: Random (no details) Duration: 4 weeks Analysis: ITT	Outpatients (83%) and inpatients. N=12. 50% female. Age: 18-65, mean=44.3. Diagnosis: DSM-III-R major depression, HRSD≥17	Fluoxetine (20mg) placebo	1. HRSD mean endpoint scores	All patients underwent dexamethosone- induced growth hormone stimulation before randomisation.	B
Valducci1992 Y M I	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT	Unclear setting. N=40, 23 female. Age: 19-67. Diagnosis: DSM-III-R major depression, HRSD≥18	1. Fluoxetine (20mg) 2. Placebo	1. Non-responders (patients not achieving ≥50% decrease in HRSD) 2. Patients reporting side effects		B
Walczak1996 Y M C	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 7-8 weeks	Inclusion Criteria: DSM-III-R Major depressive disorder Age: 31-50. N=600, HRSD analysis: N=351 Country: US Setting: Mixed Participants recruited from 10 independent centres	1. Fluvoxamine 25 mg 2. Fluvoxamine 50 mg 3. Fluvoxamine 100 mg (mean at week 6=100mg) 4. Fluvoxamine 150 mg (mean at week 6=149.22mg) 5. Placebo Data extracted only for 150mg dose group	1. Leaving the study early 2. Leaving the study early due to side effects		B
Wernicke1987	Allocation: Random (no	Outpatients. Age: 18-65, mean=39.8.	1. Fluoxetine (20mg)	1. HRSD mean change scores (20mg	Dichotomous data is	B

Y O I	details) Duration: 6 weeks	N=356 (HRSD analysis: N=345). Diagnosis: DSM-III unipolar major depressive disorder, HRSD \geq 20,	2. Fluoxetine (40mg) 3. Fluoxetine (60mg) 4. Placebo	only) 2. Non-responders (patients not achieving \geq 50% decrease in HRSD)	combined for 20, 40 and 60mg groups.	
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		Raskin depression score > Covi anxiety score		3. Leaving study early 4. Leaving study early due to side effects		
Wernicke1988 Y O I	Allocation: Random (no details) Duration: 6 weeks (+1 wk washout) Analysis: ITT (≥1 post-baseline assessment).	Outpatients. Age: 18-65, mean=39. N=363 (HRSD analysis: 61% female). Diagnosis: DSM-III unipolar depression, HRSD≥20	1. Fluoxetine (5mg) 2. Fluoxetine (20mg) 3. Fluoxetine (40mg) 4. Placebo	1. HRSD mean change scores (20mg only) 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving study early 4. Leaving study early due to side effects	Dichotomous data is combined for 20 and 40mg groups.	B

Characteristics of excluded studies

Study	Reason for exclusion
Anisman1999 Y M I	100% Dysthymia
Bakish2000	No placebo arm
Bastos1996	Not an RCT (in Portuguese - paper evaluated by native speaker)
Baumann1996	Not a relevant comparison (all patients were treated with citalopram then randomised to receive additionally placebo or lithium if they were unresponsive)
Bhagwagar2002	Not a relevant comparison (compared depressed patients with recovered patients with healthy controls)
Brunner1994	No placebo control group
Cetin1994	Paper is in Turkish unable to assess eligibility
Cook1999	All patients were receiving supportive psychotherapy
Corrigan2000	Patients on psychotherapy or behaviour therapy were allowed to continue whilst taking part in the study, number not specified, therefore unable to determine whether there was an even distribution between treatment groups of patients receiving therapy
Danjou1994	No placebo arm
Davidson02 YOI A/L P	Inadequate dose of sertraline (50-100mg)
Doogan1994	Patients on inadequate dose of sertraline (only 24% received ≥100mg)
Evans1997	Inadequate diagnosis of depression
Fabre1985	Inadequate diagnosis of depression
Fieve1986	No extractable data
Gacgoud1992	No placebo control group
Golden02 Y M I H17	Unable to ascertain how many patients were randomised to each treatment group, therefore unable to extract any data

Gottfries1992	Inadequate diagnosis and some patients with dementia
Guy1986	Not clear if randomised; very small sample (N=4 for placebo arm)

Harto1988	No extractable data
Heiligenstein1993	Patients were classified as unipolar depressed or bipolar type II depressed according to RDC, number of bipolar patients not specified
Hellerstein2000 YMI	100% Dysthymia
Hoch'sser01 Cm Y M I	Maintenance phase treatment only
Hochberg1995	1 year extension to a 6-week trial on cardiographic findings; unable to locate publication of acute phase trial.
Johnson1993	No extractable data
Kerr1993	No placebo arm
Kiev1992 Y O C	Unable to ascertain how many patients were randomised to each treatment group, therefore unable to extract any data
Klysner02 Cm E O I	Maintenance treatment phase only
Lam1995 Y O I H21	Patients were diagnosed with recurrent major depressive episode with a seasonal pattern
Lundbeck1995	Unable to locate published report
Mont'mery93B Cm ?M I	Maintenance treatment phase only
Montgomery1988	Maintenance phase study; all patients in acute phase received fluoxetine.
Moon1993	Abstract only; unable to obtain full publication.
New1999	No extractable data
Nyth1992	Inadequate diagnosis and 19% of patients had comorbid dementia
Olie1997 Y O I	Unclear whether patients received an adequate dose of sertraline ('83% received doses of either 50mg or 100mg'); 88% of sertraline group and 89% of placebo group on concomitant medication, including benzodiazepines
Pande1999	Unable to establish number of patients randomised to each group
Peselow1986 ? I I	Paper gives results of 2 trials combined (sertraline vs placebo and oxaprotiline vs placebo) - not possible to separate results by active drug
Puzynski1994	Paper is in Polish unable to assess eligibility
Rausch2002	No placebo arm
Ravindran1999	100% Dysthymia
Reimherr1984	Fluoxetine results from the double-blind study are combined with those from an open trial
Reynaert1993	No placebo arm
Robert1995 Cm Y M I	Maintenance treatment phase only
Ruhrmann1998	No placebo arm
Sacchetti1997	No placebo control group
Schneider03 EO I H17	Some participants on HRT
Thompson1991	Patients on inadequate dose of sertraline (only 27% received $\geq 100\text{mg}$)
Thompson1994 Y P I	Sertraline given at sub-therapeutic dose - 76% patients on 50mg

von Bardeleben1989	There were only 2/14 patients in the placebo arm
Wade2002 E Y P I	No citalopram arm - escitalopram versus placebo
Wakelin1986	Sub-analysis of elderly patients from Amin1984, Itil1983 and Block1983
White1990	Reports results of crossover from desipramine to fluvoxamine in desipramine non-responders; unable to locate publication of acute phase trial

TCAs versus placebo - new studies in the guideline update

Comparisons Included in this Clinical Question

Amitriptyline vs placebo
AMSTERDAM2003A
BAKISH1992B
BAKISH1992C
BREMNER1995
CLAGHORN1983
CLAGHORN1983B
FEIGHNER1979
GELENBERG1990
GEORGOTAS1982A
GOLDBERG1980
HICKS1988
HOLLYMAN1988
HORMAZABAL1985
HOSCHL1989
KLIESER1988
LAAKMAN1995
LAPIERRE1991
LYDIARD1997
MYNORSWALLIS1995
MYNORSWALLIS1997
REIMHERR1990
RICKELS1982D
RICKELS1985
RICKELS1991
ROFFMAN1982
ROWAN1982
SMITH1990
SPRING1992
STASSEN1993
WILCOX1994

Clomipramine vs placebo
LARSEN1989
PECKNOLD1976B
RAMPELLO1991

Dosulepin (dothiepin) vs placebo
FERGUSON1994B
ITIL1993
MINDHAM1991
THOMPSON2001B

Imipramine vs placebo

BARGESCHAAPVELD2002
BEASLEY1991B
BOYER1996A
BYERLEY1988
CASSANO1986
CASSANO1996
CLAGHORN1996A
COHN1984
COHN1985
COHN1990A
COHN1992
COHN1996
DOMINGUEZ1981
DOMINGUEZ1985
DUNBAR1991
ELKIN1989
ENTSUAH1994
ESCOBAR1980
FABRE1980
FABRE1992
FABRE1996
FEIGER1996A
FEIGHNER1980
FEIGHNER1982
FEIGHNER1983A
FEIGHNER1983B
FEIGHNER1989
FEIGHNER1989A
FEIGHNER1989B
FEIGHNER1989C
FEIGHNER1992B
FEIGHNER1993
FONTAINE1994
GELENBERG2002
GERNER1980B
HAYES1983
ITIL1983A
KASPER1995B
KELLAMS1979
LAIRD1993
LAPIERRE1987
LECRUBIER1997B
LIPMAN1986
LYDIARD1989
MARCH1990
MARKOWITZ1985
MENDELS1986

MERIDETH1983
 NANDI1976
 NORTON1984
 PEDERSEN2002
 PESELOW1989
 PESELOW1989B
 PHILIPP1999
 QUITKIN1989
 RICKELS1981
 RICKELS1982A
 RICKELS1987
 SCHWEIZER1994
 SCHWEIZER1998
 SHRIVASTAVA1992
 SILVERSTONE1994
 SMALL1981
 UCHA1990
 VERSIANI1989
 VERSIANI1990
 WAKELIN1986

Nortriptyline vs placebo
 GEORGOTAS1986A
 KATZ1990
 NAIR1995
 WHITE1984A

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
<p>AMSTERDAM2003A</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; zimeldine vs amitriptyline vs placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 158</p> <p>Age: Mean 41 Range 21-67</p> <p>Sex: 95 males 63 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Symptoms or a history of schizophrenia, acute mania (or a history of bipolar I disorder), dementia, mental retardation, substance misuse, significant medical illness which might contraindicate the use of TCA, significant hepatic, renal, endocrine or cardiovascular disorders.</p> <p>Notes: amitriptyline (55) + placebo (54) = 109 participants. amitriptyline (38M: 17F) and placebo (31M: 19F).</p> <p>Baseline: Zimeldine Amitriptyline Placebo Total HRSD-21 25.1 (5.8) 24.5 (4.2) 23.4 (4.9) 24.3 (5.0)</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 55</p> <p>Amitriptyline. Mean dose 182mg/day - Days 1-3: 100mg/day. Days 4-7: 200mg/day. From thereon, could be increased to 300mg/day.</p> <p>Group 2 N= 54</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Astra Pharmaceutical).</p>
<p>BAKISH1992B</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; moclobemide vs amitriptyline vs placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; Canada.</p> <p>Notes: Participants had to weigh within 20% of</p>	<p>n= 55</p> <p>Age: Mean 39 Range 20-63</p> <p>Sex: 23 males 32 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Women in their childbearing years who were not using an effective form of contraception, were pregnant or lactating, or were at risk of committing suicide. Patients who</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean change</p>	<p>Group 1 N= 19</p> <p>Amitriptyline. Mean dose 132mg/day - 50-150mg/day. Increased incrementally by 25mg up until the 4th week.</p> <p>Group 2 N= 18</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>

	<p>disorders, mental retardation, narrow angle glaucoma, or increased intraocular pressure, had a history of urinary retention or a renal, cardiovascular, respiratory, gastrointestinal, hematopoietic or cerebral disease, severe hypertension, had a suspected sensitivity to MAOI or TCA medications or had a recent history of drug or alcohol misuse. Patients who had been treated with MAOIs during the previous 2 weeks, had been treated with a TCA during the previous week, had been treated with ECT during the preceding 6 months, or were concomitantly using an antihypertensive, diuretic anticholinergic or sympathomimetic agent.</p> <p>Notes: amitriptyline (19) + placebo (18) = 37 participants. amitriptyline (14F:5M) and placebo (8F:10M).</p> <p>Baseline: Amitriptyline Moclobemide Placebo HAM-D (17) 22.37 22.94 23.35</p>			
<p>BAKISH1992C</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; moclobemide vs amitriptyline vs placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 49</p> <p>Setting: Outpatients; multicentre, Canada.</p> <p>Notes: 4 participants excluded from analysis because they failed to return after baseline. 173 participants were initially randomised.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 169</p> <p>Age: Mean 43 Range 19-64</p> <p>Sex: 95 males 74 females</p> <p>Diagnosis:</p> <p>98% Major depressive disorder by DSM-III-R</p> <p>1% Depression by Bipolar disorder</p> <p>1% Dysthymia by DSM-III-R</p> <p>Exclusions: High suicidal risk, depression associated with mood-incongruent psychotic features, manic or acute confusional states, significant organic disease, alcohol or drug misuse, and recent MAOI (within the past 2 weeks), TCA (within the past week), or ECT treatment (within the past 6 months). Women with childbearing potential who were not using an effective form of contraception and women who were pregnant or lactating. Concomitant use of antihypertensive, diuretic, anticholinergic, or pathomimetic agents prohibited.</p> <p>Notes: Amitriptyline (57) + Placebo (55) = 112 participants. Amitriptyline (28F:29M) and Placebo (20F:35M).</p> <p>Baseline: Moclobemide Amitriptyline Placebo HAM-D (17) 23.79 22.81 23.04</p>	<p>Data Used</p> <p>Weight mean change (kg)</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 58</p> <p>Amitriptyline. Mean dose 112mg/day - 50-150mg/day. 2 capsules 3 times/day. Doses were individually titrated up to an optimum over a period of 2 weeks, depending on tolerability.</p> <p>Group 2 N= 55</p> <p>Placebo - 2 capsules 3 times/day. Doses were individually titrated up to an optimum over a period of 2 weeks, depending on tolerability.</p>	<p>Funding; unknown.</p>
<p>BARGESCHAAPVELD2002</p>				

<p>Study Type: RCT</p> <p>Study Description: 2-arm study; imipramine vs placebo</p> <p>Type of Analysis: Completers (completed 1st week)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multiple primary care settings, the Netherlands.</p> <p>Info on Screening Process: 83 participants recruited. 9 did not meet inclusion criteria and 11 did not have sufficient data during the baseline sampling period. 1 participant withdrew consent and 3 participants dropped</p>	<p>n= 63</p> <p>Age: Mean 43 Range 25-59</p> <p>Sex: 17 males 46 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Current use of psychotropic medications and major medical disorders.</p> <p>Notes: Imipramine (32) + Placebo (31) = 63 participants. MDD also diagnosed by DSM-IV.</p> <p>Baseline: Imipramine Placebo HAM-D (17) 24.0 (3.5) 23.5 (2.6)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 29</p> <p>Imipramine - 50-200mg/day in the first week. Could be reduced to 100mg/day if poorly tolerated.</p> <p>Group 2 N= 30</p> <p>Placebo - 1-4 capsules/day in week 1.</p>	<p>Funding; part-pharma (Solvay Pharmaceuticals).</p>
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out in the first week.				
BEASLEY1991B				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; fluoxetine vs imipramine vs placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Patients were given chloral hydrate or flurazepam for sleep.</p> <p>Info on Screening Process: 706 entered study. 698 completed. 7 rated as both agitated and retarded, and 1 was not rated with respect to baseline psychomotor activity status and were dropped from the analysis.</p>	<p>n= 706</p> <p>Age: Mean 41</p> <p>Sex: 244 males 462 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-II</p> <p>Exclusions: Patients with bipolar illness, psychosis or active substance misuse.</p> <p>Notes: Imipramine (238) + Placebo (225) = 463 participants. Imipramine (159F:79M) and Placebo (140F:85M). Duration of current episode was at least 4 weeks. Split into agitated, retarded and neither.</p> <p>Baseline: HAM-D (21): 27.3</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>HRSD-21 mean endpoint</p> <p>Notes: 2 Fluox, 5 Imip and 3 Pbo participants discontinued prior to completing 1 visit - excluded from efficacy data</p>	<p>Group 1 N= 238</p> <p>Imipramine. Mean dose 205.6mg/day - Raised to 125mg/day by day 4 unless patients did not tolerate such an increase. From thereon, dose could be adjusted to a maximum of 300mg/day.</p> <p>Group 2 N= 225</p> <p>Placebo - No details.</p>	<p>Funding: part-pharma (Eli Lilly, Lilly Research Laboratories). Participants received =>4 weeks of treatment</p>
BOYER1996A				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; imipramine vs amisulpride vs placebo</p> <p>Type of Analysis: Both</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 168</p> <p>Setting: Outpatients, multicentre; France.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 219</p> <p>Age: Mean 43</p> <p>Sex: 99 males 120 females</p> <p>Diagnosis: 100% Dysthymia by DSM-III</p> <p>Exclusions: Other psychiatric disorders, risk of suicide, chronic misuse of alcohol or other substances, contraindication to treatment with imipramine or amisulpride. Severe somatic disease, pregnancy or lactation, participation in a therapeutic trial within 30 days of the current study, treatment with one of the two active study drugs within three months before inclusion in the current study, treatment with an antidepressant of a dosage greater than 50mg per day clomipramine-equivalent within one month before the study.</p> <p>Notes: Participants also had either or also major depression of mild or moderate severity in conjunction with primary dysthymia, or isolated major depression in partial remission. Imipramine (73) + Placebo (73) = 146 participants.</p> <p>Baseline: MADRS: 17.9 (.26)</p>	<p>Data Used</p> <p>MADRS mean change</p>	<p>Group 1 N= 73</p> <p>Imipramine. Mean dose 100mg/day - No details.</p> <p>Group 2 N= 73</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
BREMNER1995				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; mirtazapine vs amitriptyline vs placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 150</p> <p>Age: Mean 38 Range 18-93</p> <p>Sex: 48 males 102 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Primary diagnosis of schizophrenia (atypical depressive type), bipolar disorder, or adjustment disorder, anxiety as the primary disorder, known active suicidal tendencies, known cognitive deficiencies, and known alcohol or drug misuse within the last 6 months. Symptoms or a history of the following diseases; hepatic, relevant renal, respiratory, cardiovascular, or cerebrovascular diseases, narrow-angle glaucoma, clinically significant prostatic</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>MADRS mean endpoint - no data</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 50</p> <p>Amitriptyline - Week 1: 40-80mg/day, week 2: 40-160mg/day and weeks 3-6: 40-280mg/day.</p> <p>Group 2 N= 50</p> <p>Placebo - Week 1: 1-2 capsules/day, week 2: 1-4 capsules/day, and weeks 3-6: 1-7 capsules/day.</p>	<p>Funding; pharma (Organon, Inc.).</p>
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	<p>hypersensitivity reaction to TCAs or related compounds, hyperthyroidism, and clinically significant abnormal EEG. Women who were pregnant or intended to become pregnant during the study or were practicing a method of birth control assessed as unreliable by the investigators and nursing mothers. Patients who required treatment with concomitant psychotropic medication and those treated with ECT within 3 months of baseline, MAOIs within 14 days prior to baseline, study medication within 30 days of baseline or other psychotropic medication including antidepressants within 7 days of baseline.</p> <p>Notes: Amitriptyline (50) + Placebo (50) = 100 participants. Amitriptyline (37F:13M) and Placebo (35F:15M).</p> <p>Baseline: Amitriptyline Org 3770 Placebo HAM-D (17) 27.3 28.3 26.6 MADRS 36.4 37.7 36.6</p>			
<p>BYERLEY1988</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluoxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers (had to have had 2 weeks treatment)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Notes: Randomisation was carried out using a table of randomised numbers.</p> <p>Info on Screening Process: 103 participants entered; 6 excluded. 5 improved significantly during the washout period whilst 1 had an abnormal ECG.</p>	<p>n= 97</p> <p>Age: Mean 39</p> <p>Sex: 33 males 64 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients with psychotic symptoms, bipolar illness, schizophrenia, active drug or alcohol misuse, or significant medical illnesses.</p> <p>Notes: Imipramine (34) + Placebo (29) = 63 participants. Imipramine (21F:13M) and Placebo (18F:11M).</p> <p>Baseline: Imipramine Fluoxetine Placebo HAM-D (21) 28.3 (4.2) 27.2 (4.9) 27.3 (4.6)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Weight mean change (kg)</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 34</p> <p>Imipramine - 75-300mg/day. Patients took capsules three times a day for up to 6 weeks. Rate of increase depended on severity of adverse effect.</p> <p>Group 2 N= 29</p> <p>Placebo - Patients took capsules three times a day for up to 6 weeks.</p>	<p>Funding; pharma (Eli Lilly, Inc.) and research.</p>
<p>CASSANO1986</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Fluvoxamine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Mixed; multicentre, US, Canada, England, Italy and France.</p> <p>Notes: 481 participants entered study. 448 included in analysis because had at least 2 evaluations.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 448</p> <p>Age: Mean 42</p> <p>Sex: 162 males 286 females</p> <p>Diagnosis: 100% Major depressive disorder by No details</p> <p>Exclusions: Childbearing potential or pregnant women, antidepressant therapy in the past 2 weeks, electroconvulsive therapy within the last month, depressive symptoms secondary to other psychiatric illness, dependence upon licit or illicit drugs, serious organic diseases, need for concurrent medications which could interact with the study drugs or obscure their effects, and patients unwilling or unable to cooperate in the study.</p> <p>Notes: Imipramine (153) + Placebo (149) = 302 participants. Imipramine (92F: 61M) and Placebo (95F: 54M).</p> <table border="0"> <tr> <td>Baseline: Fluvoxamine</td> <td>Imipramine</td> <td>Placebo</td> </tr> <tr> <td>HAM-D 25.61</td> <td>25.92</td> <td>25.60</td> </tr> </table>	Baseline: Fluvoxamine	Imipramine	Placebo	HAM-D 25.61	25.92	25.60	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 153</p> <p>Imipramine. Mean dose 149.06mg/day - Day 1: 50mg/day, Day 2: 100mg/day, Days 3-7: 150mg/day. After week 1, could adjust the dosage according to clinical judgement. Maximum 300mg/day.</p> <p>Group 2 N= 149</p> <p>Placebo. Mean dose 3.3 capsules/day - Day 1: 1 capsule/day, day 2: 2 capsules/day, and day 3: 3 capsules/day. After 1 week, could adjust the dosage accordingly up to 6 capsules/day.</p>	<p>Funding; unknown.</p>
Baseline: Fluvoxamine	Imipramine	Placebo								
HAM-D 25.61	25.92	25.60								
<p>CASSANO1996</p>										

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Tianeptine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients; Belgium, Italy, Mexico, Portugal, Spain and Switzerland.</p> <p>Notes: Benzodiazepines allowed as associated treatment. 186 participants in ITT population. Parallel group design.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 187</p> <p>Age: Mean 47</p> <p>Sex: 82 males 105 females</p> <p>Diagnosis: 25% Major depressive disorder by DSM-III-R</p> <p>67% Depression by DSM-III-R</p> <p>9% Double depression by DSM-III-R</p> <p>Exclusions: Other types of depression, acute or chronic psychosis, non-responders to two different antidepressants for the current episode, necessity of ECT, treatment within seven days of pre-inclusion with non MAOI, treatment within 14 days of pre-inclusion with a reversibly MAOI, treatment within one month of pre-inclusion with a non-reversible MAOI, uncontrolled somatic disease, closed angle glaucoma, prostate adenoma, women without effective contraception, pregnant or lactating women, patients with a history of drug or alcohol misuse or dependence.</p> <p>Notes: Imipramine (64) + Placebo (59) = 123 participants. Imipramine (33F:31M) and Placebo (32F:27F). Depression refers to recurrent depression. Double depression refers to bipolar disorder.</p> <p>Baseline: Tianeptine Imipramine Placebo MADRS (SE) 31.2 (0.6) 31.4 (0.6) 31.0 (0.5)</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects</p> <p>Number reporting side effects</p> <p>Suicide</p> <p>Leaving treatment early for any reason</p> <p>MADRS mean endpoint</p> <p>Data Not Used</p> <p>Non-response 50% reduction in MADRS - no data</p>	<p>Group 1 N= 75</p> <p>Imipramine - Days 1-3: doses adjusted to reach 150mg/day. Days 4-14 treated at fixed dose of 150mg/day. Days 15-42 flexible doses could be prescribed (100-200mg/day) according to clinical outcomes or side effects.</p> <p>Group 2 N= 76</p> <p>Placebo - Days 1-3: up to 3 capsules daily. Days 4-14: 3 capsules/day. Days 15-42: 2-4 capsules/day according to clinical outcomes or side effects.</p>	<p>Funding; unclear.</p>
<p>CLAGHORN1983</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Zimeldine vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Unclear; multicentre, US.</p> <p>Info on Screening Process: 393 screened; 130 excluded. 90 did not return after entry or after the washout period. 22 participants responded to placebo during the washout period. 10 did not meet the inclusion criteria.</p>	<p>n= 263</p> <p>Age: Mean 39 Range 19-65</p> <p>Sex: 124 males 139 females</p> <p>Diagnosis: 4% Depression by RDC</p> <p>96% Major depressive disorder by RDC</p> <p>Exclusions: Females of childbearing potential, patients with somatic illness, pre-existing conditions, and alcohol or drug dependence. Lactating and pregnant women.</p> <p>Notes: AMI (85) + PLA (87) = 172 participants. MDD = definite. Depression = probable.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Weight mean change (kg)</p>	<p>Group 1 N= 85</p> <p>Amitriptyline. Mean dose 180mg/day - 75-300mg/day in the first two weeks. Investigators encouraged to titrate the patients to the maximum tolerable dose as rapidly as possible.</p> <p>Group 2 N= 87</p> <p>Placebo. Mean dose 230mg/day - No details.</p>	<p>Funding; unknown.</p>
<p>CLAGHORN1983B</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Zimelidine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Presented data as completer data - I have calculated ITT values.</p> <p>Info on Screening Process: 393 participants screened; 130 excluded. 90 participants did not return for treatment after entry or after washout</p>	<p>n= 263</p> <p>Age: Mean 39</p> <p>Sex: 113 males 150 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: No other pre-existing psychiatric disorders, females of childbearing potential if the possibility of pregnancy could not be definitely excluded during the study, patients with somatic illness, alcohol or drug dependence, and lactating and pregnant women.</p> <p>Notes: Amitriptyline (91) + Placebo (87) = 178 participants. Endogenous depression (72%), primary depression (68%)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason Non-response 50% reduction in HRSD</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 91</p> <p>Amitriptyline. Mean dose 180mg/day - 75-300mg/day. Dosage increased to 300mg/day over the first two weeks. Investigators were encouraged to titrate the patients to the maximum tolerable dose as rapidly as possible.</p> <p>Group 2 N= 87</p> <p>Placebo. Mean dose 230mg/day - Initial dosage was 1 capsule 3 times/day. Dosage was increase to 4 capsules 3 times/day over the first 2 weeks.</p>	<p>Funding; unknown.</p>
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22

<p>period. 22 participants responded to placebo during the washout period. 10 participants didn't meet inclusion criteria.</p>	<p>and unipolar depression (91%). Baseline: HDS (21): 27 (for all completers, ie. N=229).</p>			
<p>CLAGHORN1996A</p> <p>Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Completers (130 participants) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 150 randomised but 130 included. Info on Screening Process: Unknown.</p>	<p>n= 150 Age: Mean 39 Sex: 52 males 98 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Free of any significant health problems and free of psychoactive medications for at least 7 days before study start. Notes: 50 in each treatment group. Later reduce to Imipramine (44) + Placebo (45) = 89 participants. Baseline: HAM-D (21): 26.15</p>	<p>Data Used HRSD-21 mean change</p>	<p>Group 1 N= 44 Imipramine - 80mg-240mg/day. Initial dosage 40mg/day. Dosage increased every 3 to 4 days depending on therapeutic effect and adverse events. Each patient was to be maintained at 80mg/day after the first 2 weeks. Maximum dose: 240mg/day. Group 2 N= 45 Placebo - No details.</p>	<p>Funding: pharma (Solvay Pharmaceuticals).</p>
<p>COHN1984</p> <p>Study Type: RCT Study Description: 3-arm study; Nomifensine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Info on Screening Process: Unknown.</p>	<p>n= 63 Age: Mean 66 Sex: 23 males 40 females Diagnosis: 100% Affective disorder by Details below Exclusions: Past or present significant abnormal clinical findings or medical conditions that might affect drug metabolism. Sensitivity to tricyclic antidepressants, requirement of ECT or any psychotropic medication other than chloral hydrate, chronic alcohol or drug misuse. Notes: Affective disorder = primary affective disorder-depression (Primary Affective Disorders Checklist). Imipramine (21) + Placebo (21) = 42 participants. Imipramine (8M:13F) and Placebo (5M:19F). Baseline: Nomifensine Imipramine Placebo HAM-D (21) 31 27 28 BDI 22 22 22</p>	<p>Data Used Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects Data Not Used HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 21 Imipramine. Mean dose 137.5mg/day - 5.5 capsules (25mg each)/day. Group 2 N= 21 Placebo</p>	<p>Funding; unknown.</p>
<p>COHN1985</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluoxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: Parallel groups design.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 166</p> <p>Age: Mean 43 Range 20-64</p> <p>Sex: 68 males 98 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Concomitant physical conditions or histories of conditions that would interfere with therapy or evaluation.</p> <p>Notes: Imipramine (54) + Placebo (58) = 112 participants. Imipramine (23M:31F) and Placebo (30M:28F).</p> <p>Baseline: Fluoxetine Imipramine Placebo HAM-D (21) 25.75 25.90 25.14</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 54</p> <p>Imipramine - 100-300mg/day. Taken in the morning, at noon and at bedtime. During the first 2 weeks of drug treatment, dosages were adjusted to determine the maintenance dosage for each patients, and these dosages were given for the rest of the study.</p> <p>Group 2 N= 58</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>COHN1990A</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo.</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: 120 entered; 102 completed.</p>	<p>n= 120</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients with a primary diagnosis of schizophrenia; atypical type; anxiety as the primary disorder; disorders of adjustment; manic depressive illness; alcohol or drug misuse; or acute or unstable medical conditions. Pregnant or lactating women and women of childbearing potential not taking birth control precautions.</p> <p>Notes: Imipramine (40) + Placebo (40) = 80 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 31</p> <p>Imipramine - 65-275mg/day. Received medication in the morning and at bedtime.</p> <p>Group 2 N= 36</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>COHN1992</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Notes: 120 participants entered study; 128 excluded from analysis. Main reason was use of prohibited concomitant medication.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 102</p> <p>Age: Mean 42</p> <p>Sex: 42 males 60 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unstable systemic medical condition or clinically significant abnormal laboratory values at the initial evaluation. History of seizure disorder, alcohol or drug misuse within 6 months prior to the study, a known allergy to imipramine, or a history of glaucoma or prostatic hypertrophy. Women were excluded if they were pregnant, breast-feeding, or not using a medically acceptable form of contraception.</p> <p>Notes: Imipramine (31) + Placebo (36) = 67 participants. Imipramine (12M:19F) and Placebo (19M:17F).</p> <p>Baseline: Paroxetine Imipramine Placebo HAM-D (17) 24.9 (0.72) 24.5 (0.71) 25.6 (0.71)</p>	<p>Data Not Used</p> <p>Leaving treatment early for any reason - no data</p> <p>MADRS mean endpoint - no data</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 31</p> <p>Imipramine. Mean dose 144.9mg/day - 65-275mg/day. Treatment started with 80mg/day.</p> <p>Group 2 N= 36</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>COHN1996</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Nefazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US.</p> <p>Notes: Parallel group design. 128 participants entered study; 119 included in ITT analyses.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 119</p> <p>Age: Mean 39</p> <p>Sex: 33 males 86 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (38) + Placebo (42) = 80 participants. Imipramine (29F:9M) and Placebo (27F:15M).</p> <p>Baseline: Nefazadone Imipramine Placebo HAM-D (17) 22.8 23.6 23.4</p>	<p>Data Used</p> <p>HRSD-17 mean change</p>	<p>Group 1 N= 38</p> <p>Imipramine. Mean dose 126mg/day - 100-300mg/day.</p> <p>Group 2 N= 42</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Bristol-Myers Squibb U.S. Pharmaceuticals).</p>
<p>DOMINGUEZ1981</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amoxapine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Unsure</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p>	<p>n= 97</p> <p>Age: Mean 41 Range 21-64</p> <p>Sex: 38 males 59 females</p> <p>Diagnosis: 100% Depression by No details</p>	<p>Data Used</p> <p>Number reporting side effects Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-21 mean change - no data</p>	<p>Group 1 N= 38</p> <p>Imipramine. Mean dose 102.5mg/day - 50-200mg/day. Initial daily dose was 50-75mg/day, and was escalated to a daily dose of 100-150mg by the beginning of the second week depending the patient's response and side effects. The maximum dose was 200mg/day.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">24</p>

<p>Setting: Outpatients; US.</p> <p>Notes: 46 participants completed 6 weeks of treatment.</p> <p>Info on Screening Process: Unknown.</p>	<p>days prior to entering the study, patients with a history or signs of schizophrenia, organic brain syndrome, significant medical illness or alcohol or drug misuse.</p> <p>Notes: Imipramine (38) + Placebo (20) = 58 participants. Imipramine (15M:23F) and Placebo (10M:10F). Unipolar = 47 participants. Bipolar = 2 participants. Neurotic = 42 participants. Involutional = 4 participants. Other = 2 participants.</p> <p>Baseline: Amoxapine Imipramine Placebo HAM-D (21) 33.4 32.0 32.3</p>	<p>Notes: Unsure which HRSD version.</p>	<p>Group 2 N= 20</p> <p>Placebo. Mean dose 117.5mg/day - The initial dose was 2-3 capsules/day, and was escalated to a daily dose of 4-6 capsules by the beginning of the second week depending on the patient's response and side effects. The maximum dose was 8 capsules per day.</p>	
<p>DOMINGUEZ1985</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; US</p> <p>Notes: Excluded data from 7 participants who didn't complete 4 weeks. Only 16 of the 17 HRSD items used (excluded loss of weight).</p> <p>Info on Screening Process: 124 participants screened; 13 excluded from entering study.</p>	<p>n= 101</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: If depression was secondary to any other psychiatric illness, if they had any significant physical condition, or had a history of recent or continued substance misuse. If pregnant or of childbearing potential. Exposure to antidepressants within 3 days, lithium within a week, and/or MAO, ECT, or investigational drugs within 1 month of the washout phase.</p> <p>Notes: Imipramine (35) + Placebo (31) = 66 participants.</p> <p>Baseline: Fluvoxamine Imipramine Placebo HAM-D 17 20.4 22.0 20.9</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects Non-response 50% reduction in HRSD Number reporting side effects Leaving treatment early for any reason HRSD-17 mean endpoint</p>	<p>Group 1 N= 35</p> <p>Imipramine - All patients received 50mg on Day 1 and 100mg on Day 2. After this initial period the dosage ranged from 100-300mg/day usually in divided doses.</p> <p>Group 2 N= 31</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>DUNBAR1991</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Main reasons for exclusions from efficacy analyses were concomitant use of medication with potential CNS activity.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 717</p> <p>Age: Mean 40</p> <p>Sex: 390 males 327 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-II</p> <p>Exclusions: Patients who had a reduction of over 20% in HRSD score in the washout period.</p> <p>Notes: Imipramine (237) + Placebo (240) = 477 participants. Imipramine (101M:109F) and Placebo (115M:106F).</p> <p>Baseline: Paroxetine Imipramine Placebo HAM-D (17) 26.5 26.2 26.6</p>	<p>Data Used</p> <p>Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects MADRS mean change HRSD-17 mean change</p>	<p>Group 1 N= 237</p> <p>Imipramine - 65mg - 275mg. Started at 80mg/day. This was adjusted in the range 65-145mg/day for week 2, 65-210mg/day for week 3 and 65-275mg/day for weeks 4-6.</p> <p>Group 2 N= 240</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>ELKIN1989</p>				

<p>Study Type: RCT</p> <p>Study Description: 4-arm study; CBT vs. IPT vs. PLA-CM vs. ICM</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: 556 participants screened. The primary reason for rejection was failure to meet the MDD and/or HRSD inclusion</p>	<p>n= 239</p> <p>Age: Mean 35</p> <p>Sex: 71 males 168 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Definite bipolar II and probably or definite bipolar I, panic disorder, alcoholism, drug use disorder, antisocial personality disorder, Briquet's syndrome, and RDC diagnosis of MDD, psychotic subtype, two or more schizotypal features, history of schizophrenia, organic brain syndrome, mental retardation, concurrent treatment</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Non-response 50% reduction in HRSD</p> <p>Non-remission HRSD-17 < 7</p> <p>BDI mean endpoint</p> <p>HRSD-17 mean endpoint</p> <p>Notes: <6 for remission.</p>	<p>Group 1 N= 57</p> <p>Imipramine - Average for first two weeks 185mg/day.</p> <p>Group 2 N= 62</p> <p>Placebo - No details.</p>	<p>Funding; research (NIMH).</p>
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25

<p>criteria either at screening or at rescreening.</p>	<p>presence of specific physical illness or other medical contraindications for the use of imipramine, and presence of a clinical state inconsistent with participating in the research protocol.</p> <p>Notes: Imipramine (57) + Placebo (62) = 119 participants.</p> <p>Baseline: CBT IPT IMI-CM PLA-CM HAM-D (17) 19.2 (3.6) 18.9 (3.9) 19.2 (5.0) 19.1 (3.7)</p>			
<p>ENTSUAH1994</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Venlafaxine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 213</p> <p>Age: Mean 42</p> <p>Sex: 71 males 142 females</p> <p>Diagnosis: 100% Major depressive disorder by No details</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (71) + Placebo (78) = 149 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>MADRS mean change HRSD-21 mean change</p> <p>Notes: Cumulative mean changes given.</p>	<p>Group 1 N= 71 Imipramine - No details.</p> <p>Group 2 N= 78 Placebo - No details.</p>	<p>Funding; unclear. Work for Clinical Biostatics, Wyeth-Ayerst Research.</p>
<p>ESCOBAR1980</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Inpatients; Colombia.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 40</p> <p>Age: Mean 45 Range 25-66</p> <p>Sex:</p> <p>Diagnosis: 85% Depression by RDC</p> <p>15% Double depression by RDC</p> <p>Exclusions: No history of other psychiatric disorder or major physical illness.</p> <p>Notes: Imipramine (15) + Placebo (12) = 27 participants. Imipramine (8F:7M) and Placebo (8F:4M). Double depression = bipolar.</p> <p>Baseline: Trazodone Imipramine Placebo HAM-D (21) 30.8 31.3 30.9</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p>	<p>Group 1 N= 12 Placebo - The starting dose was 4 capsules/day. One additional capsules was permitted every second day depending on clinical condition, and up to a maximum of 12 capsules per day.</p> <p>Group 2 N= 15 Imipramine - 100-300mg/day. The starting dose was 100mg/day. An additional 25mg was permitted every second day depending on clinical condition, and up to a maximum of 300mg/day.</p>	<p>Funding; unclear.</p>
<p>FABRE1980</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completer</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 154</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Depression by No details</p> <p>Exclusions: Not suffering primarily from primary depression, were psychopathic, sociopathic or psychotic, were suffering from bipolar, involuntal or schizoaffective depressions, had significant liver or kidney disease as determined by physical examination, vital signs and laboratory tests, had uncontrolled cardiovascular, pulmonary, endocrinological or collagen diseases or glaucoma, or conditions where imipramine is contraindicated, had a history of urinary retention, paralytic ileus and convulsive disorders, were sensitive to benzodiazepines or tricyclics or actively abusing alcohol or other drugs, required other psychotropic medication, hypnotics or analgesics containing narcotics, received anticholinergic drugs or preparations containing</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 52</p> <p>Imipramine. Mean dose 128.4mg/day - No details.</p> <p>Group 2 N= 51</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
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	<p>propranolol, a methyldopa or thyroid medications, or could not read or understand the symptoms check list.</p> <p>Notes: Imipramine (52) + Placebo (51) = 103 participants. Baseline: Unknown.</p>			
FABRE1992				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: 120 participants entered the study. 111 included in efficacy analyses.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 111</p> <p>Age: Mean 36</p> <p>Sex: 42 males 69 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Another primary psychiatric diagnosis, a history of alcohol or drug misuse within the previous 6 months, an unstable hepatic, renal, respiratory or cardiovascular disorder. History of glaucoma, urinary retention or a known allergy to imipramine. Pregnant or breastfeeding women. Women not currently using a medically acceptable form of contraception.</p> <p>Notes: Imipramine (37) + Placebo (36) = 73 participants. Imipramine (12M:25F) and Placebo (13M:23F).</p> <p>Baseline: Paroxetine Imipramine Placebo HAM-D (21) 29.7 (0.64) 27.8 (0.65) 28.8 (0.66)</p>	<p>Data Used MADRS mean change HRSD-21 mean change</p> <p>Data Not Used Leaving treatment early for any reason - no data</p> <p>Notes: SDs for mean HRSD very small and gave high heterogeneity - converted to Ses and now no heterogeneity - assume error in labelling in the paper</p>	<p>Group 1 N= 37 Imipramine. Mean dose 135.2mg/day - Started at 80mg/day. Could be lowered to 65mg/day after the first week. The maximum dose could be increased to 275mg/day.</p> <p>Group 2 N= 36 Placebo - No details.</p>	Funding; unknown.
FABRE1996				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: F (46), I (48) and P (44) in ITT sample.</p> <p>Info on Screening Process: 235 participants screened; 150 entered (50 participants/group).</p>	<p>n= 150</p> <p>Age:</p> <p>Sex: 33 males 105 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Any other primary psychiatric diagnosis, an unstable medical condition, clinically significant abnormal laboratory findings and patients who demonstrated a placebo response during the washout phase.</p> <p>Notes: Imipramine (48) + Placebo (44) = 92 participants. Imipramine (8M:40F) and Placebo (14M:30F) in ITT sample.</p> <p>Baseline: Fluvoxamine Imipramine Placebo HAM-D (21) 27.7 26.5 26.0 MADRS 30.6 30.6 29.5</p>	<p>Data Used Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason Non-response 50% reduction in HRSD MADRS mean change HRSD-24 mean change</p>	<p>Group 1 N= 48 Imipramine - 72-182 mg/day. Maximum dose 240mg/day. The initial dose was 40mg/day which was increased by 40mg/day every 3-4 days to a maximum dose of 240mg/day over a 3 week period as tolerated. Minimum dose of 80mg/day for those who could not tolerate max daily dose.</p> <p>Group 2 N= 44 Placebo - No details.</p>	Funding; pharma (Solvay Pharmaceuticals).
FEIGER1996A				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Geripone vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 123</p> <p>Age: Mean 40</p> <p>Sex: 36 males 45 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Pregnant or lactating or sexually active and able to bear children but not using adequate methods of contraception. Axis I psychiatric diagnosis, delusions or hallucinations during the current episode of depression, high probability of needing other treatments during the course of the study, significant current medical conditions, meeting DSM-III-R criteria for psychoactive substance use disorder within the prior 12 months, allergy or hypersensitivity to azaperoles or tricyclic antidepressants, significant suicide</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Number reporting side effects</p> <p>MADRS mean endpoint</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p> <p>HRSD-17 mean endpoint - no data</p> <p>Notes: HAM-D 28 used where 21 denoted.</p>	<p>Group 1 N= 41</p> <p>Imipramine - Days 1-2: 50mg/day, days 3-7: 100mg/day and 50-300mg/day thereafter.</p> <p>Group 2 N= 40</p> <p>Placebo - Days 1-2: 1 capsule/day, days 3-7: 2 capsules/day and up to 6 capsules/day thereafter.</p>	<p>Funding; unclear.</p>
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	<p>risk, electroconvulsive therapy within 6 months of the study, and a history of glaucoma, urinary retention, or seizure disorders.</p> <p>Notes: I have calculated mean age and sex based on IMI and PLA only. Imipramine (41) + Placebo (40) = 80 participants. Imipramine (18M:23F) and Placebo (18M:22F).</p> <p>Baseline: Gepirone Imipramine Placebo MADRS 26.98 28.26 26.88</p>			
FEIGHNER1979				
<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Amitriptyline vs. Limbitrol (Amitriptyline + Chlordiazepoxide) vs. Chlordiazepoxide vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Randomisation was in blocks of 7 participants (2-2-2-1). 58 participants excluded from efficacy analysis.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 337</p> <p>Age: Mean 40</p> <p>Sex: 102 males 235 females</p> <p>Diagnosis: 100% Depression by Feighner criteria</p> <p>Exclusions: Patients with pre-existing psychiatric conditions such as schizophrenia, alcoholism, hysteria and antisocial personality. Patients with serious medical illnesses or who were considered marked suicidal risks. No patient who had had recent treatment with ECT or with an MAOI.</p> <p>Notes: Amitriptyline (93) + Placebo (50) = 143 participants. Amitriptyline (40M:53F) and Placebo (17M:33F). 143 unipolar and 33 bipolar depressives.</p> <p>Baseline: Limb Amit Chlord Pbo HRSD-24 34.3 36.0 35.0 34.7 BDI 19.0 19.4 18.9 19.2</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>BDI mean endpoint</p> <p>HRSD-24 mean endpoint</p> <p>Data Not Used</p> <p>Non-response 50% reduction in HRSD - no data</p>	<p>Group 1 N= 93</p> <p>Amitriptyline. Mean dose 115mg/day - Initial dosage at 100mg/day. This would be reduced to 75mg/day but investigators were encouraged to increase the dosage to 125-150mg/day.</p> <p>Group 2 N= 50</p> <p>Placebo. Mean dose 130mg/day - No details.</p>	Funding; unknown.
FEIGHNER1980				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Trazodone vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Inpatients; US</p> <p>Info on Screening Process: 50 participants admitted; 1 had pre-treatment HRSD <18, and 4 withdrew.</p>	<p>n= 45</p> <p>Age:</p> <p>Sex: 12 males 33 females</p> <p>Diagnosis: 100% Depression by Feighner criteria</p> <p>Exclusions: Females at risk of conception, patients with other psychotic disease or neurosis, poor physical health or a history of brain trauma, alcoholism, drug addiction, seizure disorder, mental deficiency or electroshock therapy in the preceding six months.</p> <p>Notes: Imipramine (18) + Placebo (10) = 28 participants. Imipramine (2M:16F) and Placebo (4M:6F).</p> <p>Baseline: Trazodone Imipramine Placebo HAMD (21) 35.4 36.6 36.0</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 18</p> <p>Imipramine - Started with 100mg/day. This could be increased by 25mg every 3-4 days up to a maximum of 300mg/day.</p> <p>Group 2 N= 10</p> <p>Placebo. Mean dose 157.5mg/day - 6.37 capsules/day.</p>	Funding; pharma.
FEIGHNER1982				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Lofepramine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 139</p> <p>Age:</p> <p>Sex: 40 males 99 females</p> <p>Diagnosis: 100% Depression by DSM-III</p> <p>Exclusions: Patients with a history of evidence of clinically significant renal disease, hepatic disease, prostatic hypertrophy, cardiovascular disease, significant laboratory abnormalities, significant pre-treatment EEG or EG abnormalities. Patients with a history or evidence of</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-21 mean endpoint</p> <p>Notes: Non-response = 40% reduction in HRSD.</p>	<p>Group 1 N= 45</p> <p>Placebo - No details.</p> <p>Group 2 N= 48</p> <p>Imipramine. Mean dose 150mg/day - Week 1: 75mg/day. From thereon could be increased to 150mg/day.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">28</p>
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	<p>glaucoma, benzodiazepine allergies or other hypersensitivity reactions. Patients who were pregnant or likely to become pregnant, those who required concomitant therapy with other psychotropic drugs, and known misusers of alcohol or drugs. All patients with other primary psychiatric diagnoses such as schizophrenia, schizoaffective disorder, anxiety etc.</p> <p>Notes: Imipramine (48) + Placebo (45) = 93 participants. Imipramine (13M:35F) and Placebo (11M:34F).</p> <p>Baseline: Lofepramine Imipramine Placebo HAM-D 26.98 (0.59) 26.94 (0.64) 27.36 (0.59)</p>			
FEIGHNER1983A				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Multicentre; US.</p> <p>Info on Screening Process: Unclear. 906 participants enrolled at start.</p>	<p>n= 723</p> <p>Age: Mean 38</p> <p>Sex: 208 males 515 females</p> <p>Diagnosis: 100% Major depressive disorder by Feighner criteria</p> <p>Exclusions: Patients who suffered primarily from other psychiatric illness, life-threatening or incapacitating physical illness, and alcoholism or other drug misuse. Depressed patients with predominant psychomotor retardation or bipolar major depressive disorder were excluded. Patients with an unstable clinically significant medical disorder, patients with known hypersensitivity to benzodiazepines or tricyclic antidepressants or who required other psychotropic medication, including anticholinergics or CNS-active antihypertensive agents.</p> <p>Notes: Imipramine (244) + Placebo (243) = 487 participants. Imipramine (78M:166F) and Placebo (64M:179F).</p> <p>Baseline: HDRS: 26.06 (5.11)</p>	<p>Data Used Number reporting side effects</p> <p>Data Not Used HRSD-17 mean endpoint - no data</p> <p>Notes: Unclear which HRDS version was used. Need to check how scores were added.</p>	<p>Group 1 N= 244 Imipramine - Started at 50mg daily. At 3 days, went up to 75mg. Maximum dosage 225mg.</p> <p>Group 2 N= 243 Placebo - No details.</p>	Funding; pharma (The Upjohn Company).
FEIGHNER1983B				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 129</p> <p>Age: Mean 39</p> <p>Sex: 24 males 105 females</p> <p>Diagnosis: 100% Major depressive disorder by Feighner criteria</p> <p>Exclusions: Patients who suffered from major bipolar affective disorders, predominantly psychomotor retarded depression, or depression secondary to other non-affective psychiatric illness. Patients with clinically unstable medical disorders and those known to be hypersensitive to benzodiazepines or TCAs. Patients who required anticholinergics, CNS active anti-hypertensives, or other psychotropic medications, except chlorhydrate.</p> <p>Notes: Imipramine (43) + Placebo (45) = 88 ppts. Imipramine (9M:34F) and Placebo (3M:42F).</p> <p>Baseline: Alprazolam Imipramine Placebo HAM-D 30.5 30.4 30.0</p>	<p>Data Used Leaving treatment early for any reason</p> <p>Data Not Used HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 43</p> <p>Imipramine. Mean dose 117.3mg/day - 25-225mg/day. Initial dose was 25mg/day. Within three days the regimen changed to 50mg/day. The investigators further increased the dose at 1-week intervals for patients for optimum clinical effect to a maximum of 225mg/day.</p> <p>Group 2 N= 45</p> <p>Placebo. Mean dose 7.2 capsules/day - 2-12 capsules/day. Initial dose was 1 capsule a day. Within 3 days the regime changed to 1 capsules twice/day. The investigators further increased the dose at 1 week intervals for patients for optimum clinical effect to a maximum of 2 capsules 3 times/day.</p>	<p>Funding; research (The Feighner Research Institute).</p>
<p>FEIGHNER1989</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Nefazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 45</p> <p>Age: Mean 45 Range 27-64</p> <p>Sex: 23 males 22 females</p> <p>Diagnosis: 100% Depression by RDC</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (15) + Placebo (15) = 30 participants. Imipramine (7M:8F) and Placebo (8M:7F). Participants met RDC Endogenous Major Depression and DSM III Major Depression with Melancholia.</p> <p>Baseline: Unknown.</p>	<p>Data Used Leaving treatment early for any reason</p> <p>Data Not Used Leaving treatment early due to side effects HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 15 Imipramine. Mean dose 135.2mg.day - Started at 50mg/day. This could be increased by up to 50mg/day to a maximum of 250mg/day. This could be decreased in the event of side effects.</p> <p>Group 2 N= 15 Placebo - Started at 2 capsules/day.</p>	<p>Funding; unknown.</p>
<p>FEIGHNER1989A</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo.</p> <p>Type of Analysis: Completers (at least 4 days of treatment)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 120</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients were excluded if they posed a serious suicidal risk, had a primary psychiatric diagnosis other than depression, a history of alcohol or other substance misuse within the past six months, were pregnant or breast feeding, had clinically significant laboratory findings, or a medical contraindication to imipramine such as a history of seizures, urinary retention, or glaucoma.</p> <p>Notes: Imipramine (40) + Placebo (37) = 77 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used Leaving treatment early due to side effects Leaving treatment early for any reason Non-response 50% reduction in HRSD - no data</p> <p>Data Not Used MADRS mean endpoint - no data</p>	<p>Group 1 N= 40 Imipramine - Maximum dose: 275mg/day.</p> <p>Group 2 N= 37 Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>FEIGHNER1989B</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients; US.</p> <p>Notes: After 2 weeks on study drug the patient could be discharged if sufficiently improved and followed as an outpatient for the remainder of the trial.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 86</p> <p>Age: Mean 41 Range 18-71</p> <p>Sex: 13 males 73 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (36) + Placebo (19) = 55 participants. Imipramine (32F:4M) and Placebo (17F:2M).</p> <p>Baseline: Unknown.</p>	<p>Data Used Leaving treatment early due to side effects</p>	<p>Group 1 N= 36 Imipramine - 150-300mg/day.</p> <p>Group 2 N= 19 Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>FEIGHNER1989C</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Fluoxetine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: 145 participants completed at least 2</p>	<p>n= 145</p> <p>Age: Mean 42</p> <p>Sex: 37 males 108 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Pregnant, not practicing medically acceptable contraception, or if they posed a serious suicide risk. Organic brain svndrome. schizophrenia. a history of</p>	<p>Data Used</p> <p>HRSD-21 mean endpoint</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 45</p> <p>Imipramine - Maximum dose: 150mg/day.</p> <p>Group 2 N= 48</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
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30

<p>weeks of treatment.</p> <p>Info on Screening Process: 198 enrolled. 178 entered double-blind treatment phase. Reasons for exclusion unknown.</p>	<p>seizures, drug or alcohol misuse within the past year, or a contraindication to imipramine such as glaucoma or chronic urinary retention. Excluded after the wash-out phase if their HDRS score was less than 20 or had decreased by 20% or more.</p> <p>Notes: Imipramine (45) + Placebo (48) = 93. Imipramine (34F:11M) and Placebo (38F:10M).</p> <p>Baseline: Fluoxetine Imipramine Placebo HAM-D (21) 25.60 25.96 25.90</p>			
<p>FEIGHNER1992B</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Notes: 120 participants entered the study.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 116</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Serious suicide risk, a primary psychiatric diagnosis other than depression, a history of alcohol or other substance misuse within the past 6 months, pregnancy or breast feeding, clinically significant laboratory abnormalities, or a medical contraindication to imipramine such as a history of seizures, urinary retention or glaucoma.</p> <p>Notes: Imipramine (40) + Placebo (37) = 77 participants.</p> <p>Baseline: HAMD (21): Approx. 25 (graphical data).</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 40</p> <p>Imipramine. Mean dose 111.3mg/day - 65mg/day-275mg/day.</p> <p>Group 2 N= 37</p> <p>Placebo. Mean dose 5.46 capsules - No details.</p>	<p>Funding; research.</p>
<p>FEIGHNER1993</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Parallel groups.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 717</p> <p>Age: Mean 40</p> <p>Sex: 347 males 370 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-II</p> <p>Exclusions: Patients had any other primary psychiatric diagnosis or progressive/unstable physical illness. Women of childbearing potential were excluded for the initial part of the study. During the latter stages of the trial, women not using adequate contraception or who were lactating were excluded.</p> <p>Notes: Imipramine (237) + Placebo (240) = 477 participants. Imipramine (112M:125F) and Placebo (122M:118F).</p> <p>Baseline: Paroxetine Imipramine Placebo HAM-D 26.4 26.2 26.6</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Non-remission HRSD-17 < 10</p> <p>HRSD-21 mean change</p>	<p>Group 1 N= 237</p> <p>Imipramine - Dose started at 80mg/day. This was altered in the range 65-145mg/day after the first week, 65-210mg/day after the second week and in the range 62-275mg/day from weeks 4-6.</p> <p>Group 2 N= 240</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>FERGUSON1994B</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Dothiepin vs. Doxepin vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 70</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: 25 participants excluded from analyses; 23 didn't return after baseline and 2 withdrew consent.</p>	<p>n= 579</p> <p>Age: Mean 40</p> <p>Sex: 214 males 340 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Active suicidal ideation or suicide attempts in the last 12 months, schizophrenia, organic mental syndromes, or seizure disorders, failure to respond to an adequate course of antidepressant therapy, recent history of alcohol or drug misuse, electroconvulsive therapy within 30 days of the</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean change</p> <p>Weight mean change (kg)</p>	<p>Group 1 N= 194</p> <p>Dosulepin (dothiepin). Mean dose 140.7mg/day - 50mg/day days 1-3, 100mg/day days 4-7, and from thereafter up to 150mg/day.</p> <p>Group 2 N= 192</p> <p>Placebo - Unknown.</p>	<p>Funding; pharma (Boots Pharmaceuticals, Inc.).</p> <p style="text-align: right;">31</p>
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<p>Info on Screening Process: 765 participants screened; 186 excluded. Reasons unknown.</p>	<p>study, monoamine oxidase inhibitors or neuroleptics within 14 days of active drug treatment, and use of other antidepressants or anxiolytics within 7 days of baseline.</p> <p>Notes: Participant demographics based on efficacy analyses. Dothiepin (194) + Placebo (192) = 386 participants. Dothiepin (118F:66M) and Placebo (112F:74M).</p> <p>Baseline: Dothiepin Doxepin Placebo HAMD (17) 23.9 (3.3) 23.8 (3.0) 23.6 (3.1) MADRS 27.7 (5.4) 27.8 (5.3) 27.4 (5.5)</p>			
<p>FONTAINE1994</p> <p>Study Type: RCT</p> <p>Study Description: 4-arm study; Nefazodone (high dose) vs. Nefazodone (low dose) vs. Imipramine vs. Placebo.</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; Canada.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 180</p> <p>Age: Mean 42 Range 20-65</p> <p>Sex: 68 males 112 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Primary psychiatric diagnosis other than depression, history of bipolar disorder, organic mental disorder, or schizophrenia; symptoms of urinary retention or prostatic hypertrophy or glaucoma; DSM-III defined diagnosis of alcoholism or substance misuse within the past year; significant medical disorder; hypersensitivity to trazodone or tricyclic antidepressants; need for concomitant medication affecting the central nervous system, except occasional chloral hydrate for sleep; serious risk of suicide; previous participation in an investigational drug trial; women breast-feeding or not using an approved method of contraception; use of a monoamine oxidase inhibitor within 14 days or any other psychotropic medications within 7 days before baseline, or electroconvulsive therapy within 28 days before baseline.</p> <p>Notes: Imipramine (45) + Placebo (45) = 90 participants. Imipramine (15M:30F) and Placebo (23M:22F).</p> <p>Baseline: HAMD (21): Nefazadone (50-250mg/day) = 25.2, Nefazadone (100-500mg/day) = 25.6, Imipramine = 25.8, Placebo = 25.9</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Non-response 50% reduction in HRSD</p> <p>HRSD-21 mean change</p>	<p>Group 1 N= 45</p> <p>Imipramine - 50-250mg/day. By day 8, patients were receiving 150mg/day.</p> <p>Group 2 N= 45</p> <p>Placebo - No details.</p>	<p>Funding: pharma (Bristol-Myers Squibb Pharmaceutical Research Institute).</p>
<p>GELENBERG1990</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Clovoxamine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: Parallel groups design.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 62</p> <p>Age: Range 21-62</p> <p>Sex: 19 males 43 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Women who were or might become pregnant, patients with other psychiatric or serious medical illnesses, or patients with chemical dependencies. Patients had to be free of lithium for at least 7 days, MAOIs for at least 2 weeks, TCAs or other antidepressants for at least 3 days and any other investigational drug for at least 4 weeks, and must not have had ECT within at least 4 weeks.</p> <p>Notes: Amitriptyline (19) + Placebo (22) = 41 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p> <p>Notes: Unsure of HAMD version.</p>	<p>Group 1 N= 19</p> <p>Amitriptyline. Mean dose 114mg/day - Day 1: 50mg/day, day 2: 100mg/day, and day 3: 150mg/day. From thereafter, the dosage could be increased to 350mg/day if required.</p> <p>Group 2 N= 22</p> <p>Placebo. Mean dose 152mg/day - No details.</p>	<p>Funding; unknown.</p>
<p>GELENBERG2002</p>				<p>32</p>

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Tyrosine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; US</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 65</p> <p>Age: Mean 40 Range 21-60</p> <p>Sex: 46 males 19 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: History of mania, symptoms of psychosis or a diagnosis of schizophrenia, those unable to give informed consent, or patients with a current diagnosis of alcoholism, other drug addiction, epilepsy or clinical evidence of serious suicidal risk with poor past response to antidepressant therapy or with medical illnesses that might interfere with treatment.</p> <p>Notes: Imipramine (22) + Placebo (22) = 44 participants. Imipramine (16M:6F) and Placebo (14M:8F).</p> <p>Baseline: Tyrosine Imipramine Placebo HAM-D (21) 24.3 24.3 24.5</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 22</p> <p>Imipramine - 2.5mg/kg/day. By study day 9 participants were to achieve a target dose of 2.5mg/kg/day in three divided doses. They were to take this for 4 weeks.</p> <p>Group 2 N= 22</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>GEORGOTAS1982A</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Zimeldine vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Unclear; US.</p> <p>Notes: 60 participants completed at least 2 weeks' treatment. Assumed 20 participants per treatment arm.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 52</p> <p>Age: Mean 40</p> <p>Sex: 31 males 21 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Intercurrent medical illness, childbearing potential, and the need to take other medications.</p> <p>Notes: AMI (15) + PLA (18) = 33 participants. Amitriptyline (12M:3F) and Placebo (10M:8F).</p> <p>Baseline: Zimeldine Amitriptyline Placebo HAM-D 21 (SE) 29.9 (1.1) 28.5 (1.5) 28.6 (1.3)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>BDI mean endpoint</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 18</p> <p>Placebo. Mean dose 223mg/day - No details.</p> <p>Group 2 N= 15</p> <p>Amitriptyline. Mean dose 206mg/day - 150mg/day by the end of week 1 and 300mg/day by the end of week 2.</p>	<p>Funding; unknown.</p>
<p>GEORGOTAS1986A</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Nortriptyline vs. Phenelzine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 49</p> <p>Setting: Outpatients; US.</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 295 screened; 137 met inclusion criteria; 126 entered washout period; 90 in double-blind study</p>	<p>n= 58</p> <p>Age: Mean 65 Range 55-76</p> <p>Sex: 22 males 36 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: HAMD-21 < 16; moderate or severe dementia; drug/alcohol dependence; mental retardation; serious neurological disorders; other pre-existing major psychiatric disorders; serious medical illness; urinary retention; narrow-angle glaucoma; supersensitivity to TCAs or MAOIs.</p> <p>Notes: Ns do not include phenelzine group; No M/F based on % M/F in ITT sample</p> <p>Baseline: Placebo Nortriptyline Phenelzine HAM-D 21 23.07 23.58 22.14</p>	<p>Data Used</p> <p>Non-remission HRSD-21 < 10</p> <p>Number reporting side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no variability measure</p> <p>Notes: Remission reported as 'response' but definition closer to that for remission on other studies</p>	<p>Group 1 N= 28</p> <p>Nortriptyline. Mean dose 79 mg/day - 1-3: 25mg/day, then days 4-7: 50mg/day. At then end of the first week, the daily dose was increased to 75mg/day. Patients who attained a plasma level between 50-180ng/ml at the end of week 2 remained on 75mg/day. Otherwise, patients took up to 125mg/day.</p> <p>Group 2 N= 30</p> <p>Placebo - Days 1-3: 1 capsules/day, then days 4-7: 2 capsules/day. At then end of the first week of treatment, the daily dose was increased to 3 capsules/day.</p>	<p>SIGN 1+; funding partly NIMH grant, no further details</p>
<p>GERNER1980B</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p>	<p>n= 60</p> <p>Age: Mean 68 Range 60-90</p> <p>Sex: 23 males 37 females</p> <p>Diagnosis: 100% Depression by RDC</p>	<p>Data Used</p> <p>Non-remission HRSD-17 < 10</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 20</p> <p>Imipramine. Mean dose 145mg/day - 50-200mg/day.</p> <p>Group 2 N= 20</p> <p>Placebo - Equivalent of 50-200mg/day.</p>	<p>Funding; part-pharma (Mead Johnson Pharmaceuticals).</p> <p style="text-align: right;">33</p>

<p>Blindness: Double blind Duration (days): Mean 28</p> <p>Setting: Outpatients; US.</p> <p>Notes: Assume 20 participants per treatment arm.</p> <p>Info on Screening Process: Unknown.</p>	<p>Exclusions: Unknown.</p> <p>Notes: Depression = unipolar depression. Imiprimine (20) + Placebo (20) = 40 participants.</p> <p>Baseline: Unknown.</p>	<p>BDI mean endpoint - no data</p> <p>Notes: 30% rather than 50% reduction in HAMD used to define responders.</p>		
<p>GOLDBERG1980</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: 184 participants entered study. Efficacy evaluated in 127 participants. Remaining 57 participants evaluated for safety only.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 127</p> <p>Age: Mean 37 Range 18-60</p> <p>Sex: 34 males 93 females</p> <p>Diagnosis: 100% Depression by Details below</p> <p>Exclusions: Unknown.</p> <p>Notes: Amitriptyline (60) + Placebo (62) = 122 participants. Amitriptyline (12M:28F) and Placebo (9M:33F). Depression = neurotic depression. Based on New York University criteria. Majority of participants had significant anxiety.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 60</p> <p>Amitriptyline - 75-200mg/day. Increased every 3-4 days.</p> <p>Group 2 N= 62</p> <p>Placebo - No details.</p>	<p>Funding; unclear. Suspect pharma.</p>
<p>HAYES1983</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 60</p> <p>Age: Mean 68</p> <p>Sex: 23 males 37 females</p> <p>Diagnosis: 100% Depression by RDC</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (19) + Placebo (15) = 34 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 19</p> <p>Imipramine. Mean dose 145mg/day - Patients took 50mg at bedtime, increased at the rate of 25mg/day until a maximum of 200mg/day was reached. Doses depended on therapeutic response and/or side effects.</p> <p>Group 2 N= 15</p> <p>Placebo - Took 2 capsules at bedtime, increased at the rate of 1 capsule per day until a maximum dose of 8 capsules/day was reached.</p>	<p>Funding; unknown.</p>
<p>HICKS1988</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Adinazolam vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: Participants admitted as inpatients and kept in the centre for 10-14 days.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 48</p> <p>Age: Mean 42</p> <p>Sex: 15 males 33 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients who were pregnant, had major medical illness, epilepsy, glaucoma, hypothyroidism, or active alcohol or drug misuse. Those who had received ECT, MAOIs or an investigational drug within the previous 2 weeks.</p> <p>Notes: Amitriptyline (16) + Placebo (15) = 31 participants. Amitriptyline (5M:11F) and Placebo (5M:10F). 6.5% dysthymia. 12.15% substance misusers. 11.8% personality diagnosis.</p> <p>Baseline: Amitriptyline Adinazolam Placebo HAMD 30.8 31.6 29.4</p>	<p>Data Used</p> <p>Weight mean change (kg)</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p> <p>Notes: Unsure of HAMD version.</p>	<p>Group 1 N= 16</p> <p>Amitriptyline. Mean dose 142mg/day - 25-300mg/day.</p> <p>Group 2 N= 15</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Upjohn Company).</p>
HOLLYMAN1988				34

<p>Study Type: RCT</p> <p>Study Description: 2-arm study; Amitriptyline vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; UK.</p> <p>Info on Screening Process: 290 participants identified by GPs for study inclusion; 112 excluded. 53 ineligible and 59 declined to enter.</p>	<p>n= 141</p> <p>Age: Range 18-64</p> <p>Sex: 24 males 117 females</p> <p>Diagnosis:</p> <p>28% Minor depression by RDC</p> <p>71% Major depressive disorder by RDC</p> <p>Exclusions: Patients that scored 27 or more on the Hamilton score, required referral for psychiatric treatment or had been under psychiatric treatment or had received an adequate course of antidepressants in the previous three months. History of drug or alcohol problems, schizophrenia, significant language problems or a diagnosis of minor of intermittent depression accompanied by a diagnosis of phobic state, generalized anxiety disorder or obsessive compulsive disorder.</p> <p>Notes: Amitriptyline (54F:13M) and Placebo (63F:11M). Minor depression = minor OR intermittent depression.</p> <p>Baseline: HRDS (17): 14.75 (3.65) (ALL)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean change</p>	<p>Group 1 N= 67</p> <p>Amitriptyline - 25-75mg/day by the end of week 1, 100mg/day by the end of week 2 and 125-175mg/day thereafter.</p> <p>Group 2 N= 74</p> <p>Placebo - Unknown.</p>	<p>Funding: pharma (Parke-Davis).</p>
<p>HORMAZABAL1985</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Cianopramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Mixed; unclear.</p> <p>Notes: Parallel groups design.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 60</p> <p>Age: Mean 44 Range 20-93</p> <p>Sex: 9 males 51 females</p> <p>Diagnosis:</p> <p>100% Depression by DSM-III</p> <p>Exclusions: Uncontrolled organic disease, pregnancy or puerperium.</p> <p>Notes: Amitriptyline (20) + Placebo (20) = 40 participants. Depression = depressive episodes. Amitriptyline (3M:17F) and Placebo (4M:16F).</p> <p>Baseline: Cianopramine Amitriptyline Placebo HAMD (21) 38.3 (6.3) 36.7 (6.8) 35.8 (8.1)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Notes: 7 participants in amitriptyline group and 2 participants in placebo group were treated concomitantly with benzodiazepines. 1 amitriptyline participant received phenobarbital.</p>	<p>Group 1 N= 20</p> <p>Amitriptyline. Mean dose 86.4mg/day - Initial dose was 1 capsule/day (25mg) which could be increased depending on efficacy and side-effects.</p> <p>Group 2 N= 20</p> <p>Placebo. Mean dose 4 capsules/day - Initial dose was 1 capsule/day (25mg) which could be increased depending on efficacy and side-effects.</p>	<p>Funding: unknown.</p>
<p>HOSCHL1989</p>				

<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Verapamil vs. Amitriptyline vs. State-adjusted treatment vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 35</p> <p>Setting: Inpatients; Czech Republic</p> <p>Notes: Amitriptyline (24F:2M) and Placebo (10F:1M).</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 86</p> <p>Age: Mean 45</p> <p>Sex: 7 males 79 females</p> <p>Diagnosis:</p> <p>14% Dysthymia by Bipolar disorder</p> <p>12% Major depressive disorder by DSM-III</p> <p>15% Depression by DSM-III</p> <p>5% Affective disorder by DSM-III</p> <p>2% Double depression by DSM-III</p> <p>2% Minor depression by DSM-III</p> <p>1% Chronic depression by DSM-III</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Non-response 50% reduction in HRSD</p> <p>HRSD-17 mean endpoint</p> <p>Notes: HRSD 16. Response was <= 10 on HRSD 16.</p>	<p>Group 1 N= 19</p> <p>Amitriptyline. Mean dose 113mg/day - 75-175mg/day. Dosage depended on the individual.</p> <p>Group 2 N= 11</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Knoll Pharmaceuticals).</p>
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	<p>Notes: Dysthymia = Bipolar (12). MDD (52). Depression = Other (13). Affective disorder = atypical depression (4). Double depression = anxiety (2). Minor depression = schizoaffective (2). Chronic = organic (1). amitriptyline (19) + placebo (11) = 30 participants.</p> <p>Baseline: Verapamil Amitriptyline Placebo HAMD (16) 20.3 (8.7) 24.4 (6.1) 22.2 (8.1)</p>			
ITIL1983A				
<p>Study Type: RCT</p> <p>Study Description: 3 arm study; fluvoxamine vs. imipramine vs. placebo.</p> <p>Type of Analysis: ITT (included if received >2 weeks' medication)</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Not known.</p>	<p>n= 69</p> <p>Age: Mean 41 Range 21-68</p> <p>Sex: 39 males 39 females</p> <p>Diagnosis: 100% Depression by RDC</p> <p>Exclusions: Pregnant women, women of child-bearing potential, patients whose depression was secondary to another illness, patients receiving imipramine or MAO inhibitors within 2 weeks of study commencement, ECT within 4 weeks of study commencement, lithium carbonate, or any short or long-term medication which might interact with either study drug. Not drug dependent, or had any significant organic disease. All had normal EEGs.</p> <p>Notes: 3 classified as bipolar depressed, 20 as single episode and 46 as recurrent MDD. A few patients took concurrent medication. Imipramine (25) + Placebo (22) = 47.</p> <p>Baseline: Placebo Imipramine Fluvoxamine HDRS-16 19.7 (2.7) 21.9 (4.2) 20.3 (3.0)</p>	<p>Data Used</p> <p>Suicide</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p> <p>Notes: HRSD-16 used.</p>	<p>Group 1 N= 25</p> <p>Imipramine. Mean dose 127 - 50-210mg/daily. Initial dose was 50mg, then increased according to participant response.</p> <p>Group 2 N= 22</p> <p>Placebo. Mean dose 173 - 50-750mg. Initial dose of 50mg, increased according to participant response.</p>	Funding; unclear.
ITIL1993				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Dothiepin vs. Doxepin vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 63</p> <p>Setting: Unclear; US.</p> <p>Notes: Parallel groups.</p> <p>Info on Screening Process: 62 participants screened; 25 participants excluded. Did not meet eligibility criteria.</p>	<p>n= 37</p> <p>Age: Mean 37 Range 18-74</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Unknown.</p> <p>Notes: MDD without psychotic features. Dothiepin (13) + Placebo (10) = 23 participants.</p> <p>Baseline: Dothiepin Doxepin Placebo HAM-D 24.9 (4.4) 23.4 (1.7) 22.8 (2.5) MADRS 27.7 (6.3) 24.7 (4.0) 25.4 (3.8)</p>	<p>Data Used</p> <p>MADRS mean endpoint</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p> <p>Data Not Used</p> <p>Non-response 50% reduction in HRSD - no data</p> <p>Notes: Unsure of HRSD version.</p>	<p>Group 1 N= 13</p> <p>Dosulepin (dothiepin) - 50-150mg/day.</p> <p>Group 2 N= 10</p> <p>Placebo - No details.</p>	Funding; pharma (Boots Pharmaceuticals, Inc.).
KASPER1995B				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Mixed; multicentre, US and Canada.</p> <p>Info on Screening Process: Unclear.</p>	<p>n= 338</p> <p>Age: Mean 42</p> <p>Sex: 148 males 194 females</p> <p>Diagnosis:</p> <p>86% Major depressive disorder by DSM-III</p> <p>14% Depression by Bipolar disorder</p> <p>Exclusions: Patients suffering from any severe physical or mental illness, were taking any drug which interact with might test medication, were abusing alcohol or drugs, were pregnant or were not using adequate contraception</p>	<p>Data Used</p> <p>Suicide</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-17 mean endpoint</p> <p>Notes: 16 item HRSD.</p>	<p>Group 1 N= 113</p> <p>Imipramine. Mean dose 151mg/day - Day 1-3: 50mg/day, then adjusted between 50-300mg/day according to response.</p> <p>Group 2 N= 109</p> <p>Placebo - 1-6 capsules/day.</p>	<p>Funding; unknown.</p>
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36

	Notes: Imipramine (113) + Placebo (109) = 222 participants. Imipramine (50M:63F) and Placebo (45M:64F). Baseline: Fluvoxamine Imipramine Placebo HAM-D (16) 23.2 (4.9) 23.1 (5.3) 23.2 (5.1)			
KATZ1990				
<p>Study Type: RCT</p> <p>Study Description: 2-arm study; Nortriptyline vs. Placebo</p> <p>Type of Analysis: Completer</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 49</p> <p>Setting: Community (nursing home or congregate housing residents); US.</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 141 screened; 22% excluded as medically unstable/contraindications to nortriptyline; 23% refused consent; 7.6% psychotic; 5.1% required immediate treatment; 3.8% spontaneous remission; 5 used as pilot patients and received open treatment; 30 in study</p>	<p>n= 30</p> <p>Age: Mean 84</p> <p>Sex: 2 males 28 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: HAM-D-24 < 18; not medically stable; contraindications to nortriptyline</p> <p>Notes: Diagnosis not formally made, but symptoms had to be consistent with DSM-III by research assistants or clinical departments of psychology and/or psychiatry</p> <p>Baseline: Placebo Nortriptyline HAM-D 24 23.7 (4.1) 24.7 (2.5)</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-24 mean endpoint</p> <p>Notes: HAM-D-24 modified to exclude item on genital symptoms</p>	<p>Group 1 N= 18</p> <p>Nortriptyline. Mean dose 65.25 mg - Plasma levels at end of treatment (SD) 75.6 (48.4) ng/mL. Week 1: 25mg/day, increase to 50mg/day during week 2 as tolerated. Further dose increases in 25mg increments were made as needed and as tolerated.</p> <p>Group 2 N= 12</p> <p>Placebo - Comparable dose increments to those in the nortriptyline group were implemented.</p>	SIGN 1+; funding NIMH
KELLAMS1979				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Inpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 28</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Depression by No details</p> <p>Exclusions: Those with a history of brain trauma, alcoholism, drug addiction, seizure disorder, or mental deficiency and patients who had recently undergone electroshock therapy or prolonged drug therapy were excluded. Women at risk of pregnancy.</p> <p>Notes: Imipramine (10) + Placebo (9) = 19 participants. Approximately equal number of each sex per treatment arm.</p> <p>Baseline: Trazadone Imipramine Placebo HAM-D (21) 23.5 25.1 26.9</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 10</p> <p>Imipramine - A maximum dose of 300mg/day. Initial dose was 100mg/day. Daily dosage could be adjusted every 2-3 days if needed, but maximum daily dose could not exceed 300mg/day.</p> <p>Group 2 N= 9</p> <p>Placebo - A maximum dose of 12 capsules/day. Initial dose was 4 capsules/day. Daily dosage could be adjusted every 2-3 days if needed, but maximum daily dose could not exceed 12 capsules.</p>	Funding; unknown.
KLIESER1988				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Trazodone vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 21</p> <p>Setting: Unclear; Germany.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 37</p> <p>Age: Mean 41</p> <p>Sex: 12 males 25 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Amitriptyline (12) + Placebo (14) = 26 participants. Amitriptyline (9F:3M) and Placebo (9F:5M).</p> <p>Baseline: Trazodone Amitriptyline Placebo HAMD 31 (6.8) 34 (8.6) 31 (7.5)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>HRSD-17 mean endpoint</p> <p>Notes: Unclear which HAMD version.</p>	<p>Group 1 N= 12</p> <p>Amitriptyline - 150mg/day</p> <p>Group 2 N= 14</p> <p>Placebo - 4 capsules/day.</p>	<p>Funding; unknown.</p>
<p>LAAKMAN1995</p>				<p>37</p>

<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Alprazolam vs. Amitriptyline vs. Lorazepam vs. Placebo</p> <p>Type of Analysis: ITT (all participated for at least 1 week)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; Germany.</p> <p>Info on Screening Process: 342 screened; 60 dropped out before baseline. Reasons; 20% reduction of HRSD score, HRSD Score <10 in week 0, severe medical condition, suicidality, not allowed additional drug treatment, non-compliance, incorrect scheduling, or documentation lost.</p>	<p>n= 282</p> <p>Age: Mean 47 Range 19-75</p> <p>Sex: 82 males 200 females</p> <p>Diagnosis: 100% Depression by ICD-9</p> <p>Exclusions: Suicidality, severe medical conditions, abnormal laboratory examinations, pregnancy, convulsive disorders, concurrent use of any psychoactive medications, schizophrenic psychosis, personality disorder, alcohol or drug misuse.</p> <p>Notes: Depression = mild to moderate depression. Amitriptyline (72) + Placebo (74) = 146 participants.</p> <p>Baseline: Lorazepam Alprazolam Amitriptyline Placebo HAMD 19.6 (4.5) 20.2 (4.5) 19.7 (4.5) 19.2 (3.7)</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects HRSD-17 mean change</p> <p>Leaving treatment early for any reason Non-response 50% reduction in HRSD</p> <p>Notes: Unsure of HRSD version.</p>	<p>Group 1 N= 72</p> <p>Amitriptyline. Mean dose 102mg/day - 50-200mg/day.</p> <p>Group 2 N= 74</p> <p>Placebo. Mean dose 2.79 tablets/day - No details.</p>	<p>Funding; unknown.</p>
<p>LAIRD1993</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 54</p> <p>Age: Mean 47</p> <p>Sex: 17 males 37 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (14) + Placebo (16) = 20 participants.</p> <p>Baseline: Unknown.</p>		<p>Group 1 N= 14</p> <p>Imipramine. Mean dose 180mg/day - No details.</p> <p>Group 2 N= 16</p> <p>Placebo. Mean dose 240mg/day - No details.</p>	<p>Funding; pharma.</p>
<p>LAPIERRE1987</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients; Canada.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 63</p> <p>Age: Mean 45</p> <p>Sex: 26 males 37 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients with other psychiatric diagnoses that would invalidate the diagnosis of major affective disorder, that had significant organic disease that would put them at risk during the study or would obscure treatment results, or that were physically dependent on licit or illicit drugs. Patients who received any of the following therapies; ECT within 4 weeks prior to the start of the study, lithium carbonate within the prior week, monoamine oxidase inhibitors within the prior 2 weeks, any other antidepressants within 3 days of starting the double-blind phase of treatment, and any drug which could not be discontinued and might interact with study medication.</p> <p>Notes: Imipramine (21) + Placebo (20) = 41 participants. Imipramine (12F:9M) and Placebo (12F:8M).</p> <p>Baseline: None.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 21</p> <p>Imipramine - No details.</p> <p>Group 2 N= 20</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>LAPIERRE1991</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Sertraline vs. Placebo</p> <p>Type of Analysis: Completers</p>	<p>n= 448</p> <p>Age:</p> <p>Sex:</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 123</p> <p>Amitriptyline. Mean dose 111mg/day - Weeks 1-3: 50-150mg/day. Maintained at 150mg/day thereafter.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">38</p>

<p>Blindness: Double blind Duration (days): Mean 56</p> <p>Setting: Outpatients; Canada and US.</p> <p>Notes: There is a H2H study also written up in this article that may be of use.</p> <p>Info on Screening Process: Unknown.</p>	<p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Amitriptyline (123) + Placebo (130) = 253 participants. Bipolar = 11 participants. MD single episode = 203 participants. MD recurrent = 234 participants.</p> <p>Baseline: Unknown. HAM-D (17) data displayed graphically.</p>		<p>Group 2 N= 130</p> <p>Placebo - No details.</p>	
<p>LARSEN1989</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Clomipramine vs. Moclobemide vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients and outpatients; Denmark.</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 38</p> <p>Age: Mean 50 Range 25-76</p> <p>Sex: 13 males 25 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: HAMD-17 < 15; previous manic episodes, adequate treatment already instituted, need for ECT, obvious suicide risk, history of drug or alcohol misuse, noncooperation or unreliability, pregnancy, lactation, abnormal hepatic or renal function, known haematopoietic, metabolic or hormonal disorders, diastolic blood pressure above 100 mmHg; contraindication to TCAs</p> <p>Baseline: Placebo Moclobemide Clomipramine HAMD 17 18.3 (15-27) 17.5 (14-24) 17.8 (15-27)</p>	<p>Data Used</p> <p>Non-remission HRSD-17 < 9</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - Data in graph; no SDs</p>	<p>Group 1 N= 20</p> <p>Clomipramine. Mean dose 150 mg - Day 1: 75mg/day, increased by 25mg/day up to 50mg three times per day (ie. 150mg/day).</p> <p>Group 2 N= 18</p> <p>Placebo - 1 capsule 3 times per day. Increased by 1 capsule daily up to 2 capsules 3 times per day (ie. 6 capsules/day).</p>	<p>SIGN: 1+; funding no details. Baseline statistics are median (range)</p>
<p>LECRUBIER1997B</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Venlafaxine vs. Placebo</p> <p>Type of Analysis: ITT; LOCF method</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 91</p> <p>Setting: Outpatients; France, Italy and UK.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 229</p> <p>Age: Mean 40</p> <p>Sex: 75 males 154 females</p> <p>Diagnosis:</p> <p>14% Minor depression by RDC</p> <p>79% Major depressive disorder by RDC</p> <p>7% Depression by RDC</p> <p>Exclusions: Fulfilled the RDC criteria for phobic anxiety, panic disorder, generalized anxiety disorder or obsessive-compulsive disorder, or if they suffered from bipolar or any psychotic disorder, required in-patient treatment, or were considered at risk from suicide, were pregnant or were using inadequate contraception, or had any significant medical conditions, eg. Seizures, organic mental disorder, or cardiovascular disease within 6 months of starting the study. Patients whose MADRS scores decreased by more than 30% during the screening period, or who had an endogenous depression score of 8 or more on the Newcastle scale (shortened form), were also excluded.</p> <p>Notes: 7% intermittent depression. Imipramine (75) + Placebo (76) = 151 pts. Imipramine (51F:24M) and Placebo (48F:28M).</p> <p>Baseline: Venlafaxine Imipramine Placebo MADRS 24.9 24.4 24.2</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Non-response 50% reduction in MADRS</p>	<p>Group 1 N= 75</p> <p>Imipramine - Day 1: 50mg/day, days 5-7: 75mg/day and days 8-15: 150mg/day. This dose maintained thereafter.</p> <p>Group 2 N= 76</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>LIPMAN1986</p>				<p>39</p>

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Placebo vs. Clordiazepoxide</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 387</p> <p>Age: Mean 38</p> <p>Sex: 158 males 229 females</p> <p>Diagnosis: 75% Major depressive disorder by DSM-III</p> <p>Exclusions: If considered to be less than 'moderately' depressed and/or 'moderately' anxious. No additional psychiatric or medical contraindications such as cardiac disease, kidney disease, glaucoma, liver disease, convulsive disorders, and a history of hypersensitivity to study medications. Psychotic, bipolar, organic, alcoholic, drug addicted, sociopathic, mentally retarded, or functionally illiterate.</p> <p>Notes: Imipramine (116) + Placebo (139) = 255 participants. Imipramine (69F:47M) and Placebo (80F:59M). Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 116</p> <p>Imipramine. Mean dose 150mg - Week 1: 25mg/day, week 2: 50mg/day, week 3: 75mg/day, week 4: 100mg/day and week 5: 150mg/day. During the last four weeks, participants could received eight capsules a day (200mg/day) unless side effects interfered.</p> <p>Group 2 N= 139</p> <p>Placebo - Week 1: 1 capsule/day, week 2: 2 capsules/day, week 3: 3 capsules/day, week 4: 4 capsules, and week 5: 6 capsules/day. Could be increased up to 8 capsules/day depending on the absence or presence of side effects.</p>	<p>Funding: pharma and research (Hoffman, La Roche and NIMH).</p>
<p>LYDIARD1989</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo.</p> <p>Type of Analysis: Completers (at least 2 weeks of treatment)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; part of multicentre study, USA.</p> <p>Notes: 54 entered; 45 completed.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 54</p> <p>Age: Mean 47 Range 23-81</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Not physically healthy, were psychotic or had organic brain syndrome, had a history of bipolar affective disorder, exhibited current depressive symptomatology of less than 1 month and greater than 18 months in duration, were currently taking any psychotropic medication, were substance misusers or exhibited a clear suicidal intent.</p> <p>Notes: Imipramine (18) + Placebo (17) = 35 participants.</p> <p>Baseline: Fluvoxamine Imipramine Placebo HRSD 24.5 26.4 26.0</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 18</p> <p>Imipramine. Mean dose 180mg/day - 100-300mg/day.</p> <p>Group 2 N= 17</p> <p>Placebo. Mean dose 240mg/day - No details.</p>	<p>Funding: pharma.</p>
<p>LYDIARD1997</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Sertraline vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Info on Screening Process: 473 participants screened; 81 excluded. Reasons unknown.</p>	<p>n= 392</p> <p>Age: Mean 40</p> <p>Sex: 131 males 261 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Acute or chronic organic mental disorder, organic brain syndrome, dysthymia, bipolar disorder, severe generalised anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, paranoid disorders, psychotic disorders not elsewhere classified, or severe personality disorders. Subjects with significant medical illness, a recent history of substance misuse or dependence, current suicide risk, history of neurologic disease, or narrow-angle glaucoma, or significant prostrate symptoms. Required additional psychotropic drugs during the study, had previously received sertraline, were within 1 month of participation in an investigational drug study, had failed to respond to adequate trials of two or more antidepressants, had received any depot neuroleptic within 6 months, had received fluoxetine within 1 month, had taken any daily psychotropic medication within 2 weeks, or had received MAOIs within 2 weeks of baseline. Patients with</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>BDI mean endpoint</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 131</p> <p>Amitriptyline. Mean dose 103.1mg./day - Initial dose at 50mg/day. This could be increased to 100mg/day at week 2, 125mg/day at week 4 and 150mg/day at week 5.</p> <p>Group 2 N= 129</p> <p>Placebo - No details.</p>	<p>Funding: pharma.</p>
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	<p>significant laboratory or ECG abnormalities.</p> <p>Notes: Amitriptyline (131) + Placebo (129) = 260 participants. Amitriptyline (90F:41M) and Placebo (86F:43M). MDD Single = 128 participants. MDD Recurrent = 264 participants.</p> <p>Baseline: Amitriptyline Sertraline Placebo (Note: SE in brackets)</p> <p>HAM-D 22.1 (0.26) 21.5 (0.24) 22.1 (0.25)</p> <p>BDI 15.0 (0.56) 14.6 (0.56) 14.3 (0.57)</p>			
MARCH1990				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US</p> <p>Notes: 54 participants entered study. 40 completed.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 54</p> <p>Age: Mean 39</p> <p>Sex: 17 males 37 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Pregnant women, lactating women, women of childbearing potential who were taking inadequate contraceptive measures, patients with schizophrenia, psychotic symptoms, organic dementias, or a diagnosis within 1 year of substance misuse or alcoholism, patients with cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, or other systemic diseases that could interfere with the diagnosis, treatment, or assessment of depression, patients who required treatment with any concurrent medication that might interact with or obscure the action of the study medications, patients with clinically significant abnormalities in electrocardiographic or laboratory results, patients with multiple drug allergies, patients who had received monoamine oxidase inhibitors or lithium in the 2 weeks preceding study entry or who had received any other antidepressant drugs in the preceding 1 week, and patients who had received any investigational drug or ECT in the previous 4 weeks.</p> <p>Notes: Imipramine (15) + Placebo (12) = 27 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>MADRS mean endpoint - no data</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 15</p> <p>Imipramine - Days 1-3: 50 mg/day, days 4-7: 100mg/day, days 8-14: 150mg/day. After day 14, dose could be increased to a maximum of 300mg/day depending on clinical response.</p> <p>Group 2 N= 12</p> <p>Placebo - Days 1-3: 1 capsule/day, days 4-7: 2 capsules/day, days 8-14: 3 capsules/day and from thereon up to 6 capsules a day depending on clinical response.</p>	<p>Funding; part-pharma (Kali-Duphar Laboratories).</p>
MARKOWITZ1985				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Phenelzine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Unclear; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 238</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Depression by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Imipramine (80) + Placebo (77) = 157 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 80</p> <p>Imipramine - At least 200mg.</p> <p>Group 2 N= 77</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>

MENDELS1986				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT: LOCF (at least 1 week of treatment)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p>	<p>n= 98</p> <p>Age: Mean 37</p> <p>Sex: 53 males 45 females</p> <p>Diagnosis: 100% Major depressive disorder by No details</p> <p>Exclusions: Pregnant women and those who could become</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 34</p> <p>Imipramine. Mean dose 167mg/day - No details.</p> <p>Group 2 N= 34</p> <p>Placebo. Mean dose 3.7 capsules/day - No details.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">41</p>

<p>Setting: Outpatients; US. Notes: 107 participants entered the study. Info on Screening Process: Unknown.</p>	<p>pregnant, patients having significant liver, kidney, gastrointestinal, cardiovascular or pulmonary disease. Patients who were allergic to benzodiazepines or imipramine or addicted to alcohol or other drugs. Individuals who were taking a psychotropic drug, a potent analgesic, or an antihistamine, who had taken another investigational drug within the past month, or who had taken other antidepressants, major tranquilizers, or benzodiazepines within the past 7 days. Notes: Imipramine (34) + Placebo (34) = 69 participants. Baseline: Unknown.</p>			
<p>MERIDETH1983</p> <p>Study Type: RCT Study Description: 3-arm study; Zimeldine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 140 randomised but efficacy data only available for 106 and safety data for 119. Info on Screening Process: Unknown.</p>	<p>n= 140 Age: Mean 43 Range 20-64 Sex: 33 males 86 females Diagnosis: 100% Major depressive disorder by RDC Exclusions: Patients not meeting entry criteria at the end of the washout study. Patients with somatic diseases, drug allergy, schizophrenia, epilepsy, or a history of drug or alcohol misuse were excluded from the trial, as were women of child-bearing age potential and lactating or pregnant women. Notes: Imipramine (38) + Placebo (42) = 80 participants. Imipramine (8M:30F) and Placebo (10M:32F). Unclear to which groups initial dropouts allocated so split 140 between 3 groups. Baseline: HAM-D (21): Unknown. Estimate about 26.0</p>	<p>Data Used Non-response 50% reduction in HRSD Data Not Used Leaving treatment early due to side effects - Only given for safety sample Leaving treatment early for any reason - Not clear HRSD-21 mean endpoint - no variability measure Notes: Number who did not take study drugs or for whom no data were available not given by treatment group; safety sample N used for leaving treatment early due to side effects so not extracted</p>	<p>Group 1 N= 46 Imipramine - Between 100-300mg/day. Group 2 N= 47 Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>MINDHAM1991</p> <p>Study Type: RCT Study Description: 4-arm study; Dothiepin vs. Diazepam vs. Sulpride vs. Placebo Type of Analysis: Completers (71 participants entered study) Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; unclear. Notes: Where a patient was lost to the study a further patient was substituted on the same treatment. Info on Screening Process: Unknown.</p>	<p>n= 51 Age: Mean 40 Range 17-64 Sex: 26 males 25 females Diagnosis: 50% Depression by ICD-10 50% Affective disorder by ICD-9 Exclusions: Unknown. Notes: Depression = depressive neurosis (ICD 300.4). Affective disorder = manic depressive psychosis depressed type (ICD 296.2). Dothiepin (17) + Placebo (20) = 37 participants. Dothiepin (6M:6F) and Placebo (6M:7F). Baseline: Dothiepin Diazepam Sulpride Placebo MADRS 29.0 29.6 30.1 29.9</p>	<p>Data Used Leaving treatment early for any reason Non-response 50% reduction in MADRS Data Not Used MADRS mean endpoint - no data Notes: MADRS <12.</p>	<p>Group 1 N= 17 Dosulepin (dothiepin). Mean dose 150mg/day - 50mg 3 times a day (150mg/day). Group 2 N= 20 Placebo - No details.</p>	<p>Funding; pharma (The Boots Company).</p>

MYNORSWALLIS1995				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Problem solving therapy vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT (at least 4 sessions completed)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p>	<p>n= 91</p> <p>Age: Mean 37 Range 18-65</p> <p>Sex: 21 males 70 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Another psychiatric disorder before the onset of the depression. receiving current psychological or</p>	<p>Data Used</p> <p>Non-remission HRSD-17 < 7</p> <p>BDI mean endpoint</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 31</p> <p>Amitriptyline. Mean dose 139mg/day - Days 1-2: 50mg/day, followed by an increase of 25mg every third night until 150mg/day taken.</p> <p>Group 2 N= 30</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Warner-Lambert).</p> <p style="text-align: right;">42</p>

<p>Notes: This was a 12 week study. However, results are reported for 6 weeks only as Placebo Non-responders were withdrawn from the study at 6 weeks.</p> <p>Info on Screening Process: 173 participants referred; 66 excluded because didn't meet entry criteria. 91 agreed to take part.</p>	<p>antidepressant drug treatment, having current psychotic symptoms, having serious suicidal intent, having a history of schizophrenia, recent drug or alcohol misuse, or physical problems that would preclude being able to take amitriptyline.</p> <p>Notes: Amitriptyline (31) + Placebo (30) = 60 participants. Amitriptyline (7M:24F) and Placebo (9M:21F).</p> <p>Baseline: Amitriptyline Problem-Solving Placebo HAM-D (17) 19.1 (4.8) 19.4 (4.9) 18.4 (3.6) BDI 26.3 (8.4) 26.5 (9.9) 25.9 (8.5)</p>			
MYNORSWALLIS1997				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Problem-solving therapy vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Primary care; UK.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 91</p> <p>Age: Mean 37</p> <p>Sex: 21 males 70 females</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Unknown.</p> <p>Notes: Amitriptyline (31) + Placebo (30) = 61 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Non-remission HRSD-17 < 10</p>	<p>Group 1 N= 31</p> <p>Amitriptyline - No details.</p> <p>Group 2 N= 30</p> <p>Placebo - No details.</p>	<p>Funding; research.</p>
NAIR1995				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Moclobemide vs. Nortriptyline vs. Placebo</p> <p>Type of Analysis: ITT (for those completing >3 wks)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 49</p> <p>Setting: Outpatients; Canada, Denmark, England.</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 115 screened</p>	<p>n= 73</p> <p>Age: Mean 71</p> <p>Sex: 21 males 52 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: HAND-17 < 18; other psychiatric/neurological diagnosis; known severe systemic diseases; acute infections; clinically significant laboratory findings; contraindications to study drugs; history of drug/alcohol misuse; cyclic ADs in past week; MAOIs or neuroleptics in past 2 weeks; sleep deprivation or ECT in past month.</p> <p>Notes: Ns don't include moclobemide group</p> <p>Baseline: Placebo Nortriptyline HAM-D 17 24.0 (18-31) 23.5 (18-32)</p>	<p>Data Used</p> <p>Non-remission HRSD-17 < 10</p> <p>Number reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-17 mean change - Data given as medians</p>	<p>Group 1 N= 38</p> <p>Nortriptyline. Mean dose 75 mg - Dose adjusted to maintain serum levels of 50-70ng/ml. 25mg/day increased to 75mg/day by day 3. Day 15, dosage was adjusted depending on the levels of serum nortriptyline on day 8. <50ng/mL=100mg/day, 171-200ng/mL=50mg/day, and >200ng/mL=25mg/day.</p> <p>Group 2 N= 35</p> <p>Placebo - Received 2 pills in the morning, afternoon and evening.</p>	<p>SIGN 1+; funding Roche International. For baseline statistics scores refer to median (range)</p>
NANDI1976				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Placebo vs. Natural Process</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Rural outpatients; India</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 41</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Depression by No details</p> <p>Exclusions: Free from any physical illness.</p> <p>Notes: Imipramine + Placebo = 27 participants.</p> <p>Baseline: Placebo Imipramine HDRS 57.0 (7.0) 60.8 (11.0)</p>	<p>Data Used</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 17</p> <p>Imipramine - 25mg twice a day for two days, then 50mg twice a day.</p> <p>Group 2 N= 10</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>NORTON1984</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo</p>	<p>n= 91</p> <p>Age: Mean 38</p> <p>Sex: 21 males 70 females</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 30</p> <p>Imipramine. Mean dose 153.3mg/day - Treatment was started at 50mg/day for 4 days, rising to 100mg/day for the</p>	<p>Funding; unknown.</p> <p style="text-align: right;">43</p>

<p>Blindness: Double blind Duration (days): Mean 28</p> <p>Setting: Outpatients; UK.</p> <p>Info on Screening Process: Unknown.</p>	<p>Diagnosis: 100% Major depressive disorder by RDC</p> <p>Exclusions: Younger than 18 and older than 65, had depressive symptoms which were manifestations of another current psychiatric illness, such as schizophrenia, an obsessional or phobic state, had previous history of another psychiatric disorder in the last year or previous history at any point of schizophrenia or schizoaffective disorder, were pregnant, had received lithium in the previous 4 weeks, an MAOI in the previous 2 weeks or any other antidepressant in the previous 3 days, had received ECT within the previous 4 weeks, were taking any other medication which could not be safely and ethically stopped or which might interact with the study drugs, had any significant organic illness, were physically dependent on drugs or other addictive agents, presented an episode of depression of less than 2 weeks duration, were unwilling or unable to cooperate in the study.</p> <p>Notes: Imipramine (30) + Placebo (25) = 55 participants. Imipramine (23F:7M) and Placebo (21F:4M).</p> <p>Baseline: Fluvoxamine Imipramine Placebo HRSD-17 19.5 19.6 19.9</p>		<p>remainder of the first week of treatment. Thereafter the dosage was adjusted according to clinical situation.</p> <p>Group 2 N= 25</p> <p>Placebo - Treatment was started at 1 capsule/day for 4 days, rising to 2 capsules/day for the remainder of the first week of treatment. Thereafter the dosage was adjusted according to clinical situation.</p>	
<p>PECKNOLD1976B</p> <p>Study Type: RCT</p> <p>Study Description: 2-arm study; Clomipramine vs. Placebo</p> <p>Type of Analysis: Unclear</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients and outpatients; Canada</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 20</p> <p>Age: Mean 41 Range 20-63</p> <p>Sex: 5 males 15 females</p> <p>Diagnosis: 100% Depression by No details</p> <p>Exclusions: No details</p> <p>Baseline: No details</p>	<p>Data Used Number reporting side effects</p> <p>Data Not Used HRSD-17 mean endpoint - No data given</p> <p>Notes: Results of statistical tests given but no data</p>	<p>Group 1 N= 10</p> <p>Clomipramine. Mean dose 140 mg - Week 1: 75mg/day, week 2: 100mg/day, week 3: 150mg/day and weeks 4-6: 200mg/day.</p> <p>Group 2 N= 10</p> <p>Placebo - Week 1: 75mg/day, week 2: 100mg/day, week 3: 150mg/day and weeks 4-6: 200mg/day.</p>	<p>SIGN 1+; funding unclear</p>
<p>PEDERSEN2002</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study: Imipramine vs. Venlafaxine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Outpatients; US</p> <p>Notes: No details of randomisation given.</p> <p>Info on Screening Process: No details given.</p>	<p>n= 459</p> <p>Age: Mean 41</p> <p>Sex: 148 males 311 females</p> <p>Diagnosis: 100% Depression by No details</p> <p>by No details</p> <p>Exclusions: No details given.</p> <p>Notes: Placebo + Imipramine = 307 participants. Placebo = 39M/81F completers, 52M/106F in total. Imipramine = 33M/62F completers, 52M/98F in total.</p> <p>Baseline: Placebo Venlafaxine Imipramine HAM-D 17 22.0 22.0 22.5</p>	<p>Data Used</p> <p>Leaving treatment early for any reason MADRS mean endpoint HRSD-17 mean endpoint</p>	<p>Group 1 N= 158 Placebo - No details.</p> <p>Group 2 N= 149 Imipramine - No details.</p>	<p>Funding; Wyeth-Ayerst Research (not stated explicitly).</p>
<p>PESELOW1989</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study: Placebo vs. Paroxetine vs. Imipramine.</p> <p>Type of Analysis: Completers</p>	<p>n= 105</p> <p>Age: Mean 45</p> <p>Sex: 67 males 38 females</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 32</p> <p>Imipramine - Dose ranged between 65-275 mg/day.</p>	<p>Funding; no details.</p> <p style="text-align: right;">44</p>

<p>Blindness: Double blind Duration (days):</p> <p>Setting: Inpatients; US Notes: No details of randomisation.</p> <p>Info on Screening Process: 137 screened; 32 excluded. 15 did not meet criteria after single-blind phase. Unclear why remaining 17 did not enter.</p>	<p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Hamilton score dropped below 18 or more than 20% from pre-single blind phase.</p> <p>Notes: No baseline or final HAM-D scores given. Imipramine + Placebo = 72 participants. Imipramine (32). Placebo (39). Imipramine = 22M/10F. Placebo = 24M/15F.</p> <p>Baseline: Placebo (HAM-D 21): 26.93</p>		<p>Group 2 N= 39 Placebo - No details.</p>	
<p>PESELOW1989B</p> <p>Study Type: RCT Study Description: 3-arm study; Paroxetine HCl vs. Imipramine HCl vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42</p> <p>Setting: Outpatients; US. Info on Screening Process: Unknown.</p>	<p>n= 122 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown. Notes: Imipramine (40) + Placebo (42) = 82 participants. Baseline: Unknown.</p>	<p>Data Used Leaving treatment early for any reason Leaving treatment early due to side effects Non-response 50% reduction in HRSD MADRS mean change HRSD-17 mean change</p>	<p>Group 1 N= 40 Imipramine - 65-275mg/day. Group 2 N= 42 Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>PHILIPP1999</p> <p>Study Type: RCT Study Description: 3-arm study: Imipramine vs. Hypericum extract vs. Placebo Type of Analysis: ITT (251 participants) Blindness: Double blind Duration (days):</p> <p>Setting: Unclear; Germany. Info on Screening Process: No details.</p>	<p>n= 263 Age: Mean 47 Sex: 66 males 197 females Diagnosis: 100% Depression by No details</p> <p>Exclusions: Mild and severe depressive disorders according to ICD-10 codes F32, F33, F32.2, F33.2, F32.3, and F33.3. Bipolar disorders according to ICD-10 codes. Comorbidity from alcohol or drug dependence according to ICD-10 codes F10-19. Suicidal risk. Long term prophylaxis with lithium or carbamazepine. Non-sufficient washout phase of previous psychotropic drug. Any interfering psychotropic drug taken concurrently. Any previous long term (>3 months) treatment with benzodiazepines. Patients at general and specific risk.</p> <p>Notes: Placebo + Imipramine = 157 participants. Placebo = 9M/38F. Imipramine = 31M/79F. Mean age = 45.5.</p> <p>Baseline: Placebo Imipramine Hypericum HDRS-17 22.7 (4.0) 22.2 (4.2) 22.7 (4.2)</p>	<p>Data Used Suicide Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change</p>	<p>Group 1 N= 47 Placebo - No details. Group 2 N= 110 Imipramine - 50mg on first treatment day, 75mg on days 2-4, and 100 mg thereafter.</p>	<p>Funding; Steiner Arzneimittel, Berlin, Germany.</p>
<p>QUITKIN1989</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Phenelzine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Unclear; US.</p> <p>Notes: Could be seen as atypical depression. May need to be excluded.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 60</p> <p>Age: Mean 38</p> <p>Sex: 26 males 34 females</p> <p>Diagnosis:</p> <p>61% Major depressive disorder by RDC</p> <p>16% Minor depression by RDC</p> <p>40% Affective disorder by RDC</p> <p>9% Depression by Bipolar disorder</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 19</p> <p>Imipramine - No details.</p> <p>Group 2 N= 20</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
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	Notes: Imipramine (27) + Placebo (27) = 54 participants. 'Affective disorder' = intermittent depression. Baseline: HAM-D: 14.52 (4.31).			
RAMPELLO1991				
Study Type: RCT Study Description: 4-arm study; Clomipramine vs. Amineptine vs. Minaprine vs. Placebo Type of Analysis: Unclear, probably completer Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients; Italy. Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 20 Age: Range 20-65 Sex: 8 males 12 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Alcoholism; organic brain syndromes; parkinsonism; serious cardiac, hepatic, renal or thyroid diseases; prostate hypertrophy; glaucoma Notes: Sex based on % in whole sample (n=40); no mean age available; diagnosed with 'retarded depression' Baseline: HRSD (SE): Placebo = 16 (0.3), Amineptine =18 (1.0), Minaprine = 19 (0.8), Clomipramine = 16 (0.5)	Data Used Leaving treatment early for any reason Data Not Used HRSD-21 mean endpoint - Ns unclear	Group 1 N= 10 Clomipramine. Mean dose 200 mg - Week 1: 50mg/day, week 2: 100mg/day, and from week 3: 200mg/day. Group 2 N= 10 Placebo - No details.	SIGN 1+; funding unclear
REIMHERR1990				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Sertraline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Parallel groups. 20.8% AMI and 14.7% PLA had concurrent medical diseases.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 448</p> <p>Age: Mean 39 Range 18-64</p> <p>Sex: 207 males 241 females</p> <p>Diagnosis:</p> <p>2% Depression by Bipolar disorder</p> <p>45% Major depressive disorder by DSM-III</p> <p>52% Double depression by DSM-III</p> <p>Exclusions: Not meeting DSM-III criteria for major depression, pregnant or lactating females, and females of childbearing potential not presently using an adequate method of contraception. Patients receiving concurrent psychotropic medication or concomitant medications other than estrogens, progesterone, and diuretics, patients with other significant medical conditions, patients receiving another investigational drug within 4 weeks of enrolling in this study, patients with a history of serious intolerance or resistance to antidepressant medications, patients with an alcohol or drug misuse conditions, and patients with schizophrenia or schizoaffective disorder.</p> <p>Notes: Depression = bipolar disorder. MDD = single episode. Double depression = recurrent depression. Amitriptyline (149) + Placebo (150) = 299 participants. Amitriptyline (65M:84F) and placebo (72M:78F).</p> <p>Baseline: Amitriptyline Sertraline Placebo HAM-D (17) 23.18 (3.63) 23.28 (3.65) 23.43 (3.73)</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change</p>	<p>Group 1 N= 149 Amitriptyline - 50, 100 or 150mg/day.</p> <p>Group 2 N= 150 Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>RICKELS1981</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amoxapine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers (at least 4 weeks' treatment)</p>	<p>n= 158</p> <p>Age: Mean 38 Range 25-57</p> <p>Sex: 58 males 100 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by DSM-III</p> <p>Exclusions: Pregnant, lactating, or planned to become</p>	<p>Data Used</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 43</p> <p>Imipramine - 75-200mg/day. Initial dosage was 75mg/day for the first week. Thereafter, dosage could be adjusted individually according to therapeutic response. Maximum dosage was 200mg/day.</p>	<p>Funding; research (NIMH) .</p> <p style="text-align: right;">46</p>

<p>Blindness: Double blind Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: 96 participants were volunteers with symptoms of depression.</p> <p>Info on Screening Process: Unknown.</p>	<p>pregnant. Patients with schizophrenia, organic brain syndrome, mental retardation, serious impairment of hepatic or renal functions, or cardiovascular or metabolic disease and those with known hypersensitivity to the study drugs. Concomitant therapy with other psychotropic drugs, thyroid medication, or anticholinergic agents was not permitted.</p> <p>Notes: Imipramine (43) + Placebo (27) = 70 participants.</p> <p>Baseline: HAM-D (21): 23.8</p>		<p>Group 2 N= 27</p> <p>Placebo - Up to 8 capsules/day. Started at 3 capsules/day in the first week.</p>	
RICKELS1982A				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Lofepramine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT?</p> <p>Blindness: Double blind Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 158</p> <p>Age: Mean 43 Range 30-56</p> <p>Sex: 54 males 104 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Pregnant, lactatings, or planned to become pregnant. Patients with schizophrenia, organic brain syndrome, or mental retardation, as well as patients suffering from serious impairment of hepatic or renal functions, or cardiovascular or metabolic disease, and those with known hypersensitivity to the study drugs. Concomitant therapy with other psychotropic drugs was not permitted.</p> <p>Notes: Depression: 54% endogenous and 46% reactive subtype. Imipramine (52) + Placebo (52) = 104 participants. Excluded participants who took less than 75mg/day of imipramine from improvement analyses.</p> <p>Baseline: HAM-D (21): 25.9 (5.7)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-21 mean endpoint</p>	<p>Group 1 N= 52</p> <p>Imipramine - 105-210mg/day.</p> <p>Group 2 N= 52</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (EM Industries).</p>
RICKELS1982D				
<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Trazodone vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: HRSD-21 scores all seem very small. Bring up in discussion.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 202</p> <p>Age: Mean 40</p> <p>Sex: 69 males 133 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: 45% endogenous depression. 55% reactive subtype. Amitriptyline (68) + placebo (68) = 136 participants.</p> <p>Baseline: HRSD (21): 1.26 (ALL)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason Number reporting side effects HRSD-21 mean endpoint</p>	<p>Group 1 N= 68</p> <p>Amitriptyline. Mean dose 123.75mg/day - 100mg/day by the end of week 1. Up to 200mg/day.</p> <p>Group 2 N= 68</p> <p>Placebo. Mean dose 135mg/day - No details.</p>	<p>Funding; part-research.</p>
RICKELS1985				

<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Alprazolam vs. Doxepin vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; multicentre, US.</p> <p>Notes: Participants had at least 2 weeks of efficacy data.</p> <p>Info on Screening Process: 605 screened; 101 excluded. Reasons; did not fulfill entry criteria, wished to withdraw for nonmedical reasons, did not cooperate with the physician or were</p>	<p>n= 504</p> <p>Age: Mean 39</p> <p>Sex: 171 males 333 females</p> <p>Diagnosis: 100% Major depressive disorder by Feighner criteria</p> <p>Exclusions: Patients who were psychopathic or psychotic, patients with bipolar, involuational, schizoaffective depression or suffering from secondary depression, patients with severe liver or kidney disease, uncontrolled cardiovascular, pulmonary, endocrinological, or collagen diseases, glaucoma, or conditions in which use of TCAs is contraindicated, including patients with a history of urinary</p>	<p>Data Used</p> <p>HRSD-21 mean endpoint</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>Non-response 50% reduction in HRSD - no data</p>	<p>Group 1 N= 124</p> <p>Amitriptyline. Mean dose 148mg/day - 50mg to start, increasing to 75mg/day by day 3. From then on could increase to 225mg/day.</p> <p>Group 2 N= 130</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
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<p>unavailable for follow-up.</p>	<p>known to be sensitive to benzodiazepines or antidepressants or actively abusing alcohol or other drugs, requiring other psychotropic medications, anticholinergics, sympathomimetic amines, guanethidine, propranolol, methyldopa or thyroid medications.</p> <p>Notes: Amitriptyline (124) + placebo (130) = 254 participants.</p> <p>Baseline: HAM-D (21): 26.6 (5.4) (ALL)</p>			
RICKELS1987				
<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Diazepam vs. Alprazolam vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 241</p> <p>Age: Mean 39</p> <p>Sex: 92 males 149 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Psychopathy or psychosis, bipolar, involuntal, schizoaffective, or secondary depression, severe liver or kidney disease, uncontrolled cardiovascular, pulmonary, endocrinological, or collagen diseases, glaucoma, history of urinary retention, paralytic ileus, convulsive disorders, and any disorder contraindicating the use of tricyclic medication. Patients known to be sensitive to benzodiazepines or antidepressants, actively abusing alcohol or other drugs, or requiring other psychotropic medications, anticholinergics, guanethidine, propranolol, methyldopa, or thyroid medications.</p> <p>Notes: Imipramine (63) + Placebo (61) = 124 participants.</p> <p>Baseline: Alprazolam Imipramine Placebo Diazepam HRSD-21 23.2 24.4 24.5 23.7</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Leaving treatment early for any reason</p> <p>Non-response 50% reduction in HRSD</p> <p>HRSD-21 mean endpoint</p>	<p>Group 1 N= 63</p> <p>Imipramine. Mean dose 143mg/day - Days 1-3: 75mg/day, and days 4-7: 100mg/day. Thereafter, dosages were increased to 150mg/day unless side effects prevented such an increase.</p> <p>Group 2 N= 61</p> <p>Placebo. Mean dose 6.8 capsules/day - Days 1-3: 3 capsules/day, and days 4-7: 4 capsules/day. Thereafter, dosage could be increased to 6 capsules/day.</p>	<p>Funding; unclear.</p>
RICKELS1991				
<p>Study Type: RCT</p> <p>Study Description: 4-arm study; Imipramine vs. Adinazolam vs. Diazepam vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: Between-participants design.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 259</p> <p>Age: Mean 42</p> <p>Sex: 114 males 145 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Patients with other psychiatric disorders, history of convulsive disorder, significant uncontrolled medical conditions, individuals adversely affected by benzodiazepines or tricyclics, and those who were abusing street drugs and/or alcohol. Patients with conditions such as glaucoma, urinary retention, or convulsive disorders.</p> <p>Notes: Imipramine (64) + placebo (67) = 131 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p> <p>Notes: Response rates correspond to patients who completed at least 2 weeks' medication only</p>	<p>Group 1 N= 64</p> <p>Imipramine - 25-150mg/day by the end of week 1.</p> <p>Group 2 N= 67</p> <p>Placebo - No details.</p>	<p>Funding; Upjohn company.</p>
ROFFMAN1982				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Oxaprotiline vs. Amitriptyline vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; USA.</p> <p>Notes: Parallel groups.</p>	<p>n= 278</p> <p>Age: Mean 44 Range 18-65</p> <p>Sex: 152 males 126 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-II</p> <p>Exclusions: History or evidence of clinically significant renal disease, BUN or creatinine elevations, hepatic disease, SGOT, SGPT, or alkaline phosphatase elevations</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 94</p> <p>Placebo - No details.</p> <p>Group 2 N= 95</p> <p>Amitriptyline - 75mg at start - could be increased to 150mg/day at visit three.</p>	<p>Funding; unknown.</p>
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48

<p>Info on Screening Process: 358 participants entered single-blind washout period; 50 excluded. 30 not included because of violations of protocol.</p>	<p>cardiovascular diseases, metabolic diseases, seizure disorders, hypersensitivity to TCAs or related compounds, cerebrovascular disease, drug misuse, alcoholism or endocrine disease. Patients with adjustment disorders, manic-depressive illness, recurrent type schizophrenia and primary anxiety disorder.</p> <p>Notes: No details of which DSM version. Amitriptyline (95) + Placebo (94) = 189 participants. Amitriptyline (53M:42F) and Placebo (54M:40F).</p> <p>Baseline: Amitriptyline Oxaprotiline Placebo HAM-D (SE) 24.2 (0.52) 24.8 (0.50) 24.5 (0.43)</p>	<p>Notes: Unsure of HRSD version.</p>		
<p>ROWAN1982</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Phenelzine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; UK.</p> <p>Notes: Randomised using minimisation.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 131</p> <p>Age: Mean 37</p> <p>Sex: 38 males 93 females</p> <p>Diagnosis: 100% Depression by RDC</p> <p>Exclusions: Severe depressives, those requiring inpatient treatment, typical endogenous depressives scoring 8 or more on the short Newcastle Scale, and bipolar manic-depressives. Those patients with physical illness, those already receiving an antidepressant in adequate dosage, and those with depressions subsidiary to another predominant syndrome were also excluded.</p> <p>Notes: Included participants with depression or depression and anxiety. Amitriptyline (44) + Placebo (45) = 89 participants. Amitriptyline (31F:13M) and Placebo (33F:12M).</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 44</p> <p>Amitriptyline - Week 1: 75mg/day, week 2: 112.5mg/day, weeks 3 and 4: 150mg/day. From thereon dosage could be increased to a maximum of 187.5mg/day during weeks 5 and 6.</p> <p>Group 2 N= 45</p> <p>Placebo - No details.</p>	<p>Funding; part-pharma (Warner-Lambert).</p>
<p>SCHWEIZER1994</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Venlafaxine vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT; LOCF method</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Info on Screening Process: 224 participants entered study. 213 completed.</p>	<p>n= 224</p> <p>Age: Mean 42</p> <p>Sex: 75 males 149 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Affective illness was bipolar, required hospitalisation, or was primarily psychotic. Reported marked suicidal ideation, recent (in the past 2 years) alcohol or drug dependence or misuse, any acute or unstable medical problem, or a history of seizures. Women capable of becoming pregnant were required to use a medically approved form of birth control and were admitted to the study only if a beta-human chorionic gonadotropin test was negative.</p> <p>Notes: Imipramine (73) + Placebo (78) = 151 participants. Imipramine (28M:45F) and Placebo (26M:52F).</p> <p>Baseline: HAM-D (21): 24.77 (3.07)</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>MADRS mean change</p> <p>HRSD-21 mean change</p>	<p>Group 1 N= 73</p> <p>Imipramine. Mean dose 176mg/day - Initiated at 25mg/day. Thereafter, patients were instructed to take their study medication twice daily immediately after meals with 50mg/day for 3-7 days before increasing to 100mg/day for 7 days. On Day 15, had the option to increase to 150mg/day.</p> <p>Group 2 N= 78</p> <p>Placebo - Initiated at 1 capsule/day. Thereafter, patients were instructed to take their study medication twice daily immediately after meals with 2 cap/day for 3-7 days before increasing to 4cap/day for 7 days. On Day 15, had the option to increase to 6cap/day.</p>	<p>Funding; pharma (Wyeth-Ayerst Laboratories).</p>
<p>SCHWEIZER1998</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Buspirone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p>	<p>n= 177</p> <p>Age: Mean 72 Range 65-89</p> <p>Sex: 83 males 94 females</p> <p>Diagnosis:</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>Number reporting side effects</p>	<p>Group 1 N= 60</p> <p>Imipramine - Week 1: 25mg/day, week 2: 100mg/day and thereafter could be increased to 150mg/day.</p>	<p>Funding; pharma (Bristol Myers Squibb Pharmaceuticals).</p> <p style="text-align: right;">49</p>

<p>Blindness: Double blind Duration (days): Mean 56 Setting: Unclear; US. Info on Screening Process: Unknown.</p>	<p>100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Alzheimer's disease or other dementia, a current or past history of psychosis, schizophrenia, schizoaffective disorder, or bipolar disorder, a current or past history of seizures or glaucoma, or any acute or unstable medical condition, including Parkinson's disease, unstable endocrine dysfunctions, or cancer in the past 5 years.</p> <p>Notes: Imipramine (60) + Placebo (60) = 120 participants.</p> <p>Baseline: Imipramine Buspirone Placebo HAM-D 17 23.9 (4.0) 24.1 (3.9) 24.1 (4.2)</p>	<p>HRSD-17 mean change</p>	<p>Group 2 N= 60 Placebo - Week 1: 1 capsule/day, week 2: 2 capsules/day and from thereon up to 3 capsules/day.</p>	
<p>SHRIVASTAVA1992</p> <p>Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 120 participants entered study. Info on Screening Process: Unknown.</p>	<p>n= 107 Age: Mean 35 Sex: 65 males 42 females Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: History of mania, alcohol or drug misuse within the previous 6 months, seizure disorder, or a clinically significant medical condition. History of glaucoma or urinary retention. Women that were pregnant, breast-feeding or not using an effective means of contraception.</p> <p>Notes: Imipramine (38) + Placebo (36) = 74 participants. Imipramine (21M:17F) and Placebo (22M:14F).</p> <p>Baseline: Paroxetine Imipramine Placebo HAM-D (17) 27.6 (0.64) 26.3 (0.60) 26.7 (0.62)</p>	<p>Data Used Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-17 mean change</p>	<p>Group 1 N= 38 Imipramine - 65-275mg/day. Week 1: 80mg/day. Week 2: could be lowered to 65mg/day. Could also be increased until by week 3, patients could be taking up to 275mg/day.</p> <p>Group 2 N= 36 Placebo - No details.</p>	<p>Funding; pharma (SmithKline Pharmaceuticals).</p>
<p>SILVERSTONE1994</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo</p> <p>Type of Analysis: Completers</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Multicentre; UK.</p> <p>Info on Screening Process: Unclear.</p>	<p>n= 249</p> <p>Age:</p> <p>Sex: 111 males 138 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: Patients at risk of suicide, with mood-incongruent symptoms, confusional states, or whose depression was due to another psychiatric illness or organic factor. Patients with any significant physical disease, or a history of increased intraocular pressure, glaucoma, or micturition disturbances. Patients who had received ECT or an investigational drug within the last 4 weeks, an MAOI within the last 2 weeks or other marketed antidepressants, lithium, or carbamazepine within the last 7 days.</p> <p>Notes: 89 participants withdrew; data is from 160 participants? Imipramine (50) + Placebo (54) = 104 participants.</p> <p>Baseline: HDRS 17: 24.9 (4.9)</p>	<p>Data Used</p> <p>Suicide</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 50</p> <p>Imipramine - Started on 25mg. 75mg for week 1. 150mg thereafter.</p> <p>Group 2 N= 54</p> <p>Placebo - No details.</p>	<p>Funding; unclear.</p>
<p>SMALL1981</p> <p>Study Type: RCT</p> <p>Study Description: 4-arm study; ECT vs. Trazodone vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT?</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p>	<p>n= 263</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis: 100% Major depressive disorder by RDC</p>	<p>Data Used</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 100</p> <p>Imipramine - No details.</p> <p>Group 2 N= 72</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">50</p>

<p>Setting: Unclear; multicentre, US. Info on Screening Process: Unknown.</p>	<p>Exclusions: Unknown. Notes: Imipramine (100) + Placebo (72) = 172 participants. Baseline: Unknown.</p>			
<p>SMITH1990</p> <p>Study Type: RCT Study Description: 3-arm study; Mirtazapine vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 10 participants (3 mirtazapine, 3 amitriptyline and 4 placebo) took medication for less than 2 weeks and were not included in efficacy analysis. Info on Screening Process: Unknown.</p>	<p>n= 150 Age: Mean 43 Sex: 64 males 86 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Primary diagnosis of schizophrenia, atypical depression, anxiety, adjustment disorder, bipolar disorder, if they were known drug or alcohol misusers or had known active suicidal tendencies of known cognitive deficiencies. Free of significant renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease, free of narrow angle glaucoma, prostatic hypertrophy, and seizure disorders, and with no clinically relevant abnormal laboratory values or significantly abnormal ECG findings. Notes: Amitriptyline (47) + Placebo (46) = 93 participants. Baseline: Mirtazapine Amitriptyline Placebo HAM-D 17 23.4 23.7 23.3</p>	<p>Data Used Leaving treatment early for any reason Leaving treatment early due to side effects Non-response 50% reduction in HRSD MADRS mean change HRSD-17 mean change</p>	<p>Group 1 N= 47 Amitriptyline. Mean dose 111mg/day - Week 1: max 80mg/day, week 2: max 160mg/day, and weeks 3-6: max 280mg/day. Group 2 N= 46 Placebo. Mean dose 4.6 capsules/day - Week 1: 2 capsules/day, week 2: 4 capsules/day and weeks 3-6: seven capsules/day.</p>	<p>Funding; unknown but suspect pharma.</p>
<p>SPRING1992</p> <p>Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Clovoxamine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Info on Screening Process: Unknown.</p>	<p>n= 35 Age: Mean 35 Sex: 13 males 22 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Women who were pregnant or of childbearing potential and not taking effective contraceptive measures, patients whose depression was secondary to another psychiatric disorder, and patients with significant organic disease or drug dependency. Notes: Amitriptyline (10) + Placebo (15) = 25 participants. Amitriptyline (2M:8F) and Placebo (6M:9F). Baseline: Amitriptyline Clovoxamine Placebo HAM-D (21) 25.2 (2.8) 24.2 (2.3) 24.8 (4.5)</p>	<p>Data Used HRSD-21 mean endpoint</p>	<p>Group 1 N= 10 Amitriptyline. Mean dose 114 mg/day - 50-350 mg/day. Group 2 N= 15 Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>STASSEN1993</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Amitriptyline vs. Oxaprotiline vs. Placebo</p> <p>Type of Analysis: ITT; LOCF</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 40</p> <p>Setting: Unclear; multicentre, US.</p> <p>Notes: Says it is a meta-analysis. Appears to be a secondary analysis of an earlier study.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 429</p> <p>Age: Range 17-73</p> <p>Sex: 154 males 275 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Unknown.</p> <p>Notes: Amitriptyline (120) + Placebo (189) = 309 participants.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Leaving treatment early due to side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Data Not Used</p> <p>HRSD-21 mean endpoint - no data</p>	<p>Group 1 N= 189</p> <p>Placebo - No details.</p> <p>Group 2 N= 120</p> <p>Amitriptyline - Weeks 1 and 2: 75-225mg/day. Kept at 225mg/day thereafter.</p> <p>Group 3 N=</p>	<p>Funding; unclear.</p>
<p>THOMPSON2001B</p>				

<p>Study Type: RCT</p> <p>Study Description: 2-arm study; Dothiepin vs. Placebo</p> <p>Type of Analysis: ITT; LVCF (included those who returned at 2-weeks)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Unclear; UK.</p> <p>Notes: This study should not be read as a clinical trial of the efficacy of dothiepin. GPs administered all tests after receiving training. Sex ratio only.</p> <p>Info on Screening Process: 79 participants screened; 27 did not enter trial. Reasons unknown for 11 participants. 6 attempted suicide, 7 had treatment for depression in the past 6 months and for 3 there was refusal of consent and/or moving out of the area during the study.</p>	<p>n= 52</p> <p>Age:</p> <p>Sex:</p> <p>Diagnosis:</p> <p>58% Major depressive disorder by RDC</p> <p>27% Depression by RDC</p> <p>Exclusions: Pregnant, breast-feeding, had a known allergy to dothiepin, a history of glaucoma, existing or potential urinary retention, epilepsy, or cardiovascular disorder, or impaired renal or hepatic function. Patients who had received antipsychotic therapy within the previous 5 years or antidepressant therapy within 6 months, who required a referral to hospital or immediate medication, or who were unlikely to be able to complete self-rating questionnaires.</p> <p>Notes: Estimate roughly 30F and 20M. participants entered according to 'existing' diagnoses of depression unless otherwise suspected by GP. Depression = endogenous (RDC). Remaining participants either probable major and/or endogenous depression.</p> <p>Baseline: Unknown. Used HRSD-17.</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Number reporting side effects</p> <p>Data Not Used</p> <p>HRSD-17 mean endpoint - no data</p>	<p>Group 1 N= 25</p> <p>Dosulepin (dothiepin). Mean dose 75mg/day - 75mg/day.</p> <p>Group 2 N= 27</p> <p>Placebo - No details.</p>	<p>Funding: part-pharma (Boots Company PLC).</p>
<p>UCHA1990</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT?</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; Argentina.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 72</p> <p>Age: Mean 43 Range 19-66</p> <p>Sex: 18 males 44 females</p> <p>Diagnosis:</p> <p>Exclusions: Unknown.</p> <p>Notes: Very little data provided. Summarised. May need to be excluded.</p> <p>Baseline: Unknown.</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Data Not Used</p> <p>HRSD-17 mean change - no data</p>	<p>Group 1 N= 24</p> <p>Imipramine - 33.3mg-200mg/day.</p> <p>Group 2 N= 24</p> <p>Placebo - No details.</p>	<p>Funding: unclear.</p>
<p>VERSIANI1989</p>				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; South America.</p> <p>Notes: 1 M patient and 2 I patients were receiving lithium on entry and continued to be treated with it throughout the study.</p> <p>Info on Screening Process: Unknown.</p>	<p>n= 490</p> <p>Age: Mean 42 Range 18-69</p> <p>Sex: 117 males 373 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Marked suicidal intent, other psychiatric illness, severe organic disease, alcoholism, and drug misuse. Patients were also required not to have the usual contraindications to treatment with TCAs.</p> <p>Notes: Imipramine (164) + Placebo (162) = 326 participants. Imipramine (38M:126F) and Placebo (39M:123F). Monopolar = 51.8%. Bipolar = 6.8%.</p> <p>Baseline: Moclobemide Imipramine Placebo HRSD-17 26 (5.4) 25.5 (5.1) 25.4 (5.0)</p>	<p>Data Used</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HRSD-17 mean endpoint</p>	<p>Group 1 N= 164</p> <p>Imipramine. Mean dose 159mg/day - Day 1: 33.3mg/day, Day 2: 66.6mg/day, Day 4: 100mg/day and from thereon up to 200mg/day.</p> <p>Group 2 N= 162</p> <p>Placebo - No details.</p>	<p>Funding; unknown.</p>
<p>VERSIANI1990</p> <p>Study Type: RCT</p> <p>Study Description: 3-arm study; Imipramine vs. Moclobemide vs. Placebo.</p> <p>Type of Analysis: Unclear</p>	<p>n= 75</p> <p>Age:</p> <p>Sex: 25 males 50 females</p>		<p>Group 1 N= 25</p> <p>Imipramine. Mean dose 200mg/day - No details.</p>	<p>Funding; unknown.</p> <p style="text-align: right;">52</p>

Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; South America. Info on Screening Process: Unknown.	Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Unknown. Notes: Summarised. Parallel groups. Imipramine (25) + Placebo (25) = 50 participants. Baseline: Unknown.		Group 2 N= 25 Placebo - No details.	
WAKELIN1986				
Study Type: RCT Study Description: 3-arm study; Imipramine vs. Fluvoxamine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients and inpatients; Netherlands. Info on Screening Process: Unclear.	n= 76 Age: Mean 65 Sex: 20 males 55 females Diagnosis: 100% Affective disorder by DSM-III Exclusions: Unknown. Notes: Imipramine (29) + Placebo (14) = 43 participants. Imipramine (6M:23F) and Placebo (6M:8F). Data is taken from previous studies. Baseline: HRSD (17): 25.1	Data Used Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint	Group 1 N= 29 Imipramine. Mean dose 160mg/day - 150-300mg/day. Group 2 N= 14 Placebo. Mean dose 170mg/day - No details.	Funding; unclear.
WHITE1984A				
Study Type: RCT Study Description: 3-arm study; Nortriptyline vs. Tranylcypromine vs. Placebo. Type of Analysis: Completer Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Notes: RANDOMISATION: randomised, no details except stratified by endogenous/non-endogenous and by gender Info on Screening Process: No details	n= 120 Age: Mean 37 Sex: 66 males 54 females Diagnosis: 100% Major depressive disorder by Spitzer Exclusions: Schizophrenia; cerebral dysfunction; glaucoma; urinary retention; hyperthyroidism; diabetes; asthma; cardiovascular disease; hypertension; pheochromocytoma; liver disease. Notes: N male/female based on % male of total N (183); patients classified endogenous (20%) or not (80%) based on RDC criteria Baseline: Placebo Nortriptyline Tranylcypromine HAM-D 27.0 (6.9) 25.2 (6.7) 26.8 (7.4)	Data Used HRSD-21 mean change Leaving treatment early for any reason Notes: Assumed HAMD-21 as baseline scores high	Group 1 N= 61 Nortriptyline. Mean dose 109.4 mg - Dosage could be varied at the discretion of the treating psychiatrist between 75 to 150mg/day. Group 2 N= 59 Placebo - Dosage could be varied at the discretion of the treating psychiatrist between 2-6 capsules/day.	SIGN 1+; funding unclear
WILCOX1994				

<p>Study Type: RCT</p> <p>Study Description: 3-arm study; Placebo vs. Mianserin vs. Amitriptyline</p> <p>Type of Analysis: ITT (at least 1 evaluable visit 2wks post-base)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; US.</p> <p>Notes: 10 participants excluded from ITT analyses because there were no post-baseline data available.</p> <p>Info on Screening Process: 217 enrolled; 68 excluded. Reasons unknown.</p>	<p>n= 149</p> <p>Age: Mean 41</p> <p>Sex: 76 males 73 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III</p> <p>Exclusions: Clinically significant renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease, narrow-angle glaucoma, clinically significant prostatic hypertrophy, seizure disorders, drug allergies or other hypersensitivity reactions to TCAs or related compounds, hyperthyroidism, history of blood dyscrasias from the use of TCAs for prior episodes of depression, primary psychiatric diagnoses of schizophrenia, anxiety, adjustment disorder or bipolar disorder.</p> <p>Notes: Amitriptyline (50) + Placebo (49) = 99 participants. Amitriptyline (26M:24F) and Placebo (26M:23F), 58 participants = recurrent depression. 91 participants = single</p>	<p>Data Used</p> <p>HRSD-21 mean endpoint</p> <p>Number reporting side effects</p> <p>Non-response 50% reduction in HRSD</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to side effects</p> <p>MADRS mean endpoint</p> <p>Weight mean change (kg)</p>	<p>Group 1 N= 50</p> <p>Amitriptyline. Mean dose 121.8mg/day - Week 1: 120mg/day and weeks 2-6: 300mg/day.</p> <p>Group 2 N= 49</p> <p>Placebo. Mean dose 3.1 capsules/day - 2-5 capsules/day.</p>	<p>Funding; pharma (Organon, Inc.).</p>
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	episode.			
	Baseline: Amitriptyline	Mianserin	Placebo	
	HAM-D (21) 25.8	25.7	25.5	
	MADRS 30.6	30.6	29.4	

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
36	No data to extract. (Fluvoxamine vs. Imipramine vs. Placebo).
37	No data to extract. (Imipramine vs. Placebo vs. CBT vs. IPT).
AGOSTI1991	Couldn't extract any data. (Imipramine vs. Placebo vs. Phenelzine vs. L-Deprenyl).
AGOSTI1993	No data to extract. (Phenelzine vs. Imipramine vs. Placebo).
AGOSTI1999A	No data to extract. (IPT vs. CBT vs. ICM vs. P-CM).
AGOSTI2002	No data to extract. (Imipramine vs. Fluoxetine vs. Placebo).
AGOSTI2002A	Sample drawn from a series of studies. (Imipramine vs. Phenelzine vs. L-deprenyl vs. Mianserin vs. Desipramine vs. Placebo).
AINSLIE1965	No formal diagnosis
ALEXOPOULOS2000	Continuation study
ANON1993H	Continuation therapy
ANON1995H	Case study
ANON2005F	Bipolar
ANTON1994	Continuation trial
ARNOLD1981	Healthy Ss
ASBERG1973	Not an RCT
ASBERG1974	Not a controlled study
ASHTON1978	Healthy participants
BAKISH1993A	Dysthymia (Imipramine vs. Ritanserin vs. Placebo).
BAKISH1994	Dysthymia only
BALESTRIERI2004	Not RCT
BAN1982	N too small (8)
BASSA1965	No data to extract. (Imipramine vs. Placebo).
BAUER2000	Augmentation study
BECH1978	No relevant comparison
BECH1989	Not diagnosed according to recognised formal system; focus of study is on pain symptoms (clomipramine vs placebo vs mianserin)
BELL1992	Augmentation study
BELLAK1966	No data to extract. (Imipramine vs. MAO).

BENDTSEN1996 Not depression
BENEDETTI1930 Bipolar
BERTILSSON1974 Not RCT
BERTRAM1979 Maintenance study with no control group
BHAT1984 No data to extract. (Amitriptyline vs. Phenelzine vs. Placebo).
BHATIA1991A Not depression
BLASHKI1971 Dysthymia

BLATT2000	Secondary analysis of previously reported data. (Imipramine vs. Placebo vs. CBT vs. IPT)
BLIER1998	Augmentation study
BODNAR1972	Not depression
BOUSLEH1995	Treatment arm 'antidepressants' included Amitriptyline, Rolipram OR Fluparoxan. No pure measure. (ECT vs. Antidepressant vs. Placebo).
BOYER1996	Dysthymia
BRADY1994	Original data reported elsewhere. No data to extract. (Fluvoxamine vs. Imipramine vs. Placebo).
BRANCONNIER1981	No formal diagnosis (mild to moderate depressive symptomatology) and impaired cognitive function
BRANCONNIER1983	No data to extract. (High-dose Bupropion vs. low-dose Bupropion vs. Imipramine vs. Placebo).
BREMNER1996A	Continuation trial
BROWN1988	Reported placebo responders only. (Imipramine vs. Fluoxetine vs. Placebo).
BROWNE1963	No formal diagnosis. (Amitriptyline vs. Placebo).
BUCHSBAUM1988	Trial lasted 2 days only. (Placebo vs. Imipramine vs. Amoxapine).
BUNI1997	Dysthymia
BURROWS1977	Uncontrolled study
BUYSE1996	Maintenance trial
BYSTRITSKY1994	Not RCT
CALABRESE1998	Bipolar
CALABRESE2003	Bipolar
CARMAN1991	No data to extract. (Mianserin vs. Amitriptyline vs. Placebo).
CHANG2005	Withdrawal
CHAUDHRY1998	All previously treated with CBT
CHESROW1964	Depression and chronic physical health problems guideline
CHOUINARD1981	Not RCT
CLAGHORN1984	No data to extract. (Dothiepin vs. Amitriptyline vs. Placebo).
CLAGHORN1993	Secondary analysis of data; continuation study (Imipramine vs. Paroxetine vs. Placebo).
CLEARE1997	N too small per treatment arm (Desipramine vs. Imipramine vs. Org 4428 vs. Placebo).
COHN1989	Bipolar disorder (Fluoxetine vs. imipramine vs. placebo).
COOK1986	N too small per treatment arm (Desipramine vs. Amitriptyline vs. Doxepin vs. Imipramine).
COOK1993	Case study
COOKSON1985	Bipolar

COPPEN1978B	Continuation trial
COVI1981	No data to extract; short summary.
CUNNINGHAM1994A	Not RCT
DAL POZZO1997	Healthy participants
DAVIES1977	Not RCT
DAVIS1968	No data to extract. (Amitriptyline vs. Amitriptyline Perphenazine vs. Placebo).

DEBUS1980	Healthy participants
DECASTRO1985	Case study
DIMASCIO1968	Patients were classified as 'depressed' according to scores on MMPI; not recognised (Imipramine vs. Placebo)
DINGEMANSE1995	Healthy participants
DOWNING1972	Not an RCT
DOWNING1973	Not an RCT
EBERT1995	Bipolar
EHSANULLAH1977	Health volunteers; non-RCT
ELKIN1995	No data to extract. (Imipramine vs. Placebo vs. CBT vs. IPT).
ELSENGA1982	All participants sleep deprived
EXTEIN1979	Case studies
FAVA1997C	Could not extract any data. (Imipramine vs. Sertraline vs. Placebo).
FEET1985	Combination drugs (Imipramine + placebo vs. Imipramine + diazepam vs. Imipramine + Dixyrazine).
FEET1993	All imipramine treatments were combined with other drugs (Imipramine + dixyrazine vs. imipramine + diazepam vs. imipramine + placebo).
FEET1994	Treated with imipramine in combination with a variety of drugs (Imipramine + dixyrazine vs. imipramine + diazepam vs. imipramine + placebo).
FEIGHNER1992A	Didn't give N per group. (Paroxetine vs. Imipramine vs. Placebo).
FERGUSON1994A	Non-responders
FERRERI1997	Relapse prevention
FIEVE1968	All ppts took lithium at the start of the trial. No recognised rating scales were used. (Lithium vs. Imipramine vs. Placebo).
FINK1965	Secondary analysis of earlier study; included regardless of diagnosis (Chloropromazine + Procyclidine vs. Imipramine + Placebo).
FISCH1992	Pooled data from four studies
FRANK1990A	Maintenance trial
FRANK1991	No data to extract (Imipramine-clinical management vs. IPT-management vs. IPT-management + placebo vs. IPT-management + imipramine vs. placebo-clinical management)
FRIEDMAN1966	Psychotic depression
FRIEDMAN1975	No formal diagnosis
FRIEDMAN1979	Not RCT
FRIEDMAN1995A	Relapse
FRIEDMAN1999	Dysthymia
FUX1995	Panic patients only
GAERTNER1982	Not RCT

GANNON1970 N too small (10)
GASTPAR1980 Crossover study
GELENBERG1979 Case study
GEORGE1998 Bipolar
GEORGOTAS1989A Relapse prevention study (follow-up of Georgotas1986A)
GEORGOTAS1989B Maintenance and relapse prevention study (follow-up of Georgotas1986A)

GHAZIUDDIN1995	Crossover
GHOSE1980	Crossover
GHOSE1980A	Not RCT
GILLER1980	Continuation trial
GILLER1985	Discontinuation trial
GLASS1981	Crossover trial
GLEN1984	Relapse prevention
GOLDBERG1980A	Length of study unknown. (Trazodone vs. Amitriptyline vs. Placebo).
GOLDBERG1981	No data to extract. (Amitriptyline vs. Trazodone vs. Placebo).
GOLDBERG2004	Bipolar
GRACIOUS1991	Not depressed
GRACIOUS2005	Postpartum depression
GREEN1999	Maintenance trial
GUNDERTREMY1983	Healthy participants
GUY1982	Pooled together data from a series of studies
HAIDER1967	Amitriptyline + AP; Combination drugs
HAMEROFF1982A	Chronic conditions
HANLON1975	Combination drugs
HARKNESS1982	Follow-on study of relapse prevention strategies
HARRISON1986	Difficulty extracting data (Phenelzine vs. Imipramine vs. Placebo).
HARRISON1988	Continuation trial
HARTMANN1973	Not depressed
HAYDU1974	Not RCT
HECHT1986	No data to extract. (Trazodone vs. Amitriptyline vs. Placebo).
HELLERSTEIN2000	Dysthymia
HENINGER1983	Augmentation study
HERMAN2005	Augmentation study
HERRMANN1991	Crossover
HERRMANN1991A	Crossover
HINDMARCH1998A	Healthy participants
HOHN1961A	Crossover trial
HONIGFELD1962	No data could be extracted. (Imipramine vs. Placebo vs. Isocarboxazid vs. Destro-amphetamine-amobarbital).
HONORE1982	Not RCT
HUSSAIN1970	Not full trial report; Ami tablet included an AP
IMBER1990	Secondary analysis of others' data.
IMLAH1985	No details of diagnosis (reactive or neurotic secondary depression)
IRWIN1978	No data to extract. (Imipramine vs. Mianserin vs. Placebo).

ITIL1977	Participants not depressed
JARVIK1982	Single blind; no extractable data
JEFFERSON1983	Not RCT
JINDAL2003	Not RCT
JOHNSON1993	Results reported elsewhere; no data to extract (Imipramine vs. Fluvoxamine vs. Placebo)
JOHNSON2005	Bipolar

JOHNSTONE1980A	Neurotic illness = no diagnoses made on purpose
JUNGKUN2001	Healthy subjects
KAHN1986	Anxiety disorders only
KALIN2000	Bipolar
KANE1982	N too small per treatment arm
KANE1983	Too few participants in placebo arm (n=5) (imipramine vs placebo)
KANTOR1986	Augmentation study
KARP1994	Maintenance trial
KARP2004	Maintenance treatment study
KATON1993	Chronic illness
KATZ1993A	No data to extract. (2 studies - a) Amitriptyline vs. Oxaprotiline vs. Placebo, and b) Amitriptyline vs. Levoprotiline vs. Placebo).
KELLER1993	Panic disorder
KERR1996A	Healthy participants
KHAN1988	Collated results from two separate samples. (Placebo vs. Adinazolam vs. Imipramine vs. Fluvoxamine).
KHAN1989	Not rct
KLEBER1983	Drug misuse
KLEIN1967	Collated results from two studies when they used different samples (Imipramine vs. Chlorpromazine-Procyclidine vs. Placebo)
KLEIN1968	Included participants regardless of diagnosis
KLEIN1993	No formal diagnostic criteria (Phenelzine vs. Imipramine vs. Placebo)
KLIESER1989	No formal diagnosis (Trazodone vs. Haloperidol vs. Amitriptyline vs. Placebo)
KOCSIS1988	Dysthymia only
KOCSIS1988A	Dysthymia only
KOCSIS1989	Dysthymia only
KOCSIS1990	Over 15% bipolar
KOCSIS1996	Maintenance trial
KOCSIS1997	Dysthymia only (Sertraline vs. Imipramine vs. Placebo)
KONGSAKON2005	Drug misuse
KORN1986	Not RCT
KOWALSKI1985	Not RCT
KRAGHSORENSEN1974	Uncontrolled maintenance study
KRAGHSORENSEN1976	Dose-finding study
KRAMER1965	No data to extract. (Imipramine).
KROGMAYER1984	Maintenance trial
KRUPNICK1994	Not RCT

KUPFER1977	25% bipolar
KUPFER1979	28% bipolar
KUPFER1979A	30% psychotic
KUPFER1992	Maintenance trial data
KUPFER1992A	Not RCT
KUPFER1994	Dose-finding study
KUSALIC1993	Not RCT

LANGLOIS1985A No data to extract. (Amitriptyline vs. Zimeldine vs. Placebo).
LAPIERRE1974 Trial lasted one week only (Chlorimipramine vs. Imipramine vs. Placebo)
LAROCHELLE1979 N too small (6) (Tyramine vs. Norepinephrine after Imipramine vs. Trazodone)
LAURITZEN1992 Combination treatment (Imipramine + mianserin vs. Imipramine + placebo)
LAURITZEN1996 All received ECT
LECRUBIER1996 Dysythymia
LEE1993 Continuation trial
LEGG1976 No data to extract. (Imipramine vs. Chlorpromazine vs. Placebo).
LENZE2002 Maintenance trial
LICHT2002 Augmentation study
LIEBOWITZ1981 Atypical depression
LIEBOWITZ1984A No data to extract. Phenelzine and Imipramine combined. (Phenelzine vs. Imipramine vs. Placebo).
LIEBOWITZ1984B Atypical depression
LIEBOWITZ1984C No data to extract (Phenelzine vs. Imipramine vs. Placebo)
LIEBOWITZ1988 Continuation trial
LIPMAN1981 No data to extract. (Imipramine vs. Chlordiazepoxide vs. Placebo).
LOUIE1984 Not RCT
MALITZ1971 No data to extract. (Amitriptyline vs. Nortriptyline vs. Diphenylhydantoin vs. Dextroamphetamine vs. Amitriptyline-Perphenazine vs. Amitriptyline-Diazepam vs. Ay-62014 vs. Placebo).
MALT1999 Combination therapy
MANN1981 Too few participants (n=18) (imipramine vs placebo)
MARRACCINI1999 Maintenance trial
MASON1996 Drug misuse
MATUZAS1982 N too small (N = 10 Imipramine, N = 6 placebo) (Imipramine vs. Placebo)
MAX1987 Not depressed population
MCCANCE-KATZ1992 Not RCT
MCCONAGHY1968 Not RCT
MCDONALD1966 N too small (Amitriptyline vs. ECT vs. Placebo)
MCGRATH1982 No data to extract (Amitriptyline vs. Imipramine vs. Mianserin vs. Placebo)
MCGRATH1992 Couldn't extract data (Imipramine vs. Phenelzine vs. Placebo)
MCGRATH1993A Crossover trial
MCGRATH2000A Atypical depression
MERIDETH1984 No data to extract (Nomifensine vs. Imipramine vs. Placebo)

MILLER1998A	Maintenance trial
MINDHAM1972	Continuation therapy
MOLL1990	All TCAs lumped together no detail
MONTGOMERY1982	Not RCT
MORAKINYO1970	No formal diagnosis
MORENO1997	Augmentation study
MOSCOVICH1984	N too small

MULSANT2001B	Irrelevant comparison (augmentation); psychotic depression
MURPHY1978A	Expressly looks at anxiety and NOT depression
MYERS1984	Not focused on depression but on compliance
NARUSHIMA2000	Non-depressed participants
NATALE1979	Not RCT
NESHKES1985	Not RCT
NEWTON1981	No data to extract (Study a: Trazodone vs. Imipramine vs. Placebo and b: Trazodone vs. Amitriptyline vs. Placebo)
NIERENBERG2004	Continuation trial
NORMAN1983	Not RCT
NORMAN1992	Not RCT
NUNES1998	Drug misuse
NURNBERG2003	Sexual dysfunction
OPPENHEIM1983	Not RCT
OTTEVANGER1993	No data to extract (Fluvoxamine vs. Imipramine vs. Placebo)
OTTEVANGER1994	21.2% bipolar
OVERALL1962	No data to extract (Imipramine vs. Isocarboxazide vs. Dextroamphetamine-amobarbital vs. Placebo)
OZCANKAYA1997	N too small
PANDE1993	Not RCT
PARK1971	N too small
PATAT1997	N too small and crossover
PATKAR2006	Augmentation study
PAYKEL1973A	Not RCT
PAYKEL1975	Maintenance trial
PAYKEL1976A	Maintenance trial
PAYKEL1982	No data to extract (Amitriptyline vs. Phenelzine sulfate vs. Placebo)
PAYKEL1988A	No data to extract
PAYKEL1988B	Ps withdrawn for poor compliance; no efficacy trial
PEET1981	102 normal male volunteers separated according to level of depression Zung Self-Rating Scale. (Imipramine vs. Diazepam vs. Placebo) - no formal diagnosis
PERRY1978	41.3% psychotic depression
PESELOW1981	Maintenance trial
PESELOW1989A	Crossover and continuation trial
PESELOW1990A	Lumped all drugs together under 'drugs' so could not extract data. (Fluoxetine vs. Clovoxamine vs. Imipramine vs. Placebo).
PESELOW1992B	No post-treatment data available per treatment group
PESELOW1994	Not RCT

PORTER1970 No data to extract (Imipramine vs. Imipramine + Riboflavin vs. Placebo vs. Placebo + Riboflavin)
PRANGE1972 No placebo control
PRESKORN1983 No data to extract (Bupropion vs. Amitriptyline vs. Placebo)
PRICE1986 Not RCT; li augmentation
PRICE1990 Augmentation study
PRIEN1984A Maintenance trial

PRIEN1986	Maintenance trial
PUIGANTICH1987	Age
QUADRI1980	All took amphetamines beforehand
QUINTKIN1985	Not RCT
QUITKIN1978	Delusional depression
QUITKIN1978A	Drug combinations (Lithium + imipramine vs. Lithium + placebo imipramine vs. Placebo lithium + imipramine vs. Placebo lithium + placebo imipramine)
QUITKIN1982	Atypical depression
QUITKIN1984C	Incomplete data set
QUITKIN1986	Couldn't extract data (Phenelzine vs. Imipramine vs. Placebo)
QUITKIN1987	Replication study but used results from both studies (each had different participants). (Phenelzine sulphate vs. Imipramine vs. Placebo).
QUITKIN1988	Atypical depression
QUITKIN1990	Atypical depression
QUITKIN1993A	Entered responders and non-responders in a previous trial to two separate trials (Imipramine vs. Phenelzine vs. Placebo)
QUITKIN1993B	No data to extract (Imipramine vs. Phenelzine vs. Placebo)
QUITKIN2005	No data to extract
RABKIN1986	Included ppts with bulimia and anxiety disorders
RAFT1981	N too small (29) (Amitriptyline vs. Phenelzine vs. Placebo)
RAMPELLO1995	Unclear how many bipolar ppts included (Amitriptyline vs. Amineptine vs. Placebo)
RASKIN1973	Did not need to be depressed to be included in study
RASKIN1974	Did not need to be depressed to be included in study
RASKIN1975	Did not need to be depressed to be included in study
RASKIN1976	Did not need to be depressed to be included in study
RASKIN1976A	participants didn't need to be depressed
RASKIN1978	Continuation trial; follow-up data from one year later only (Imipramine vs. Chlorpromazine vs. Placebo)
REISBY1979	Not RCT
REYNOLDS1992A	Maintenance trial (acute phase has no nort or pbo only arms)
RICKELS1964	Crossover trial
RICKELS1970	Randomised participants within two given populations but reported pooled results for both populations, therefore could not extract data (Amitriptyline vs. Chlordiazepoxide vs. Amitriptyline + Chlordiazepoxide vs. Placebo)
RICKELS1970A	No data to extract
RICKELS1982	No data to extract (Alprazolam vs. Imipramine vs. Placebo)

RICKELS1982B No data to extract (Nomifensine vs. Imipramine vs. Placebo)
RICKELS1994 No data to extract (Nefazadone vs. Imipramine vs. Placebo)
RICKELS1995 Continuation trial; pooled data
RIFKIN1973 Not RCT
ROBINSON2000B Post-stroke depression (nortriptyline vs placebo)
ROFFMAN1983 No data to extract (Amitriptyline vs. Oxaprotiline vs. Placebo)
ROSEN1993 No placebo control

61

ROTHBLUM1982	Combination therapy
ROTHSCHILD1994	Participants were bulimic
ROWAN1980	No data to extract (Amitriptyline vs. Phenelzine vs. Placebo)
ROWAN1981	No data presented for Amitriptyline (Amitriptyline vs. Phenelzine vs. Placebo)
ROWAN1983	Not RCT
RUSH1984	Bipolar
SANDERS2005	Post-partum depression
SCHIFANO1990	Chronic illness
SCHILDKRAUT1964	N too small per treatment arm (Imipramine vs. Phenelzine vs. Placebo)
SCHILDKRAUT1965	
SCHULTERBRANDT1974	Diagnosis of depression not necessary to be included in study (Imipramine vs. Chlorpromazine vs. Placebo)
SHALAL1996	Not RCT
SHAMMAS1977	No formal diagnosis
SHAPIRA1989	All treated with fenfluramine first (Imipramine + Fenfluramine vs. Imipramine + Placebo)
SHAPIRA1992	Not RCT
SHAPIRA1993	Not RCT
SHARMA1980	Dosing trial (time of day)
SHEA1992A	Follow-up trial
SHELTON1997	Looked at participants with dysthymia only and excluded all patients with 'depression'. (Sertraline vs. Imipramine vs. Placebo).
SHEPHERD1981	Continuation trial
SHERWOOD1993	Not RCT
SHIPLEY1981	16% psychotic depression
SHOPSIN1971	N too small (eg. Only 1 participant on imipramine) (Imipramine vs. Naphthylamine vs. Lithium carbonate vs. Amobarbytol vs. Nicotinamide adenine dinucleotide vs. Chlorpromazine)
SIRIS1982	Post-psychotic
SIRIS1987A	All patients had schizophrenia or schizoaffective disorder
SIRIS1988A	Post-psychotic depression
SIRIS2001A	Continuation trial
SJOQVIST1971	Not an RCT
SOLOFF1989	Not depression
SPIKER1988	Pooled data from two earlier studies (Amitriptyline vs. Placebo)
STANER1993	Did not provide data for Imipramine or Placebo groups. (Tianeptine vs. Imipramine vs. Placebo).
STEINBOOK1979	N too small per treatment arm (Amoxapine vs. Imipramine vs. Placebo)

STEWART1988 No data to extract (Imipramine vs. Phenelzine vs. Placebo)
STEWART1988A No data to extract (Imipramine vs. Phenelzine vs. Placebo)
STEWART1989 Too many dysthymic patients
STEWART1989A No data to extract (Imipramine vs. Phenelzine vs. Mianserin vs. Placebo)
STEWART1992 No data to extract (Phenelzine vs. Imipramine vs. Placebo)
STEWART1993 No data to extract (Phenelzine vs. Imipramine vs. Placebo)
STEWART1993A N too small per treatment arm (Imipramine vs. Placebo)

STEWART1997	Continuation study (Imipramine vs. Phenelzine vs. Placebo)
STEWART1999	No data to extract (Imipramine vs. Placebo)
STRATAS1984	No data to extract (Dothiepin vs. Amitriptyline vs. Placebo)
SUSSEX1985	No formal depression diagnosis (nortriptyline vs placebo)
SZABADI1980	Not depressed
TAN1994	No formal diagnosis (score =>15 on GDS). (Lofepramine vs. Placebo)
TAYLOR1999A	Maintenance trial
THASE1996A	Dysthymia only
TOLLEFSON1994	Pooled all AD data together
TYRER1988A	Dysthymia only
TYRER1990	Ppts not depressed
TYRER1990A	Case study
UHLENHUTH1964	Crossover - could not extract after first phase. (Imipramine vs. Placebo)
VAN1981B	No data to extract (Maprotiline vs. Imipramine vs. Placebo)
VAN1984	N too small
VAN1984A	N too small
VAN2006	Follow-up trial
VERSIANI1990A	Pooled data
VERSIANI1997	Dysthymia only
VINAR1985	Amitriptyline + Nortriptyline combination
VOGEL1983	No antidepressants administered
WALLERSTEIN1967	Combination drugs
WEINTRAUB1963	No data to extract (Imipramine vs. Placebo)
WEISSMAN1992	Combination treatment; all received IPT (Alprazolam vs. Imipramine vs. Placebo).
WHEATLEY1972B	Not depressed
WILCOX1992	Retrospective analysis
WILKINSON2002	Combination therapies
WISNER2001	Postpartum depression; also prophylaxis trial
WOLFE1989	No data to extract
ZIS1991	All participants receiving ECT
ZLOTNICK1996	Follow-up data only

References of Included Studies

AMSTERDAM2003A (Published Data Only)

Amsterdam, J. D., Case, W. G., Csanalosi, E., Singer, M., & Rickels, K. (1986). A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. *Pharmacopsychiatry*, 19, 115-119.

BAKISH1992B (Published Data Only)

Bakish, D., Wiens, A., Ellis, J., Alda, M., & Lapierre, Y. (1992). A double-blind placebo-controlled comparison of moclobemide and amitriptyline in the treatment of depression. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*, 37 (Suppl. 1), 12-17.

BAKISH1992C (Published Data Only)

Bakish, D., Bradwejn, J., Nair, N., McClure, J., Remick, R., & Bulger, L. (1992). A comparison of moclobemide, amitriptyline and placebo in depression: a Canadian multicentre study. *Psychopharmacology*, 106 (Suppl. 1), S98-S101.

BARGESCHAAPVELD2002 (Published Data Only)

Barge-Schaapveld, D. Q. & Nicolson, N. A. (2002). Effects of antidepressant treatment on the quality of daily life: an experience sampling study. *Journal of Clinical Psychiatry*, 63, 477-485.

63

- BEASLEY1991B** (Published Data Only)
Beasley, C. M. J., Saylor, M. E., Bosomworth, J. C., & Wernicke, J. F. (1991). High-dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. *Journal of Clinical Psychopharmacology*, 11, 166-174.
- BOYER1996A** (Published Data Only)
Boyer, P., & Lecrubier, Y. (1996). Atypical antipsychotic drugs in dysthymia: placebo controlled studies of amisupride versus imipramine, versus amineptine. *European Psychiatry*, 11 (Suppl. 3), S135-S140.
- BREMNER1995** (Published Data Only)
Bremner, J. D. (1995). A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression. *Journal of Clinical Psychiatry*, 56, 519-525.
- BYERLEY1988** (Published Data Only)
Byerley, W. F., Reimherr, F. W., Wood, D. R., & Grosser, B. I. (1988). Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. *Journal of Clinical Psychopharmacology*, 8, 112-115.
- CASSANO1986** (Published Data Only)
Cassano, G. B., Conti, L., Massimetti, G., Mengali, F., Waekelin, J. S., & Levine, J. (1986). Use of a standardized documentation system (BLIPS/BDP) in the conduct of a multicenter international trial comparing fluvoxamine, imipramine, and placebo. *Psychopharmacology Bulletin*, 22, 52-58.
- CASSANO1996** (Published Data Only)
Cassano, G. B., Heinze, G., Loo, H., Mendlewicz, J., & Paes, D. (1996). A double-blind comparison of tianeptine, imipramine and placebo in the treatment of major depressive episodes. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 11, 254-259.
- CLAGHORN1983** (Published Data Only)
Claghorn, J., Gershon, S., & Goldstein, B. J. (1983). Zimelidine tolerability in comparison to amitriptyline and placebo: Findings from a multicentre trial. *Acta Psychiatrica Scandinavica Supplementum*, 308, 104-114.
- CLAGHORN1983B** (Published Data Only)
Claghorn, J., Gershon, S., Goldstein, B. J., Behmetz, S., Bush, D. F., & Huitfeldt, B. (1983). A double-blind evaluation of zimelidine in comparison to placebo and amitriptyline in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 7, 367-382.
- CLAGHORN1996A** (Published Data Only)
Claghorn, J. L., Earl, C. Q., Walczak, D. D., Stoner, K. A., Wong, L. F., Kanter, D. et al. (1996). Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. *Journal of Clinical Psychopharmacology*, 16, 113-120.
- COHN1984** (Published Data Only)
Cohn, J. B., Varga, L., & Lyford, A. (1984). A two-center double-blind study of nomifensine, imipramine, and placebo in depressed geriatric outpatients. *Journal of Clinical Psychiatry*, 45, 68-72.
- COHN1985** (Published Data Only)
Cohn, J. B. & Wilcox, C. (1985). A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. *Journal of Clinical Psychiatry*, 46, 26-31.
- COHN1990A** (Published Data Only)
Cohn, J. B., Crowder, J. E., Wilcox, C. S., & Ryan, P. J. (1990). A placebo- and imipramine-controlled study of paroxetine. *Psychopharmacology Bulletin*, 26, 185-189.
- COHN1992** (Published Data Only)
Cohn, J. B. & Wilcox, C. S. (1992). Paroxetine in major depression: a double-blind trial with imipramine and placebo. *Journal of Clinical Psychiatry*, 53 (Suppl.), 52-56.
- COHN1996** (Published Data Only)
Cohn, C. K., Robinson, D. S., Roberts, D. L., Schwiderski, U. E., O'Brien, K., & Ieni, J. R. (1996). Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. *Journal of Clinical Psychiatry*, 57 (Suppl. 2), 15-18.

DOMINGUEZ1981 (Published Data Only)

Dominguez, R. A., Jacobson, A. F., Weiss, B. L., et al. (1981). A placebo-controlled comparison of amoxapine and imipramine in the treatment of depressed outpatients. *Current Therapeutic Research, Clinical & Experimental*, 29, 714-727.

DOMINGUEZ1985 (Published Data Only)

Dominguez, R. A., Goldstein, B. J., Jacobson, A. F., & Steinbook, R. M. (1985). A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. *Journal of Clinical Psychiatry*, 46, 84-87.

- DUNBAR1991** (Published Data Only)
Dunbar, G. C., Cohn, J. B., Fabre, L. F., Feighner, J. P., Fieve, R. R., Mendels, J. et al. (1991). A comparison of paroxetine, imipramine and placebo in depressed out-patients. *British Journal of Psychiatry*, 159, 394-398.
- ELKIN1989** (Published Data Only)
*Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F. et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments.[see comment]. *Archives of General Psychiatry*, 46, 971-982.
Watkins, J. T., Leber, W. R., Imber, S. D., Collins, J. F., Elkin, I., Pilkonis, P. A. et al. (1993). Temporal course of change of depression. *Journal of Consulting & Clinical Psychology*, 61, 858-864.
Sotsky, S. M., Glass, D. R., Shea, M. T., Pilkonis, P. A., Collins, J. F., Elkin, I. et al. (1991). Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. *American Journal of Psychiatry*, 148, 997-1008.
Agosti, V. & Ocepek-Welikson, K. (1997). The efficacy of imipramine and psychotherapy in early-onset chronic depression: a reanalysis of the National Institute of Mental health Treatment of Depression Collaborative Research Program. *Journal of Affective Disorders*, 43, 181-186.
- ENTSUAH1994** (Published Data Only)
Entsuaah, A. R., Bradley, M. M., & Littman, G. S. (1994). Cumulative mean change procedure: application to a comparative trial of venlafaxine, imipramine, and placebo in the treatment of major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 18, 695-706.
- ESCOBAR1980** (Published Data Only)
Escobar, J. I., Gomez, J., Constain, C., et al. (1980). Controlled clinical trial with trazodone, a novel antidepressant. A South American experience. *Journal of Clinical Pharmacology*, 20, 124-130.
- FABRE1980** (Published Data Only)
Fabre, L. F. & McLendon, D. M. (1980). A double-blind study comparing the efficacy and safety of alprazolam with imipramine and placebo in primary depression. *Current Therapeutic Research, Clinical & Experimental*, 27, 474-482.
- FABRE1992** (Published Data Only)
Fabre, L. F. (1992). A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. *Journal of Clinical Psychiatry*, 53 (Suppl.), 40-43.
- FABRE1996** (Published Data Only)
Fabre, L., Birkhimer, L. J., Zaborny, B. A., Wong, L. F., & Kapik, B. M. (1996). Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *International Clinical Psychopharmacology*, 11, 119-127.
- FEIGER1996A** (Published Data Only)
Feiger, A. D. (1996). A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. *Psychopharmacology Bulletin*, 32, 659-665.
- FEIGHNER1979** (Published Data Only)
Feighner, J. P., Brauzer, B., Gelenberg, A. J., Gomez, E., Kiev, A., Kurland, M. L. et al. (1979). A placebo-controlled multicenter trial of Limbitrol versus its components (amitriptyline and chlordiazepoxide) in the symptomatic treatment of depressive illness. *Psychopharmacology*, 61, 217-225.
- FEIGHNER1980** (Published Data Only)
Feighner, J. P. (1980). Trazodone, a triazolopyridine derivative, in primary depressive disorder. *Journal of Clinical Psychiatry*, 41, 250-255.
- FEIGHNER1982** (Published Data Only)
Feighner, J. P., Meridith, C. H., Dutt, J. E., & Hendrickson, G. G. (1982). A double blind comparison of lofepramine, imipramine and placebo in patients with depression. *Acta Psychiatrica Scandinavica*, 66, 100-108.
- FEIGHNER1983A** (Published Data Only)
Feighner, J. P., Aden, G. C., Fabre, L. F., Rickels, K., & Smith, W. T. (1983). Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA*, 249, 3057-3064.
- FEIGHNER1983B** (Published Data Only)
Feighner, J. P., Meredith, C. H., Frost, N. R., Chammas, S., & Hendrickson, G. (1983). A double-blind comparison of alprazolam vs. imipramine and placebo in the treatment of major depressive

disorder. *Acta Psychiatrica Scandinavica*, 68, 223-233.

FEIGHNER1989

Feighner, J. P., Pambakian, R., Fowler, R. C., Boyer, W. F., & D'Amico, M. F. (1989). A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. *Psychopharmacology Bulletin*, 25, 219-221.

FEIGHNER1989A (Published Data Only)

Feighner, J. P. & Boyer, W. F. (1989). Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *Acta Psychiatrica Scandinavica Supplementum*, 350, 125-129.

65

- FEIGHNER1989B** (Published Data Only)
Feighner, J. P., Boyer, W. F., Meredith, C. H., & Hendrickson, G. G. (1989). A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. *International Clinical Psychopharmacology*, 4, 239-244.
- FEIGHNER1989C** (Published Data Only)
Feighner, J. P., Boyer, W. F., Meredith, C. H., & Hendrickson, G. G. (1989). A double-blind comparison of fluoxetine, imipramine and placebo in outpatients with major depression. *International Clinical Psychopharmacology*, 4, 127-134.
- FEIGHNER1992B** (Published Data Only)
Feighner, J. P. & Boyer, W. F. (1992). Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *Journal of Clinical Psychiatry*, 53 (Suppl.), 44-47.
- FEIGHNER1993** (Published Data Only)
Feighner, J. P., Cohn, J. B., Fabre, L. F. J., Fieve, R. R., Mendels, J., Shrivastava, R. K. et al. (1993). A study comparing paroxetine placebo and imipramine in depressed patients. *Journal of Affective Disorders*, 28, 71-79.
- FERGUSON1994B** (Published Data Only)
Ferguson, J. M., Mendels, J., & Manowitz, N. R. (Prothiaden Collaborative Study Group). (1994). Dothiepin versus doxepin in major depression: results of a multicenter, placebo-controlled trial. *Journal of Clinical Psychiatry*, 55, 258-263.
- FONTAINE1994** (Published Data Only)
Fontaine, R., Ontiveros, A., Elie, R., Kensler, T. T., Roberts, D. L., Kaplita, S. et al. (1994). A double-blind comparison of nefazodone, imipramine, and placebo in major depression. *Journal of Clinical Psychiatry*, 55, 234-241.
- GELENBERG1990** (Published Data Only)
Gelenberg, A. J., Wojcik, J. D., Falk, W. E., Spring, B., Brotman, A. W., & Galvin-Nadeau, M. (1990). Clovoxamine in the treatment of depressed outpatients: a double-blind, parallel-group comparison against amitriptyline and placebo. *Comprehensive Psychiatry*, 31, 307-314.
- GELENBERG2002** (Published Data Only)
Gelenberg, A. J., Wojcik, J. D., Falk, W. E., Baldessarini, R. J., Zeisel, S. H., Schoenfeld, D. et al. (1990). Tyrosine for depression: a double-blind trial. *Journal of Affective Disorders*, 19, 125-132.
- GEORGOTAS1982A** (Published Data Only)
Georgotas, A., Krakowski, M., & Gershon, S. (1982). Controlled trial of zimelidine, a 5-HT reuptake inhibitor, for treatment of depression. *American Journal of Psychiatry*, 139, 1057-1058.
- GEORGOTAS1986A** (Published Data Only)
Georgotas, A., McCue, R. E., Friedman, E., & Cooper, T. B. (1987). Response of depressive symptoms to nortriptyline, phenelzine and placebo. *British Journal of Psychiatry*, 151, 102-106.
Georgotas, A., McCue, R. E., Friedman, E., & Cooper, T. B. (1987). A placebo-controlled comparison of the effect of nortriptyline and phenelzine on orthostatic hypotension in elderly depressed patients. *Journal of Clinical Psychopharmacology*, 7, 413-416.
Georgotas, A., Stokes, P., McCue, R. E., Dubow, A., Welkowitz, J., Friedman, E. et al. (1986). The usefulness of DST in predicting response to antidepressants: a placebo-controlled study. *Journal of Affective Disorders*, 11, 21-28.
Georgotas, A., McCue, R. E., Cooper, T., Chang, I., Mir, P., & Welkowitz, J. (1987). Clinical predictors of response to antidepressants in elderly patients. *Biological Psychiatry*, 22, 733-740.
Georgotas, A., McCue, R. E., Friedman, E., & Cooper, T. B. (1987). Electrocardiographic effects of nortriptyline, phenelzine, and placebo under optimal treatment conditions. *American Journal of Psychiatry*, 144, 798-801.
Georgotas, A., McCue, R. E., Reisberg, B., Ferris, S. H., Nagachandran, N., Chang, I. et al. (1989). The effects of mood changes and antidepressants on the cognitive capacity of elderly depressed patients.[see comment]. *International Psychogeriatrics*, 1, 135-143.
Georgotas, A., McCue, R. E., Hapworth, W., Friedman, E., Kim, O. M., Welkowitz, J. et al. (1986). Comparative efficacy and safety of MAOIs versus TCAs in treating depression in the elderly. *Biological Psychiatry*, 21, 1155-1166.
- GERNER1980B** (Published Data Only)

Gerner, R., Estabrook, W., Steuer, J., & Jarvik, L. (1980). Treatment of geriatric depression with trazodone, imipramine, and placebo: a double-blind study. *Journal of Clinical Psychiatry*, 41, 216-220.

GOLDBERG1980 (Published Data Only)

Goldberg, H. L. & Finnerty, R. J. (1980). Trazodone in the treatment of neurotic depression. *Journal of Clinical Psychiatry*, 41, 430-434.

HAYES1983 (Published Data Only)

Hayes, R. L., Gerner, R. H., Fairbanks, L., Moran, M., & Waltuch, L. (1983). ECG findings in geriatric depressives given trazodone, placebo, or imipramine. *Journal of Clinical Psychiatry*, 44, 180-183.

66

- HICKS1988** (Published Data Only)
Hicks, F., Robins, E., & Murphy, G. E. (1988). Comparison of adinazolam, amitriptyline, and placebo in the treatment of melancholic depression. *Psychiatry Research*, 23, 221-227.
- HOLLYMAN1988** (Published Data Only)
Hollyman, J. A., Freeling, P., Paykel, E. S., Bhat, A., & Sedgwick, P. (1988). Double-blind placebo-controlled trial of amitriptyline among depressed patients in general practice. *Journal of the Royal College of General Practitioners*, 38, 393-397.
- HORMAZABAL1985** (Published Data Only)
Hormazabal, L., Omer, L. M., & Ismail, S. (1985). Cianopramine and amitriptyline in the treatment of depressed patients--a placebo-controlled study. *Psychopharmacology*, 86, 205-208.
- HOSCHL1989** (Published Data Only)
Hoschl, C. & Kozeny, J. (1989). Verapamil in affective disorders: a controlled, double-blind study. *Biological Psychiatry*, 25, 128-140.
- ITIL1983A** (Published Data Only)
Itil, T. M., Shrivastava, R. K., Mukherjee, S., et al. (1983). A double-blind placebo-controlled study of fluvoxamine and imipramine in out-patients with primary depression. *British Journal of Clinical Pharmacology*, 15 (Suppl. 3), S433-S438.
- ITIL1993** (Published Data Only)
Itil, T. M., Arikan, M. K., Itil, K. Z., et al. (1993). Clinical CEEG/DBM findings with a new antidepressant: Dothiepin. *Integrative Psychiatry*, 8, 241-251.
- KASPER1995B** (Published Data Only)
Kasper, S., Moller, H. J., Montgomery, S. A., et al. (1995). Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. *International Clinical Psychopharmacology*, 9 (Suppl. 4), 3-12.
- KATZ1990** (Published Data Only)
Katz, I. R., Simpson, G. M., Curlik, S. M., et al. (1990). Pharmacologic treatment of major depression for elderly patients in residential care settings. *Journal of Clinical Psychiatry*, 51 (Suppl.), 41-47.
- KELLAMS1979** (Published Data Only)
Kellams, J. J., Klapper, M. H., & Small, J. G. (1979). Trazodone, a new antidepressant: efficacy and safety in endogenous depression. *Journal of Clinical Psychiatry*, 40, 390-395.
- KLIESER1988** (Published Data Only)
Klieser, E. & Lehmann, E. (1988). Experimental comparison between the effect of standardized trazodone-amitriptyline and placebo treatment in vitalized depressive patients. *Psychopharmacology*, 95 (Suppl.), S3-S5.
- LAAKMAN1995** (Published Data Only)
Laakman, G., Faltermaier-Temizel, M., Bossert-Zaudig, S., Baghai, T., & Lorkowski, G. (1995). Treatment of depressive outpatients with lorazepam, alprazolam, amitriptyline and placebo. *Psychopharmacology*, 120, 109-115.
- LAIRD1993** (Published Data Only)
Laird, L. K., Lydiard, R. B., Morton, W. A., Steele, T. E., Kellner, C., Thompson, N. M. et al. (1993). Cardiovascular effects of imipramine, fluvoxamine, and placebo in depressed outpatients. *Journal of Clinical Psychiatry*, 54, 224-228.
- LAPIERRE1987** (Published Data Only)
Lapierre, Y. D., Browne, M., Horn, E., Oyewumi, L. K., Sarantidis, D., Roberts, N. et al. (1987). Treatment of major affective disorder with fluvoxamine. *Journal of Clinical Psychiatry*, 48, 65-68.
- LAPIERRE1991** (Published Data Only)
Lapierre, Y. D. (1991). Controlling acute episodes of depression. *International Clinical Psychopharmacology*, 6 (Suppl. 2), 23-35.
- LARSEN1989** (Published Data Only)
Larsen, J. K., Holm, P., Hoyer, E., Mejlhede, A., Mikkelsen, P. L., Olesen, A. et al. (1989). Moclobemide and clomipramine in reactive depression. A placebo-controlled randomized clinical trial. *Acta Psychiatrica Scandinavica*, 79, 530-536.

LECRUBIER1997B (Published Data Only)

Lecrubier, Y., Bourin, M., Moon, C. A., Schifano, F., Blanchard, C., Danjou, P. et al. (1997). Efficacy of venlafaxine in depressive illness in general practice. *Acta Psychiatrica Scandinavica*, 95, 485-493.

LIPMAN1986 (Published Data Only)

Lipman, R. S., Covi, L., Rickels, K., McNair, D. M., Downing, R., Kahn, R. J. et al. (1986). Imipramine and chlordiazepoxide in depressive and anxiety disorders. I. Efficacy in depressed outpatients. *Archives of General Psychiatry*, 43, 68-77. 67

- LYDIARD1989** (Published Data Only)
Lydiard, R. B., Laird, L. K., Morton, W. A. J., Steele, T. E., Kellner, C., Laraia, M. T. et al. (1989). Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. *Psychopharmacology Bulletin*, 25, 68-70.
- LYDIARD1997** (Published Data Only)
Lydiard, R. B., Stahl, S. M., Hertzman, M., & Harrison, W. M. (1997). A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *Journal of Clinical Psychiatry*, 58, 484-491.
- MARCH1990** (Published Data Only)
March, J. S., Kobak, K. A., Jefferson, J. W., Mazza, J., & Greist, J. H. (1990). A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. *Journal of Clinical Psychiatry*, 51, 200-202.
- MARKOWITZ1985** (Published Data Only)
Markowitz, J. S., Rabkin, J. G., McGrath, P. J., Stewart, J., & Quitkin, F. M. (1985). Attrition and its consequences in a clinical trial of placebo, imipramine, and phenelzine. *Psychopharmacology Bulletin*, 21, 107-109.
- MENDELS1986** (Published Data Only)
Mendels, J. & Schless, A. P. (1986). Comparative efficacy of alprazolam, imipramine, and placebo administered once a day in treating depressed patients. *Journal of Clinical Psychiatry*, 47, 357-361.
- MERIDETH1983** (Published Data Only)
Merideth, C. H. & Feighner, J. P. (1983). A double-blind, controlled evaluation of zimeldine, imipramine and placebo in patients with primary affective disorders. *Acta Psychiatrica Scandinavica Supplementum*, 308, 70-79.
- MINDHAM1991** (Published Data Only)
Mindham, R. H. S., Jerram, T. C., Cole, H. L., Oswald, A. G., & Khan, S. (1991). A comparison of sulpiride, dothiepin, diazepam and placebo in the treatment of depressed out-patients. *Journal of Psychopharmacology*, 5, 259-262.
- MYNORSWALLIS1995** (Published Data Only)
Mynors-Wallis, L. M., Gath, D. H., Lloyd-Thomas, A. R., & Tomlinson, D. (1995). Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *British Medical Journal*, 310, 441-445.
- MYNORSWALLIS1997** (Published Data Only)
Mynors-Wallis, L. & Gath, D. (1997). Predictors of treatment outcome for major depression in primary care. *Psychological Medicine*, 27, 731-736.
- NAIR1995** (Published Data Only)
Nair, N. P., Amin, M., Holm, P., Katona, C., Klitgaard, N., Ng, Y. et al. (1995). Moclobemide and nortriptyline in elderly depressed patients. A randomized, multicentre trial against placebo. *Journal of Affective Disorders*, 33, 1-9.
Ng, Y., Nair, N. P. V., Amin, M., Schwartz, G., Ahmed, S. K., Holm, P. et al. (1997). The dexamethasone suppression test and treatment outcome in elderly depressed patients participating in a placebo-controlled multicenter trial involving moclobemide and nortriptyline. *Biological Psychiatry*, 42, 925-931.
Ng, Y., Klitgaard, N., Nair, N. P. V., Amin, M., Kragh-Sorensen, P., Schwartz, G. et al. (1996). Clinical relevance of serum nortriptyline and 10-Hydroxy-Nortriptyline measurements in the depressed elderly: A multicenter pharmacokinetic and pharmacodynamic study. *Neuropsychopharmacology*, 15, 1-6.
- NANDI1976** (Published Data Only)
Nandi, D. N., Ajmany, S., Ganguli, H., Banerjee, G., Boral, G. C., Ghosh, A. et al. (1976). A clinical evaluation of depressives found in a rural survey in India. *British Journal of Psychiatry*, 128, 523-527.
- NORTON1984** (Published Data Only)
Norton, K. R., Sireling, L. I., Bhat, A. V., Rao, B., & Paykel, E. S. (1984). A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. *Journal of Affective Disorders*, 7, 297-308.

PECKNOLD1976B (Published Data Only)

Pecknold, J. C., Amin, M. M., Ban, T. A., & Orbach, L. (1976). Proceedings: Systematic clinical studies with clomipramine in depressed psychiatric patients--II. Report on a placebo-controlled clinical trial. *Psychopharmacology Bulletin*, 12, 24-25.

PEDERSEN2002 (Published Data Only)

Pedersen, R. D., Pally, A. G., & Rudolph, R. L. (2002). Can improvement in well-being and functioning be distinguished from depression improvement in antidepressant clinical trials? *Quality of Life Research*, 11, 9-17.

- PESELOW1989** (Published Data Only)
Peselow, E. D., Stanley, M., Filippi, A. M., Barouche, F., Goodnick, P., & Fieve, R. R. (1989). The predictive value of the dexamethasone suppression test. A placebo-controlled study. *British Journal of Psychiatry*, 155, 667-672.
- PESELOW1989B** (Published Data Only)
Peselow, E. D., Filippi, A. M., Goodnick, P., Barouche, F., & Fieve, R. R. (1989). The short- and long-term efficacy of paroxetine HCl: A. Data from a 6-week double-blind parallel design trial vs. imipramine and placebo. *Psychopharmacology Bulletin*, 25, 267-271.
- PHILIPP1999** (Published Data Only)
Philipp, M., Kohnen, R., & Hiller, K. O. (1999). Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *British Medical Journal*, 319, 1534-1538.
- QUITKIN1989** (Published Data Only)
Quitkin, F. M., McGrath, P. J., Stewart, J. W., Harrison, W., Wager, S. G., Nunes, E. et al. (1989). Phenelzine and imipramine in mood reactive depressives. Further delineation of the syndrome of atypical depression. *Archives of General Psychiatry*, 46, 787-793.
- RAMPELLO1991** (Published Data Only)
Rampello, L., Nicoletti, G., & Raffaele, R. (1991). Dopaminergic hypothesis for retarded depression: a symptom profile for predicting therapeutical responses. *Acta Psychiatrica Scandinavica*, 84, 552-554.
- REIMHERR1990** (Published Data Only)
Reimherr, F. W., Chouinard, G., Cohn, C. K., Cole, J. O., Itil, T. M., Lapierre, Y. D. et al. (1990). Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *Journal of Clinical Psychiatry*, 51 (Suppl. B), 18-27.
- RIKELS1981** (Published Data Only)
Rickels, K., Case, W. G., Werblowsky, J., Csanalosi, I., Schless, A., & Weise, C. C. (1981). Amoxapine and imipramine in the treatment of depressed outpatients: a controlled study. *American Journal of Psychiatry*, 138, 20-24.
- RIKELS1982A** (Published Data Only)
Rickels, K., Weise, C. C., Zal, H. M., et al. (1982). Lofepramine and imipramine in unipolar depressed outpatients. A placebo controlled study. *Acta Psychiatrica Scandinavica*, 66, 109-120.
- RIKELS1982D** (Published Data Only)
Rickels, K. & Case, W. G. (1982). Trazodone in depressed outpatients. *American Journal of Psychiatry*, 139, 803-806.
- RIKELS1985** (Published Data Only)
Rickels, K., Feighner, J. P., & Smith, W. T. (1985). Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Archives of General Psychiatry*, 42, 134-141.
- RIKELS1987** (Published Data Only)
Rickels, K., Chung, H. R., Csanalosi, I. B., Hurowitz, A. M., London, J., Wiseman, K. et al. (1987). Alprazolam, diazepam, imipramine, and placebo in outpatients with major depression. *Archives of General Psychiatry*, 44, 862-866.
- RIKELS1991** (Published Data Only)
Rickels, K., London, J., Fox, I., Hassman, H., Csanalosi, I., & Weise, C. (1991). Adinazolam, diazepam, imipramine, and placebo in major depressive disorder: a controlled study. *Pharmacopsychiatry*, 24, 127-131.
- ROFFMAN1982** (Published Data Only)
Roffman, M., Gould, E. E., Brewer, S. J., et al. (1982). A double-blind comparative study of oxaprotiline with amitriptyline and placebo in moderate depression. *Current Therapeutic Research, Clinical & Experimental*, 32, 247-256.
- ROWAN1982** (Published Data Only)
Rowan, P. R., Paykel, E. S., & Parker, R. R. (1982). Phenelzine and amitriptyline: effects on symptoms of neurotic depression. *British Journal of Psychiatry*, 140, 475-483.

SCHWEIZER1994 (Published Data Only)

Schweizer, E., Feighner, J., Mandos, L. A., & Rickels, K. (1994). Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. *Journal of Clinical Psychiatry*, 55, 104-108.

SCHWEIZER1998 (Published Data Only)

Schweizer, E., Rickels, K., Hassman, H., & Garcia-Espana, F. (1998). Buspirone and imipramine for the treatment of major depression in the elderly. *Journal of Clinical Psychiatry*, 59, 175-183.

69

- SHRIVASTAVA1992** (Published Data Only)
Shrivastava, R. K., Shrivastava, S. H., Overweg, N., & Blumhardt, C. L. (1992). A double-blind comparison of paroxetine, imipramine, and placebo in major depression. *Journal of Clinical Psychiatry*, 53 (Suppl.), 48-51.
- SILVERSTONE1994** (Published Data Only)
Silverstone, T., bou-Saleh, M. T., Pathak, R., Lock, T., Bennie, E., Mohammed, Y. et al. (1994). A multicentre comparative trial of moclobemide, imipramine and placebo in major depressive disorder. UK moclobemide study group. *International Clinical Psychopharmacology*, 9, 109-113.
- SMALL1981** (Published Data Only)
Small, J. G., Milstein, V., Kellams, J. J., & Small, I. F. (1981). Comparative onset of improvement in depressive symptomatology with drug treatment, electroconvulsive therapy, and placebo. *Journal of Clinical Psychopharmacology*, 1 (Suppl.), S62-S69.
- SMITH1990** (Published Data Only)
Smith, W. T., Glaudin, V., Panagides, J., & Gilvary, E. (1990). Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. *Psychopharmacology Bulletin*, 26, 191-196.
- SPRING1992** (Published Data Only)
Spring, C., Gelenberg, A. J., Garvin, R., & Thompson, S. (1992). Amitriptyline, clovoxamine and cognitive function: A placebo-controlled comparison in depressed outpatients. *Psychopharmacology*, 108, 327-332.
- STASSEN1993** (Published Data Only)
Stassen, H. H., Delini-Stula, A., & Angst, J. (1993). Time course of improvement under antidepressant treatment: a survival-analytical approach. *European Neuropsychopharmacology*, 3, 127-135.
- THOMPSON2001B** (Published Data Only)
Thompson, C. & Thompson, C. M. (2001). The prescribing of antidepressants in general practice. II: A placebo-controlled trial of low-dose dothiepin. *Human Psychopharmacology*, 4, 191-204.
- UCHA1990** (Published Data Only)
Ucha, U., Marquez, C. A., Traballi, C. A., & Portes, N. (1990). Double-blind comparison of moclobemide, imipramine and placebo in depressive patients. *Acta Psychiatrica Scandinavica Supplementum*, 360, 54-56.
- VERSIANI1989** (Published Data Only)
Versiani, M., Oggero, U., Alterwain, P., Capponi, R., Dajas, F., Heinze-Martin, G. et al. (1989). A double-blind comparative trial of moclobemide v. imipramine and placebo in major depressive episodes. *British Journal of Psychiatry Supplementum*, 6, 72-77.
- VERSIANI1990** (Published Data Only)
Versiani, M., Nardi, A. E., Mundim, F. D., Alves, A., & Schmid-Burgk, W. (1990). Moclobemide, imipramine and placebo in the treatment of major depression. *Acta Psychiatrica Scandinavica Supplementum*, 360, 57-58.
- WAKELIN1986** (Published Data Only)
Wakelin, J. S. (1986). Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data. *International Clinical Psychopharmacology*, 1, 221-230.
- WHITE1984A** (Published Data Only)
White, K., Razani, J., Cadow, B., Gelfand, R., Palmer, R., Simpson, G. et al. (1984). Tranylcypromine vs nortriptyline vs placebo in depressed outpatients: a controlled trial. *Psychopharmacology*, 82, 258-262.
- WILCOX1994** (Published Data Only)
Wilcox, C. S., Cohn, J. B., Katz, B. B., Mijares, C. P., Guarino, J. J., Panagides, J. et al. (1994). A double-blind, placebo-controlled study comparing mianserin and amitriptyline in moderately depressed outpatients. *International Clinical Psychopharmacology*, 9, 271-279.

References of Excluded Studies

- 36** (Published Data Only)

Brady, K. T., Lydiard, R. B., Kellner, C. H., Joffe, R., Laird, L. K., Morton, W. A. et al. (1994). A comparison of the effects of imipramine and fluvoxamine on the thyroid axis. *Biological Psychiatry*, 36, 778-779.

37

(Published Data Only)

Blatt, S. J., Zuroff, D. C., Bondi, C. M., & Sanislow, I. C. A. (2000). Short- and long-term effects of medication and psychotherapy in the brief treatment of depression: further analyses of data from the NIMH TDCRP. *Psychotherapy Research*, 10, 215-234.

70

- AGOSTI1991** (Published Data Only)
Agosti, V., Stewart, J. W., & Quitkin, F. M. (1991). Life satisfaction and psychosocial functioning in chronic depression: effect of acute treatment with antidepressants. *Journal of Affective Disorders*, 23, 35-41.
- AGOSTI1993** (Published Data Only)
Agosti, V., Stewart, J. W., Quitkin, F. M., & Ocepek-Welikson, K. (1993). How symptomatic do depressed patients remain after benefiting from medication treatment? *Comprehensive Psychiatry*, 34, 182-186.
- AGOSTI1999A** (Published Data Only)
Agosti, V. (1999). Predictors of persistent social impairment among recovered depressed outpatients. *Journal of Affective Disorders*, 55, 215-219.
- AGOSTI2002** (Published Data Only)
Agosti, V., Quitkin, F. M., Stewart, J. W., & McGrath, P. J. (2002). Somatization as a predictor of medication discontinuation due to adverse events. *International Clinical Psychopharmacology*, 17, 311-314.
- AGOSTI2002A** (Published Data Only)
Agosti, V. & McGrath, P. J. (2002). Comparison of the effects of fluoxetine, imipramine and placebo on personality in atypical depression. *Journal of Affective Disorders*, 71, 113-120.
- AINSLIE1965** (Published Data Only)
Ainslie, J.D., Jones, M. B., & Stiefel, J. R. (1965). Practical drug evaluation method: Imipramine in depressed outpatients. *Archives of General Psychiatry*, 12, 368-373.
- ALEXOPOULOS2000**
Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kalayam, B., Kakuma, T., Gabrielle, M. et al. (2000). Executive dysfunction and long-term outcomes of geriatric depression. *Archives of General Psychiatry*, 57, 285-290.
- ANON1993H** (Published Data Only)
How long should the elderly take antidepressants? A double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin. Old Age Depression Interest Group. (1993). *British Journal of Psychiatry*, 162, 175-182.
- ANON1995H** (Published Data Only)
Fluoxetine (1995). *New Zealand Medical Journal*, 108.
- ANON2005F**
Drug treatments for bipolar disorder: 1 - Acute manic or depressive episodes (2005). *Drug & Therapeutics Bulletin*, 43.
- ANTON1994** (Published Data Only)
Anton, S. F., Robinson, D. S., Roberts, D. L., Kensler, T. T., English, P. A., & Archibald, D. G. (1994). Long-term treatment of depression with nefazodone. *Psychopharmacology Bulletin*, 30, 165-169.
- ARNOLD1981** (Published Data Only)
Arnold, S. E., Kahn, R. J., Faldetta, L. L., Laing, R. A., & McNair, D. M. (1981). Tricyclic antidepressants and peripheral anticholinergic activity. *Psychopharmacology*, 74, 325-328.
- ASBERG1973**
Asberg, M., Bertilsson, L., Tuck, D., Cronholm, B., & Sjoqvist, F. (1973). Indoleamine metabolites in the cerebrospinal fluid of depressed patients before and during treatment with nortriptyline. *Clinical Pharmacology & Therapeutics*, 14, 277-286.
- ASBERG1974**
Asberg, M. (1974). Plasma nortriptyline levels--relationship to clinical effects. *Clinical Pharmacology & Therapeutics*, 16, 215-229.
- ASHTON1978**
Ashton, H., Millman, J. E., Telford, R., & Thompson, J. W. (1978). A comparison of some physiological and psychological effects of Motival (fluphenazine and nortriptyline) and diazepam in normal

subjects. *British Journal of Clinical Pharmacology*, 5, 141-147.

BAKISH1993A (Published Data Only)

Bakish, D., Lapierre, Y. D., Weinstein, R., Klein, J., Wiens, A., Jones, B. et al. (1993). Ritanserin, imipramine, and placebo in the treatment of dysthymic disorder. *Journal of Clinical Psychopharmacology*, 13, 409-414.

BAKISH1994 (Published Data Only)

Bakish, D., Ravindran, A., Hooper, C., & Lapierre, Y. (1994). Psychopharmacological treatment response of patients with a DSM-III diagnosis of dysthymic disorder. *Psychopharmacology Bulletin*, 30, 53-59.

71

BALESTRIERI2004

Balestrieri, M., Carta, M. G., Leonetti, S., Sebastiani, G., Starace, F., & Bellantuono, C. (2004). Recognition of depression and appropriateness of antidepressant treatment in Italian primary care. *Social Psychiatry & Psychiatric Epidemiology*, 39.

BAN1982 (Published Data Only)

Ban, T. A., Fujimori, M., Petrie, W. M., Ragheb, M., & Wilson, W. H. (1982). Systematic studies with amoxapine, a new antidepressant. *International Pharmacopsychiatry*, 17, 18-27.

BASSA1965 (Published Data Only)

Bassa, D. M. & Voro, H. D. (1965). Evaluation of efficacy of imipramine in depressive disorders: a double-blind study. *American Journal of Psychiatry*, 121, 1116-1117.

BAUER2000 (Published Data Only)

Bauer, M., Bschor, T., Kunz, D., Berghofer, A., Strohle, A., & Muller-Oerlinghausen, B. (2000). Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *American Journal of Psychiatry*, 157, 1429-1435.

BECH1978

Bech, P. (1978). Depressive symptomatology and drug response. *Communications in Psychopharmacology*, 2, 409-418.

BECH1989 (Published Data Only)

Bech, P., Jorgensen, B., Norrelund, N., Loldrup, D., Langemark, M., Hansen, H. J. et al. (1989). Pains as presentation symptoms of depression in liaison psychiatry as evidenced by outcome of clomipramine treatment: two placebo-controlled trials. *Nordic Journal of Psychiatry*, 43, 89-94.

BELL1992 (Published Data Only)

Bell, I. R., Edman, J. S., Morrow, F. D., Marby, D. W., Perrone, G., Kayne, H. L. et al. (1992). Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction. *Journal of the American College of Nutrition*, 11, 159-163.

BELLAK1966 (Published Data Only)

Bellak, L. & Rosenberg, S. (1966). Effects of anti-depressant drugs on psychodynamics. *Psychosomatics*, 7, 106-114.

BENDTSEN1996 (Published Data Only)

Bendtsen, L., Jensen, R., & Olesen, J. (1996). A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. *Journal of Neurology, Neurosurgery & Psychiatry*, 61, 285-290.

BENEDETTI1930

Benedetti, F., Campori, E., Barbini, B., Fulgosi, M. C., & Colombo, C. (1930). Dopaminergic augmentation of sleep deprivation effects in bipolar depression. *Psychiatry Research*, 104, 239-246.

BERTILSSON1974

Bertilsson, L., Asberg, M., & Thoren, P. (1974). Differential effect of chlorimipramine and nortriptyline on cerebrospinal fluid metabolites of serotonin and noradrenaline in depression. *European Journal of Clinical Pharmacology*, 7, 365-368.

BERTRAM1979

Bertram, U., Kragh-Sorensen, P., Rafaelsen, O. J., & Larsen, N. E. (1979). Saliva secretion following long-term antidepressant treatment with nortriptyline controlled by plasma levels. *Scandinavian Journal of Dental Research*, 87, 58-64.

BHAT1984 (Published Data Only)

Bhat, A. V., Rowan, P. R., & Paykel, E. S. (1984). Responses to phenelzine and amitriptyline: absence of differential predictors by multiple regression analysis. *Journal of Affective Disorders*, 6, 209-218.

BHATIA1991A (Published Data Only)

Bhatia, S. C., Hsieh, H. H., Theesen, K. A., Townley, R. G., Andersen, J. M., Weiss, S. et al. (1991). Platelet alpha-2 adrenoreceptor activity pre-treatment and post-treatment in major depressive disorder with melancholia. *Research Communications in Chemical Pathology & Pharmacology*, 74, 47-57.

BLASHKI1971

Blashki, T. G., Mowbray, R., & Davies, B. (1971). Controlled trial of amitriptyline in general practice. *British Medical Journal*, 1, 133-138.

BLATT2000 (Published Data Only)

Blatt, S.J., Zuroff, D.C., Bondi, C.M., & Sanislow III, C.A. (2000). Short- and long-term effects of medication and psychotherapy in the brief treatment of depression: further analyses of data from the NIMH TDCRP. *Psychotherapy Research*, 10 (2), 215-234.

BLIER1998 (Published Data Only)

Blier, P., Bergeron, R., Sussman, N., Emrich, H. M., Nelson, J. C., Thase, M. E. et al. (1998). The use of pindolol to potentiate antidepressant medication. *Journal of Clinical Psychiatry*, 59, 16-25.

72

- BODNAR1972** (Published Data Only)
Bodnar, S. & Catterill, T. B. (1972). Amitriptyline in emotional states associated with the climacteric. *Psychosomatics*, 13, 117-119.
- BOUSLEH1995** (Published Data Only)
bou-Saleh, M. T., Anderson, D. N., Collins, J., Hughes, K., Cattell, R. J., Hamon, C. G. et al. (1995). The role of pterins in depression and the effects of antidepressive therapy. *Biological Psychiatry*, 38, 458-463.
- BOYER1996** (Published Data Only)
Boyer, P. & Lecrubier, Y. (1996). Atypical antipsychotic drugs in dysthymia: Placebo controlled studies of amisulpride versus imipramine, versus amineptine. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 11 (Suppl. 3), 5135-5140.
- BRADY1994** (Published Data Only)
Brady, K.T., Lydiard, R.B., Kellner, C.H., Joffe, R., Laird, L.K., Morton, W.A., & Steele, T.E. (1992). A comparison of the effects of imipramine and fluvoxamine on the thyroid axis. *Biological Psychiatry*, 36, 778-779.
- BRANCONNIER1981** (Published Data Only)
Branconnier, R. J., Cole, J. O., & Ghazvinian, S. (1981). The therapeutic profile of mianserin in mild elderly depressives [proceedings]. *Psychopharmacology Bulletin*, 17, 129-131.
- BRANCONNIER1983** (Published Data Only)
Branconnier, R. J., Cole, J. O., Ghazvinian, S., Spera, K. F., Oxenkrug, G. F., & Bass, J. L. (1983). Clinical pharmacology of bupropion and imipramine in elderly depressives. *Journal of Clinical Psychiatry*, 44, 130-133.
- BREMNER1996A** (Published Data Only)
Bremner, J. D. & Smith, W. T. (1996). Org 3770 VS amitriptyline in the continuation treatment of depression: A placebo controlled trial. *European Journal of Psychiatry*, 10.
- BROWN1988** (Published Data Only)
Brown, W. A., Dornseif, B. E., & Wernicke, J. F. (1988). Placebo response in depression: a search for predictors. *Psychiatry Research*, 26, 259-264.
- BROWNE1963** (Published Data Only)
Browne, M. W., Kreeger, L. C., & Kazamias, N. G. (1963). A clinical trial of amitriptyline in depressive patients. *British Journal of Psychiatry*, 109, 692-694.
- BUCHSBAUM1988** (Published Data Only)
Buchsbaum, M. S., Lee, S., Haier, R., Wu, J. C., Green, M., & Tang, S. W. (1988). Effects of amoxapine and imipramine on evoked potentials in the Continuous Performance Test in patients with affective disorder. *Neuropsychobiology*, 20, 15-22.
- BUNI1997**
Buni, T. M. (1997). Treatment of dysthymia. *Journal of Family Practice*, 44, 528-529.
- BURROWS1977**
Burrows, G. D., Maguire, K. P., Scoggins, B. A., Stevenson, J., & Davies, B. (1977). Plasma nortriptyline and clinical response--a study using changing plasma levels. *Psychological Medicine*, 7, 87-91.
- BUYSSE1996**
Buysse, D. J., Reynolds, C. F., Hoch, C. C., Houck, P. R., Kupfer, D. J., Mazumdar, S. et al. (1996). Longitudinal effects of nortriptyline on EEG sleep and the likelihood of recurrence in elderly depressed patients. *Neuropsychopharmacology*, 14, 243-252.
- BYSTRITSKY1994**
Bystritsky, A. & Waikar, S. V. (1994). Inert placebo versus active medication. Patient blindability in clinical pharmacological trials. *Journal of Nervous and Mental Disease*, 182, 485-487.
- CALABRESE1998**
Calabrese, J. R., Rapport, D. J., Shelton, M. D., & Kimmel, S. E. (1998). Clinical studies on the use of lamotrigine in bipolar disorder. *Neuropsychobiology*, 38, 185-191.

CALABRESE2003

Calabrese, J. R., Bowden, C. L., Sachs, G., Yatham, L. N., Behnke, K., Mehtonen, O. P., et al. (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *Journal of Clinical Psychiatry*, 64, 1013-1024.

CARMAN1991 (Published Data Only)

Carman, J. S., Ahdieh, H., Wyatt-Knowles, E., Warga, E., & Panagides, J. (1991). A controlled study of mianserin in moderately to severely depressed outpatients. *Psychopharmacology Bulletin*, 27, 135-139.

73

CHANG2005

Chang, F. (2005). Strategies for benzodiazepine withdrawal in seniors. *Canadian Pharmacists Journal*, 138, 38-40.

CHAUDHRY1998 (Published Data Only)

Chaudhry, H. R., Najam, N., & Naqvi, A. (1998). The value of amineptine in depressed patients treated with cognitive behavioural psychotherapy. *Human Psychopharmacology*, 13, 419-424.

CHESROW1964 (Published Data Only)

Chesrow, E. J., Kaplitz, S. E., Breme, J. T., Sabatini, R., Vetra, H., & Marquardt, G. H. (1964). Nortriptyline for the treatment of anxiety and depression in chronically ill and geriatric patients. *Journal of the American Geriatrics Society*, 12, 271-277.

CHOUINARD1981

Chouinard, G., Annable, L., & Langlois, R. (1981). Absence of orthostatic hypotension in depressed patients treated with bupropion. *Progress in Neuro-Psychopharmacology*, 5, 483-490.

CLAGHORN1984 (Published Data Only)

Claghorn, J. L., Schroeder, J., & Goldstein, B. J. (1984). Comparison of the electrocardiographic effect of dothiepin and amitriptyline. *Journal of Clinical Psychiatry*, 45, 291-293.

CLAGHORN1993 (Published Data Only)

Claghorn, J. L. & Feighner, J. P. (1993). A double-blind comparison of paroxetine with imipramine in the long-term treatment of depression. *Journal of Clinical Psychopharmacology*, 13, 23S-27S.

CLEARE1997 (Published Data Only)

Cleare, A. J., Murray, R. M., & O'Keane, V. (1997). Do noradrenergic reuptake inhibitors affect serotonergic function in depression? *Psychopharmacology*, 134, 406-410.

COHN1989 (Published Data Only)

Cohn, J. B., Collins, G., Ashbrook, E., & Wernicke, J. F. (1989). A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. *International Clinical Psychopharmacology*, 4, 313-322.

COOK1986 (Published Data Only)

Cook, B. L., Helms, P. M., Smith, R. E., & Tsai, M. (1986). Unipolar depression in the elderly. Reoccurrence on discontinuation of tricyclic antidepressants. *Journal of Affective Disorders*, 10, 91-94.

COOK1993

Cook, D. J., Guyatt, G. H., Davis, C., Willan, A., & McIlroy, W. (1993). A diagnostic and therapeutic N-of-1 randomized trial. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*, 38, 251-254.

COOKSON1985

Cookson, J. C. (1985). Drug treatment of bipolar depression and mania. *British Journal of Hospital Medicine*, 34, 172-175.

COPPEN1978B (Published Data Only)

Coppen, A., Ghose, K., Montgomery, S., Rama, R., Bailey, J., & Jorgensen, A. (1978). Continuation therapy with amitriptyline in depression. *British Journal of Psychiatry*, 133, 28-33.

COVI1981 (Published Data Only)

Covi, L., Rickels, K., Lipman, R. S., et al. (1981). Effects of psychotropic agents on primary depression. *Psychopharmacology Bulletin*, 17, 100-103.

CUNNINGHAM1994A

Cunningham (1994). Erratum: A comparison of venlafaxine, trazodone, and placebo in major depression (*Journal of Clinical Psychopharmacology* [April 1994] 14 [99-106]) *Journal of Clinical Psychopharmacology*, 14, 87-157.

DAL POZZO1997

Dal Pozzo, C., Kerr, J. S., Balguranidis, C., Yoon, J. S., & Hindmarch, I. (1997). The effects of acute doses of dothiepin (25, 50, and 75 mg) versus placebo on psychomotor performance and cognitive function. *Human Psychopharmacology*, 12, 337-345.

DAVIES1977

Davies, G., Hamilton, S., Hendrickson, E., Levy, R., & Post, F. (1977). The effect of cyclandelate in depressed and demented patients: a controlled study in psychogeriatric patients. *Age & Ageing*, 6,

156-162.

DAVIS1968 (Published Data Only)

Davis, W. G. (1968). Treating psychological disturbances induced by physical disorders: a double-blind study of perphenazine-amitriptyline in anxiety and depression. *Psychosomatics*, 9, 44-46.

DEBUS1980 (Published Data Only)

Debus, G. & Ehrhardt, J. (1980). Emotional effects of an antidepressant drug (lofepramine) after single drug administration in physically healthy subjects varying in their level of depression. *Arzneimittel-Forschung*, 30.

74

DECASTRO1985

DeCastro, R. M. (1985). Antidepressants and myoclonus: case report. *Journal of Clinical Psychiatry*, 46, 284-287.

DIMASCIO1968 (Published Data Only)

DiMascio, A., Meyer, R. E., & Stifler, L. (1968). Effects of imipramine on individuals varying in level of depression. *American Journal of Psychiatry*, 124 (Suppl. 8), 55-58.

DINGEMANSE1995 (Published Data Only)

Dingemans, J., Kneer, J., Fotteler, B., Groen, H., Peeters, P. A., & Jonkman, J. H. (1995). Switch in treatment from tricyclic antidepressants to moclobemide: a new generation monoamine oxidase inhibitor. *Journal of Clinical Psychopharmacology*, 15, 41-48.

DOWNING1972

Downing, R. W. & Rickels, K. (1972). Predictors of amitriptyline response in outpatient depressives. *The Journal of Nervous and Mental Disease*, 154, 248-263.

DOWNING1973

Downing, R. W. & Rickels, K. (1973). Predictors of response to amitriptyline and placebo in three outpatient treatment settings. *The Journal of Nervous and Mental Disease*, 156, 109-129.

EBERT1995

Ebert, D., Jaspert, A., Murata, H., & Kaschka, W. P. (1995). Initial lithium augmentation improves the antidepressant effects of standard TCA treatment in non-resistant depressed patients. *Psychopharmacology*, 118, 223-225.

EHSANULLAH1977 (Published Data Only)

Ehsanullah, R. S., Ghose, K., Kirby, M. J., Turner, P., & Witts, D. (1977). Clinical pharmacological studies of tandamine, a potential antidepressive drug. *Psychopharmacology*, 52, 73-77.

ELKIN1995 (Published Data Only)

Elkin, I., Gibbons, R. D., Shea, M. T., Sotsky, S. M., Watkins, J. T., Pilkonis, P. A. et al. (1995). Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Journal of Consulting & Clinical Psychology*, 63, 841-847.

ELSENGA1982 (Published Data Only)

Elsenga, S. (1982). Clinical effects of sleep deprivation and clomipramine in endogenous depression. *Journal of Psychiatric Research*, 17, 361-374.

EXTEIN1979 (Published Data Only)

Extein, I., Potter, W. Z., Wehr, T. A., & Goodwin, F. K. (1979). Rapid mood cycles after a noradrenergic but not a serotonergic antidepressant. *American Journal of Psychiatry*, 136, 1602-1603.

FAVA1997C (Published Data Only)

Fava, M., Nierenberg, A. A., Quitkin, F. M., Zisook, S., Pearlstein, T., Stone, A. et al. (1997). A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. *Psychopharmacology Bulletin*, 33, 101-103.

FEET1985 (Published Data Only)

Feet, P. O., Larsen, S., & Robak, O. H. (1985). A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dixyrazine. *Acta Psychiatrica Scandinavica*, 72, 334-340.

FEET1993 (Published Data Only)

Feet, P. O., Gotestam, K. G., & Norman, N. (1993). Gender differences in prolactin and aldosterone in primary non-agitated depressed patients and normal controls. *European Journal of Psychiatry*, 7, 77-88.

FEET1994 (Published Data Only)

Feet, P. O. & Gotestam, K. G. (1994). Cortisol responses to imipramine combined treatments. *European Journal of Psychiatry*, 8, 45-52.

FEIGHNER1992A (Published Data Only)

Feighner, J. P. (1992). A double-blind comparison of paroxetine, imipramine and placebo in depressed outpatients. *International Clinical Psychopharmacology*, 6 (Suppl. 4), 31-35.

FERGUSON1994A

Ferguson, J., Cunningham, L., Merideth, C., Apter, J., Feighner, J., Ionescu-Pioggia, M., et al. (1994). Bupropion in tricyclic antidepressant nonresponders with unipolar major depressive disorder. *Annals of Clinical Psychiatry*, 6, 153-160.

FERRERI1997

Ferreri, M., Colonna, L., & Leger, J. M. (1997). Efficacy of amineptine in the prevention of relapse in unipolar depression. *International Clinical Psychopharmacology*, 12 (Suppl. 3), S39-S45.

FIEVE1968 (Published Data Only)

Fieve, R. R., Platman, S. R., & Plutchik, R. R. (1968). The use of lithium in affective disorders. II. Prophylaxis of depression in chronic recurrent affective disorder. *American Journal of Psychiatry*, 125, 492-498.

75

- FINK1965** (Published Data Only)
Fink, M., Klein, D. F., & Kramer, J. C. (1965). Clinical efficacy of chlorpromazine-procyclidine combination, imipramine and placebo in depressive disorders. *Psychopharmacologia*, 7, 27-36.
- FISCH1992** (Published Data Only)
Fisch, C. & Knoebel, S. B. (1992). Electrocardiographic findings in sertraline depression trials. *Drug Investigation*, 4, 305-312.
- FRANK1990A** (Published Data Only)
Frank, E., Kupfer, D. J., Perel, J. M., Cornes, C., Jarrett, D. B., Mallinger, A. G. et al. (1990). Three-year outcomes for maintenance therapies in recurrent depression. *Archives of General Psychiatry*, 47, 1093-1099.
- FRANK1991** (Published Data Only)
Frank, E., Kupfer, D. J., Wagner, E. F., McEachran, A. B., & Cornes, C. (1991). Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression. Contributing factors. [Erratum appears in *Arch Gen Psychiatry* 1992 May;49(5):401]. *Archives of General Psychiatry*, 48, 1053-1059.
- FRIEDMAN1966** (Published Data Only)
Friedman, A.S., Granick, S., Cohen, H.W., & Cowitz, B. (1966). Imipramine (Tofranil) vs. placebo in hospitalized psychotic depressives (a comparison of patients' self-ratings, psychiatrists' ratings and psychological test scores). *Journal of Psychiatric Research*, 4, 13-36.
- FRIEDMAN1975** (Published Data Only)
Friedman, A. S. (1975). Interaction of drug therapy with marital therapy in depressive patients. *Archives of General Psychiatry*, 32, 619-637.
- FRIEDMAN1979**
Friedman, J. & Meares, R. (1979). The effect of placebo and tricyclic antidepressants on cortical evoked potentials in depressed patients. *Biological Psychology*, 8, 291-302.
- FRIEDMAN1995A** (Published Data Only)
Friedman, R. A., Mitchell, J., & Kocsis, J. H. (1995). Retreatment for relapse following desipramine discontinuation in dysthymia. *American Journal of Psychiatry*, 152, 926-928.
- FRIEDMAN1999**
Friedman, R. A., Markowitz, J. C., Parides, M., Gniwesch, L., & Kocsis, J. H. (1999). Six months of desipramine for dysthymia: can dysthymic patients achieve normal social functioning? *Journal of Affective Disorders*, 54, 283-286.
- FUX1995** (Published Data Only)
Fux, M. & Taub, M. (1995). Relapse rate and expression of anger in a double-blind. *European Journal of Psychiatry*, 9.
- GAERTNER1982**
Gaertner, H. J., Kreuter, F., Scharek, G., et al. (1982). Do urinary MHPG and plasma drug levels correlate with response to amitriptyline therapy? *Psychopharmacology*, 76, 236-239.
- GANNON1970** (Published Data Only)
Gannon, P., Itil, T., Keskiner, A., & Hsu, B. (1970). Clinical and quantitative electroencephalographical effects of MK 940. *Arzneimittel-Forschung*, 20, 971-974.
- GASTPAR1980**
Gastpar, M., Hobi, V., Poldinger, W., et al. (1980). A placebo-controlled comparative study of the combined effects of oxprenolol and clomipramine in depressed patients. *International Pharmacopsychiatry*, 15, 24-58.
- GELENBERG1979**
Gelenberg, A. J. (1979). Amoxapine, a new antidepressant, appears in human milk. *Journal of Nervous Mental Disease*, 167, 635-636.
- GEORGE1998**
George, M. S., Speer, A. M., Molloy, M., Nahas, Z., Teneback, C. C., Risch, S. C. et al. (1998). Low frequency daily left prefrontal rTMS improves mood in bipolar depression: A placebo-controlled case report. *Human Psychopharmacology*, 13, 271-275.
- GEORGOTAS1989A**

Georgotas, A., McCue, R. E., & Cooper, T. B. (1989). A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. *Archives of General Psychiatry*, 46, 783-786.

GEORGOTAS1989B

Georgotas, A. & McCue, R. E. (1989). Relapse of depressed patients after effective continuation therapy. *Journal of Affective Disorders*, 17, 159-164.

GHAZIUDDIN1995

Ghaziuddin, N., Naylor, M. W., & King, C. A. (1995). Fluoxetine in tricyclic refractory depression in adolescents. *Depression*, 2, 287-291.

GHOSE1980

Ghose, K. (1980). Sympathomimetic amines and tricyclic antidepressant drugs. *Neuropharmacology*, 19, 251-254.

GHOSE1980A

Ghose, K. (1980). Decreased tyramine sensitivity after discontinuation of amitriptyline therapy. An index of pharmacodynamic half-life. *European Journal of Clinical Pharmacology*, 18, 151-157.

GILLER1980 (Published Data Only)

Giller, E. J., Jatlow, P., Bialos, D., Harkness, L., & Docherty, J. P. (1980). Platelet MAO and amitriptyline treatment. *Psychiatry Research*, 2, 259-265.

GILLER1985 (Published Data Only)

Giller, E. J., Bialos, D., Harkness, L., Jatlow, P., & Waldo, M. (1985). Long-term amitriptyline in chronic depression. *Hillside Journal of Clinical Psychiatry*, 7, 16-33.

GLASS1981 (Published Data Only)

Glass, R. M., Uhlenhuth, E. H., Hartel, F. W., et al. (1981). Cognitive dysfunction and imipramine in outpatient depressives. *Archives of General Psychiatry*, 38, 1048-1051.

GLEN1984

Glen, A. I., Johnson, A. L., & Shepherd, M. (1984). Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized, double-blind, controlled trial. *Psychological Medicine*, 14, 37-50.

GOLDBERG1980A (Published Data Only)

Goldberg, H. M. & Finnerty, R. J. (1980). A double-blind study of trazodone. *Psychopharmacology Bulletin*, 16, 47-49.

GOLDBERG1981 (Published Data Only)

Goldberg, H. L., Rickels, K., & Finnerty, R. (1981). Treatment of neurotic depression with a new antidepressant. *Journal of Clinical Psychopharmacology*, 1 (Suppl. 6), 355-385.

GOLDBERG2004

Goldberg, J. F., Burdick, K. E., & Endick, C. J. (2004). Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *American Journal of Psychiatry*, 161, 564-566.

GRACIOUS1991

Gracious, B. & Wisner, K. L. (1991). Nortriptyline in chronic fatigue syndrome: a double blind, placebo-controlled single case study. *Biological Psychiatry*, 30, 405-408.

GRACIOUS2005

Gracious, B. L., Hanusa, B. H., Wisner, K. L., et al. (2005). Weight changes in postpartum women with remitted depression. *Journal of Clinical Psychiatry*, 66, 291-293.

GREEN1999

Green, T. D., Reynolds, C. F., Mulsant, B. H., et al. (1999). Accelerating antidepressant response in geriatric depression: a post hoc comparison of combined sleep deprivation and paroxetine versus monotherapy with paroxetine, nortriptyline, or placebo. *Journal of Geriatric Psychiatry & Neurology*, 12, 67-71.

GUNDERTREMY1983 (Published Data Only)

Gundert-Remy, U., Amann, E., Hildebrandt, R., & Weber, E. (1983). Lack of interaction between the tetracyclic antidepressant maprotiline and the centrally acting antihypertensive drug clonidine. *European Journal of Clinical Pharmacology*, 25, 595-599.

GUY1982 (Published Data Only)

Guy, W., Ban, T. A., McEvoy, J. P., Petrie, W. M., Wilson, W. H., & Schaffer, J. D. (1982). A collaborative study of a new antidepressant, viloxazine, in neurotic and endogenous depressives. *International Pharmacopsychiatry*, 17, 36-42.

HAIDER1967 (Published Data Only)

Haider, I. (1967). Amitriptyline and perphenazine in depressive illness: a controlled trial. *British Journal of Psychiatry*, 113, 195-199.

HAMEROFF1982A

Hameroff, S. R., Cork, R. C., Scherer, K., Crago, B. R., Neuman, C., Womble, J. R. et al. (1982). Doxepin effects on chronic pain, depression and plasma opioids. *Journal of Clinical Psychiatry*, 43,

22-27.

HANLON1975 (Published Data Only)

Hanlon, T. E., Blatchley, R. J., & Kurland, A. A. (1975). Effects of control techniques on therapeutic outcome in a controlled clinical trial. *International Pharmacopsychiatry*, 10, 169-176.

HARKNESS1982 (Published Data Only)

Harkness, L., Giller, E. L., Bialos, D., & Waldo, M. C. (1982). Chronic depression: response to amitriptyline after discontinuation. *Biological Psychiatry*, 17, 913-917.

77

HARRISON1986 (Published Data Only)

Harrison, W. M., Rabkin, J. G., Ehrhardt, A. A., Stewart, J. W., McGrath, P. J., Ross, D. et al. (1986). Effects of antidepressant medication on sexual function: a controlled study. *Journal of Clinical Psychopharmacology*, 6, 144-149.

HARRISON1988 (Published Data Only)

Harrison, W., Stewart, J. W., McGrath, P. J., Tricamo, E., & Quitkin, F. M. (1988). Is loss of antidepressant effect during continuation therapy related to placebo effect? *Psychopharmacology Bulletin*, 24, 91-113.

HARTMANN1973

Hartmann, E. & Cravens, J. (1973). The effects of long term administration of psychotropic drugs on human sleep. 3. The effects of amitriptyline. *Psychopharmacologia*, 33, 185-202.

HAYDU1974

Haydu, G. G., Goldschmidt, L., & Drymiotis, A. D. (1974). Effect of imipramine on the rheumatoid factor titre of psychotic patients with depressive symptomatology. *Annals of the Rheumatic Diseases*, 33, 273-275.

HECHT1986 (Published Data Only)

Hecht, O., Cole, J. O., Friedman, L., Bird, M., & McEachern, J. (1986). Weight changes in antidepressants: a comparison of amitriptyline and trazodone. *Neuropsychobiology*, 15 (Suppl. 1), 28-30.

HELLERSTEIN2000 (Published Data Only)

Hellerstein, D. J., Kocsis, J. H., Chapman, D., Stewart, J. W., & Harrison, W. (2000). Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: effects on personality. *American Journal of Psychiatry*, 157, 1436-1444.

HENINGER1983 (Published Data Only)

Heninger, G. R., Charney, D. S., & Sternberg, D. E. (1983). Lithium carbonate augmentation of antidepressant treatment. An effective prescription for treatment-refractory depression. *Archives of General Psychiatry*, 40, 1335-1342.

HERMAN2005 (Published Data Only)

Herman, I., Shamir, D., Bar-Hamburger, R., Pick, C. G., & Schreiber, S. (2005). The effect of mianserin add-on, on the intensity of opioid withdrawal symptoms during detoxification program--a randomized, double blind, placebo controlled, prospective study. *Addictive Behaviors*, 30, 1154-1167.

HERRMANN1991

Herrmann, W. M., Scharer, E., Wendt, G., & ini-Stula, A. (1991). Pharmacology-EEG profile of maroxepine: third example to discuss the predictive value of pharmacology-electroencephalography in early human pharmacological evaluations of psychoactive drugs. *Pharmacopsychiatry*, 24, 214-224.

HERRMANN1991A

Herrmann, W. M., Scharer, E., Wendt, G., & ini-Stula, A. (1991). Pharmacology-EEG profile of levoprotiline: second example to discuss the predictive value of pharmacology-electroencephalography in early human pharmacological evaluations of psychoactive drugs. *Pharmacopsychiatry*, 24, 206-213.

HINDMARCH1998A (Published Data Only)

Hindmarch, I. (1998). Effect of antidepressants on cognitive and psychomotor function: The lack of effect of reboxetine. *Human Psychopharmacology*, 13, 521-527.

HOHN1961A (Published Data Only)

Hohn, R., Gross, G. M., Gross, M., & Lasagna, L. (1961). A doubleblind comparison of placebo and imipramine in the treatment of depressed patients in a state hospital. *Journal of Psychiatric Research*, 1, 76-91.

HONIGFELD1962

Honigfeld, G. & Lasky, J. J. (1962). One year follow-up of depressed patients treated in a multi-hospital drug study. I. Social workers' evaluations. *Diseases of the Nervous System*, 23, 555-562.

HONORE1982

Honore, P., Moller, S. E., & Jorgensen, A. (1982). Lithium+L-tryptophan compared with amitriptyline in endogenous depression. *Journal of Affective Disorders*, 4, 79-82.

HUSSAIN1970 (Published Data Only)

Hussain, Z. (1970). Drugs in depressive illness. *British Medical Journal*, 1, 482.

IMBER1990 (Published Data Only)

Imber, S. D., Pilkonis, P. A., Sotsky, S. M., et al. (1990). Mode-specific effects among three treatments for depression. *Journal of Consulting & Clinical Psychology*, 58, 352-359.

IMLAH1985 (Published Data Only)

Imlah, N. W. (1985). An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. *British Journal of Psychiatry*, 146, 515-519.

78

- IRWIN1978** (Published Data Only)
Irwin, P. & Fink, M. (1978). Electroencephalogram study of mianserin in depressed patients. *British Journal of Clinical Pharmacology*, 5 (Suppl. 1), 43S-47S.
- ITIL1977** (Published Data Only)
Itil, T. M., Bhattacharyya, A., Polvan, N., et al. (1977). Fluvoxamine (Du-23,000), a new antidepressant. Quantitative pharmaco-electroencephalography and pilot clinical trials. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 1, 309-322.
- JARVIK1982** (Published Data Only)
Jarvik, L. F., Mintz, J., Steuer, J., et al. (1982). Treating geriatric depression: a 26-week interim analysis. *Journal of the American Geriatrics Society*, 30, 713-717.
- JEFFERSON1983**
Jefferson, J. W. & Ayd, J. (1983). Combining lithium and antidepressants. *Journal of Clinical Psychopharmacology*, 3, 303-307.
- JINDAL2003**
Jindal, R. D. & Thase, M. E. (2003). Integrating psychotherapy and pharmacotherapy to improve outcomes among patients with mood disorders. *Psychiatric Services*, 54, 1484-1490.
- JOHNSON1993** (Published Data Only)
Johnson, M. R., Lydiard, R. B., Morton, W. A., et al. (1993). Effect of fluvoxamine, imipramine and placebo on catecholamine function in depressed outpatients. *Journal of Psychiatric Research*, 27, 161-172.
- JOHNSON2005**
Johnson, G. F. (2005). Mood stabilisers in bipolar disorder. *Medicine Today*, 6.
- JOHNSTONE1980A** (Published Data Only)
Johnstone, E. C., Owens, D. G., Frith, C. D., et al. (1980). Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychological Medicine*, 10, 321-328.
- JUNGKUN2001**
Jungkun, G., Kuss, H. J., & Gsell, W. (2001). Long-term effects of tricyclic antidepressants on norepinephrine kinetics in humans. *Journal of Neural Transmission*, 108, 349-362.
- KAHN1986** (Published Data Only)
Kahn, R. J., McNair, D. M., Lipman, R. S., et al. (1986). Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. *Archives of General Psychiatry*, 43, 79-85.
- KALIN2000**
Kalin, N. H. (2000). Management of the depressive component of bipolar disorder. *Depression & Anxiety*, 4, 190-198.
- KANE1982** (Published Data Only)
Kane, J. M., Quitkin, F. M., Rifkin, A., et al. (1982). Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. *Archives of General Psychiatry*, 39, 1065-1069.
- KANE1983** (Published Data Only)
Kane, J. M., Cole, K., Sarantakos, S., et al. (1983). Safety and efficacy of bupropion in elderly patients: preliminary observations. *Journal of Clinical Psychiatry*, 44, 134-136.
- KANTOR1986** (Published Data Only)
Kantor, D., McNevin, S., Leichner, P., et al. (1986). The benefit of lithium carbonate adjunct in refractory depression - fact of fiction? *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*, 31, 416-418.
- KARP1994**
Karp, J. F., Frank, E., Ritenour, A., et al. (1994). Imipramine and sexual dysfunction during the long-term treatment of recurrent depression. *Neuropsychopharmacology*, 11, 21-27.
- KARP2004** (Published Data Only)
Karp, J. F., Buysse, D. J., Houck, P. R., Cherry, C., Kupfer, D. J., & Frank, E. (2004). Relationship of variability in residual symptoms with recurrence of major depressive disorder during

maintenance treatment. *American Journal of Psychiatry*, 161, 1877-1884.

KATON1993

Katon, W., Sullivan, M., Russo, J., et al. (1993). Depressive symptoms and measures of disability: a prospective study. *Journal of Affective Disorders*, 27, 245-254.

KATZ1993A

(Published Data Only)

Katz, R. J., Lott, M., Landau, P., et al. (1993). A clinical test of noradrenergic involvement in the therapeutic mode of action of an experimental antidepressant. *Biological Psychiatry*, 33, 261-266.

79

- KELLER1993**
Keller, M. B., Lavori, P. W., Goldenberg, I. M., et al. (1993). Influence of depression on the treatment of panic disorder with imipramine, alprazolam and placebo. *Journal of Affective Disorders*, 28, 27-38.
- KERR1996A** (Published Data Only)
Kerr, J. S., Powell, J., & Hindmarch, I. (1996). The effects of reboxetine and amitriptyline, with and without alcohol on cognitive function and psychomotor performance. *British Journal of Clinical Pharmacology*, 42, 239-241.
- KHAN1988** (Published Data Only)
Khan, A., Johnson, F., Avery, D. H., et al. (1988). DST results in nonpsychotic depressed outpatients. *American Journal of Psychiatry*, 145.
- KHAN1989**
Khan, A., Cohen, S., Dager, S., et al. (1989). Onset of response in relation to outcome in depressed outpatients with placebo and imipramine. *Journal of Affective Disorders*, 17, 33-38.
- KLEBER1983**
Kleber, H. D., Weissman, M. M., Rounsaville, B. J., et al. (1983). Imipramine as treatment for depression in addicts. *Archives of General Psychiatry*, 40, 649-653.
- KLEIN1967** (Published Data Only)
Klein, D. F. (1967). Importance of psychiatric diagnosis in prediction of clinical drug effects. *Archives of General Psychiatry*, 16, 118-126.
- KLEIN1968** (Published Data Only)
Klein, D. F. (1968). Psychiatric diagnosis and a typology of clinical drug effects. *Psychopharmacologia*, 13, 359-386.
- KLEIN1993** (Published Data Only)
Klein, D. F. (1993). The treatment of atypical depression. *European Psychiatry*, 8.
- KLIESER1989** (Published Data Only)
Klieser, E. & Lehmann, E. (1989). Experimental examination of trazodone. *Clinical Neuropharmacology*, 12 (Suppl. 1), S18-S24.
- KOCSIS1988** (Published Data Only)
Kocsis, J. H., Frances, A. J., Voss, C., et al. (1988). Imipramine and social-vocational adjustment in chronic depression. *American Journal of Psychiatry*, 145, 997-999.
- KOCSIS1988A** (Published Data Only)
Kocsis, J. H., Frances, A. J., Voss, C., et al. (1988). Imipramine treatment for chronic depression. *Archives of General Psychiatry*, 45, 253-257.
- KOCSIS1989** (Published Data Only)
Kocsis, J. H., Mason, B. J., Frances, A. J., et al. (1989). Prediction of response of chronic depression to imipramine. *Journal of Affective Disorders*, 17, 255-260.
- KOCSIS1990** (Published Data Only)
Kocsis, J. H., Croughan, J. L., Katz, M. M., et al. (1990). Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. *American Journal of Psychiatry*, 147, 621-624.
- KOCSIS1996** (Published Data Only)
Kocsis, J. H., Friedman, R. A., Markowitz, J. C., et al. (1996). Maintenance therapy for chronic depression. A controlled clinical trial of desipramine. *Archives of General Psychiatry*, 53, 769-774.
- KOCSIS1997** (Published Data Only)
Kocsis, J. H., Zisook, S., Davidson, J., et al. (1997). Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. *American Journal of Psychiatry*, 154, 390-395.
- KONGSAKON2005**
Kongsakon, R., Papadopoulos, K. I., & Saguansiritham, R. (2005). Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *International Clinical Psychopharmacology*, 20, 253-256.

KORN1986

Korn, A., Eichler, H. G., Fischbach, R., & Gasic, S. (1986). Moclobemide, a new reversible MAO inhibitor - interaction with tyramine and tricyclic antidepressants in healthy volunteers and depressive patients. *Psychopharmacology*, 88, 153-157.

KOWALSKI1985

Kowalski, A., Stanley, R. O., Dennerstein, L., Burrows, G., & Maguire, K. P. (1985). The sexual side-effects of antidepressant medication: a double-blind comparison of two antidepressants in a non- 80
psychiatric population. *British Journal of Psychiatry*, 147, 413-418.

KRAGHSORENSEN1974

Kragh-Sorensen, P., Hansen, C. E., Larsen, N. E., Nasestoft, J., & Hvidberg, E. F. (1974). Long-term treatment of endogenous depression with nortriptyline with control of plasma levels. *Psychological Medicine*, 4, 174-180.

KRAGHSORENSEN1976

Kragh-Sorensen, P., Hansen, C. E., Baastrup, P. C., & Hvidberg, E. F. (1976). Self-inhibiting action of nortriptylin's antidepressive effect at high plasma levels: a randomized double-blind study controlled by plasma concentrations in patients with endogenous depression. *Psychopharmacologia*, 45, 305-312.

KRAMER1965 (Published Data Only)

Kramer, M., Whitman, R. M., Baldridge, B., & Lansky, L. (1965). Depression: dreams and defenses. *American Journal of Psychiatry*, 122, 411-419.

KROGMAYER1984 (Published Data Only)

Krog-Meyer, I., Kirkegaard, C., Kijne, B., et al. (1984). Prediction of relapse with the TRH test and prophylactic amitriptyline in 39 patients with endogenous depression. *American Journal of Psychiatry*, 141, 945-948.

KRUPNICK1994

Krupnick, J. L., Collins, J., Pilkonis, P. A., Elkin, I., Simmens, S., Sotsky, S. M. et al. (1994). Therapeutic alliance and clinical outcome in the NIMH treatment of depression collaborative research program: Preliminary findings. *Psychotherapy: Theory, Research, Practice, Training*, 31, 28-35.

KUPFER1977 (Published Data Only)

Kupfer, D. J., Hanin, I., Spiker, D. G., Grau, T., & Coble, P. (1977). Amitriptyline plasma levels and clinical response in primary depression. *Clinical Pharmacology & Therapeutics*, 22, 904-911.

KUPFER1979 (Published Data Only)

Kupfer, D. J., Hanin, I., Spiker, D. G., et al. (1979). EEG sleep and tricyclic plasma levels in primary depression. *Communications in Psychopharmacology*, 3, 73-80.

KUPFER1979A (Published Data Only)

Kupfer, D. J., Coble, P. A., & Rubinstein, D. (1979). Changes in weight during treatment for depression. *Psychosomatic Medicine*, 41, 535-544.

KUPFER1992 (Published Data Only)

Kupfer, D. J., Frank, E., Perel, J. M., et al. (1992). Five-year outcome for maintenance therapies in recurrent depression. *Archives of General Psychiatry*, 49, 769-773.

KUPFER1992A

Kupfer, D. J. (1992). Maintenance treatment in recurrent depression: current and future directions. The first William Sargant Lecture. *British Journal of Psychiatry*, 161, 309-316.

KUPFER1994

Kupfer, D. J., Pollock, B. G., Perel, J. M., et al. (1994). Effect of pulse loading with clomipramine on EEG sleep. *Psychiatry Research*, 54, 161-175.

KUSALIC1993

Kusalic, M., Engelsmann, F., & Bradwejn, J. (1993). Thyroid functioning during treatment for depression. *Journal of Psychiatry & Neuroscience*, 18, 260-263.

LANGLOIS1985A (Published Data Only)

Langlois, R., Cournoyer, G., De, M., & Caille, G. (1985). High incidence of multisystemic reactions to zimeldine. *European Journal of Clinical Pharmacology*, 28, 67-71.

LAPIERRE1974 (Published Data Only)

Lapierre, Y. D. (1974). Galvanic skin responses (GSR) and plethysmographic changes induced by chlorimipramine, imipramine and placebo. *Current Therapeutic Research, Clinical & Experimental*, 16, 461-469.

LAROCHELLE1979 (Published Data Only)

Larochelle, P., Hamet, P., & Enjalbert, M. (1979). Responses to tyramine and norepinephrine after imipramine and trazodone. *Clinical Pharmacology & Therapeutics*, 26, 24-30.

LAURITZEN1992 (Published Data Only)

Lauritzen, L., Clemmesen, L., Klysner, R., et al. (1992). Combined treatment with imipramine and mianserin. A controlled pilot study. *Pharmacopsychiatry*, 25, 182-186.

LAURITZEN1996 (Published Data Only)

Lauritzen, L., Odgaard, K., Clemmesen, L., Lunde, M., et al. (1996). Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy.[see comment]. *Acta Psychiatrica Scandinavica*, 94, 241-251.

LECRUBIER1996

Lecrubier, Y. (1996). Pharmacological interventions in dysthymia. *European Psychiatry*, 11, 129s-133s.

81

LEE1993

Lee, J. H., Reynolds, C. F., Hoch, C. C., Buysse, D. J., Mazumdar, S., George, C. J. et al. (1993). Electroencephalographic sleep in recently remitted, elderly depressed patients in double-blind placebo-maintenance therapy. *Neuropsychopharmacology*, 8, 143-150.

LEGG1976 (Published Data Only)

Legg, J. F. & Stiff, M. P. (1976). Drug-related test patterns of depressed patients. *Psychopharmacology*, 50, 205-210.

LENZE2002

Lenze, E. J., Dew, M. A., Mazumdar, S., et al. (2002). Combined pharmacotherapy and psychotherapy as maintenance treatment for late-life depression: effects on social adjustment. *American Journal of Psychiatry*, 159, 466-468.

LICHT2002 (Published Data Only)

Licht, R. W. & Qvitzau, S. (2002). Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. *Psychopharmacology*, 161, 143-151.

LIEBOWITZ1981

Liebowitz, M. R., Quitkin, F. M., Stewart, J. W., et al. (1981). Phenelzine and imipramine in atypical depression. *Psychopharmacology Bulletin*, 17.

LIEBOWITZ1984A (Published Data Only)

Liebowitz, M. R., Quitkin, F. M., Stewart, J. W., McGrath, P. J., Harrison, W., Rabkin, J. G. et al. (1984). Psychopharmacologic validation of atypical depression. *Journal of Clinical Psychiatry*, 45, 22-25.

LIEBOWITZ1984B (Published Data Only)

Liebowitz, M. R., Quitkin, F. M., Stewart, J. W., McGrath, P. J., Harrison, W., Rabkin, J. et al. (1984). Phenelzine v imipramine in atypical depression. A preliminary report. *Archives of General Psychiatry*, 41, 669-677.

LIEBOWITZ1984C (Published Data Only)

Liebowitz, M.R., Quitkin, F.M., Stewart, J.M., McGrath, P., Harrison, W., Rabkin, J.G., & Klein, D.F. (1984). Methodological issues in developing nosological systems for chronic depressive illness: Psychopharmacological dissection of nonendogenous depression. *Psychopharmacology Bulletin*, 20, 390-393.

LIEBOWITZ1988 (Published Data Only)

Liebowitz, M. R., Quitkin, F. M., Stewart, J. W., McGrath, P. J., Harrison, W. M., Markowitz, J. S. et al. (1988). Antidepressant specificity in atypical depression. *Archives of General Psychiatry*, 45, 129-137.

LIPMAN1981 (Published Data Only)

Lipman, R. S., Covi, L., Downing, R. W., & et, a. (1981). Pharmacotherapy of anxiety and depression: Rationale and study design. *Psychopharmacology Bulletin*, 17.

LOUIE1984

Louie, A. K. & Meltzer, H. Y. (1984). Lithium potentiation of antidepressant treatment. *Journal of Clinical Psychopharmacology*, 4.

MALITZ1971 (Published Data Only)

Malitz, S. & Kanzler, M. (1971). Are antidepressants better than placebo? *American Journal of Psychiatry*, 127, 1605-1611.

MALT1999 (Published Data Only)

Malt, U. F., Robak, O. H., Madsbu, H. P., Bakke, O., & Loeb, M. (1999). The Norwegian naturalistic treatment study of depression in general practice (NORDEP)-I: randomised double blind study. *British Medical Journal*, 318, 1180-1184.

MANN1981 (Published Data Only)

Mann, J. J., Georgotas, A., Newton, R., et al. (1981). A controlled study of trazodone, imipramine, and placebo in outpatients with endogenous depression. *Journal of Clinical Psychopharmacology*, 1, 75-80.

MARRACCINI1999

Marraccini, R. L., Reynolds, C. F., Houck, P. R., et al. (1999). A double-blind, placebo-controlled assessment of nortriptyline's side-effects during 3-year maintenance treatment in elderly patients with recurrent major depression. *International Journal of Geriatric Psychiatry*, 14, 1014-1018.

MASON1996

Mason, B. J., Kocsis, J. H., Ritvo, E. C., et al. (1996). A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA*, 275, 761-767.

- MATUZAS1982** (Published Data Only)
Matuzas, W., Javaid, J. I., Glass, R., et al. (1982). Plasma concentrations of imipramine and clinical response among depressed outpatients. *Journal of Clinical Psychopharmacology*, 2.
- MAX1987** (Published Data Only)
Max, M. B., Culnane, M., Schafer, S. C., Gracely, R. H., Walther, D. J., Smoller, B. et al. (1987). Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology*, 37, 589-596.
- MCCANCE-KATZ1992**
McCance-Katz, E., Price, L. H., Charney, D. S., & Heninger, G. R. (1992). Serotenergic function during lithium augmentation of refractory depression. *Psychopharmacology*, 108, 93-97.
- MCCONAGHY1968**
McConaghy, N., Joffe, A. D., Kingston, W. R., Stevenson, H. G., Atkinson, I., Cole, E. et al. (1968). Correlation of clinical features of depressed out-patients with response to amitriptyline and proprityline. *British Journal of Psychiatry*, 114, 103-106.
- MCDONALD1966** (Published Data Only)
McDonald, I. M., Perkins, M., Marjerrison, G., & Podilsky, M. (1966). A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. *American Journal of Psychiatry*, 122, 1427-1431.
- MCGRATH1982**
McGrath, P. J., Quitkin, F. M., Blood, D., et. al. (1982). The effect of mianserin on cardiac conduction: A controlled study. *Psychopharmacology Bulletin*, 18, 71-72.
- MCGRATH1992** (Published Data Only)
McGrath, P. J., Stewart, J. W., Harrison, W. M., Ocepek-Welikson, K., Rabkin, J. G., Nunes, E. N. et al. (1992). Predictive value of symptoms of atypical depression for differential drug treatment outcome. *Journal of Clinical Psychopharmacology*, 12, 197-202.
- MCGRATH1993A**
McGrath, P. J., Stewart, J. W., Nunes, E. V., Ocepek-Welikson, K., Rabkin, J. G., Quitkin, F. M. et al. (1993). A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *American Journal of Psychiatry*, 150, 118-123.
- MCGRATH2000A** (Published Data Only)
McGrath, P. J., Stewart, J. W., Janal, M. N., Petkova, E., Quitkin, F. M., & Klein, D. F. (2000). A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. *American Journal of Psychiatry*, 157, 344-350.
- MERIDETH1984** (Published Data Only)
Merideth, C. H., Feighner, J. P., & Hendrickson, G. (1984). A double-blind comparative evaluation of the efficacy and safety of nomifensine, imipramine, and placebo in depressed geriatric outpatients. *Journal of Clinical Psychiatry*, 45, 73-77.
- MILLER1998A**
Miller, M. D., Curtiss, E. I., Marino, L., Houck, P. R., Paradis, C. F., Mazumdar, S. et al. (1998). Long-term ECG changes in depressed elderly patients treated with nortriptyline. A double-blind, randomized, placebo-controlled evaluation. *American Journal of Geriatric Psychiatry*, 6, 59-66.
- MINDHAM1972**
Mindham, R. H., Howland, C., & Shepherd, M. (1972). Continuation therapy with tricyclic antidepressants in depressive illness. *Lancet*, 2, 854-855.
- MOLL1990** (Published Data Only)
Moll, E. & Hetzel, W. (1990). Moclobemide (Ro 11-1163) safety in depressed patients. *Acta Psychiatrica Scandinavica, Supplementum*, 360, 69-70.
- MONTGOMERY1982**
Montgomery, S. A. & Montgomery, D. (1982). Pharmacological prevention of suicidal behaviour. *Journal of Affective Disorders*, 4.
- MORAKINYO1970** (Published Data Only)

Morakinyo, V. O. (1970). Amytriptyline and chlordiazepoxide (Limbitrol) in depressive states in Nigerians--a double-blind study. *African Journal of Medical Sciences*, 1, 409-414.

MORENO1997 (Published Data Only)

Moreno, F. A., Gelenberg, A. J., Bachar, K., & Delgado, P. L. (1997). Pindolol augmentation of treatment-resistant depressed patients. *Journal of Clinical Psychiatry*, 58, 437-439.

MOSCOVICH1984

Moscovich, D. & Mester, R. (1984). Tricyclic antidepressive treatment reinforced by reserpine. *Israel Journal of Psychiatry & Related Sciences*, 21, 283-289.

MULSANT2001B

Mulsant, B. H., Sweet, R. A., Rosen, J., Pollock, B. G., Zubenko, G. S., Flynn, T. et al. (2001). A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. *Journal of Clinical Psychiatry*, 62, 597-604.

MURPHY1978A (Published Data Only)

Murphy, J. E. (1978). Mianserin in the treatment of depressive illness and anxiety states in general practice. *British Journal of Clinical Pharmacology*, 5 (Suppl. 1), 81S-85S.

MYERS1984

Myers, E. D. & Calvert, E. J. (1984). Information, compliance and side-effects: a study of patients on antidepressant medication. *British Journal of Clinical Pharmacology*, 17, 21-25.

NARUSHIMA2000

Narushima, K., Kosier, J. T., & Robinson, R. G. (2000). Preventing poststroke depression: a 12-week double-blind randomized treatment trial and 21-month follow-up. *Journal of Nervous and Mental Disease*, 190, 296-303.

NATALE1979

Natale, M. (1979). The relationship of imipramine plasma levels and verbalized hostility in nondelusional endogenous depressives. *Journal of Nervous and Mental Disease*, 167, 620-625.

NESHKES1985

Neshkes, R. E., Gerner, R., Jarvik, L. F., Mintz, J., Joseph, J., Linde, S. et al. (1985). Orthostatic effect of imipramine and doxepin in depressed geriatric outpatients. *Journal of Clinical Psychopharmacology*, 5, 102-106.

NEWTON1981 (Published Data Only)

Newton, R. (1981). The side effect profile of trazodone in comparison to an active control and placebo. *Journal of Clinical Psychopharmacology*, 1, 895-935.

NIERENBERG2004 (Published Data Only)

Nierenberg, A. A., Quitkin, F. M., Kremer, C., Keller, M. B., & Thase, M. E. (2004). Placebo-controlled continuation treatment with mirtazapine: acute pattern of response predicts relapse. *Neuropsychopharmacology*, 29, 1012-1018.

NORMAN1983

Norman, T. R., Burrows, G. D., Maguire, K. P., et al. (1983). Maprotiline in affective illness. plasma concentration and clinical response. *Journal of Affective Disorders*, 5, 147-154.

NORMAN1992

Norman, T. R., Judd, F. K., & Burrows, G. D. (1992). New pharmacological approaches to the management of depression: from theory to clinical practice. *Australian & New Zealand Journal of Psychiatry*, 26, 73-81.

NUNES1998

Nunes, E. V., Quitkin, F. M., Donovan, S. J., Deliyannides, D., Ocepek-Welikson, K., Koenig, T. et al. (1998). Imipramine treatment of opiate-dependent patients with depressive disorders. A placebo-controlled trial. *Archives of General Psychiatry*, 55, 153-160.

NURNBERG2003

Nurnberg, H. G., Hensley, P. L., Gelenberg, A. J., Fava, M., Lauriello, J., & Paine, S. (2003). Treatment of antidepressant-associated sexual dysfunction with sildenafil: A randomized controlled trial. *JAMA*, 289, 56-64.

OPPENHEIM1983

Oppenheim, G. (1983). Estrogen in the treatment of depression: Neuropharmacological mechanisms. *Biological Psychiatry*, 18, 721-725.

OTTEVANGER1993 (Published Data Only)

Ottevanger, E. A. (1993). Fluvoxamine superior to imipramine in suicidal depressed patients. *European Neuropsychopharmacology*, 3, 362-363.

OTTEVANGER1994 (Published Data Only)

Ottevanger, E. A. (1994). The efficacy of fluvoxamine in patients with severe depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 18, 731-740.

OVERALL1962 (Published Data Only)

Overall, J. E., Hollister, L. E., POKORNY, A. D., CASEY, J. F., & KATZ, G. (1962). Drug therapy in depressions. Controlled evaluation of imipramine, isocarboxazide, dextroamphetamineamobarbital, and placebo. *Clinical Pharmacology & Therapeutics*, 3, 16-22.

OZCANKAYA1997

Ozcankaya, R., Delibas, N., & Ozguner, M. F. (1997). The clomipramine challenge test in major cases of depression and schizophrenia. *Turkish Journal of Medical Sciences*, 27.

84

PANDE1993

Pande, A. C. & Saylor, M. E. (1993). Severity of depression and response to fluoxetine. *International Clinical Psychopharmacology*, 8, 243-245.

- PARK1971** (Published Data Only)
Park, S., Glick, B., Floyd, A., & Gershon, S. (1971). Ketipramine fumarate as compared to imipramine in depressed outpatients. *Current Therapeutic Research, Clinical & Experimental*, 13, 322-325.
- PATAT1997** (Published Data Only)
Patat, A., Dubruc, C., Deschamp, C., Durrieu, G., Trocherie, S., Cimarosti, I. et al. (1997). EEG, MAO-A inhibition, pharmacokinetics and safety of befloxtone in the elderly. *Human Psychopharmacology*, 12, 557-571.
- PATKAR2006** (Published Data Only)
Patkar, A. A., Masand, P. S., Pae, C. U., Peindl, K., Hooper-Wood, C., Mannelli, P. et al. (2006). A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. *Journal of Clinical Psychopharmacology*, 26.
- PAYKEL1973A**
Paykel, E. S., Prusoff, B. A., Klerman, G. L., Haskell, D., & DiMascio, A. (1973). Clinical response to amitriptyline among depressed women. *Journal of Nervous and Mental Disease*, 156, 149-165.
- PAYKEL1975**
Paykel, E. S., DiMascio, A., Haskell, D., & Prusoff, B. A. (1975). Effects of maintenance amitriptyline and psychotherapy on symptoms of depression. *Psychological Medicine*, 5, 67-77.
- PAYKEL1976A**
Paykel, E. S., DiMascio, A., Klerman, G. L., Prusoff, B. A., & Weissman, M. M. (1976). Maintenance therapy of depression. *Pharmakopsychiatrie Neuro-Psychopharmakologie*, 9, 127-139.
- PAYKEL1982** (Published Data Only)
Paykel, E. S., Rowan, P. R., Parker, R. R., & Bhat, A. V. (1982). Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Archives of General Psychiatry*, 39, 1041-1049.
- PAYKEL1988A** (Published Data Only)
Paykel, E. S., Freeling, P., & Hollyman, J. A. (1988). Are tricyclic antidepressants useful for mild depression? A placebo controlled trial. *Pharmacopsychiatry*, 21, 15-18.
- PAYKEL1988B** (Published Data Only)
Paykel, E. S., Hollyman, J. A., Freeling, P., & Sedgwick, P. (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders*, 14, 83-95.
- PEET1981** (Published Data Only)
Peet, M., Ellis, S., & Yates, R. A. (1981). The effect of level of depression on the use of visual analogue scales by normal volunteers. *British Journal of Clinical Pharmacology*, 12, 171-178.
- PERRY1978** (Published Data Only)
Perry, G. F., Fitzsimmons, B., Shapiro, L., & Irwin, P. (1978). Clinical study of mianserin, imipramine and placebo in depression: blood level and MHPG correlations. *British Journal of Clinical Pharmacology*, 5 (Suppl. 1.), S35-S41.
- PESELOW1981** (Published Data Only)
Peselow, E. D., Dunner, D. L., Fieve, R. R., et al. (1981). Maintenance treatment of unipolar depression. *Psychopharmacology Bulletin*, 17, 53-56.
- PESELOW1989A** (Published Data Only)
Peselow, E. D., Filippi, A. M., Goodnick, P., Barouche, F., & Fieve, R. R. (1989). The short- and long-term efficacy of paroxetine HCl: B. Data from a double-blind crossover study and from a year-long term trial vs. imipramine and placebo. *Psychopharmacology Bulletin*, 25, 272-276.
- PESELOW1990A** (Published Data Only)
Peselow, E. D., Robins, C., Block, P., Barouche, F., & Fieve, R. R. (1990). Dysfunctional attitudes in depressed patients before and after clinical treatment and in normal control subjects. *American Journal of Psychiatry*, 147, 439-444.
- PESELOW1992B** (Published Data Only)
Peselow, E. D., Robins, C. J., Sanfilipo, M. P., Block, P., & Fieve, R. R. (1992). Sociotropy and autonomy: relationship to antidepressant drug treatment response and endogenous-nonendogenous dichotomy. *Journal of Abnormal Psychology*, 101, 479-486.

PESELOW1994

Peselow, E. D., Sanfilipo, M. P., & Fieve, R. R. (1994). Patients' and informants' reports of personality traits during and after major depression. *Journal of Abnormal Psychology*, 103.

PORTER1970 (Published Data Only)

Porter, A. M. W. (1970). Depressive illness in a general practice. A demographic study and a controlled trial of imipramine. *British Medical Journal*, 1, 773-778.

PRANGE1972 (Published Data Only)

Prange, J. A. J., Wilson, I. C., Knox, A. E., McClane, T. K., Breese, G. R., Martin, B. R. et al. (1972). Thyroid-imipramine clinical and chemical interaction: evidence for a receptor deficit in depression. *Journal of Psychiatric Research*, 9, 187-205.

85

- PRESKORN1983** (Published Data Only)
Preskorn, S. H. (1983). Antidepressant response and plasma concentrations of bupropion. *Journal of Clinical Psychiatry*, 44, 137-139.
- PRICE1986** (Published Data Only)
Price, L. H., Charney, D. S., & Heninger, G. R. (1986). Variability of response to lithium augmentation in refractory depression. *American Journal of Psychiatry*, 143, 1387-1392.
- PRICE1990** (Published Data Only)
Price, L. H., Charney, D. S., Delgado, P. L., & Heninger, G. R. (1990). Fenfluramine augmentation in tricyclic-refractory depression. *Journal of Clinical Psychopharmacology*, 10, 312-317.
- PRIEN1984A**
Prien, R. F., Kupfer, D. J., Mansky, P. A., Small, J. G., Tuason, V. B., Voss, C. B. et al. (1984). Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Archives of General Psychiatry*, 41, 1096-1104.
- PRIEN1986** (Published Data Only)
Prien, R. F. & Kupfer, D. J. (1986). Continuation drug therapy for major depressive episodes: how long should it be maintained? *American Journal of Psychiatry*, 143, 18-23.
- PUIGANTICH1987**
Puig-Antich, J., Perel, J. M., Lupatkin, W., Chambers, W. J., Tabrizi, M. A., King, J. et al. (1987). Imipramine in prepubertal major depressive disorders. *Archives of General Psychiatry*, 44, 81-89.
- QUADRI1980** (Published Data Only)
Quadri, A. A., Shalini, K., & Channabasavanna, S. M. (1980). d-Amphetamine as a predictor for response to imipramine and amitriptyline. *Indian Journal of Psychiatry*, 22, 182-184.
- QUINTKIN1985**
Quintkin, F. M. & Quitkin (1985). The importance of dosage in prescribing antidepressants. *British Journal of Psychiatry*, 147, 593-597.
- QUITKIN1978**
Quitkin, F., Rifkin, A., & Klein, D. F. (1978). Imipramine response in deluded depressive patients. *American Journal of Psychiatry*, 135, 806-811.
- QUITKIN1978A** (Published Data Only)
Quitkin, F., Rifkin, A., Kane, J., Ramos-Lorenzi, J. R., & Klein, D. F. (1978). Prophylactic effect of lithium and imipramine in unipolar and bipolar II patients: a preliminary report. *American Journal of Psychiatry*, 135, 570-572.
- QUITKIN1982**
Quitkin, F. M., Schwartz, D., Liebowitz, M. R., et al. (1982). Atypical depressives: A preliminary report of antidepressant response and sleep patterns. *Psychopharmacology Bulletin*, 18, 78-80.
- QUITKIN1984C** (Published Data Only)
Quitkin, F. M., Harrison, W., Liebowitz, M., McGrath, P., Rabkin, J. G., Stewart, J. et al. (1984). Defining the boundaries of atypical depression. *Journal of Clinical Psychiatry*, 45, 19-21.
- QUITKIN1986**
Quitkin, F. M., Rabkin, J. G., Stewart, J. W., McGrath, P. J., & Harrison, W. (1986). Study duration in antidepressant research: advantages of a 12-week trial. *Journal of Psychiatric Research*, 20, 211-216.
- QUITKIN1987** (Published Data Only)
Quitkin, F. M., Rabkin, J. D., Markowitz, J. M., Stewart, J. W., McGrath, P. J., & Harrison, W. (1987). Use of pattern analysis to identify true drug response. A replication. *Archives of General Psychiatry*, 44, 259-264.
- QUITKIN1988** (Published Data Only)
Quitkin, F. M., Stewart, J. W., McGrath, P. J., Liebowitz, M. R., Harrison, W. M., Tricamo, E. et al. (1988). Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. *American Journal of Psychiatry*, 145, 306-311.
- QUITKIN1990** (Published Data Only)
Quitkin, F. M., McGrath, P. J., Stewart, J. W., Harrison, W., Tricamo, E., Wager, S. G. et al. (1990). Atypical depression, panic attacks, and response to imipramine and phenelzine. A replication.

Archives of General Psychiatry, 47, 935-941.

QUITKIN1993A (Published Data Only)

Quitkin, F. M., Stewart, J. W., McGrath, P. J., Nunes, E., Ocepek-Welikson, K., Tricamo, E. et al. (1993). Further evidence that a placebo response to antidepressants can be identified. American Journal of Psychiatry, 150, 566-570.

QUITKIN1993B (Published Data Only)

Quitkin, F. M., Stewart, J. W., McGrath, P. J., Nunes, E., Ocepek-Welikson, K., Tricamo, E. et al. (1993). Loss of drug effects during continuation therapy. American Journal of Psychiatry, 150, 562-565.

86

- QUITKIN2005** (Published Data Only)
Quitkin, F. M., McGrath, P. J., Stewart, J. W., Deliyannides, D., Taylor, B. P., Davies, C. A. et al. (2005). Remission rates with 3 consecutive antidepressant trials: effectiveness for depressed outpatients. *Journal of Clinical Psychiatry*, 66, 670-676.
- RABKIN1986** (Published Data Only)
Rabkin, J. G. & Markowitz, J. S. (1986). Side effect assessment with SAFTEE: Pilot study of the instrument. *Psychopharmacology Bulletin*, 22, 389-396.
- RAFT1981** (Published Data Only)
Raft, D., Davidson, J., Wasik, J., & Mattox, A. (1981). Relationship between response to phenelzine and MAO inhibition in a clinical trial of phenelzine, amitriptyline and placebo. *Neuropsychobiology*, 7, 122-126.
- RAMPELLO1995** (Published Data Only)
Rampello, L., Nicoletti, G., Raffaele, R., & Drago, F. (1995). Comparative effects of amitriptyline and amineptine in patients affected by anxious depression. *Neuropsychobiology*, 31, 130-134.
- RASKIN1973** (Published Data Only)
Raskin, A., Boothe, H., Schulterbrandt, J.G., Reatig, N., & Odle, D. (1973). A model for drug use with depressed patients. *The Journal of Nervous and Mental Disease*, 156, 130-142.
- RASKIN1974** (Published Data Only)
Raskin, A. (1974). Age-sex differences in response to antidepressant drugs. *Journal of Nervous and Mental Disease*, 159, 120-130.
- RASKIN1975** (Published Data Only)
Raskin, A. & Crook, T. H. (1975). Antidepressants in black and white inpatients. Differential response to a controlled trial of chlorpromazine and imipramine. *Archives of General Psychiatry*, 32, 643-649.
- RASKIN1976** (Published Data Only)
Raskin, A. & Crook, T. H. (1976). The endogenous--neurotic distinction as a predictor of response to antidepressant drugs. *Psychological Medicine*, 6, 59-70.
- RASKIN1976A**
Raskin, A. & Crook, T. H. (1976). Sensitivity of rating scales completed by psychiatrists, nurses and patients to antidepressant drug effects. *Journal of Psychiatric Research*, 13, 31-41.
- RASKIN1978** (Published Data Only)
Raskin, A., Boothe, H., Reatig, N., & Schulterbrandt, J. G. (1978). Initial response to drugs in depressive illness and psychiatric and community adjustment a year later. *Psychological Medicine*, 8, 71-79.
- REISBY1979**
Reisby, N., Gram, L. F., Bech, P., et al. (1979). Clomipramine: Plasma levels and clinical effects. *Communications in Psychopharmacology*, 3, 341-351.
- REYNOLDS1992A**
*Reynolds, C. F., Frank, E., Perel, J. M., Imber, S. D., Cornes, C., Morycz, R. K. et al. (1992). Combined pharmacotherapy and psychotherapy in the acute and continuation treatment of elderly patients with recurrent major depression: a preliminary report. *American Journal of Psychiatry*, 149, 1687-1692.
Dew, M. A., Reynolds, C. F., Mulsant, B., Frank, E., Houck, P. R., Mazumdar, S. et al. (2001). Initial recovery patterns may predict which maintenance therapies for depression will keep older adults well. *Journal of Affective Disorders*, 65, 155-166.
Reynolds, C. F., Frank, E., Dew, M. A., Houck, P. R., Miller, M., Mazumdar, S. et al. (1999). Treatment of 70(+)-year-olds with recurrent major depression. Excellent short-term but brittle long-term response. *American Journal of Geriatric Psychiatry*, 7, 64-69.
Reynolds, C. F., Miller, M. D., Pasternak, R. E., Frank, E., Perel, J. M., Cornes, C. et al. (1999). Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *American Journal of Psychiatry*, 156, 202-208.
Reynolds, C. F., Frank, E., Perel, J. M., Imber, S. D., Cornes, C., Miller, M. D. et al. (1999). Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA*, 281, 39-45.
Reynolds, C. F., Frank, E., Houck, P. R., Mazumdar, S., Dew, M. A., Cornes, C. et al. (1997). Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy

after discontinuation of antidepressant medication? *American Journal of Psychiatry*, 154, 958-962.

Reynolds, C. F., Buysse, D. J., Brunner, D. P., Begley, A. E., Dew, M. A., Hoch, C. C. et al. (1997). Maintenance nortriptyline effects on electroencephalographic sleep in elderly patients with recurrent major depression: double-blind, placebo- and plasma-level-controlled evaluation. *Biological Psychiatry*, 42, 560-567.

Reynolds, C. F., Frank, E., Perel, J. M., Mazumdar, S., Dew, M. A., Begley, A. et al. (1996). High relapse rate after discontinuation of adjunctive medication for elderly patients with recurrent major depression. *American Journal of Psychiatry*, 153, 1418-1422.

Reynolds, I. I. C., Frank, E., Perel, J. M., Miller, M. D., Paradis, C. F., Stack, J. A. et al. (1995). Nortriptyline side effects during double-blind, randomized, placebo- controlled maintenance therapy in older depressed patients. *American Journal of Geriatric Psychiatry*, 3. 87

- RIKELS1964** (Published Data Only)
Rickels, K., Ward, C. H., & Schut, L. (1964). Different populations, different drug responses. a comparative study of two anti-depressants, each used in two different patient groups. *American Journal of the Medical Sciences*, 247, 328-335.
- RIKELS1970** (Published Data Only)
Rickels, K., Hesbacher, P. T., Weise, C. C., Gray, B., & Feldman, H. S. (1970). Pills and improvement: a study of placebo response in psychoneurotic outpatients. *Psychopharmacologia*, 16, 318-328.
- RIKELS1970A**
Rickels, K., Gordon, P. E., Jenkins, B. W., Perloff, M., Sachs, T., & Stepansky, W. (1970). Drug treatment in depressive illness. *Diseases of the Nervous System*, 31, 30-42.
- RIKELS1982** (Published Data Only)
Rickels, K., Cohen, D., Csanalosi, I., et al. (1982). Alprazolam and imipramine in depressed outpatients: A controlled study. *Current Therapeutic Research, Clinical & Experimental*, 32.
- RIKELS1982B** (Published Data Only)
Rickels, K., Weise, C. C., Sandler, K., et al. (1982). Nomifensine, imipramine and placebo in depressed outpatients. *International Pharmacopsychiatry*, 17 (Suppl. 1), 73-88.
- RIKELS1994** (Published Data Only)
*Rickels, K., Schweizer, E., Clary, C., Fox, I., & Weise, C. (1994). Nefazodone and imipramine in major depression: a placebo-controlled trial. *British Journal of Psychiatry*, 164, 802-805.
Zajecka, J. M. (1996). The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. *Journal of Clinical Psychiatry*, 57 (Suppl. 2), 10-14.
- RIKELS1995** (Published Data Only)
Rickels, K., Robinson, D. S., Schweizer, E., Marcus, R. N., & Roberts, D. L. (1995). Nefazodone: aspects of efficacy. *Journal of Clinical Psychiatry*, 56 (Suppl. 6), 43-46.
- RIFKIN1973**
Rifkin, A. E., Quitkin, F. M., & Klein, D. F. (1973). Plasma-nortriptyline levels in depression. *Lancet*, 1, 1258.
- ROBINSON2000B** (Published Data Only)
Robinson, R. G., Schultz, S. K., Castillo, C., Kopel, T., Kosier, J. T., Newman, R. M. et al. (2000). Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *American Journal of Psychiatry*, 157, 351-359.
- ROFFMAN1983** (Published Data Only)
Roffman, M., Gould, E., Brewer, S., et al. (1983). Comparative anticholinergic activity of oxaprotiline and amitriptyline. *Drug Development Research*, 3, 56-66.
- ROSEN1993** (Published Data Only)
Rosen, J., Sweet, R., Pollock, B. G., & Mulsant, B. H. (1993). Nortriptyline in the hospitalized elderly: tolerance and side effect reduction. *Psychopharmacology Bulletin*, 29, 327-331.
- ROTHBLUM1982** (Published Data Only)
Rothblum, E. D., Sholomskas, A. J., Berry, C., & Prusoff, B. A. (1982). Issues in clinical trials with the depressed elderly. *Journal of the American Geriatrics Society*, 30, 694-699.
- ROTHSCHILD1994** (Published Data Only)
Rothschild, R., Quitkin, H. M., Quitkin, F. M., Stewart, J. W., Ocepek-Welikson, K., McGrath, P. J. et al. (1994). A double-blind placebo-controlled comparison of phenelzine and imipramine in the treatment of bulimia in atypical depressives. *International Journal of Eating Disorders*, 15, 1-9.
- ROWAN1980**
Rowan, P., Paykel, E. S., Parker, R. R., & West, E. (1980). Comparative effects of phenelzine and amitriptyline: a placebo controlled trial. *Neuropharmacology*, 19, 1223-1225.
- ROWAN1981** (Published Data Only)
Rowan, P. R., Paykel, F. S., West, P. S., et al. (1981). Effects of phenelzine and acetylator phenotype. *Neuropharmacology*, 20, 353-354.
- ROWAN1983**

Rowan, P. (1983). Monoamine oxidase inhibitors in depression. *British Medical Journal*, 286, 225-226.

RUSH1984

Rush, A. J., Schlessler, M. A., Erman, M., & Fairchild, C. (1984). Alprazolam in bipolar-I depressions. *Pharmacotherapy*, 4, 40-42.

SANDERS2005

Sanders, S., Del, M., Purdy, S., Spinks, A., Tait, L., & McAvoy, B. (2005). Evidence in practice - Number 7: Can postpartum depression be prevented? *British Journal of General Practice*, 55, 398.

SCHIFANO1990

Schifano, F., Garbin, A., Renesto, V., De, D., Trinciarelli, G., Silvestri, A. et al. (1990). A double-blind comparison of mianserin and maprotiline in depressed medically ill elderly people. *Acta Psychiatrica Scandinavica*, 81, 289-294.

SCHILDKRAUT1964 (Published Data Only)

Schildkraut, J. J., Klerman, G. L., Hammond, R., & Friend, D. G. (1964). Excretion of 3-methoxy-4-hydroxymandelic acid (VMA) in depressed patients treated with antidepressant drugs. *Journal of Psychiatric Research*, 2, 266.

SCHILDKRAUT1965

Schildkraut, J. J., Gordon, E. K., & Durell, J. (1965). Catecholamine metabolism in affective disorders. I. Normetanephrine and VMA excretion in depressed patients treated with imipramine. *Journal of Psychiatric Research*, 3, 213-228.

SCHULTERBRANDT1974 (Published Data Only)

Schulterbrandt, J.G., Raskin, A., & Reatig, N. (1974). True and apparent side effects in a controlled trial of Chlorpromazine and Imipramine in Depression. *Psychopharmacologia*, 38, 303-317.

SHALAL1996

Shalal, B., Piel, E., Mecz, L., Kremer, I., & Klein, E. (1996). Lack of advantage for imipramine combined with lithium versus imipramine alone in the treatment of major depression - a double-blind controlled study. *Biological Psychiatry*, 40, 1181-1183.

SHAMMAS1977 (Published Data Only)

Shammas, E. (1977). Controlled comparison of bromazepam, amitriptyline, and placebo in anxiety-depressive neurosis. *Diseases of the Nervous System*, 38, 201-207.

SHAPIRA1989 (Published Data Only)

Shapira, B., Reiss, A., Kaiser, N., Kindler, S., & Lerer, B. (1989). Effect of imipramine treatment on the prolactin response to fenfluramine and placebo challenge in depressed patients. *Journal of Affective Disorders*, 16, 1-4.

SHAPIRA1992

Shapira, B., Yagmur, M. J., Gropp, C., Newman, M., & Lerer, B. (1992). Effect of clomipramine and lithium on fenfluramine-induced hormone release in major depression. *Biological Psychiatry*, 31, 975-983.

SHAPIRA1993

Shapira, B., Cohen, J., Newman, M. E., & Lerer, B. (1993). Prolactin response to fenfluramine and placebo challenge following maintenance pharmacotherapy withdrawal in remitted depressed patients. *Biological Psychiatry*, 33, 531-535.

SHARMA1980

Sharma, S. & Hegde, R. (1980). Therapeutic efficacy of doxepin in divided and single dose regime. *Indian Journal of Psychiatry*, 22, 283-287.

SHEA1992A (Published Data Only)

Shea, M. T., Elkin, I., Imber, S. D., Sotsky, S. M., Watkins, J. T., Collins, J. F. et al. (1992). Course of depressive symptoms over follow-up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Archives of General Psychiatry*, 49, 782-787.

SHELTON1997 (Published Data Only)

Shelton, R. C., Davidson, J., Yonkers, K. A., Koran, L., Thase, M. E., Pearlstein, T. et al. (1997). The undertreatment of dysthymia. *Journal of Clinical Psychiatry*, 58, 59-65.

SHEPHERD1981 (Published Data Only)

Shepherd, M. (1981). Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a controlled clinical trial. *Psychological Medicine*, 11, 409-416.

SHERWOOD1993

Sherwood, N. & Hindmarch, I. (1993). A comparison of five commonly prescribed antidepressants with particular reference to their behavioural toxicity. *Human Psychopharmacology*, 8, 417-422.

SHIPLEY1981 (Published Data Only)

Shibley, J. E., Kupfer, D. J., Spiker, D. G., Shaw, D. H., Coble, P. A., Neil, J. F. et al. (1981). Neuropsychological assessment and EEG sleep in affective disorders. *Biological Psychiatry*, 16, 907-918.

SHOPSIN1971 (Published Data Only)

Shopsin, B. & Gershon, S. (1971). Plasma cortisol response to dexamethasone suppression in depressed and control patients. *Archives of General Psychiatry*, 24, 320-326.

SIRIS1982

Siris, S. G., Rifkin, A. E., & Reardon, G. T. (1982). Response of postpsychotic depression to adjunctive imipramine or amitriptyline. *Journal of Clinical Psychiatry*, 43, 485-486.

89

- SIRIS1987A** (Published Data Only)
Siris, S. G., Morgan, V., Fagerstrom, R., Rifkin, A., & Cooper, T. B. (1987). Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Archives of General Psychiatry*, 44, 533-539.
- SIRIS1988A** (Published Data Only)
Siris, S. G., Adan, F., Cohen, M., Mandeli, J., Aronson, A., & Casey, E. (1988). Postpsychotic depression and negative symptoms: an investigation of syndromal overlap. *American Journal of Psychiatry*, 145, 1532-1537.
- SIRIS2001A**
Siris, S. G., Rifkin, A. E., Reardon, G. T., & November, M. (2001). Comparison of imipramine and benzotropine in the prevention of extrapyramidal side effects of fluphenazine. *Psychopharmacology Bulletin*, .
- SJOQVIST1971**
Sjoqvist, F. (1971). A pharmacokinetic approach to the treatment of depression. *International Pharmacopsychiatry*, 6, 147-169.
- SOLOFF1989** (Published Data Only)
Soloff, P. H., George, A., Nathan, S., Schulz, P. M., Cornelius, J. R., Herring, J. et al. (1989). Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *Journal of Clinical Psychopharmacology*, 9, 238-246.
- SPIKER1988** (Published Data Only)
Spiker, D. G. & Kupfer, D. J. (1988). Placebo response rates in psychotic and nonpsychotic depression. *Journal of Affective Disorders*, 14, 21-23.
- STANER1993** (Published Data Only)
Staner, L. & Mendlewicz, J. (1993). Efficacy of tianeptine in the treatment of major depression and depressed bipolar disorders. Illustration of the interest of surveillance of a European multicentre double-blind study in progress: Tianeptine versus placebo and imipramine. *European Psychiatry*, 8, 11S-15S.
- STEINBOOK1979** (Published Data Only)
Steinbook, R. M., Jacobson, A. F., Weiss, B. L., & Goldstein, B. J. (1979). Amoxapine, imipramine and placebo: A double-blind study with pretherapy urinary 3-methoxy-4-hydroxyphenylglycol levels. *Current Therapeutic Research, Clinical & Experimental*, 26.
- STEWART1988** (Published Data Only)
Stewart, J. W., Quitkin, F. M., McGrath, P. J., Rabkin, J. G., Markowitz, J. S., Tricamo, E. et al. (1988). Social functioning in chronic depression: effect of 6 weeks of antidepressant treatment. *Psychiatry Research*, 25, 213-222.
- STEWART1988A** (Published Data Only)
Stewart, J. W., Harrison, W., Cooper, T. B., & Quitkin, F. M. (1988). Tyramine sulfate excretion may be a better predictor of antidepressant response than monoamine oxidase activity. *Psychiatry Research*, 25, 195-201.
- STEWART1989** (Published Data Only)
Stewart, J. W., McGrath, P. J., Quitkin, F. M., Harrison, W., Markowitz, J., Wager, S. et al. (1989). Relevance of DMS-III depressive subtype and chronicity of antidepressant efficacy in atypical depression. Differential response to phenelzine, imipramine, and placebo. *Archives of General Psychiatry*, 46, 1080-1087.
- STEWART1989A** (Published Data Only)
Stewart, J. W. & Halbreich, U. (1989). Plasma melatonin levels in depressed patients before and after treatment with antidepressant medication. *Biological Psychiatry*, 25, 33-38.
- STEWART1992** (Published Data Only)
Stewart, J. W., McGrath, P. J., & Quitkin, F. M. (1992). Can mildly depressed outpatients with atypical depression benefit from antidepressants? *American Journal of Psychiatry*, 149, 615-619.
- STEWART1993** (Published Data Only)
Stewart, J. W., McGrath, P. J., Quitkin, F. M., Rabkin, J. G., Harrison, W., Wager, S. et al. (1993). Chronic depression: response to placebo, imipramine, and phenelzine. *Journal of Clinical Psychopharmacology*, 13, 391-396.

STEWART1993A (Published Data Only)

Stewart, J. W., Mercier, M. A., Agosti, V., Guardino, M., & Quitkin, F. M. (1993). Imipramine is effective after unsuccessful cognitive therapy: sequential use of cognitive therapy and imipramine in depressed outpatients. *Journal of Clinical Psychopharmacology*, 13, 114-119.

STEWART1997 (Published Data Only)

Stewart, J. W., Tricamo, E., McGrath, P. J., & Quitkin, F. M. (1997). Prophylactic efficacy of phenelzine and imipramine in chronic atypical depression: likelihood of recurrence on discontinuation after 6 months' remission. *American Journal of Psychiatry*, 154, 31-36.

90

- STEWART1999** (Published Data Only)
Stewart, J. W., Quitkin, F. M., McGrath, P. J., & Bruder, G. E. (1999). Do tricyclic responders have different brain laterality? *Journal of Abnormal Psychology*, 108, 707-710.
- STRATAS1984** (Published Data Only)
Stratas, N. E. (1984). A double-blind study of the efficacy and safety of dothiepin hydrochloride in the treatment of major depressive disorder. *Journal of Clinical Psychiatry*, 45, 466-469.
- SUSSEX1985** (Published Data Only)
Separate and combined anxiolytic and anti-depressant treatment of mixed anxiety/depression. A double-blind, placebo controlled comparison. Sussex Clinical Trials Group (1985). *Acta Psychiatrica Scandinavica*, 72, 81-88.
- SZABADI1980**
Szabadi, E., Gaszner, P., & Bradshaw, C. M. (1980). The peripheral anticholinergic activity of tricyclic antidepressants: Comparison of amitriptyline and desipramine in human volunteers. *British Journal of Psychiatry*, 137.
- TAN1994** (Published Data Only)
Tan, R. S., Barlow, R. J., Abel, C., Reddy, S., Palmer, A. J., Fletcher, A. E. et al. (1994). The effect of low dose lofepramine in depressed elderly patients in general medical wards. *British Journal of Clinical Pharmacology*, 37, 321-324.
- TAYLOR1999A**
Taylor, M. P., Reynolds, C. F., Frank, E., Cornes, C., Miller, M. D., Stack, J. A. et al. (1999). Which elderly depressed patients remain well on maintenance interpersonal psychotherapy alone?: report from the Pittsburgh study of maintenance therapies in late-life depression. *Depression & Anxiety*, 10, 55-60.
- THASE1996A** (Published Data Only)
Thase, M. E., Fava, M., Halbreich, U., Kocsis, J. H., Koran, L., Davidson, J. et al. (1996). A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia.[see comment]. *Archives of General Psychiatry*, 53, 777-784.
- TOLLEFSON1994** (Published Data Only)
Tollefson, G. D., Tollefson, S. L., Saylor, M. E., & Luxenberg, M. G. (1994). Absence of emergent suicidal ideation during treatment: A comparative, controlled, double-blind analysis employing several distinct antidepressants. *Depression*, 2, 50-59.
- TYRER1988A** (Published Data Only)
Tyrer, P., Seivewright, N., Murphy, S., Ferguson, B., Kingdon, D., Barczak, P. et al. (1988). The Nottingham study of neurotic disorder: comparison of drug and psychological treatments. *Lancet*, 2, 235-240.
- TYRER1990** (Published Data Only)
Tyrer, P., Seivewright, N., Ferguson, B., Murphy, S., Darling, C., Brothwell, J. et al. (1990). The Nottingham Study of Neurotic Disorder: relationship between personality status and symptoms. *Psychological Medicine*, 20, 423-431.
- TYRER1990A**
Tyrer, P. & Murphy, S. (1990). Efficacy of combined antidepressant therapy in resistant neurotic disorder.[see comment]. *British Journal of Psychiatry*, 156, 115-118.
- UHLENHUTH1964** (Published Data Only)
Uhlenhuth, E.H., & Park, L.C. (1964). The influence of medication (Imipramine) and doctor in relieving depressed psychoneurotic outpatients. *Journal of Psychiatric Research*, 2, 101-122.
- VAN1981B** (Published Data Only)
van, d. (1981). Maprotiline versus imipramine and placebo in neurotic depression. *Journal of Clinical Psychiatry*, 42, 138-141.
- VAN1984** (Published Data Only)
Van, d., Silverstone, T., & Ankier, S. I. (1984). Electrophysiological and haemodynamic changes with trazodone, amitriptyline and placebo in depressed out-patients. *Current Medical Research & Opinion*, 9, 339-352.

VAN1984A (Published Data Only)

Van, d., Silverstone, T., Ankier, S. I., Warrington, S. J., & Turner, P. (1984). A double-blind non-crossover placebo-controlled study between group comparison of trazodone and amitriptyline on cardiovascular function in major depressive disorder. *Psychopathology*, 17 (Suppl. 2), 64-76.

VAN2006 (Published Data Only)

Van, D., Birkenhager, T. K., Mulder, P. G., Bruijn, J. A., & Moleman, P. (2006). Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. *Journal of Clinical Psychiatry*, 67, 263-268.

91

- VERSIANI1990A** (Published Data Only)
Versiani, M., Nardi, A. E., Figueira, I. L., & Stabl, M. (1990). Tolerability of moclobemide, a new reversible inhibitor of monoamine oxidase-A, compared with other antidepressants and placebo. *Acta Psychiatrica Scandinavica, Supplementum*, 360, 24-28.
- VERSIANI1997** (Published Data Only)
Versiani, M., Amrein, R., Stabl, M., Magistris, Udabe, R. U., Da, C. et al. (1997). Moclobemide and imipramine in chronic depression (dysthymia): An international double-blind, placebo-controlled trial. *International Clinical Psychopharmacology*, 12, 183-193.
- VINAR1985**
Vinar, O., Zapletalek, M., Kazdova, E., et al. (1985). Antidepressant effects of lisuride are not different from effects of amitriptyline and nortriptyline. *Activitas Nervosa Superior*, 27, 249-251.
- VOGEL1983** (Published Data Only)
Vogel, G. W. (1983). Evidence for REM sleep deprivation as the mechanism of action of antidepressant drugs. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 7, 343-349.
- WALLERSTEIN1967** (Published Data Only)
Wallerstein, E., Dykyj, R., & Nodine, J. H. (1967). Fluphenazine and amitriptyline in the anxious depressed patient. *American Journal of Psychiatry*, 124, 397-398.
- WEINTRAUB1963**
Weintraub, W. & Aronson, H. (1963). Clinical judgment in psychopharmacological research. *Journal of Neuropsychiatry*, 4, 65-70.
- WEISSMAN1992** (Published Data Only)
Weissman, M. M., Prusoff, B., Sholomskas, A. J., & Greenwald, S. (1992). A double-blind clinical trial of alprazolam, imipramine, or placebo in the depressed elderly. *Journal of Clinical Psychopharmacology*, 12, 175-182.
- WHEATLEY1972B**
Wheatley, D. (1972). Potentiation of amitriptyline by thyroid hormone. *Archives of General Psychiatry*, 26, 229-233.
- WILCOX1992** (Published Data Only)
Wilcox, C. S., Cohn, J. B., Linden, R. D., Heiser, J. F., Lucas, P. B., Morgan, D. L. et al. (1992). Predictors of placebo response: A retrospective analysis. *Psychopharmacology Bulletin*, 28, 157-162.
- WILKINSON2002** (Published Data Only)
Wilkinson, D., Holmes, C., Woolford, J., Stammers, S., & North, J. (2002). Prophylactic therapy with lithium in elderly patients with unipolar major depression. *International Journal of Geriatric Psychiatry*, 17, 619-622.
- WISNER2001**
Wisner, K. L., Perel, J. M., Peindl, K. S., Hanusa, B. H., Findling, R. L., & Rapport, D. (2001). Prevention of recurrent postpartum depression: a randomized clinical trial. *Journal of Clinical Psychiatry*, 62, 82-86.
- WOLFE1989** (Published Data Only)
Wolfe, N., Gelenberg, A. J., & Lydiard, R. B. (1989). Alpha2-adrenergic receptor sensitivity in depressed patients: Relation between 3H-yohimbine binding to platelet membranes and clonidine-induced hypotension. *Biological Psychiatry*, 25, 382-392.
- ZIS1991** (Published Data Only)
Zis, A. P., Goumeniouk, A. D., Clark, C. M., Grant, B. E. K., Remick, R. A., Lam, W. et al. (1991). ECT-induced prolactin release: Effect of sex, electrode placement and serotonin uptake inhibition. *Human Psychopharmacology*, 6, 155-160.
- ZLOTNICK1996** (Published Data Only)
Zlotnick, C., Shea, M. T., Pilkonis, P. A., Elkin, I., & Ryan, C. (1996). Gender, type of treatment, dysfunctional attitudes, social support, life events, and depressive symptoms over naturalistic follow-up. *American Journal of Psychiatry*, 153, 1021-1027.

Amitriptyline - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Beasley 1993b Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Duration: 5 weeks	Inclusion Criteria: RDC Major depressive disorder, 20+ HRSD (21 item), no more than 20% decrease in HRSD during placebo week, Raskin score of at least 8, and higher than Covi score Age: 21-70 Country: US & Canada Setting: Outpatients	Fluoxetine versus amitriptyline (75mg -> 100mg on day 2 -> 125mg on day 4, 100-150mg on day 8, 150-200mg on day 12, 150-300mg after day 15, 85.2% patients achieved 125 mg/day)	1. HRSD mean change scores 2. Leaving the study early 3. Non-responders (patients not achieving ≥50% decrease in HRSD) 4. Leaving the study early due to side effects	[Geddes2002]	B
Blacker1988 Y P E	Allocation: Random double-blind 6-week trial	Primary care patients, n = 227, HRSD analysis: n=177; mean age: trazodone - 45 years (+-12.8), mianserin - 46 years (+-12.7), dosulepin/dothiepin - 43 years (+-13.2), amitriptyline - 42 years (+-12.5); (number of women not given) Diagnosis: DSM III for major depression, HRSD 17+	1. Trazodone (150 mg) 2. Mianserin (30 mg - 60 mg) 3. Dosulepin/dothiepin (75 mg starting, increased to 150 mg) 4. Amitriptyline (75 mg starting, increased to 100mg) (Data extracted for 3 & 4)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD-21 mean endpoint scores	Setting: UK [Barbui2001]	B
Bremner 1995 Y O I	Allocation: random (no details) Double-blind 6-week trial	Primary care and outpatients n=275, c.64% women, mean age: mirtazapine group - 47.2 years (+-11.1); paroxetine group - 47.3 years (+-10.3) Diagnosis: DSM-IV for major depressive episode, and HRSD-17 ≥ 18	1. Mirtazapine (mean 22mg/day; max 35mg) 2. Amitriptyline (mean = 168.4mg/day; max 280 mg) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD mean endpoint scores	Setting: US	B
Carman 1991 Y O I	Allocation: Random double-blind 6-week trial	Outpatients, n = 150; age: 18+ Diagnosis: DSM III major depression, HRSD-17≥18	1. Mianserin (mean=104 mg) 2. Amitriptyline (mean = 200 mg) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US [Barbui2001]	B
Cohn1990 E O I	Double-blind Random Double-blind 8-week trial	Outpatients; n = 241; 49% female; mean age 70.4 years; Diagnosis: DSM III R major depressive episode or bipolar disorder (only 6/241 [2.5%] with bipolar disorder)	1. Sertraline (mean 116.2 mg) 2. Amitriptyline (mean 88.3 mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US [Barbui2001]	B

Cournoyer 1987 Y I I	Allocation: Random Double-blind 3-week trial	Inpatients, n = 34, 71% women; mean age 46.6 years (range 26-72) Diagnosis: DSM III and RDC criteria major depressive episode, unipolar (89%) and bipolar (11%) , HRSD≥20	1. Trimipramine 2. Amitriptyline (in both groups, 100 mg starting dose)	1. HRSD-17 mean endpoint scores 2. Leaving the study early	Setting: Canada [Barbui2001]	B
Donlon1981	Allocation: Random	Outpatients, n = 46, 72% women; age: 24-58	1. Amoxapine (150 mg/300	1. Leaving the study early	Setting: US	B

Y O I	Double-blind 4-week trial	Diagnosis: RDC major depressive disorder, HRSD 25+, Raskin 8+, Zung 50+	mg, mean=250mg) 2. Amitriptyline (75 mg-150 mg, mean=125mg)	2. Leaving the study early due to side effects 3. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD)	[Barbui2001]	
Doongaji 1993 Y M I	Allocation: Random Double-blind 6-week trial	Inpatients and outpatients, n = 156; 53% female; age: 20-65 Diagnosis: DSM-III major depression, HRSD ≥ 20	1. Lofepramine (all patients on day 42 received 140 mg) 2. Amitriptyline (all patients on day 42 received 100 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD mean endpoint scores	Setting: India [Barbui2001]	B
Edwards 1996 Y O I	Allocation: Random Double blind 6-week trial	Outpatients, n = 531; 61% female, age: 18-70 Diagnosis: DSM IIIR major depression, HRSD-17 ≥ 17	1. Minaprine (maximum dose of 300 mg) 2. Amitriptyline (150 mg) 3. Minaprine (100 mg) 4. Minaprine (100 mg, t.i.d)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients with side effects	Setting: UK Data extracted for 1 and 2 only. [Barbui2001]	B
Fawcett 1989 Y O I	Allocation: Random Double-blind 6-week trial	Outpatients, n = 51, 71% women; mean age: fluoxetine 41 years (range 24-57), amitriptyline 39 years (range 24-59). Diagnosis: RDC major depressive disorder, HAMD 20+, Raskin greater than Covi	1. Fluoxetine (20 mg starting, increased to 60mg) 2. Amitriptyline (87.5% received > 100 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD-21 mean endpoint scores 4. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD)	Setting: Canada [Barbui2001]	B
Geretsegger 95 E I E	Allocation: Random Double blind 6-week trial	Inpatient for the first 3 weeks, n = 91; 86% female; mean age: paroxetine 71 years (+5.9), amitriptyline 71.3 years (+ 5.6) Diagnosis: DSM III R major depressive episode, HRSD 18+	1. Paroxetine (20 mg starting) 2. Amitriptyline (all received 100 mg on day 3)	1. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects 5. HRSD mean endpoint scores	Setting: Germany & Austria [Barbui2001]	B
Guy1983 Y I I	Allocation: Random Double blind 6-week trial	Inpatients; n=40;77% female; mean age=40.2. Diagnosis: RDC major (90% patients), minor (10% patients), intermittent depressive disorder, HRSD 19+. When DSM-II diagnosis was applied: Involutional melancholia-2%, Manic depressive-depressed-63%, manic depressive-circular, depressed-7%, depressive neurosis-28%	1. Mianserin (30 mg -> 300 mg) 2. Amitriptyline (60mg->150 mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US [Barbui2001]	B
Hutchinson 92 E P E	Allocation: Random Double blind 6-week trial	Primary care patients, n = 90; 77% female; mean age: paroxetine 72 years (+5.6), amitriptyline 71.5 years (+9.5) Diagnosis: DSM III major depressive episode, HRSD 18+	1. Paroxetine (20 mg starting) 2. Amitriptyline (100 mg starting)	1. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: UK [Barbui2001]	B

				4. Patients reporting side effects 5. HRSD-21 mean endpoint scores		
Judd1993 Y M E	Allocation: Random Double-blind 6- week trial	Inpatients and outpatients, n = 58; 66% female; mean age 41.7 years (+- 9.8) Diagnosis: DSM-III-R for major depression and HRSD > 17	1. Fluoxetine (20 mg) 2. Amitriptyline (50 mg starting, raised to 150 mg in all by 2nd week)	1. HRSD-17 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: Australia [Barbui2001]	B
Keegan1991 Y M I	Allocation: Random Double-blind 6- week trial	Not clear whether inpatients or outpatients; n = 43; % female not clear; mean age 39.5 years (+- 13.6); Diagnosis: DSM-III for major depression, HRSD >20	1. Fluoxetine (40 mg starting - 80 mg) 2. Amitriptyline (150 mg starting - 250 mg)	1. Non-responders (Patients not achieving ≥ 50% decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: Canada [Barbui2001]	B
Kerkhofs 1990 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active treatment: 6 weeks	Inclusion Criteria: RDC, 17+ HRSD (?) and less than 20% improvement during washout phase, Not receiving oxazepam within 5 days of sleep assessment. Age: 18-64 Country: Belgium Setting: Inpatient for at least part of time	Fluoxetine versus amitriptyline (100mg -> 150mg on day 8)	HRSD mean endpoint scores	[Geddes2002]	B
Kuhs 1989 Y I E	Allocation: Random; Duration: 6-week	Inpatients; n = 40; mean age and % female not clear. Diagnosis: DSM-III for major depression; HRSD > 17	1. Paroxetine (30 mg) 2. Amitriptyline (150 mg)	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: Germany [Barbui2001]	B
Laakmann 1991 Y I E	Allocation: Random Double-blind 5-week trial	Outpatients; n = 130; 72% (76/105) female (25 dropouts not included in analyses). Age: 19-74 (mean age not given) Diagnosis: ICD-9 for endogenous depressive patients, HRSD 17+, Raskin 8+	1. Fluoxetine (40 mg starting and reduced to 20mg or increased to 60mg) 2. Amitriptyline (100mg starting, and reduced to 50 mg or increased to 150mg)	1. HRSD mean endpoint scores 2. Leaving the study early	Setting: Germany [Barbui2001]	B
Lehmann 1982 Y I E	Allocation: Random Double-blind 4-week trial	Inpatients; n = 22, HRSD analysis: n=11; mean age: nortriptyline 44.2 years, amitriptyline 44 years Diagnosis: RDC major unipolar depression, HRSD 20+	1. Nortriptyline (mean daily dosage: 95 mg) 2. Amitriptyline (mean daily dosage: 131 mg)	1. HRSD mean scores at endpoint 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving ≥50% decrease in HRSD)	Setting: US [Barbui2001]	B

Loga1992 Y II	Allocation: Random Double-blind 6-week trial	Inpatients; n = 90; 62% (51/82) female (8 dropouts not included in analyses). Mean age: dosulepin/dothiepin 45.7 years (+9.1), amitriptyline 43.6 years (+8.9). Diagnosis:	1. Dosulepin/dothiepin (mean dosage at week 3 - 137.8 mg +/- 41.5) 2. Amitriptyline (mean	1. Leaving the study early	Setting: Yugoslavia [Barbui2001]	B
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		DSM III R recurrent major depression(66%), bipolar depression(2%), depressive neurosis (32%)	dosage at week 3 - 137.2 mg +/- 35.8)			
Marchesi 1998 Y O I	Allocation: Random Double-blind 10-week trial	N = 142; 74% female, mean age: females 44.1 years (+- 11.8), males 42.1 years (+- 12.2) Diagnosis: DSM III R major depression, HRSD 16+	1. Fluoxetine (20 mg throughout) 2. Amitriptyline (mean dosage - 115+/- 39.2 mg)	1. HRSD-17 mean score at endpoint 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving ≥50% decrease on HRSD)	Setting: Italy [Barbui2001]	B
Moises1981 Y I E	Allocation: Random Double-blind 4-week trial	Inpatients, n = 43; 86% female; mean age 48.7 years (range 22-70) Diagnosis: ICD and Feighner criteria of primary affective disorder. Further diagnosis according to ICD: unipolar depression (77%), bipolar (7%), neurotic (14%) or schizoaffective disorder (2%)	1. Trazodone (starting dosage: 450 mg) 2. Amitriptyline (starting dosage - 150 mg)	1. Non-responders (Patients not achieving > 50% reduction on HRSD) 2. HRSD-17 mean endpoint scores 3. Leaving the study early	Setting: Germany [Barbui2001]	B
Moller1993 ? I E	Allocation: Random Double-blind 6-week trial	Inpatients; n = 223; % female and mean age not given, but inclusion criteria for age: +18 years Diagnosis: DSM III major depressive disorder, HRSD 18+	1. Paroxetine (30 mg/day throughout) 2. Amitriptyline (150 mg/day throughout)	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: Germany & Hungary [Barbui2001]	B
Moller1995 Y I I	Allocation: Random Double-blind 4-week trial	Inpatients; n = 51; 82% female; mean age: mianserin 41.8 years (+- 11.3), amitriptyline 48.9 years (+-14.8) Diagnosis: DSM III major depressive episode, HRSD 18+	1. Mianserin (90 mg throughout) 2. Amitriptyline (150 mg throughout)	1. Leaving the study early	Setting: Germany [Barbui2001]	B
Molnar1977 Y O E	Allocation: Random Double blind 4-week trial	Outpatients, n = 25, HRSD analysis: n=21, 48% (10/21) female; mean age: maprotiline 40.6 years (range 21-62), amitriptyline 38.3 years (range 21-59) Diagnosis: ICD-8 depression requiring hospitalisation, HRSD 15+, MMPI 60-. Moderate depressive episode (72%), Depressive neurosis (28%)	1. Maprotiline 2. Amitriptyline (150 mg/day throughout in both groups)	1. Patients with side effects	Setting: Canada [Barbui2001]	B
Montgomery80 Y I E	Allocation: Random Double blind 6-week trial	Inpatients, n = 41, HRSD analysis: n=34; 69% (25/36) female (5 dropouts not included in analyses); mean age: maprotiline 42.83 years (+-3.43), amitriptyline 42.8 years (+- 3.36) Diagnosis: Feighner criteria of primary depressive illness, HRSD?=17	1. Maprotiline 2. Amitriptyline (150 mg/day throughout in both groups)	1. HRSD-17 mean scores at endpoint 2. Leaving the study early	Setting: UK [Barbui2001]	B

Mullin1996 Y M I	Allocation: random (no details)	Inpatients and outpatients n=156, 116 women, mean age: mirtazapine	1. Mirtazapine (modal 40mg/day by weeks 4-5)	1. Leaving the study early 2. Leaving the study early due to	Setting: UK	B
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	Double-blind 5-week trial	group - 45.4 years (+11.8); amitriptyline group - 44.2 years (+10.3) Diagnosis: DSM-III and RDC for major depressive episode, and HRSD-21 \geq 18	2. Amitriptyline (modal 150 mg/day by weeks 4-5)	side effects 3. Non-responders (Patients not achieving \geq 50% decrease on HRSD) 4. HRSD mean endpoint scores		
Nelson1982 Y I I	Allocation: Random Double-blind 4-week trial	Inpatients, n = 28, 86% female; mean age 38 years (+13.8) Diagnosis: RDC major depressive disorder	1. Imipramine (150 mg) 2. Amitriptyline (150 mg)	1. Leaving the study early	Setting: US [Barbui2001]	B
Peters1990 Y O E	Allocation: Random Double-blind 5-week trial	Outpatients; n = 102; 63% female; mean age: fluoxetine 48 years (+11), amitriptyline 41 years (+10) Diagnosis: ICD 9 endogenous depression, unipolar or bipolar, HRSD 17+, Raskin 8+ and greater than Covi	1. Fluoxetine (20mg) 2. Amitriptyline (75 mg starting, increased to 100 mg)	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. HRSD-17 mean scores at endpoint 3. Leaving the study early	Setting: Germany [Barbui2001]	B
Preskorn 1991 Y O I	Allocation: Random Double blind 6-week trial	Outpatients, n = 61, % female and mean age not given, but inclusion criteria for age: +18 Diagnosis: DSM III major depressive disorder, HRSD 20+	1. Fluoxetine (20 mg starting) versus 2. Amitriptyline (50 mg, increased to 200 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD mean change scores	Setting: US [Barbui2001]	B
Prusoff1981 Y O I	Allocation: Random Double blind 6-week trial	Outpatients, n = 67; 68% female; age, 70% > 35 years; Diagnosis: RDC major depression, Raskin 7+	1. Amoxapine (mean daily dosage: 230mg) 2. Amitriptyline (mean daily dosage: 108mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US [Barbui2001]	B
Rabkin1984 Y M I	Allocation: Random Double-blind 6-week trial	Inpatients and outpatients, n = 49, HRSD analysis: n=34; 56% female (based on number who completed treatment); mean age: mianserin 43 years (+17), amitriptyline 45 years (+10) Diagnosis: RDC for major depressive disorder, HRSD-21 \geq 18	1. Mianserin (30 mg starting - 150 mg in all patients) 2. Amitriptyline (60 mg starting - 300 mg in all patients)	HRSD-21 mean endpoint scores	Setting: US [Barbui2001]	B
Raft1981 ? O ?	Allocation: Random (no details) Duration: 5 weeks	Outpatients. N=29. Diagnosis: Definite primary depression according Feighner criteria.	1. Phenelzine (30mg ->90mg at day 12) 2. Amitriptyline (100mg ->300mg at day 12) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	All patients were recruited from the N.C. Memorial Hospital Pain Clinic.	B

Reimherr 1990 Y O E	Allocation: Random Double-blind 8-week trial	Outpatients; n = 448; 54% female. Mean age: sertraline 39 years (range 20-64), amitriptyline 38 years (range 18-62, placebo 40 years (range 19-64) Diagnosis: DSM III major depression, HRSD 18+, Raskin greater than Covi	1. Sertraline (mean final dose: 159 mg) 2. Amitriptyline (mean final dose: 111 mg) 3. Placebo (Data extracted for 1 & 2 only)	1. HRSD-18 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: US & Canada Extracted data for the 'evaluable patients' group since the mean daily dose of	B
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					amitriptyline for the 'all patients' group was too low. [Barbui2001]	
Remick1994 Y O I	Allocation: Random Double-blind 7-week trial	Outpatients, n = 33; 64% female; mean age: fluvoxamine 41.7 years, amitriptyline 41 years. Diagnosis: DSM III R major depressive disorder, HRSD 20+	1. Fluvoxamine (mean daily dosage: 135 mg) 2. Amitriptyline (mean daily dosage: 175 mg)	1. HRSD-17 mean scores at endpoint 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: Canada [Barbui2001]	B
Rickels1982 Y M I	Allocation: Random Double-blind 6-week trial	Family practice and outpatients; n = 202; 66% female; mean age 40 years (+- 13) Diagnosis: DSM-III for major unipolar depression	1. Trazodone (mean final dose 275 mg) 2. Amitriptyline (mean final dose 140 mg) 3. Placebo (Data extracted for 1 & 2)	1. Leaving the study early	Setting: US [Barbui2001]	B
Rickels1985 Y O I	Allocation: Random Double-blind 6-week trial	Outpatients; n = 605; 66% female (based on 504 patients included in efficacy analysis). Mean age 39 years (+- 11.7). Diagnosis: Feighner Diagnostic criteria for primary depression, HRSD-21≥18.	1. Doxepin (mean final dose 143 mg) 2. Amitriptyline (mean final dose 148 mg) 3. Alprazolam 4. Placebo (Data extracted for 1 & 2)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US [Barbui2001]	B
Robinson83 Y O C	Allocation: Random (no details) Duration: 6 weeks	Outpatients. N=130, aged: 19-67 years. Diagnosis: RDC major depressive(71.6%) disorder or probable major depressive disorder (16%) or DSM-III dysthymic disorder or atypical depression (12.4%).	1. Phenelzine (30mg -> 60mg on day 6) 2. Amitriptyline (75mg ->150mg on day 6)	1. HRSD mean change scores 2. Leaving the study early		B
Rush1989 Y O I	Allocation: Random Double-blind 6-week trial	Outpatients, n = 42, 57% women, mean age 40.7 years (+-10.2). Diagnosis: RDC criteria of non-psychotic major depressive disorder, unipolar (95%) or bipolar (5%)	1. Desipramine (50->150mg, mean=154.5mg) 2. Amitriptyline (as above)	1. Leaving the study early	Setting: US [Barbui2001]	B
Shaw1986 Y M I	Allocation: Random Double-blind 6-week trial	Inpatients and outpatients, n = 44; % female not known; age - included patients between 18 and 70 years Diagnosis: DSM-III for major depression	1. Citalopram (mean final dose 46 mg) 2. Amitriptyline (mean final dose 148 mg)	1. HRSD-17 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: UK [Barbui2001]	B

Smith1990 Y O I	Allocation: random (no details) Double-blind 6-week trial	Outpatients n=150, 57% women, mean age 43 years Diagnosis: DSM-III for major depressive illness, and HRSD-17 \geq 18	1. Mirtazapine (mean 18 mg/day) 2. Amitriptyline (mean 111mg/day)	1. Leaving the study early due to side effects 2 .HRSD mean endpoint scores 3. Non-responders (patients not	Setting: US	B
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			3. Placebo	achieving $\geq 50\%$ decrease in HRSD)		
Staner1995 Y I I	Allocation: Random Double-blind 4-week trial	Inpatients, n = 40; 83% female; mean age: paroxetine 41.7 years (+10.8), amitriptyline 42.5 years (+11.7) Diagnosis: RDC major depression, HRSD 18+	1. Paroxetine (25 mg for first 5 days, then 30 mg for next 4 weeks) 2. Amitriptyline (50 mg for first 5 days, then 150 mg for next 4 weeks)	1. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 2. HRSD-21 mean endpoint scores 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Setting: Belgium [Barbui2001]	B
Stuppaeck 1994 Y I E	Allocation: Random Double-blind 6-week trial	Inpatients, n = 153; 60% female, mean age 74.5 years (+11.6) Diagnosis: DSM III major depression, melancholic subtype, HRSD 18+	1. Paroxetine (30 mg starting) 2. Amitriptyline (all received 150 mg within first 3 days)	1. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 2. HRSD-21 mean endpoint scores 3. Leaving the study early 4. Leaving the study early to side effects	Setting: Austria & Germany [Barbui2001]	B
Veith1983 Y O E	Allocation: Random Double-blind 3-week trial	Outpatients; n = 77, HRSD analysis: n=49; 43% (25/49) female (28 dropouts not included in analyses). Mean age: desipramine 36 years (+2), amitriptyline 34 years (+2). Diagnosis: Feighner criteria of primary unipolar affective disorder, Zung Self-rating Depression Scale 54+	1. Desipramine (100mg up to 200mg) 2. Amitriptyline (100mg up to 200mg)	1. HRSD-17 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: US [Barbui2001]	B
Versiani 1999 Y ? E	Allocation: Random Double-blind 8- week trial	Patient setting not known, n = 157; 75.8% female, mean age 41.3 years Diagnosis: DSM-IV for major depression and HRSD > 17	1. Fluoxetine (20 mg) 2. Amitriptyline (mean final dose 138.1 mg)	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: South America [Barbui2001]	B
Wilcox1994 Y O I	Allocation: Random Double blind 6-week trial	Outpatients; n = 149; 49% female; mean age: mianserin 44 years, amitriptyline 40 years, placebo 40 years; Diagnosis: DSM III major depression, HRSD 18+	1. Mianserin (mean=74.1mg) 2. Amitriptyline (mean = 121.8 mg) 3. Placebo (Data extracted for 1 & 2)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD)	Setting: US [Barbui2001]	B
Young1987 Y O E	Allocation: Random Double blind 6-week trial	Outpatients; n = 50; 68% female; mean age: fluoxetine 46.1 years, amitriptyline 46.6 years; Diagnosis: RDC moderately to severe unipolar depression, HRSD 18+	1. Fluoxetine (mean = 73 mg) 2. Amitriptyline (mean = 122 mg)	1. HRSD mean scores at endpoint 2. Leaving the study early 3. Leaving the study early due to side effects	Setting: UK [Barbui2001]	B

Zivkov1995 Y I E	Allocation: random (no details) Double-blind 6-week trial	Inpatients n=251, 174 women (in 'efficacy' sample n=224). Mean age: mirtazapine group - 46.8 years (+-10.9); amitriptyline group - 46.9 years (+-10.5). Diagnosis: DSM-III and RDC for major depressive episode, and HRSD-21 \geq 20	1. Mirtazapine (mean = 52.8 (+-1.2) mg) 2. Amitriptyline (mean =196.9 (+-45) mg - completers only)	1. Leaving the study early due to side effects 2. Leaving the study early 3. HRSD mean endpoint scores 4. Non-responders (patients not	Setting: Yugoslavia 'Efficacy' sample - all patients completing at	B
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				achieving $\geq 50\%$ decrease in HRSD)	least 14 days of treatment	
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Characteristics of excluded studies

Study	Reason for exclusion
Aberg1977 YII	* Patients not diagnosed against recognised classification system
Altamura1989 OIE	* Dosage below therapeutic level for amitriptyline
Altamura1989a OII	* Dosage below therapeutic level for amitriptyline
Amin1973 YII	* Method of depression diagnosis not specified
Amin1978 YOI	* Method of depression diagnosis not specified
Anderson1972	No efficacy/safety data available
Anonymous1971	No efficacy/safety data available
Anton1990 YIE	* Study used a combination of amitriptyline and perphenazine
Ather1985 OMI	* No formal depression diagnostic assessment conducted
Balestrieri1971 YII	* No formal depression diagnostic assessment conducted
Bascara1989 Y?I	* Dosage below therapeutic level for amitriptyline
Battegay1985 YOI	* Patients not diagnosed against recognised classification system
Beaini1980 YOE	No efficacy/safety data available
Beckmann1975 YII	* Randomisation method not clear
Bennie1976 YOE	* Patients not diagnosed against recognised classification system
Bersani1994 YOE	* Dosage below therapeutic level for amitriptyline and sertraline
Bianchi1971 YMI	* Patients not diagnosed against recognised classification system
Bignamini1992 ?OI	* Randomisation method not clear
Botros1989 YOI	* No formal depression diagnostic assessment conducted
Branconnier1981	No efficacy/safety data available
Browne1969 YMI	* Study used amitriptyline and perphenazine combination
Burke1967 YII	* Patients not diagnosed against recognised classification system
Burrows1980 YII	* No formal depression diagnostic assessment conducted
Burt1962 YIE	* No formal depression diagnostic assessment conducted
Byrne1989 YII	* Meta-analysis of phase II clinical trials
Carney1984 YMI	* Patients not diagnosed against recognised classification system
Chouinard1985 Y P E	* Included in Beasley1993
Christiansen Y P E	* Patients not diagnosed against recognised classification system

Claghorn1984	No efficacy/safety data available
Click1982 YOI	* No formal depression diagnostic assessment conducted

Coppen1976	No efficacy/ safety data available
Dahl1981 YPI	* No formal depression diagnostic assessment conducted
Daly1979 YII	* No formal depression diagnostic assessment conducted
DeRonchi1998 YMI	* One third of the patients received benzodiazepine (lorazepam) throughout the study
Deering1974 OM?	* No formal depression diagnostic assessment conducted
DelZompo1990 YO E	* Dosage below therapeutic level for amitriptyline
Delaunay1978 YO I	* Patients not diagnosed against recognised classification system
Dell1977 YPI	* Patients not diagnosed against recognised classification system
Demyttenaere1998 YO?	* Dosage below therapeutic level for amitriptyline
Demyttenaere2001	No efficacy/ safety data available
Dorman1980 YO I	* Patients not diagnosed against recognised classification system
Dorn1980	* No formal depression diagnostic assessment conducted
Elwan1976	No efficacy/ safety data available
Feighner1983 YO I	* Randomisation method not clear
Ferrari1987 YII	* Benzodiazepines were permitted as additional treatment
Forrest1964 YMI	* Method of depression diagnosis not specified
Forrest1975 YPI	* Patients not diagnosed against recognised classification system
Freed1999 YP?	* Patients not diagnosed against recognised classification system
Friedel1979	No efficacy/ safety data available
Fruensgaard1979 YII	* Patients not diagnosed against recognised classification system
Gasperini1992 YII	* Included patients with bipolar disorder
Goldberg1977 YO I	* Patients not diagnosed against recognised classification system
Goldberg1980 YO I	* Dosage below therapeutic level for amitriptyline and trazodone
Goldstein1969 YO I	* Patients not diagnosed against recognised classification system
Gomez-Martinez Y?E	* No formal depression diagnostic assessment conducted
Gravem1987 YMI	* Patients not diagnosed against recognised classification system
Grof1974 YMI	* Patients not diagnosed against recognised classification system
Grof1977 YMI	No efficacy/ safety data available
Guelfi1989 YO I	* Dosage below therapeutic level for amitriptyline
Hackett1967	No efficacy/ safety data available
Harding1973 YO I	* No formal depression diagnostic assessment conducted
Harris1991 Y O E	* Dosage below therapeutic level for amitriptyline
Hegerl1997	* Abstract to Moller 1998 which was excluded because dosage was below recommended level for amitriptyline

Hekimian1978 YOI	* Patients not diagnosed against recognised classification system
Hollister1964	No efficacy/safety data available

Hosak2000 YOI	* Dosage below therapeutic level for amitriptyline
Hutchinson1963	No efficacy/safety data available
Invernizzi1994 YMI	* Dosage below therapeutic level for amitriptyline
James1982 YII	* Patients not diagnosed against recognised classification system
Jaskari1977 YII	* Patients not diagnosed against recognised classification system
Jessel1981	No efficacy/safety data available
Kamijima1997	* Unable to assess paper in terms of diagnostic criteria and dosage (language - Japanese)
Kampman1978 YO?	* Patients not diagnosed against recognised classification system
Kaumeier1980 YII	* Patients not diagnosed against recognised classification system
Kay1974 YPE	* Patients not diagnosed against recognised classification system
Kerr1984 M	* Dosage below recommended level
Khan1981 OOI	* Patients not diagnosed against recognised classification system
Khan1982 YII	* Method of depression diagnosis not specified
Kiebach1982	No efficacy/safety data available
Kiloh1979 ?MI	* Patients not diagnosed against recognised classification system
Klieser1988 Y I E	* Patients were receiving 20 minutes of CBT daily
Kline1982 YIE	* 54% of patients with bipolar disorder
Kocsis1986 ?II	* 34% of patients with bipolar disorder
Kyle1998 OPI	* Dosage below therapeutic level for amitriptyline
Laakmann1988	* Patients not diagnosed against recognised classification system
Lambourn1974	No efficacy/safety data available
Lapierre1980 YMI	* Dosage below therapeutic level for amitriptyline and trazodone
Lauritsen1974 YII	* No formal depression diagnostic assessment conducted
Laursen1985 OIE	* ICD for bipolar disorder in all patients
Leahy1967 YII	* No formal depression diagnostic assessment conducted
Lennox1978 YPI	* No formal depression diagnostic assessment conducted
Levin1974 YM?	* No formal depression diagnostic assessment conducted
Lipsedge1971 YOI	*No formal depression diagnostic assessment conducted
Lloyd1981	No efficacy/safety data available
Loo1988 YMI	* All patients were alcoholic with depression or dysthymia
Lopez-Ibor1979 Y?I	* No formal depression diagnostic assessment conducted
Lydiard1997 YOI	* Dosage below therapeutic level for amitriptyline
Lyons1985	No efficacy/safety data available

Magnus1977 YOI	* No formal depression diagnostic assessment conducted
Maier1989	No efficacy/safety data available

Marais1974 YMI	* No formal depression diagnostic assessment conducted
Mariategui1978 YOI	* Patients not diagnosed against recognised classification system
Marjerrison1969	No efficacy/safety data available
Marneros1979 YII	* Patients not diagnosed against recognised classification system
Masco1985 YOI	* Included in Beasley1993
Mason1990 M	* Only responders - patients with HRSD scores < 20 for 2 consecutive weeks, extracted. Did not meet criteria for response
McCallum1975 YOE	* No formal depression diagnostic assessment conducted
McClelland1979 YME	* Dosage below recommended level
McConaghy1965 ?OI	* No formal depression diagnostic assessment conducted
Melo de Paula YII	* Patients not diagnosed against recognised classification system
Mendels1968 YMI	* No formal depression diagnostic assessment conducted
Mendlewicz1980 YII	* Included patients with bipolar disorder (25%)
Mendlewicz1982 YII	* Patients were treated for 2 weeks only
Metha1980 YPE	* Method of depression diagnosis not specified
Mindham1977 YPI	* Method of depression diagnosis not specified
Moller1998 YII	* Dosage for amitriptyline and sertraline below therapeutic levels
Moller2000 YMI	* Dosage below therapeutic levels for amitriptyline and sertraline
Montbrun1976	* Patients not diagnosed against recognised classification system
Monteleone1994 OOI	* Dosage below therapeutic level for amitriptyline
Montgomery1978	No efficacy/safety data available
Moyes1980	No efficacy/safety data available
Muller-Oerling YII	* Patients not diagnosed against recognised classification system
Murphy1978 YPI	* Method of depression diagnosis not specified
Murphy1980YPI	* Method of depression diagnosis not specified
Naftulin1972 YOE	* Study used a combination of amitriptyline and perphenazine
Nieto1973 YOI	* Patients not diagnosed against recognised classification system
Nugent1979 OII	* Patients not diagnosed against recognised classification system
Okasha1976 YOI	* Patients not diagnosed against recognised classification system
Peet1977	No efficacy/safety data available
Petrie1982 YOI	* Patients not diagnosed against recognised classification system
Pugh 1982 YOI	* Patients not diagnosed against recognised classification system
Quadri1980 I	* Randomisation method not clear. Some patients received d-amphetamine before receiving treatment drug
Querol1970 YOI	* Dosage below therapeutic level for amitriptyline and doxepin

Rampello1995 YOE	* Included patients with either unipolar or bipolar depression (proportions not given)
Rees1976 YOE	* No formal depression diagnostic assessment conducted

Rego1974 YM?	* Method of depression diagnosis not specified
Renfordt1976	No efficacy/safety data available
Richmond1964 ?OI	* No formal depression diagnostic assessment conducted
Rickels1970 YMI	* No formal depression diagnostic assessment performed
Rickels1972 YMI	* Study used a combination of amitriptyline and perphenazine
Rickels1974 YMI	* No formal depression diagnostic assessment performed
Rickels1982a YMI	* Study used a combination of amitriptyline and perphenazine
Rose1965 YMI	* Method of depression diagnosis not specified
Rush1988 YII	* Method of depression diagnosis not specified
Rybakowski1991 Y??	* In 6 patients the drugs were switched because of lack of response in the first used compound
Saletu1979	No efficacy/safety data available
Sandifer1965 YII	* Patients not diagnosed against recognised classification system
Sedman1977 YII	* No formal depression diagnostic assessment performed
Sethi1979 YI?	* Patient diagnosis based on HRSD, BDI and clinical interviews
Shipley1985 Y I E	* 7/35 (20%) patients were diagnosed with bipolar disorder
Silverstone1977 YPI	* Patients not diagnosed against recognised classification system
Sims1980 YIE	* No formal depression diagnostic assessment performed
Sinclair1975 OPI	* No formal depression diagnostic assessment performed
Solis1970 ?MI	* No formal depression diagnostic assessment conducted
Stier1982 Y O E	* 4/20 (20%) patients were diagnosed with bipolar disorder
Stott1993 YPI	* Patients not diagnosed against recognised classification system
Straker1966 YOI	* Method of depression diagnosis not specified
Stratas1984	No efficacy/safety data available
Taverna1969	No efficacy/safety data available
Toru1972 YMI	* No formal depression diagnostic assessment performed
Trappe1973 YOI	* Method of depression diagnosis not specified
Trick1975 Y?I	* No formal depression diagnostic assessment performed
Tsaras1981 YO E	* No formal depression diagnostic assessment conducted
Upward1988 YOI	* No formal depression diagnostic assessment performed
Van Amerongen YO?	* No formal depression diagnostic assessment performed
Van De Merwe1984a	No efficacy/safety data available
Van De Merwe1984b	No efficacy/safety data available
Vartanian1984	No efficacy/safety data available

Vogel1976	No efficacy/safety data available
Von Bauer1969 YII	* No formal depression diagnostic assessment conducted

Waite1986 OII	* Dosage levels not given - left to discretion of clinicians
Watanabe1978 YII	* No formal depression diagnostic assessment conducted
Weissman1975 YOI	* Patients not diagnosed against recognised classification system
Wheatley1975	No efficacy/safety data available
Wright 1976 YOI	* No formal depression diagnostic assessment conducted
Yamhure1977	No efficacy/safety data available
Ziegler1977 Y O I	*Not double blind

* Indicates that study was originally included in Barbui2001.

Antidepressants versus TCAs sub-analysis

Study	Source review
Amin1984 Y M I	SSRI
Amore1989 Y I I	SSRI
Anon1988 Y M E	SSRI
Anon1990 Y I E	SSRI
Arminen1992 Y I E	SSRI
Ban1998 Y I I	Reboxetine
Beasley1993a Y I I	SSRI
Beasley1993b Y O I	SSRI
Benkert96 Y I I	Venlafaxine
Berzowski1997 Y M	Reboxetine
Bowden1993 Y M I	SSRI
Bramanti1988 Y M I	SSRI
Bremner1994 Y O I	SSRI
Bremner1995 Y O I	Mirtazapine
Bruijn1996 Y I I	Mirtazapine
Byerley1988 Y O E	SSRI
Chiu1996 Y M E	SSRI
Claghorn1996 Y O C	SSRI
Cohn1985 Y O I	SSRI

Cohn1990 E O I	SSRI
Cohn1990a Y O E	SSRI

Dalery1992 Y O E	SSRI
Davidson81 Y I C	Phenelzine
Davidson87 Y O C	Phenelzine
De Wilde1983 Y O I	SSRI
Dick1983 Y I E	SSRI
Dominguez85 Y O I	SSRI
Dowling1990 Y ? I	SSRI
Fabre1991 Y O I	SSRI
Fabre1996 Y O I	SSRI
Fawcett1989 Y O I	SSRI
Feighner1985a E O I	SSRI
Feighner1989 Y I I	SSRI
Feighner1989a Y O E	SSRI
Feighner92 Y O I	SSRI
Ferreri1989 Y O I	SSRI
Fournier1997 Y O I	SSRI
Georgotas86 E O I	Phenelzine
Geretsegger95 E I E	SSRI
Guillibert89 E O ?	SSRI
Hutchinson92 E P E	SSRI
Itil1983 Y O E	SSRI
Judd1993 Y M E	SSRI
Katona1999 E M I	Reboxetine
Keegan1991 Y M I	SSRI
Kerkhofs1990 Y I E	SSRI
Kuhs1989 Y I E	SSRI
Laakmann1991 Y I E	SSRI
Lapierre1987 Y I E	SSRI
Lecrubie97 Y P I	Venlafaxine
Lydiard1989 Y O E	SSRI
Mahapatra97 E M I	Venlafaxine
March1990 Y O I	SSRI
Marchesi1998 Y O I	SSRI
Marttila1995 Y M I	Mirtazapine

McGrath2000 Y M I	SSRI
Moller1993 ? I E	SSRI
Moon1996 Y P I	SSRI
Mullin1988 Y O E	SSRI
Mullin1996 Y M I	Mirtazapine
Nathan1990 Y I ?	SSRI
Noguera1991 Y O I	SSRI
Norton1984 Y O E	SSRI
Ohrberg1992 Y O E	SSRI
Ottevanger95 Y I I	SSRI
Pelicier1993 E O I	SSRI
Peters1990 Y O E	SSRI
Preskorn1991 Y O I	SSRI
Quitkin1990 Y O I	Phenelzine
Raft1981 ? O ?	Phenelzine
Rahman1991 E I E	SSRI
Ravindram1995 Y O E	SSRI
Reimherr1990 Y O I	SSRI
Remick1989 Y M I	SSRI
Remick1993 Y M E	SSRI
Remick1994 Y O I	SSRI
Richou1995 Y I I	Mirtazapine
Robinson83 Y O C	Phenelzine
Roth1990 Y O E	SSRI
Samuelian98 Y O I	Venlafaxine
Schweizer94 Y O I	Venlafaxine
Shaw1986 Y M I	SSRI
Smeraldi98 E M I	Venlafaxine
Smith1990 Y O I	Mirtazapine
Staner1995 Y I I	SSRI
Stark1985 Y O I	SSRI
Stuppaeck1994 Y I E	SSRI
Swann1997 Y O I	Phenelzine
Tollefson1994 Y O I	SSRI

Vallejo87A Melan YOC	Phenelzine
Versiani1999 Y ? E	SSRI
Volkers2002 Y I I	SSRI
Young1987 Y O E	SSRI
Zivkov1995 Y I E	Mirtazapine

Atypical depression sub-analysis

Study	Source review
McGrath2000 Y M I	SSRI
Pande1996 Y O I	Phenelzine
Quitkin1990 Y O I	Phenelzine

SSRIs versus antidepressants - studies from previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Alves1999 Y O I	Allocation: Random (using a balanced randomisation from randomly permuted blocks. Duration: 12 weeks Analysis: ITT - LOCF	Outpatients N = 87, 80 female, aged 18-68 Diagnosis: DSM-IV Major Depression, HRSD-21 ≥ 20	1. Venlafaxine IR (75mg up to 150mg) 2. Fluoxetine (20mg up to 40mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD-17 mean endpoint scores 4. Patients reporting side effects	Conducted at 3 clinical sites in Portugal Baseline HRSD scores: venlafaxine: 27.9(+5.2), fluoxetine: 26.9(+3.9).	B
Amin1984 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM III R Depression (Major depression (86%) single or recurrent episodes, bipolar disorder (14%) with or without melancholia), 15+ HRSD Age: 18+ N=338 (HRSD analysis: N=313) Country: Canada, US, UK, Netherlands Setting: Inpatients & outpatients	1. Fluvoxamine (mean = 158.5mg) 2. Imipramine (mean = 151mg) 3. Placebo	1. HRSD-16 mean endpoint score 2. Leaving study early due to side effects	Data used is from 5 North American centres reported in Kasper1995. [Geddes2002]	B

Amore1989 Y I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not	Inclusion Criteria: DSM III R Major Depression without psychotic features. 21+ on 21 item HRSD Age: 20-70	1. Fluvoxamine 2. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
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	Applicable Active Treatment: 4 weeks	Country: Italy Setting: Inpatients				
Andreoli2002 Y M I	Allocation: Random (no details) Duration: 8 weeks (+4-28 day washout) Analysis: ITT	Inpatients and outpatients. N=381, aged: 18-65. Diagnosis: DSM-III-R major depression without psychotic features, HRSD≥22. Baseline HRSD: reboxetine - 26.8 +3.4, fluoxetine - 26.9 +3.6, placebo - 27.4 +3.6	1. Reboxetine (8mg up to 10mg after 4 weeks) 2. Fluoxetine (20mg up to 40mg after 4 weeks) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	Conducted in 33 centres in 6 countries.	B
Anon1988 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥ 2 weeks of treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive episode, 17+ HRSD Age: 16-70. N=59, HRSD analysis: N=47. Country: Wales Setting: Inpatients & outpatients	1. Fluoxetine 2. Dosulepin/dothiepin (50mg -> 100mg on day 4 -> 150mg on day 8, up to 225mg thereafter, mean = 172mg +/- 7mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Anon1990 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 18+ HRSD, 9+ Hamilton depression subscale Age: 19-68. N=120 (HRSD analysis: N=70) Country: Denmark Setting: Inpatient	Paroxetine versus clomipramine (150mg)	1. HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	HRSD endpoint score: includes unpublished data [Geddes2002]	B
Arminen1992 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥ 2 weeks treatment) Active Treatment: 12 weeks	Inclusion Criteria: DSM III R major depression, 18+ HRSD Age: 18-70. N=57, HRSD analysis: N=50. Country: Finland Setting: Inpatients	Paroxetine versus imipramine (100-200mg)	1. HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects (based on investigators' opinion)	HRSD endpoint score: includes unpublished data [Geddes2002]	B
Barrelet1991 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: DSM III Major Depression, 18+ points on HRSD Age: mean 54 years. N=61, HRSD analysis: N=51. Country: Switzerland Setting: Inpatients & outpatients	Fluvoxamine versus moclobemide (300-450mg, mean = 323mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects (based on number not tolerating drug well)	[Geddes2002]	B
Beasley1991 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat	Inclusion Criteria: DSM III criteria for non-psychotic major depressive episode for 4 weeks, 20 + HRSD(21), >20 HRSD 21 at end of wash out period, and less than 20% improvement. Age: 18+. N=126, HRSD analysis: N=120.	Fluoxetine versus trazodone (100mg -> 150mg on day 4 -> 200mg on day 8 -> 250mg on day 11, range	1. HRSD-21 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B

	Active Treatment: 6 weeks	Country: US Setting: Outpatients	after 21 days 50-400mg, mean = 244.1 +/- 74.9mg, 79-7% patients received 200mg/day)			
Beasley1993a Y I I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive disorder, 20+ HRSD (21 item), no more than 20% decrease in HRSD during placebo week, Raskin score of at least 8, and higher than Covi score Age: 18-70. N=118, HRSD analysis: N=104 Country: US Setting: Inpatients for at least 3 days	Fluoxetine versus imipramine (75mg -> 100mg on day 2-> 125mg on day 4, 100-150 mg on day 8, 150-200mg on day 12, 150-300 mg after day 15)	1.HRSD-21 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Beasley1993b Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 5 weeks	Inclusion Criteria: RDC Major depressive disorder, 20+ HRSD (21 item), no more than 20% decrease in HRSD during placebo week, Raskin score of at least 8, and higher than Covi score Age: 21-70. N=136. Country: US & Canada Setting: Outpatients	Fluoxetine versus amitriptyline (75mg -> 100mg on day 2 -> 125mg on day 4, 100-150mg on day 8, 150-200mg on day 12, 150-300mg after day 15, 85.2% Patients achieved 125 mg/day)	1. HRSD-21 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Benkert2000 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM-IV for major depressive episode, and HRSD-17 ≥ 18 Age: mean=47 Country: Germany Setting: Inpatients and outpatients	Paroxetine versus mirtazapine (mean 32.7 mg/day)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		
Bougerol1992 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 4 weeks	Inclusion Criteria: DSM-III-R, major depression, 17+ on HRSD Age: 18+. N=130, HRSD analysis: N=126 Country: Switzerland & France Setting: Inpatients & outpatients	Fluvoxamine versus moclobemide (300mg, up to 450mg on day 8, mean at day 28 = 336mg)	1.HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	2 patients on adjunctive lithium. [Geddes2002]	B

Bowden1993 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable	Inclusion Criteria: DSM-III-R major depressive disorder, 20+ HRSD (21) at admission to study, 18+ HRSD (21) at beginning of active treatment phase, less than a 20% decrease in HRSD (21) during washout phase.	Fluoxetine versus desipramine	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
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	Active Treatment: 6 weeks	Age: 18-60 Country: US Setting: Inpatients & outpatients				
Bramanti1988 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: DSM-III-R major depression, 18+ 21 item HRSD Age: 18+. N=60, HRSD analysis: N=57 Country: Italy Setting: Not Clear	Fluvoxamine versus imipramine (50mg -> 100mg on day 4, up to 150mg on day 7)	1.HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Bremner1994 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active Treatment: 5 weeks	Inclusion Criteria: RDC major depressive disorder, at least 'moderately depressed', 20+ HRSD (version unclear), 8+ Raskin and greater than Covi. Age: 23-69 Country: US Setting: Outpatients	1. Fluoxetine 2. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Geddes2002]	B
Byerley1988 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression of at least 1 month 20+ HRSD (21) Age: mean age 39. N=97, HRSD analysis: N=60 Country: US Setting: Outpatients	Fluoxetine versus imipramine (75mg -> 150mg by day 15) versus placebo	1.HRSD-21 mean endpoint score	[Geddes2002]	B
Chiu1996 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 18+ HRSD (15) Age: 18-70 years. N=40, HRSD analysis: N=30. Country: China Setting: Inpatients and outpatients	Paroxetine versus imipramine (75mg -> 125 mg on day 8 up to 150mg on day 15)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Barbui2002]	B
Claghorn1996 Y O C	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active treatment: 6 weeks	Inclusion Criteria: DSM-III major depression Age: 39 (+-10.9) years; N=150, HRSD analysis: N=61 Country: US Setting: Outpatient	1. Fluvoxamine (mean dose during 4th week 128.5 mg) 2. Imipramine (mean dose during 4th week 186.8 mg) 3. Placebo	1.Leaving the study early 2. Leaving the study early due to side effects		B
Clerc1994 Y I I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention	Inclusion Criteria: DSM-III-R major depression with melancholia, MADRS \geq 25 Age: 18+ Country: France and Belgium	Fluoxetine versus venlafaxine (200mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects		B

	to treat Active Treatment: 6 weeks	Setting: Inpatients		4. Patients reporting side effects		
Cohn1985 Y O I	Allocation: Random (no details) Duration: 6 weeks (+1 week washout) Analysis: ITT	Outpatients. N=166. 98 female. Age: 20-64. Diagnosis: DSM-III major depressive illness, HRSD≥20	1. Fluoxetine (20-80mg) 2. Placebo 3. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects	Same protocol as Stark1985 but different patients. [Geddes2002]	B
Cohn1990 E O I	Double-blind Random Double-blind 8-week trial	Outpatients; n = 241; 49% female; mean age 70.4 years. Diagnosis: DSM-III-R major depressive episode or bipolar disorder (only 6/241 [2.5%] with bipolar disorder)	1. Sertraline (mean 116.2 mg) 2. Amitriptyline (mean 88.3 mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: US. [Geddes2002]	B
Cohn1990a Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, recurrent or single episode 18 + HRSD (no more than 20% improvement during washout period) Age: 18+ Country: US Setting: Outpatients	1. Paroxetine (10-50mg, mean=30.9mg) 2. Imipramine (65-275 mg, mean=144.9mg)	1. HRSD mean endpoint scores	*Includes unpublished data. This was 1 centre from the multi-centre trial in Feighner1992, efficacy data used for Feighner1992 is from 1 other centre (Fabre 1992) therefore these are a different set of patients. [Geddes2002]	B
Costa1998 Y O I	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT - LOCF	Outpatients. N=382, 301 female, aged 18-60 Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 20	1. Venlafaxine IR (75mg up to 150mg) 2. Fluoxetine (75mg up to 40mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Conducted at clinical sites in South America Baseline HRSD scores: venlafaxine: 30.4 (+-6.2) or fluoxetine: 29.7 (+-5.3)	B

Dalery1992 Y O E	Double-blind RCT Concealment of	Inclusion Criteria: DSM-III-R major depressive disorder, single or recurrent episode	Fluoxetine versus amineptine (200mg)	1.MADRS mean endpoint scores 2. Leaving the study early	[Geddes2002]	B
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	Allocation: Unclear Analysis: Completer Active Treatment: 90 days	Age: 18-70. N=169, HRSD analysis: N=141 Country: France Setting: Outpatients		3. Leaving the study early due to side effects		
De Wilde1983 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active Treatment: 4 weeks	Inclusion Criteria: 4+ Feighner Criteria, 16+ HRSD, Endogenously depressed Age: 18-70 Country: Belgium Setting: Outpatients	1. Fluvoxamine 2. Clomipramine	1. Leaving the study early 2. Patients reporting side effects	[Geddes2002]	B
De Wilde1985 Y I I	Double Blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: RDC Endogenous depression or chronic dysthymic disorder. 25+ on 10-item CPRS. Age: 18-70 Country: Belgium Setting: Inpatients	1. Citalopram 2. Mianserin	Leaving the study early Patients reporting side effects	[Geddes2002]	B
Dick1983 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: 16+ HRSD, persistent depressed mood accompanied by at least 5 Feighner Criteria Age: mean 49. N=32, HRSD analysis: N=26. Country: Switzerland Setting: Inpatients	Fluvoxamine versus clomipramine (150mg by day 3, mean = 132.8mg +/- 16.6mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Dierick1996 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depressive episode, HRSD≥20 Age: 18-83 Country: Europe Setting: Outpatients	Fluoxetine versus venlafaxine (75mg up to 150mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B
Dominguez85 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active treatment: 4 weeks	Inclusion Criteria: DSM-III major depression Age: 21-64 years; N=101 Country: America Setting: Outpatient	1. Fluvoxamine (100-300mg) 2. Imipramine 3. Placebo	1. Leaving the study early	Leaving study early due to side effects and mean endpoint data included in Amin 1984. [Geddes2002]	B
Dorman1992 E O E	Double-blind RCT Concealment of	Inclusion Criteria: DSM-III-R unipolar depression, 17+ HRSD	Paroxetine versus mianserin (30mg, up to	1.HRSD-17 mean endpoint score 2. Leaving the study early	HRSD endpoint score: includes	B

	Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Age: 65+. N=60, HRSD analysis: N=49. Country: UK Setting: Outpatients	60mg after day 7)	3. Leaving the study early due to side effects 4. Patients reporting side effects	unpublished data [Geddes2002]	
Dowling1990 Y ? I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive disorder, unipolar illness. 17+ HRSD (version unclear) Age: mean 43 Country: Eire Setting: Not Clear	1. Fluoxetine 2. Dosulepin/dothiepin	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
Fabre1991 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 5 weeks	Inclusion Criteria: DSM-III-R major depression (single episode or recurrent), 18-27 HRSD (number of items unclear) Age: 18-65 Country: US Setting: Outpatients	Fluoxetine versus nortriptyline	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Geddes2002]	B
Fabre1996 Y O I	Allocation: Random (no details). Duration: 6 weeks (+ 7-14 day placebo washout). Analysis: ITT (≥1 dose & ≥1 post-baseline assessment)	Outpatients. N=150. Age: 18-65. Diagnosis: DSM-III major depressive disorder, HRSD-21≥20, Raskin depression ≥8 and > Covi anxiety score	1. Fluvoxamine (mean at week 6 =117mg) 2. Placebo 3. Imipramine	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Barbui2002]	B
Falk1989 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive episode, unipolar either single or recurrent, current episode at least 4 weeks, 20+ 21 item HRSD Age: 62+. N=27, HRSD analysis: N=25 Country: US Setting: Outpatients	Fluoxetine versus trazodone (100mg -> 150mg on day 4 -> 200mg on day 8 -> 250mg on day 11, 50-400mg after day 21, mean = 350mg)	1. HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B

Fawcett1989 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	Inclusion Criteria: DSM-III unipolar major depression, 20+ HRSD (21) Age: 18+. N=40, HRSD analysis: N=38 Country: US Setting: Outpatients	Fluoxetine versus amitriptyline (100mg up to 200mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Barbui2001]	B
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Feighner1985a E O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, at least 1 month, 20+ HRSD (number of items unclear) Age: 61+ Country: US Setting: Outpatients	1. Fluoxetine 2. Doxepin	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
Feighner1989 Y I I	Allocation: Random (no details). Duration: 6 weeks (+3 day placebo washout). Analysis: ITT	Inpatients. N=86, 85% female. Age: 18-71, mean=41. Diagnosis: DSM-III major depression	1. Fluvoxamine (150-300mg, mean=145mg) 2. Placebo 3. Imipramine	1. Leaving the study early due to side effects		B
Feighner1989a Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥2 weeks treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, 20+ HRSD (21), 8+ Raskin scale, and greater than Covi Age: 18-70. N=179, HRSD analysis: N=145 Country: US Setting: Outpatients	Fluoxetine versus imipramine (72% achieved >150mg) versus placebo	1. HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Feighner92 Y O I	Random (no details). Duration: 6 weeks. Analysis: ITT (> 1 post baseline efficacy)	Outpatients. N=726. Age: 18-65, mean=40. Diagnosis: DSM-III major depressive episode, HRSD-17≥18. Raskin depression > Covi anxiety score. Mean Baseline HRSD: Paroxetine - 26.4, placebo - 26.6	1. Paroxetine (10-20mg, mean= 28.7-45.5mg) 2. Placebo 3. Imipramine	1. HRSD-17 mean change scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	* This was a multicentre trial. Mean endpoint data was available for two centres, one reported in Fabre 1992 (N=120) and used here the other is Cohn1990a (N=120). N reported in Feighner1992. [Geddes2002]	B

Ferreri 1989 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not	Inclusion Criteria: DSM-III major depressive disorder, 18-25 HRSD (21) Age: 18-65 Country: France	1. Fluoxetine 2. Amineptine	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Geddes2002]	B
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	Applicable Active Treatment: 6 weeks	Setting: Outpatients				
Fournier1997 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion Criteria: DSM-III major depressive disorder, HRSD-17>=18 Raskin score > Covi anxiety score Age: 18-65 Country: Canada Setting: Outpatients	Sertraline versus imipramine (50mg-200mg, mean = 168mg)	1. Leaving the study early	[Barbui2002]	B
Fudge1990 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive disorder unipolar affective illness, 20+ HRSD (21) Age: 18+ Country: US Setting: Outpatients	Fluoxetine versus trazodone (100-250mg, 50-400mg after day 21)	1. HRSD mean endpoint scores* 2. Leaving the study early	* Includes unpublished data. [Geddes2002]	B
Gattaz1995 Y I I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: DSM-III-R major depression, and HRSD 18 + Age: 18-65. N=70, HRSD analysis: N=52 Country: Germany Setting: Inpatients	Fluoxetine versus moclobemide (300mg, up to 600mg after day 7, mean=344mg +/- 75mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
Geerts1994 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression without psychotic features. 17+ on 17-item HRSD Age: 18 - 70. N=49, HRSD analysis: N=28 Country: Belgium Setting: Inpatients & outpatients	Fluoxetine versus moclobemide (300mg, up to 600mg on day 22)	1.HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
Geretsegger95 E I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥2 weeks treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 18+ HRSD, inpatient at least 3 weeks Age: 65+. N=91, HRSD analysis: N=59 Country: Germany & Austria Setting: Inpatient for at least 3 weeks	Paroxetine versus amitriptyline (50mg - >100mg on day 3, up to 150mg on day 21)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	* Includes unpublished data. [Geddes2002]	B
Guillibert89 E O ?	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 20+ HRSD (21 item) - declining less than 20% in washout period, Newcastle Scale score 6+ Age: 65+. N=79.	Paroxetine versus clomipramine (25mg -> 50mg on day 4 -> 75mg on day 8)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	*Includes unpublished data. [Geddes2002]	B

	weeks	Country: France Setting: Outpatients				
Hackett1996 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depression, HRSD-21≥20 Age: 18+ Country: Europe Setting: Outpatients	Paroxetine versus venlafaxine (150mg)	1.HRSD-21 mean endpoint score		B
Hutchinson92 E P E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 18+ HRSD (21-item) Age: 65+. N=90, HRSD analysis: N=67. Country: UK Setting: Family practice	Paroxetine versus amitriptyline (100mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	*Includes unpublished data. [Geddes2002]	B
Itil1983 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: RDC major affective disorder Age: 21-68. N=69, HRSD analysis: N=37 Country: US Setting: Outpatients	Fluvoxamine versus imipramine (50mg -> 150mg on day 3, up to 300mg on day 8, mean=127mg +/- 46mg) versus placebo	1.HRSD-16 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	4% patients diagnosed with bipolar disorder. [Geddes2002]	B
Judd1993 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 1-month episode minimum, 17+ on HRSD Age: 21-63. N=58, HRSD analysis: N=46 Country: Australia Setting: Inpatients and outpatients	Fluoxetine versus amitriptyline (50mg -> 150mg by end of week 2, up to 200mg thereafter)	1.HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Kasper1990 Y I I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 4 weeks	Inclusion Criteria: ICD-9 endogenous depression, RDC/DSM-III unipolar major depression (39 patients). Age: 28-71. N=42, HRSD analysis: N=41 Country: Germany Setting: Inpatients	Fluvoxamine versus maprotiline (50mg -> 100-300mg on day 2, mean = 236mg +/- 32mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Total sleep deprivation at day 1 and day 8 for all patients. [Geddes2002]	B
Keegan1991 Y M I	Allocation: Random Double-blind 6-week trial	Not clear whether inpatients or outpatients; n = 43; % female not clear. Mean age 39.5 years (+- 13.6).	1. Fluoxetine (40 mg starting - 80 mg) 2. Amitriptyline (150 mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: Canada. [Geddes2002]	B

Diagnosis: DSM-III for maior depression. HRSD starting - 250 mg)
>20.



Kerkhofs1990 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: RDC unipolar major depressive disorder, 17+ HRSD (?) and less than 20% improvement during washout phase, not receiving oxazepam within 5 days of sleep assessment. Age: 18-64. N=34, HRSD analysis: N=19. Country: Belgium Setting: Inpatient for at least part of time	Fluoxetine versus amitriptyline (100mg -> 150mg on day 8)	1. HRSD mean endpoint scores	[Geddes2002]	B
Kuhs1989 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive illness, 18+ HRSD (21-item) Age: 18-65. N=40, HRSD analysis: N=31 Country: Germany Setting: Inpatients	Paroxetine versus amitriptyline (150mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects (taken from 'number tolerating drug well')	* Includes unpublished data. [Geddes2002]	B
La Pia1992 E M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorders, 18+ HRSD 21, 20+ Mini Mental State. Age: 60-80. N=40, HRSD analysis: N=35 Country: Italy Setting: Outpatients & inpatients	Fluoxetine versus mianserin (40?mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Patients reporting side effects	* Includes unpublished data. [Geddes2002]	B
Laakmann1991 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: ICD-9 endogenous depression, HRSD 17+, Raskin 8+ Age: 18-70. N=174, HRSD analysis: N=124 Country: Germany Setting: Inpatients	Fluoxetine versus amitriptyline (100mg up to 200mg)	1. HRSD mean endpoint scores 2. Leaving the study early	Includes unpublished data. [Geddes2002]	B
Lapierre1987 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 15+ HRSD Age: 20-69. N=63, HRSD analysis: N=10 Country: Canada Setting: Inpatients	1. Fluvoxamine (50-300mg, mean=180.3mg) 2. Imipramine 3. Placebo	1. Leaving the study early	Leaving study early due to side effects and mean endpoint data included in Amin1984. [Geddes2002]	B

Leinonen1999 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment:	Inclusion criteria: DSM-IV major depressive episode, MADRS≥ 22 Age: mean=42 Country: Europe Setting: Outpatient	Citalopram versus mirtazapine (mean 35.9 mg)	1.MADRS mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	* Includes unpublished data	B
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119

	8 weeks					
Lydiard1989 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 22+ HRSD Age: 18+. N=54, HRSD analysis: N=52. Country: US Setting: Outpatients	Fluvoxamine versus imipramine (> 100 - 300mg, mode = 180mg +/- 97mg) versus placebo	1. HRSD mean endpoint scores* 2. Leaving the study early due to side effects	* Includes unpublished data. [Geddes2002]	B
March1990 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major affective disorder, HRSD-17>=22 Age: 18-67, mean =39.4. N=54 (37 female). Country: US Setting: Outpatients	Fluvoxamine versus imipramine (100- 300mg) versus placebo	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
Marchesi1998 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 10 weeks	Inclusion Criteria: DSM-III-R major depression, 16+ HRSD (17) Age: 18+. N=142 Country: Italy Setting: Outpatient	Fluoxetine versus amitriptyline (25mg -> 75mg on day 7 up to 225mg, mean = 115mg +- 39.2)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Barbui2001]	B
Martenyi2001 Y I C	Allocation: Random (no details). Duration: 6 weeks. Analysis: Completer	Inclusion Criteria: DSM-III-R non-psychotic major depression, HRSD-17≥18. Age: 18-65. Setting: Inpatient. Country: Former Yugoslavia	Fluoxetine versus maprotiline (100- 200mg)	1. HRSD mean change scores 2. Leaving the study early		B
Massana1999 Y M I	Allocation: Random (no details) Duration: 8 weeks (up to 28-day washout) Analysis: ITT	N=168. Age: 18-65. Diagnosis: DSM-III-R acute major depressive episodes not accompanied by psychotic features, HRSD-21≥22. Setting: Inpatients & outpatients.	1. Reboxetine (8mg up to 10mg) 2. Fluoxetine (20mg up to 40mg)	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Conducted at 16 centres in four countries.	B
McGrath2000 Y M I	Allocation: Random (no details) Duration: 10 weeks. Analysis: ITT-LOCF	N=154. Age: 18-65, mean=41.6. Diagnosis: DSM- IV major depressive episode and Columbia criteria for atypical depression. Setting unclear.	Fluoxetine versus Imipramine (50mg- >300mg, mean=204.9+- 90.7mg) versus placebo	1. HRSD-17 mean endpoint score 2. Leaving the study early		B

McPartlin98 Y PCI	Double Blind RCT Concealment of Allocation: Unclear Analysis: Intention	Inclusion Criteria: DSM-IV major depression, MADRS \geq 19 Age: 18-83 Country: UK	Paroxetine versus venlafaxine (75mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects		B
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	to treat Active Treatment: 12 weeks	Setting: Outpatients				
Moller1993 ? I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 18+ HRSD (21 item) Age: Not Clear. N=223, HRSD analysis: N=140 Country: Germany + Hungary Setting: Inpatients	Paroxetine versus amitriptyline (150mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Moon1991 Y P I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	N= 62. 40 female. Age: 18-70. Diagnosis: DSM III major depressive episodes, MADRS>24. Setting: primary care.	1. Fluvoxamine (100mg up to 300mg) 2. Mianserin (60mg up to 180mg)	1. Leaving the study early due to side effects 2. Patients reporting side effects	[Barbui2002]	B
Moon1996 Y P I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	N= 138. 87 females. Age: 18-65, mean=45.1. Diagnosis: DSM-III-R major depressive episode, MADRS>=18. Setting: primary care.	1. Paroxetine (20mg up to 30mg) 2. Lofepramine (140mg up to 210mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Barbui2002]	B
Mullin1988 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 17+ HRSD Age: 18-70. N=73, HRSD analysis: N=50 Country: UK Setting: Outpatients	Fluvoxamine versus dosulepin/dothiepin (75mg -> 112.5mg after 1 week up to 225mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	* Includes unpublished data. [Geddes2002]	B
Nathan1990 Y I ?	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: RDC major depressive disorder, 15+ HRSD, 7+ Raskin Severity of Depression Scale Age: mean 39.7. N=37, HRSD analysis: N=35 Country: US Setting: Inpatients	Fluvoxamine versus desipramine (100mg -> 150mg on day 3 -> 200mg on day 5)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Noguera1991 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major unipolar depression, 17+ HRSD, less than 20% reduction in HRSD during washout period, 8+ Raskin, and > Covi. Age: 18-65. N=120. Country: Spain	Fluoxetine versus clomipramine (100mg)	1. HRSD mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B

	weeks	Setting: Outpatients				
Norton1984 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 4 weeks	Inclusion Criteria: RDC for major depressive disorder (probable or definite), 15+ HRSD Age: 18-65. N=91, HRSD analysis: N=88 Country: UK Setting: Outpatients	Fluvoxamine versus imipramine (50mg -> 100mg on day 5, mean in week 4 =153.3) versus placebo	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	* Includes unpublished data. [Geddes2002]	B
Ohrberg1992 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression Age: 18-70. N=159, HRSD analysis: N=120 Country: Denmark Setting: Outpatients	Paroxetine versus imipramine (100- 250mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	*Includes unpublished data. [Geddes2002]	B
Ottevanger95 Y I I	Double Blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 4 weeks	Inclusion Criteria: Depression (Feighner Criteria), 17+ HRSD, Age: mean 49 Country: Netherlands Setting: Inpatients	Fluvoxamine versus clomipramine (50- 150mg, mean=106mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Pande1996 Y O I	Allocation: Random (no details) Duration: 6 weeks (+7 day placebo washout) Analysis: ITT	N=40. Age: 18-65. Diagnosis: DSM- III-R major depressive disorder (38 patients), dysthymia or depressive disorder NOS, HRSD- 17≥10 and Columbia criteria for atypical depression. Setting: outpatients.	1. Phenelzine (45-90mg) 2. Fluoxetine (20-60mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD-17 mean change scores		B
Pelicier1993 E O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 5 weeks	Inclusion Criteria: Reactive Depression according to Feighner criteria Age: 60+ Country: France Setting: Outpatients	1. Paroxetine 2. Clomipramine	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Geddes2002]	B
Perez1990 Y ? I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 6	Inclusion Criteria: DSM-III-R major depressive episode, 30+ MADRS Age: 18+ Country: UK Setting: Not Clear	1. Fluvoxamine 2. Mianserin	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects	[Geddes2002]	B

	weeks					
Peters1990 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Endpoint Active Treatment: 5 weeks	Inclusion Criteria: 17+ HRSD, 8+ Raskin, higher than Covi. Age: 25-63. Country: Germany. Setting: Outpatients	Fluoxetine versus amitriptyline (75mg -> 100mg by day 4)	1. HRSD mean endpoint scores 2. Leaving the study early	[Geddes2002]	B
Phanjoo1991 E M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 30+ MADRS Age: 65+. N=50, HRSD analysis: N=31 Country: Scotland Setting: Inpatients & outpatients	Fluvoxamine versus mianserin (20mg -> 40mg up to 80mg, mean = 60mg)	1. MADRS mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	MADRS endpoint scores includes unpublished data [Geddes2002]	B
Poirier1999 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 4 weeks	Inclusion Criteria: DSM-III-R major depression, HRSD≥18 Age: 21-62 Setting: Inpatients and outpatients	Paroxetine versus venlafaxine (75mg -> 200mg on day 5, mean = 269 +- 46.7)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B
Preskorn1991 Y O I	Double-blind RCT Concealment of allocation: Unclear. Analysis: ITT Active treatment: 6 weeks	Inclusion criteria: DSM-III major depressive disorder, HRSD 20+ Age: 18+. N=61, HRSD analysis: N=60. Country: US Setting: Outpatients	Fluoxetine versus amitriptyline (200mg)	1. HRSD mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Barbui2001]	B
Rahman1991 E I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 30+ MADRS Age: 65+. N=52, HRSD analysis: N=36. Country: UK Setting: Inpatients	Fluvoxamine versus dosulepin/dothiepin (50mg -> 100mg on day 4, up to 200mg on day 7, mean during weeks 4-6 =159mg)	1. MADRS mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	MADRS endpoint scores includes unpublished data [Geddes2002]	B

Ravindram1995 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥11 days treatment) Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depression (mild to moderate severity), 15+ on HRSD Age: 18-65. N=103, HRSD analysis: N=86 Country: Canada Setting: Outpatients	Sertraline versus desipramine (50-225mg, mean after week 4=163.75mg) versus placebo	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	* Includes unpublished data. [Geddes2002]	B
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Reimherr1990 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 18+ HRSD (18) without 25% reduction during washout, higher score on Raskin than Covi Age: 18-65. N=448, HRSD analysis: N= 376. Country: US Setting: Outpatients	Sertraline versus amitriptyline (50mg, up to 150mg by day 21, mean = 111mg) versus placebo	1. HRSD mean change scores* 2. Leaving the study early 3. Leaving the study early due to side effects	*Extracted data for the 'evaluable patients' group because the mean daily dose of amitriptyline for the 'all patients' group was too low. [Geddes2002]	B
Remick1989 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Not Applicable Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depressive disorder, 20+ HRSD (21) (including after washout week) Age: mean 43 Country: Canada Setting: Outpatients & inpatients	Fluoxetine versus doxepin (50-200mg, mean=146.8mg)	1. Leaving the study early 2. Leaving the study early due to side effects	[Geddes2002]	B
Remick1993 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive disorder for 1 month minimum, 20+ HRSD (21), 20% or below 20 on HRSD after washout led to exclusion. Age: 18-65. N=47, HRSD analysis: N=39. Country: Canada Setting: Outpatients & inpatients	Fluoxetine versus desipramine (50mg -> 100mg on day 4 -> 150mg on day 11, up to 300mg after day 21, mean = 160mg)	1.HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	HRSD endpoint scores include unpublished data [Geddes2002]	B
Remick1994 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 7 weeks	Inclusion Criteria: DSM-III-R major depressive episode, 20+ HRSD Age: 18-65. N=33. Country: Canada Setting: Outpatients	Fluvoxamine versus amitriptyline (>50mg, mean at week 7 =135 mg) versus placebo	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	* Unpublished data. [Geddes2002]	B
Reynaert1995 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 16+ on 17 item HRSD Age: mean 47 year. N=101, HRSD analysis: N=80 Country: Belgium Setting: Inpatients & outpatients	Fluoxetine versus moclobemide (300mg, up to 600mg on day 23)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B

Roth1990 Y O E	Double-blind RCT Concealment of	Inclusion Criteria: DSM-III-R major depressive episode, 22+ HRSD	Fluvoxamine versus desipramine (50mg ->	1. HRSD mean endpoint scores 2. Leaving the study early	[Geddes2002]	B
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	Allocation: Unclear Analysis: ITT (≥ 3 weeks treatment) Active Treatment: 6 weeks	Age: 18+. N=90, HRSD analysis: N=80. Country: US Setting: Outpatients	100mg by day 14, 100-300mg thereafter, mean at week 3 =195.8mg, mean at week 6 =224.6) versus placebo			
Rudolph1999 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion Criteria: DSM-IV major depressive disorder, HRSD-21 ≥ 20 Age: 18-40, mean=40 Country: US Setting: outpatient	Fluoxetine versus venlafaxine XR (75-225mg, mean = 175mg)	1.HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects		B
Schatzberg02 E O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion criteria: DSM-IV major depressive episode, HRSD-17 ≥ 18 Age: 65+ Country: US Setting: Outpatients	Paroxetine versus mirtazapine (mean = 25.7+- 6.7mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	*Includes unpublished data	B
Shaw1986 Y M I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive illness. 18+ HRSD Age: 18-70. N=44. Country: South Wales Setting: Inpatients & outpatients	Citalopram versus amitriptyline (75mg -> 150mg on day 4, 112.5-225mg after day 21, mean at week 6 =148mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Silverstone99 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 12 weeks	Inclusion Criteria: DSM-IV major depressive disorder, HRSD-17 ≥ 20 Age: 18-71. Setting: Outpatients	Fluoxetine versus Venlafaxine SR (mean = 111.2 mg in week 4)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B

Staner1995 Y II	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 34 days	Inclusion Criteria: RDC major Depression, 18+ HRSD Age: 18-65. N=40. Country: Belgium Setting: Inpatients	Paroxetine versus amitriptyline (100mg -> 150mg on day 6)	1.HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
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Stark1985 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: IIT (≥ 1 post baseline assessment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III unipolar major depressive disorder for 4 weeks, 20+ HRSD (21), less than 20% reduction in HRSD during wash out period, 8+ on Raskin Scale, and greater than Covi scale. Age: 18-70. N=540, HRSD analysis: N=539. Country: US Setting: Outpatients	Fluoxetine versus imipramine (125mg at day 4, up to 300mg thereafter) versus placebo	1. HRSD-21 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Stuppaeck1994 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: IIT (≥ 1 week treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III major depression, melancholic subtype, 18+ HRSD (21item) Age: 18-65. N=153, HRSD analysis: N=134. Country: Austria & Germany Setting: Inpatients	Paroxetine versus amitriptyline (50mg -> 150mg by day 3, up to 200mg on day 14, up to 250 mg on day 28, mean = 166mg)	1.HRSD-21 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Timmerman 1987 Y I E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer Active Treatment: 4 weeks	Inclusion Criteria: DSM-III-R major depressive disorder, 18+ HRSD Age: 18-69. N=29, HRSD analysis: N=27. Country: Netherlands Setting: Inpatients (all women)	Citalopram versus maprotiline (75mg -> 150mg on day 15 for 77% of patients)	1.HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Geddes2002]	B
Tollefson1994 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: Intention to treat Active Treatment: 8 weeks	Inclusion Criteria: DSM-III-R major depressive disorder (unipolar, non psychotic depressed) for 1 month + sub tag 'agitated' according to RDC, 14+ HRSD at washout and for first 2 visits, 2+ score on at least 2 items on agitation rating scale. Age: 18-65. N=124, HRSD analysis: N=122. Country: US Setting: Outpatients	Fluoxetine versus imipramine (50mg -> 150mg on day 15, up to 300mg on day 28)	1.HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B

Tylee1997 Y P I	Allocation: Random (by the permuted blocks method) Duration: 12 weeks Analysis: ITT	N = 341, 97 female, aged 18-85. Diagnosis: DSM-IV major depression, MADRS ≥ 19. Setting: primary care.	1. Venlafaxine IR (75mg) 2. Fluoxetine (20mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Patients recruited through 34 general practices in the UK Baseline HRSD scores: venlafaxine: 22.4(+5), fluoxetine: 22.5(+4.4)	B
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Tzanakaki00 Y M I	Allocation: Random (no details) Duration: 6 weeks (+ 7 day placebo) Analysis: ITT - LOCF	N=109, 86 female, aged 18-64. Diagnosis: DSM-IV major depression with melancholia, MADRS 25 or higher Setting: Inpatients & outpatients	1. Venlafaxine IR (75mg -> 150mg) 2. Fluoxetine (20mg -> 40mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Baseline HRSD scores: venlafaxine: 27.8(+5.6), fluoxetine: 27.1(+5.6)	B
Versiani1999 Y ? E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 8 weeks	Inclusion Criteria: DSM-IV major depression, 18+ HRSD(17), 18+ HAM-A Age: 18+. N=157, HRSD analysis: N=156 Country: Various South American	Fluoxetine versus amitriptyline (50-250mg, mean = 114.1 +- 29.9mg)	1.HRSD-17 mean endpoint score 2. Leaving the study early 3. Leaving the study early due to side effects	[Barbui2001]	B
Volkers2002 Y I I	Double-blind RCT. Concealment of allocation: unclear. Duration: 4 weeks. Analysis: ITT	Inclusion criteria: DSM-IV unipolar major depressive disorder, HRSD-17>13. Age: 18+, mean=52.5. Country: The Netherlands. Setting: Inpatients.	Fluvoxamine versus imipramine (mean=220.7mg)	1.HRSD-17 mean endpoint score		B
Wade2003 Y P I	Allocation: Random (no details). Double blind. 24-week trial.	N=197 (ITT=177), 130 female. Age: 18+, mean=40. Diagnosis: DSM-IV major depressive disorder, HRSD-17>18. Baseline HRSD-17: Mirtazapine=23.8+-3.76, paroxetine=24.4 +-3.51. Country: UK. Setting: primary care.	1. Mirtazapine (30mg-45mg, mean=34.6+-5.7mg) 2. Paroxetine (20-30mg, mean=23.9+-3.96mg)	1. HRSD-17 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B
Wheatley1998 Y O I	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depressive episode, HRSD-17 ≥ 21 Age: 18-65 Country: Europe Setting: Inpatients and outpatients	Fluoxetine versus mirtazapine (mean 39.8 mg)	1. HRSD mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	* Unpublished data	B
Williams1993 Y M E	Double-blind RCT Concealment of Allocation: Unclear Analysis: ITT (≥3 weeks treatment) Active Treatment: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 17+ on 21 item HRSD Age: 20-86. N=122, HRSD analysis: N=92 Country: New Zealand Setting: Not Clear	Fluoxetine versus moclobemide (150?mg -> 300-600mg at day 15, mean at week 6 =505.1mg)	1.HRSD-21 mean endpoint scores* 2.Leaving the study early 3. Leaving the study early due to side effects	*Unpublished data. [Geddes2002]	B
Young1987 Y O E	Double-blind RCT Concealment of Allocation: Unclear Analysis: Completer	Inclusion Criteria: RDC moderately severe unipolar depression, 18+ HRSD Age: 20-65. N=64, HRSD analysis: N=50 Country: UK	Fluoxetine versus amitriptyline (50-150mg, mean at week 6 =122mg)	1. Leaving the study early 2. HRSD mean endpoint scores* 3. Leaving the study early due to side effects	* Unpublished data. [Geddes2002]	B

	Active Treatment: 6 weeks	Setting: Outpatients				
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Characteristics of excluded studies

Study	Reason for exclusion
Ahlfors1988	Inadequate diagnosis of depression [Geddes2002*]
Altamura1989	No interpretable data available [Geddes2002]
Anonymous1986	Inadequate diagnosis of depression [Geddes2002*]
Anseau1994	Nefazodone used to represent SSRIs [Geddes2002*]
Ballus2000	Inclusion criteria was ICD-10 mild-moderate depression or dysthymia; number of patients diagnosed with dysthymia not given
Bascara1989	No interpretable data available [Geddes2002*]
Battegay1985	Inadequate diagnosis of depression [Geddes2002*]
Benkert1996	Venlafaxine used to represent SSRIs [Geddes2002*]
Bersani1994	Average daily dose of amitriptyline was less than 105% of its therapeutic level [Geddes2002*]
Besancon1993	24% patients were diagnosed with dysthymia or cyclothymia (not concurrent with major depression). [Geddes2002*]
Bignamini1992	No interpretable data available [Barbui2001]
Blanchard1995	No interpretable data available [Geddes2002]
Bocksberger93	Some patients were receiving adjunctive lithium, numbers not specified. [Geddes2002*]
Bouchard1987	Less than 75% patients achieved a therapeutic dose of maprotiline [Geddes2002*]
Bressa1989	No interpretable data available; no address for correspondence [Geddes2002]
Byrne1989	Not an RCT [Barbui2001]
Chouinard1985	Included in Beasley1993b [Geddes2002]
Christiansen1996	Inadequate diagnosis of depression [Barbui2001]
Cohn1984	Unable to locate paper to confirm eligibility; reference quoted by Geddes is incorrect [Geddes2002*]
Cohn1989	All patients were diagnosed with bipolar depression [Geddes2002*]
Corne1989	Majority of patients received less than therapeutic dose of dosulepin/dothiepin (4 received 50mg, 43 received 75mg, 4 received 100mg) [Geddes2002*]
Cunningham1994	Venlafaxine used to represent SSRIs [Geddes2002*]
De Wilde1982	Repeated in De Wilde1983 [Geddes2002]
Debus1988	Included in Beasley1991 [Geddes2002]
deJonghe1991a	Unable to ascertain whether patients received an adequate dose of maprotiline (range 50-150mg) [Geddes2002*]

deJonghe1991b	54% patients were diagnosed with dysthymia (not concurrent with major depression) [Geddes2002*]
Demyttenaere1998	Inadequate use of randomisation [Barbui2001]

DeNayer2002	Inadequate diagnosis of depression
Diaz-Martinez1998	Not double blind - open label
Doogan1994	No interpretable data available [Geddes2002]
Dunner1992	No interpretable data available [Barbui2002]
Entsuah1994	Same study as Schwiezer1994 [Geddes2002]
Entsuah2001	Not an RCT
Fairweather1993	No interpretable data available [Geddes2002]
Feighner1985b	Included in Beasley1993b [Geddes2002]
Feighner1989d	Nefazodone used to represent SSRIs [Geddes2002*]
Feighner1991	Not a relevant comparison - fluoxetine versus busprione [Barbui 2002]
Fontaine1991	No interpretable data available [Geddes2002]
Fontaine1994	Nefazodone used to represent SSRIs [Geddes2002*]
Freed1999	Inadequate diagnosis of depression [Barbui2001]
Gagiano1989	No interpretable data available [Geddes2002]
Gasperini1992	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Barbui2001]
Ginestet1989	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Geddes2002*]
Gonella1990	5% patients diagnosed with bipolar disorder, 30% diagnosed with dysthymia (not concurrent with major depression) [Geddes2002*]
Gravem1987	Inadequate diagnosis of depression [Geddes2002*]
Guelfi1983	Inadequate diagnosis of depression [Geddes2002*]
Guy1984	No interpretable data available [Geddes2002]
Harris1991	Average daily dose of amitriptyline was less than 105% of its therapeutic level [Geddes2002*]
Hegerl1997	Inadequate use of randomisation [Barbui2001]
Hewer1994	No interpretable data available [Geddes2002]
Jakovljevic1998	Less than 75% patients achieved a therapeutic dose of maprotiline - 71% of patients received 75mg/day maprotiline [Barbui2002]
Kamijima1997	Unable to assess eligibility of trial - published in Japanese [Barbui2001]
Keller1998	Some patients had comorbid psychiatric disorder [Barbui2002]
Klok1981	Inadequate diagnosis of depression [Geddes2002*]
Kuha1991	Only 61% of patients were receiving an adequate dose of maprotiline [Geddes2002*]
Kyle1998	No interpretable data available [Barbui2001]
Laakmann1988	Inadequate diagnosis of depression [Geddes2002*]

Laursen1985	All patients were diagnosed with bipolar depression [Geddes2002*]
Levine1989	50% of patients were only receiving 50mg of imipramine [Geddes2002*]

Link1992	Not an RCT [Barbui2002]
Loeb1989	No interpretable data available; no address for correspondence [Geddes2002]
Lonnqvist1994	Only 60.76% patients had major depression; 17% diagnosed with dysthymia, 11% with adjustment disorder [Geddes2002*]
Lydiard1997	Average daily dose of amitriptyline was less than 105% of its therapeutic level; mean final dose = 103.1mg [Barbui2001]
Mahapatra1996	Venlafaxine used to represent SSRIs [Geddes2002*]
Manna1989	Daily dose of clomipramine (75mg) was less than therapeutic level [Geddes2002*]
Masco1985	Included in Beasley1993b [Geddes2002]
Mehtonen2000	Less than 75% patients were on a therapeutic daily dose of sertraline; 64% of patients received 100mg/day sertraline
Mertens1988	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Geddes2002*]
Michelson338	Not an RCT
Moller1998	Less than 75% patients achieved a therapeutic dose of amitriptyline; 32% of patients received 75mg amitriptyline/day [Barbui2001]
Moon1989	No interpretable data available [Geddes2002]
Moon1994	75% of patients were receiving an inadequate dose of sertraline, 79% were receiving an inadequate dose of clomipramine [Geddes2002*]
Muijen1988	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Geddes2002*]
Mulsant2001	At least 14 patients were diagnosed with comorbid Alzheimer's disease; unable to ascertain whether patients received an adequate dose of nortriptyline [Geddes2002*]
Murasaki1997	Unable to assess eligibility of trial - published in Japanese [Barbui2002]
Nielsen1991	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Geddes2002*]
Nielsen1993	30% of patients were only receiving 75mg of imipramine [Geddes2002*]
Pakesch1991	Inadequate diagnosis of depression [Geddes2002*]
Perry1989	Included in Beasley1991 [Geddes2002]
Poelinger1989	Inadequate diagnosis of depression [Geddes2002*]
Ravindran1997	Inadequate diagnosis of depression [Geddes2002*]
Rickels1994	Nefazodone used to represent SSRIs [Geddes2002*]
Robertson1994	Bipolar depression formed part of inclusion criteria, number of patients in study with bipolar not specified [Geddes2002*]
Ropert1989	Daily dose of clomipramine was less than its therapeutic level. [Geddes2002*]
Rosenberg1994	Inadequate diagnosis of depression [Geddes2002*]
Schweizer1994	Venlafaxine used to represent SSRIs [Geddes2002*]
Shillingford1990	No interpretable data available [Geddes2002*]
Shrivastava1994	Venlafaxine used to represent SSRIs [Geddes2002*]

Stott1993	Inadequate diagnosis of depression [Geddes2002*]
Stratta1991	Inadequate diagnosis of depression [Geddes2002*]

Szegedi1997	No interpretable data available [Barbui2002]
Taneri1989	No interpretable data available; no address for correspondence [Geddes2002]
Tapani1989	40% patients were only receiving 50mg of doxepin during weeks 2-5 [Geddes2002*]
Thompson1991	Patients on inadequate dose of sertraline (only 27% received ≥ 100 mg) [Geddes2002*]
Upward1988	Inadequate description of diagnosis. [Geddes2002*]
Van Moffaert1994	No interpretable data available [Geddes2002]
Zanardi2000	More than 15% patients were diagnosed with bipolar disorder - 16/28 patients = 21.4%

[Geddes2002*] indicates that this study was originally included in Geddes2002.

Escitalopram - studies from previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Alexopoulos 2003 Y O I	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT	Outpatients. N=212. Age: 18-80, mean = 40.6/38.1. Diagnosis: DSM -IV major depressive disorder, MADRS \geq 22. Baseline scores: escitalopram - MADRS = 29.5, HRSD = 26.8, sertraline-MADRS=29, HRSD=26.8.	1. Escitalopram (10mg) 2. Sertraline (50-200mg, 86% patient received \geq 100mg, mean=148.75mg)	1. Non-responders (patients not achieving \geq 50% decrease in MADRS) 2. Non-remitters (patients not achieving MADRS \leq 10) 3. Leaving the study early 4. Leaving the study early due to side effects	Unpublished trial.	B

Bielski2003	Allocation: Random (no	Setting unclear. N=198. Aged 18-65,	1. Escitalopram (20mg)	1. HRSD mean change scores	Unpublished	B
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Y ? I	details). Duration: 8 weeks. Analysis: ITT	mean=37. Diagnosis: DSM-IV major depressive disorder, HRSD≥20. Baseline scores: escitalopram HRSD=28.6, venlafaxine - MADRS=28.9+4.6, HRSD=27.4	2. Venlafaxine (225mg)	2. MADRS mean change scores 3. Non-responders (patients not achieving ≥50% decrease in MADRS) 4. Non-remitters (patients not achieving MADRS≤12) 5. Leaving the study early 6. Leaving the study early due to side effects	trial.	
Burke2002 Y O I	Allocation: Random (no details). Duration: 8 weeks (+1 week placebo washout). Analysis: ITT	Outpatients. N=491. Aged 18-65. Diagnosis: DSM-IV major depressive disorder, MADRS ≥22. Baseline scores: escitalopram 10mg - MADRS=28, HRSD-24=24.3+6.2, escitalopram 20mg - MADRS=28.9, HRSD-24=25.8, citalopram- MADRS = 29.2, HRSD-24=25.9, placebo - MADRS=29.5, HRSD-24=25.8.	1. Escitalopram (10mg) 2. Escitalopram (20mg) 3. Citalopram (40mg) 4. Placebo (Data from 1 and 2 collapsed for dichotomous outcomes, 2 used for continuous measures)	1. MADRS mean change scores (escitalopram vs placebo, escitalopram vs citalopram) 2. HRSD mean change scores (escitalopram vs citalopram) 3. Non-responders (patients not achieving ≥50% decrease in MADRS) 4. Leaving the study early 5. Leaving the study early due to side effects 6. Patients reporting side effects	Conducted at 35 centres in the US.	B
Montgomery 2001 Y P I	Allocation: Random (no details). Duration: 8 weeks (+1 week placebo washout). Analysis: responder/remission data given for observed cases only (extracted as ITT for this review).	Primary care patients. N=471. Age: 18-65, mean= 43. Diagnosis: DSM-IV major depressive disorder, MADRS ≥22 & ≤40. Baseline scores: escitalopram - MADRS=29, citalopram - MADRS=29.2, placebo - MADRS=28.7.	1. Escitalopram (10mg up to 20mg, mean=14mg, 41% patients received 20mg) 2. Citalopram (20mg up to 40mg, mean = 28.4mg) 3. Placebo	1. Non-responders (patients not achieving ≥50% decrease in MADRS) 2. Non-remitters (patients not achieving MADRS<12) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted at 69 primary care centres in Europe.	B
Montgomery 2002 Y P I	Allocation: Random (no details). Duration: 8 weeks Analysis: responder /remission data given for observed cases only (extracted as ITT for this review).	Primary care patients. N=293. Aged 18-85. Diagnosis: DSM-IV major depressive disorder, MADRS ≥18. Baseline scores: escitalopram - MADRS = 28.7, venlafaxine - MADRS = 29.	1. Escitalopram (10mg-20mg, mean = 12.1mg, 22% patients received 20mg) 2. Venlafaxine (75-150mg, mean=95.2mg)	1. Non-responders (patients not achieving ≥50% decrease in MADRS) 2. Non-remitters (patients not achieving MADRS≤12) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Unpublished trial.	B
Wade2002 Y P I	Allocation: Random (no details). Duration: 8 weeks (+1 week placebo washout). Analysis: ITT (patients receiving ≥1 dose and ≥1 assessment)	Primary care patients. N=380. Age: 18-65, mean=40. 288 female. Diagnosis: DSM-IV major depressive disorder, 40 => MADRS ≥ 22. Baseline scores: escitalopram - MADRS = 29.2, placebo - MADRS = 28.7.	1. Escitalopram (10mg) 2. Placebo	1. MADRS mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in MADRS) 3. Non-remitters (patients not achieving MADRS≤12) 4. Leaving the study early 5. Leaving the study early due to side effects 6. Patients reporting side effects		B

Characteristics of excluded studies

Study	Reason for exclusion
Rapaport2004	Not an acute phase RCT. Reports on a maintenance phase study.

Acute-phase escitalopram - new studies in the guideline update

Comparisons Included in this Clinical Question

Escitalopram v bupropion XL v escitalopram+ bupropion XL v placebo	Escitalopram v bupropion XL v placebo CLAYTON2006C study1 CLAYTON2006C study2	Escitalopram v citalopram COLONNA2005 MOORE2005	Escitalopram v citalopram 10 mg v citalopram 20 mg YEVTUSHENKO2007
Escitalopram v citalopram v placebo LEPOLA2003 SCT-MD-02	Escitalopram v fluoxetine MAO2008 SCT-MD-09 SCT-MD-16	Escitalopram v fluoxetine v placebo KASPER2005	Escitalopram v paroxetine BALDWIN2006D BOULENGER2006
Escitalopram v placebo BOSE2008 SCT-MD-26	Escitalopram v sertraline VENTURA2007	Escitalopram v sertraline v placebo SCT-MD-27	Escitalopram v venlafaxine BIELSKI2004
Escitalopram 10mg v escitalopram 20 mg v citalopram 40 mg v placebo	Escitalopram v duloxetine KHAN2007B NIERENBERG2007B WADE2007	Escitalopram v duloxetine v placebo	

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BALDWIN2006D				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Followup: 19 week continuation phase</p> <p>Setting: Primary care; multinational (36 sites)</p> <p>Notes: RANDOMISATION: no details (1:1)</p>	<p>n= 325</p> <p>Age: Mean 45</p> <p>Sex: 87 males 238 females</p> <p>Diagnosis: 100% Current episode of major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS <22 or >40; abnormal physical examination; other axis I in past 6 months; alcohol or drug misuse; mania or hypomania, schizophrenia or psychotic disorder, bipolar disorder, OCD, eating disorder; learning disability or cognitive disorder; MADRS score =>5 on item 10; nonresponse or hypersensitivity to citalopram or paroxetine; drug allergy/hypersensitivity; lactose intolerance; taken psychoactive drug, in past 2 weeks; triptans, oral anticoagulants, sildenafil citrate, cimetidine, type 1c anti-arrhythmics, cardiac glycosides, narcotic analgesics, investigational drug in past 3 months; formal psychotherapy</p> <p>Notes: 1 week placebo lead in Continuation data not extracted because contains treatment interruption n= 325 randomised; 323 'ITT'</p> <p>Baseline: MADRS: Escit 29.6 (4.2); Prx 29.7 (4.1)</p>	<p>Data Used</p> <p>HAMD-17 mean change HAMD-17 mean endpoint MADRS mean change MADRS mean endpoint Remission: MADRS <= 12 Response: 50% reduction in MADRS Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>DESS - not relevant ASEX - not relevant</p> <p>Notes: Data available for end of 8 week acute phase and end of 19 week maintenance phase, but acute phase only extracted as maintenance phase contains medication interruption period</p>	<p>Group 1 N= 166</p> <p>Escitalopram. Mean dose 10-20 mg/d - mean 13.9 mg/d</p> <p>Group 2 N= 159</p> <p>Paroxetine. Mean dose 20-40 mg/d - mean 26.3 mg/g</p>	<p>Funding: sponsored by Lundbeck</p>
<p>BIELSKI2004</p> <p>Study Type: RCT</p> <p>Study Description: Was BIELSKI2003 in original guideline (based on conference</p>	<p>n= 198</p> <p>Age: Mean 37</p> <p>Sex: 83 males 115 females</p>	<p>Data Used</p> <p>Remission: MADRS <= 12 MADRS mean change</p>	<p>Group 1 N= 98</p> <p>Escitalopram. Mean dose 20 mg/d - Titrated as per US label instructions</p>	<p>Funding: unclear - two authors from Forest Laboratories Inc 135</p>

<p>abstract)</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Unclear</p> <p>Notes: RANDOMISATION: no details</p>	<p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 <20 No other exclusion criteria reported</p> <p>Notes: n= 198 randomised; 195 'ITT'</p> <p>Baseline: HAMD-17: Escit 28.6; Vfx 27.4</p>	<p>HAMD-17 mean change</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: HAMD-17 <= 7</p> <p>Response: 50% reduction in HAMD-17</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 2 N= 100</p> <p>Venlafaxine XR. Mean dose 225 mg/d - Titrated as per US label instructions</p>	
<p>BOSE2008</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': min 1 dose and 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Outpatients; US</p> <p>Notes: RANDOMISATION: computer generated schedule</p>	<p>n= 267</p> <p>Age: Mean 68</p> <p>Sex: 107 males 156 females</p> <p>Diagnosis: 100% MDD with ongoing episode of at least 4 weeks by DSM-IV</p> <p>Exclusions: MMSE score <24; MADRS score <22; abnormal physical examination results; bipolar disorder, schizophrenia, OCD, mental retardation, cognitive or developmental disorder; other axis I diagnosis; severe personality disorder; history of psychotic disorder; suicide risk; substance misuse in past 6 months; clinically significant medical conditions; use of depot neuroleptic in past 6 months; any neuroleptic, antidepressant or anxiolytic in past 2 weeks; previously treated with escitalopram or failed to respond to citalopram or two other SSRIs; ECT in past 3 months; participation in investigational drug study in past month; treatment with any psychotropic medication (except zolpidem or zalepon)</p> <p>Notes: 1 week placebo lead in n=267 randomised; 264 'safety'; 263 'ITT'</p> <p>Baseline: MADRS: Escit 29.4 (4.1); Plb 28.4 (3.6) HAMD-17: Escit 20.3 (4.3); Plb 19.6 (3.9)</p>	<p>Data Used</p> <p>Number of people reporting side effects</p> <p>MADRS mean change</p> <p>Leaving treatment early due to side effects</p> <p>CGI</p> <p>HAMD-24 mean change</p> <p>Remission: MADRS <= 10</p> <p>Response: 50% reduction in MADRS</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>QoL - not relevant</p> <p>Hamilton Anxiety Scale - not relevant</p> <p>Geriatric Depression Scale - not relevant</p> <p>Mini-Mental State Examination - not relevant</p>	<p>Group 1 N= 132</p> <p>Escitalopram. Mean dose 10 mg/d - Adjustable after week 4 up to 20 mg/d</p> <p>Group 2 N= 135</p> <p>Placebo</p>	<p>Funding: funded by Forest Laboratories</p>
<p>BOULENGER2006</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF (not all randomised; criteria unclear)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 168</p> <p>Setting: Outpatients; 6 countries (49 centres)</p> <p>Notes: RANDOMISATION: no details (1:1)</p>	<p>n= 459</p> <p>Age: Mean 44</p> <p>Sex: 143 males 311 females</p> <p>Diagnosis: 100% Major depressive disorder with current episode by DSM-IV-TR</p> <p>Exclusions: MADRS <30; duration of depressive episode <2 weeks or >1 year; anxiety disorder if primary diagnosis was not MDD; bipolar, psychotic, OC or eating disorder; mental retardation or developmental disorder; alcohol or drug disorder in past year; suicide risk or score =>5 on item 10 MADRS; receiving behaviour or systematic psychotherapy; preganant or breast-feeding; lactose intolerance; hypersensitivity or nonresponse to citalopram, escitalopram or paroxetine, taking (stipulated) psychotropic drug in past 2 weeks; ECT in past 6 months.</p> <p>Notes: 2 week taper period at end n= 459 randomised; 454 treated; 451 'ITT'</p> <p>Baseline: MADRS: Escit 35.2 (3.7); Prx 34.8 (3.8) HAMD-17: Escit 24.7 (4.8); Prx 24.3 (5.0)</p>	<p>Data Used</p> <p>HAMD-17 mean change MADRS mean change Remission: MADRS <= 12 Response: 50% reduction in MADRS Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>Hamilton Anxiety Scale - not relevant CGI - not relevant</p>	<p>Group 1 N= 232</p> <p>Escitalopram. Mean dose 10-20 mg/d - 10 mg/d 1st week then increased</p> <p>Group 2 N= 227</p> <p>Paroxetine. Mean dose 20-40 mg/d - 20 mg/d 1st week, 30 mg/d 2nd week, then increased</p>	<p>Funding: sponsored by Lundbeck</p>
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<p>CLAYTON2006C study1</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT':LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Unclear</p> <p>Notes: RANDOMISATION: no details (1:1:1)</p>	<p>n= 420</p> <p>Age: Mean 36</p> <p>Sex: 164 males 256 females</p> <p>Diagnosis: 100% MDD with current episode =>12 weeks and =<12 years by DSM-IV</p> <p>Exclusions: HAMD-17 <19; abnormal orgasm function; did not engage in sexual activity leading to orgasm at least once every 2 weeks; any sexual dysfunction; anorexia nervosa, bulimia, seizure disorder, brain injury; panic disorder, OCD, PTSD, acute stress disorder in past 12 months; bipolar disorder, schizophrenia or other psychotic disorder; suicide attempt in past 6 months; prescribed medications that might affect sexual functioning.</p> <p>Notes: 1 week screening n= 425 randomised; 420 'safety'; 397 'ITT'</p> <p>Baseline: HAMD-17: Escit 23.3 (0.3); Bpn 23.9 (0.3); Plb 23.3 (0.2)</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>HAMD-17 mean change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 <= 7</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>Hospital Anxiety and Depression Scale - not relevant</p> <p>CGI - not relevant</p> <p>CSFQ - not relevant</p>	<p>Group 1 N= 142</p> <p>Escitalopram. Mean dose 10-20 mg/d - mean (sd) 13 mg/d (2.6)</p> <p>Group 2 N= 142</p> <p>Bupropion XL. Mean dose 150-450 mg/d - mean (sd) 323 mg/d (59.4)</p> <p>Group 3 N= 141</p> <p>Placebo</p>	<p>Funding: supported by GlaxoSmithKline</p>
<p>CLAYTON2006C study2</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT':LOCF 1 dose&no orgasm dysfrctn&postbln evltn</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Unclear</p> <p>Notes: RANDOMISATION: no details (1:1:1)</p>	<p>n= 424</p> <p>Age: Mean 37</p> <p>Sex: 180 males 230 females</p> <p>Diagnosis: 100% MDD with current episode =>12 weeks and =<12 years by DSM-IV</p> <p>Exclusions: HAMD-17 <19; abnormal orgasm function; did not engage in sexual activity leading to orgasm at least once every 2 weeks; any sexual dysfunction; anorexia nervosa, bulimia, seizure disorder, brain injury; panic disorder, OCD, PTSD, acute stress disorder in past 12 months; bipolar disorder, schizophrenia or other psychotic disorder; suicide attempt in past 6 months; prescribed medications that might affect sexual functioning.</p> <p>Notes: 1 week screening n= 424 randomised; 410 'safety'; 388 'ITT'</p> <p>Baseline: HAMD-17: Escit 23.3 (0.3); Bpn 23.2 (0.3); Plb 23.3 (0.3)</p>	<p>Data Used</p> <p>HAMD-17 mean change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 <= 7</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>Hospital Anxiety and Depression Scale - not relevant</p> <p>CGI - not relevant</p> <p>CSFQ - not relevant</p>	<p>Group 1 N= 149</p> <p>Escitalopram. Mean dose 10-20 mg/d - mean (sd) 13 mg/d (3.2)</p> <p>Group 2 N= 138</p> <p>Bupropion XL. Mean dose 150-450 mg/d - mean (sd) 309 mg/d (58.3)</p> <p>Group 3 N= 137</p> <p>Placebo</p>	<p>Funding: supported by GlaxoSmithKline</p>
<p>COLONNA2005</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT':LOCF min 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 168</p> <p>Setting: Outpatients; multi-national (6 sites)</p> <p>Notes: RANDOMISATION: computer-generated randomisation list (1:1)</p>	<p>n= 357</p> <p>Age: Mean 46</p> <p>Sex: 92 males 265 females</p> <p>Diagnosis: 100% Major depressive disorder with current episode by DSM-IV</p> <p>Exclusions: MADRS <22 or >40; any other serious illness; pregnant, breast-feeding or not using contraception; mania or bipolar, schizophrenia or other psychotic disorder; OCD, eating disorder, mental retardation, developmental or cognitive disorder, MADRS =>5 on item 10; antipsychotic, antidepressant, hypnotic, anxiolytic, antiepileptic, barbiturates, chloral hydrate, 5-HT agonist treatment; ECT, behaviour therapy or psychotherapy, any investigational drug</p>	<p>Data Used</p> <p>MADRS mean change</p> <p>MADRS mean endpoint</p> <p>Remission: MADRS <= 12</p> <p>Response: 50% reduction in MADRS</p> <p>Leaving treatment early due to side effects</p> <p>Side effects reported</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>CGI - not relevant</p>	<p>Group 1 N= 175</p> <p>Escitalopram. Mean dose 10 mg/d</p> <p>Group 2 N= 182</p> <p>Citalopram. Mean dose 20 mg/d</p>	<p>Funding: sponsored by Lundbeck</p>
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	<p>drug misuse; drug hypersensitivity or allergy; lack of response to more than one AD treatment.</p> <p>Notes: 1 week placebo lead in</p> <p>Baseline: MADRS: Escit 29.5 (4.3); Cital 30.2 (4.7)</p>			
KASPER2005				
<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Primary Care and Specialist; 11 countries</p> <p>Notes: RANDOMISATION: no details</p>	<p>n= 518</p> <p>Age: Mean 75</p> <p>Sex: 125 males 393 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS <22 or >40; MMSE <22; mania or any bipolar disorder; schizophrenia or any psychotic disorder; OCD; eating disorder; mental retardation or cognitive disorder; MADRS <5 on item 10; treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, barbiturates, chloral hydrate, antiparkinsonian drugs, diuretics, 5-HT receptor agonists, lithium, sodium valproate, carbamazepine, ECT, behaviour therapy or psychotherapy, investigational drug in past month; history of schizophrenia, psychotic disorder or drug misuse; drug allergy or hypersensitivity; lack of response to more than one antidepressant during current depressive episode</p> <p>Notes: 1 week placebo lead in</p> <p>n= 518 randomised; 517 treated</p> <p>Baseline: MADRS: Escit 28.2 (3.8); Fluox 28.5 (3.8); Plb 28.6 (4.2)</p>	<p>Data Used</p> <p>MADRS mean endpoint</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 12</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>CGI - not relevant</p>	<p>Group 1 N= 174</p> <p>Escitalopram. Mean dose 10 mg/d</p> <p>Group 2 N= 164</p> <p>Fluoxetine. Mean dose 20 mg/d</p> <p>Group 3 N= 180</p> <p>Placebo</p>	<p>Funding: unclear - two authors are full-time employees of Lundbeck and third author has received pharmaceutical funding for past research (and this trial?)</p>
KHAN2007B				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US (12 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 382 people screened; 104 did not meet inclusion criteria</p>	<p>n= 278</p> <p>Age: Mean 42</p> <p>Sex: 112 males 166 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS < 26; MADRS at baseline within 25% of score at screening; abnormal findings on physical exam, laboratory tests and 12-lead ECT; pregnant or breastfeeding; Axis I disorder other than MDD; mental retardation or pervasive developmental disorder or cognitive disorder; recent history or current diagnosis of drug or alcohol dependence; suicidal ideation or attempt within past year; history of psychotic disorder or psychotic features; personality disorder likely to interfere with study; history of seizure disorder or risk of seizure; history of narrow-angle glaucoma or inappropriate antidiuretic hormone secretion syndrome; current diagnosis or history of clinically significant medical illness unstable in last year; women not using adequate contraception</p> <p>Notes: 1 week placebo lead in and 16 week extension phase</p> <p>Baseline: HAMD-17 (SD) 21 (4)</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 10</p> <p>MADRS mean change</p> <p>MADRS mean endpoint</p> <p>HAMD-17 mean endpoint</p> <p>Response: 50% reduction in HAMD-24</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 138</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 140</p> <p>Escitalopram. Mean dose 10 mg - 20 mg - Dose increased to 20 mg after 4 weeks if lack of response</p>	<p>SIGN: 1+; funding: National Institutes of Health Center and Forest Research Institute; 1-week no-drug screening phase</p>
<p>LEPOLA2003</p> <p>Study Type: RCT</p> <p>Study Description: Was MONTGOMERY2001 in original guideline (based on conference abstract)</p>	<p>n= 471</p> <p>Age: Mean 43</p> <p>Sex: 133 males 338 females</p>	<p>Data Used</p> <p>Remission: MADRS <= 12</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p>	<p>Group 1 N= 156</p> <p>Escitalopram. Mean dose 10 mg/d (min) - Dose could be doubled at week 4 or 6</p>	<p>Funding: sponsored by Lundbeck 138</p>

<p>Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Primary Care; multinational</p> <p>Notes: RANDOMISATION: no details (1:1:1)</p>	<p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: Baseline MADRS <22 or >40; suffering from any bipolar disorder or psychotic disorder, OCD, eating disorder, mental retardation, developmental or cognitive disorder; MADRS=>5 on item 10; treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, barbiturates, chloral hydrate or other 5-hydroxytryptamine receptor agonists, ECT, behaviour therapy or psychotherapy</p> <p>Notes: 1 week placebo lead in n=471 randomised; 468 'ITT'</p> <p>Baseline: MADRS: Plb 28.7; Escit 29.0; Cital 29.2</p>	<p>Leaving treatment early for any reason</p> <p>Response: 50% reduction in MADRS</p> <p>MADRS mean change</p> <p>MADRS mean endpoint</p> <p>Data Not Used</p> <p>CGI - not relevant</p>	<p>Group 2 N= 161</p> <p>Citalopram. Mean dose 20 mg/d (min) - Dose could be doubled at week 4 or 6</p> <p>Group 3 N= 154</p> <p>Placebo</p>	
<p>MAO2008</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients and inpatients; China (6 sites)</p> <p>Notes: RANDOMISATION: no details (1:1)</p>	<p>n= 240</p> <p>Age: Mean 39</p> <p>Sex: 105 males 135 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: CGI <4; HAMD-17 <18; any other primary axis I diagnosis; any anxiety disorder as primary diagnosis in past year; substance misuse in past year; suicidal risk; medical illness; currently taking St John's wort or other Chinese herbal medicine for depression.</p> <p>Notes: 2 week washout period n= 240 randomised; 231 'ITT'</p> <p>Baseline: MADRS: Escit 30.1 (5.4); Fluox 31.2 (5.1) HAMD-17: Escit 24.7 (5.4); Fluox 24.1 (4.5)</p>	<p>Data Used</p> <p>MADRS mean change</p> <p>MADRS mean endpoint</p> <p>HAMD-17 mean change</p> <p>HAMD-17 mean endpoint</p> <p>Response: 50% reduction in MADRS</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: MADRS <= 12</p> <p>Remission: HAMD-17 <= 7</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 123</p> <p>Escitalopram. Mean dose 10 mg/d - + placebo fluoxetine</p> <p>Group 2 N= 117</p> <p>Fluoxetine. Mean dose 20 mg/d - + placebo escitalopram</p>	<p>Funding: Contract grant sponsor - Xian-Janssen Pharmaceutical Company</p>
<p>MOORE2005</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF min 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; France (multicentre)</p> <p>Notes: RANDOMISATION: block randomisation</p>	<p>n= 294</p> <p>Age: Mean 45</p> <p>Sex: 97 males 197 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS <30; any other axis I disorder; mania or any bipolar disorder; schizophrenia or any psychotic disorder; OCD; eating disorder; mental retardation or cognitive disorder; personality disorder; treatment with depot antipsychotic in past 6 months; any antipsychotic, anxiolytics or anticonvulsant in past 2 weeks; substance misuse in past 12 months.</p> <p>Notes: n= 294 randomised; 294 'safety'; 280 'ITT'</p> <p>Baseline: MADRS: Escit 36.3 (4.8); Cit 35.7 (4.4)</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 12</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>MADRS mean endpoint</p> <p>Data Not Used</p> <p>MADRS-S endpoint - no variability measure</p> <p>CGI - not relevant</p> <p>Notes: 'Adjusted' means reported</p>	<p>Group 1 N= 142</p> <p>Escitalopram. Mean dose 10-20 mg/d - 10 mg/d week 1 then increased</p> <p>Group 2 N= 152</p> <p>Citalopram. Mean dose 20-40 mg/d - 20 mg/d week 1 then increased</p>	<p>Funding: funded by Lundbeck</p>
<p>NIERENBERG2007B</p> <p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Followup: 6-month continuation phase</p>	<p>n= 684</p> <p>Age: Mean 42 Range 18-79</p> <p>Sex: 238 males 446 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p>	<p>Data Used</p> <p>Number with palpitation</p> <p>Number with abnormal orgasmia</p> <p>Number with decreased libido</p> <p>Number with ventricular dysfunction</p> <p>Number with hypertension</p> <p>Number with suicidal depression</p>	<p>Group 1 N= 273</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 274</p> <p>Escitalopram. Mean dose 10 mg</p> <p>Group 3 N= 137</p> <p>Placebo</p>	<p>SIGN 1++; funding Eli Lilly (code HMCR); variable-duration placebo washout; continuation phase data in Pigott2007 data not extracted as report 139 incomplete - requested full report</p>

<p>Setting: Outpatients; US (36 sites)</p> <p>Notes: RANDOMISATION: randomised using 'interactive voice response system'</p> <p>Info on Screening Process: 1049 people screened, 365 failed to meet entry criteria</p>	<p>and ECT; pregnant or lactating; Axis I disorder other than MDD; previous diagnosis of bipolar disorder, schizophrenia or other psychotic disorder in past 2 years; axis II disorder that would interfere with protocol compliance; primary diagnosis of anxiety in past 6 months; history of substance dependence in last 6 months; failed >=2 adequate courses of antidepressants during current episode; history of lack of response to adequate trial of study drugs for depression; serious suicidal risk; serious medical illness likely to need intervention, hospitalisation or use of excluded medication during study, use of MAOI or fluoxetine with 30 days of 3rd visit; positive drug urine screen for substances of misuse, ECT or TMS in last year, initiating, stopping or changing psychotherapy frequency or modality after study entry</p> <p>Notes: placebo lead in</p> <p>Baseline: HAMD-17 17.6 (4.8) (dul); 17.8 (5.1) (esc); 17.7 (5.2) (pbo)</p>	<p>Number with chronic airways disease exacerbated</p> <p>Number with cardiac failure congestive</p> <p>Number with arrhythmia</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Weight change</p> <p>Notes: Not possible to calculate SDs for weight change</p> <p>Author emailed for n at randomisation 07/10/08</p>		
<p>SCT-MD-02</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': min 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US (22 sites)</p> <p>Notes: RANDOMISATION: no details</p>	<p>n= 386</p> <p>Age: Mean 42</p> <p>Sex: 176 males 199 females</p> <p>Diagnosis:</p> <p>Exclusions: MADRS score <22; HAMD item 1 score <2; abnormal physical examination; pregnant or nursing or not using birth control; Bipolar or psychotic disorder, OCD, mental retardation, cognitive or developmental disorder; personality or any other axis I disorder; history of psychotic disorder; suicide risk; substance MISuse in past 6 months; clinically significant medical condition; abnormal blood pressure; treatment with depot neuroleptic in past 6 months; any neuroleptic, antidepressant or anxiolytic in past 2 weeks; treatment with psychotropic drug or prohibited or over the counter medication; investigational drug study or treatment in past 2 months; previous study escitalopram; allergy to citalopram; failure to respond to SSRI or two other antidepressants; ECT current or past 6 months; psychotherapy or behaviour therapy in past 3 months; unable to follow protocol; not suitable for study (investigator opinion)</p> <p>Notes: 1 week placebo lead in</p> <p>Baseline: MADRS: Escit 28.7 (4.3); Cit 28.3 (5.0); Plb 28.8 (5.0)</p> <p>HAMD: Escit 24.8 (5.4); Cit 25.0 (5.5); Plb 25.0(5.3)</p>	<p>Data Used</p> <p>MADRS mean endpoint</p> <p>Response: 50% reduction in MADRS</p> <p>MADRS mean change</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>CGI - not relevant</p>	<p>Group 1 N= 129</p> <p>Escitalopram. Mean dose 10-20 mg/d</p> <p>Group 2 N= 128</p> <p>Citalopram. Mean dose 20-40 mg/d</p> <p>Group 3 N= 129</p> <p>Placebo</p>	<p>Funding: Forest Laboratories Inc</p>
<p>SCT-MD-09</p> <p>Study Type: RCT</p> <p>Type of Analysis: Completers (and no prohibited meds)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 35</p> <p>Setting: Outpatients; US</p> <p>Notes: RANDOMISATION: no details</p>	<p>n= 30</p> <p>Age: Mean 39</p> <p>Sex: 4 males 26 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD score <18 or sleep disturbance scale score <1</p> <p>No other criteria reported - need appendices from Lundbeck</p> <p>Notes: n= (original n randomised unclear); 30 'safety' (received at least one dose of double blind medication); 27 completers; 24 'evaluable' (no prohibited meds)</p>	<p>Data Used</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>HAMD-17 mean change</p> <p>MADRS mean change</p> <p>Data Not Used</p> <p>CGI - not relevant</p> <p>Hamilton Anxiety Scale - not relevant</p>	<p>Group 1 N= 16</p> <p>Escitalopram. Mean dose 10-20 mg/d - Lower dose for initial 7 days then increased to max dose</p> <p>Group 2 N= 14</p> <p>Fluoxetine. Mean dose 20-40 mg/d - Lower dose for initial 7 days then increased to max dose</p>	<p>Funding: Sponsored by Forest Research Institute</p>

Baseline: MADRS: Escit 24.4 (2.36); Fluox 25.3 (3.74)

	HAMD: Escit 21.5 (3.10); Fluox 21.5 (2.70)			
SCT-MD-16				
<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US (9 sites)</p> <p>Notes: RANDOMISATION: no details</p>	<p>n= 205</p> <p>Age: Mean 37</p> <p>Sex: 69 males 128 females</p> <p>Diagnosis: Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS score <22 No other criteria reported</p> <p>Notes: 1 week placebo lead in 8 patients unaccounted for between randomisation and treatment - need to email Lundbeck for details</p> <p>Baseline: MADRS: Escit 30.4 (4.31); Fluox 30.2 (5.15) HAMD-24: Escit 25.9 (5); Fluox 26.5 (5.74)</p>	<p>Data Used</p> <p>Remission: MADRS <= 10</p> <p>Response: 50% reduction in MADRS</p> <p>HAMD-24 mean change</p> <p>MADRS mean endpoint</p> <p>MADRS mean change</p> <p>Leaving treatment early due to side effects</p> <p>Data Not Used</p> <p>CES-D - not relevant</p> <p>QoL - not relevant</p> <p>CGI - not relevant</p> <p>Hamilton Anxiety Scale - not relevant</p> <p>Notes: HAMD response and remission data also reported but exact definition unclear</p>	<p>Group 1 N= 98</p> <p>Escitalopram. Mean dose 10-20 mg/d - Started on minimum dose and raised to maximum dose after 3 weeks</p> <p>Group 2 N= 99</p> <p>Fluoxetine. Mean dose 20-40 mg/d - Started on minimum dose and raised to maximum dose after 3 weeks</p>	<p>Funding: Sponsored by Forest Research Institute</p>
SCT-MD-26				

<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 14</p> <p>Followup: 6 week continuation phase</p> <p>Setting: Unclear; US (20 sites)</p> <p>Notes: RANDOMISATION: no details</p>	<p>n= 309</p> <p>Age: Mean 39</p> <p>Sex: 117 males 183 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: Not reported</p> <p>Notes: 1 week placebo lead in Extracted as 8 week study as no difference between acute and continuation phases n= 309 randomised; 300 'safety'; 294 'ITT'</p> <p>Baseline: MADRS: Escit 30.4 (4.0); Plb 30.5 (4.13) HAMD: Escit 30.4 (4.1); Plb 29.7 (3.61)</p>	<p>Data Used</p> <p>Remission: HAMD-17 <= 7</p> <p>Response: 50% reduction in MADRS</p> <p>Response: 50% reduction in HAMD-17</p> <p>HAMD-17 mean change</p> <p>HAMD-17 mean endpoint</p> <p>MADRS-S endpoint</p> <p>MADRS mean change</p> <p>Side effects reported</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>Remission: MADRS <= 10 - 'sustained' remission</p> <p>QoL - not relevant</p> <p>CES-D - not relevant</p> <p>CGI - not relevant</p> <p>Hamilton Anxiety Scale - not relevant</p> <p>Notes: HAMD assumed to be 17 item; Remission data available for HAMD also but criteria unclear - have emailed Lundbeck for clarification of this 15.10.08</p>	<p>Group 1 N= 147</p> <p>Escitalopram. Mean dose 10-20 mg/d - Started at 10 mg and possibly increased after 1 week</p> <p>Group 2 N= 153</p> <p>Placebo</p>	<p>Funding: supported by Lundbeck</p>
<p>SCT-MD-27</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p>	<p>n= 409</p> <p>Age: Mean 40</p> <p>Sex: 179 males 224 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p>	<p>Data Used</p> <p>HAMD-17 mean change</p> <p>MADRS mean change</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 10</p> <p>Side effects reported</p>	<p>Group 1 N= 136</p> <p>Escitalopram. Mean dose 10-20 mg/d - minimum dose for first week then could be increased up to maximum dose (mean: 16.6 mg/d)</p>	<p>Funding: Sponsored by Forest Research Institute</p> <p style="text-align: right;">141</p>

<p>Setting: Outpatients; US (24 sites) Notes: RANDOMISATION: no details</p>	<p>Exclusions: None reported Notes: 1 week placebo lead in n= 409 randomised; 403 'safety'; 398 'ITT' Baseline: MADRS: Escit 30.4 (4.58); Srl 30.1 (4.65); Plb 30.7 (4.6) HAMD baseline data also available</p>	<p>Leaving treatment early due to side effects Leaving treatment early for any reason Data Not Used Sheehan Disability Scale - not relevant QoL - not relevant Hamilton Anxiety Scale - not relevant CGI - not relevant</p>	<p>Group 2 N= 138 Sertraline. Mean dose 50-200 mg/d - minimum dose for first week then could be increased up to maximum dose (mean: 113.1 mg/d) Group 3 N= 135 Placebo</p>	
<p>VENTURA2007 Study Type: RCT Study Description: Was ALEXPOLOUS2003 in original guideline (based on conference abstract) Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US Notes: RADOMISATION: no details (1:1)</p>	<p>n= 215 Age: Mean 39 Sex: 93 males 119 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS <22; abnormal physical examination; pregnant, lactating or not using contraception; other primary axis I disorder; psychotic disorder; bipolar disorder, schizophrenia, OCD; substance misuse; suicide risk; personality disorder; depot neuroleptic in past 6 months; any neuroleptic, antidepressant, anxiolytic in past 2 weeks; previous treatment with study drug; failure to respond to two SSRIs; in investigational study or treatment with investigational drug in past month; use of psychotropic drug Notes: 1 week placebo lead in n= 215 randomised; 212 'safety'; 211 'ITT' Baseline: MADRS: Escit 29.5 (4.31); Srl 29.0 (4.02) HAMD-24: Escit 26.8 (4.74); Srl 26.8 (4.51)</p>	<p>Data Used HAMD-24 mean change HRDS 24 mean endpoint MADRS mean change MADRS mean endpoint Response: 50% reduction in HAMD-24 Response: 50% reduction in MADRS Remission: HAMD-17 <= 7 Remission: MADRS <= 10 Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason Data Not Used QoL - not relevant CES-D - not relevant Hamilton Anxiety Scale - not relevant CGI - not relevant Notes: Author emailed 07/10/08 for clarification on dosing regime and on version of HAMD that was used (discrepancy between published article and ctr)</p>	<p>Group 1 N= 107 Escitalopram. Mean dose 10 mg/d - placebos added if 'dose increase' needed Group 2 N= 108 Sertraline. Mean dose 50-200mg/d</p>	<p>Funding: funded by Forest Laboratories</p>
<p>WADE2007</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: LOCF (at least one post-baseline evaluation)</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Outpatients and primary care; Belgium, Canada, Czech Republic, France, Germany, Italy, Spain, Sweden, UK (35 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 294</p> <p>Age: Mean 44</p> <p>Sex: 212 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV-TR</p> <p>Exclusions: MADRS < 26; comorbid OCD, PTSD or panic disorder; bipolar disorder, psychotic disorder or fetures, current eating disorders, mental retardation, pervasive developmental disorder or cognitive disorder, alcohol or drug misuse-related disorders with 12 months of the study; serious suicide risk; receiving formal behaviour therapy, systematic psychotherapy, pregnant, breastfeeding, history of lactose intolerance; hypersensitivity or non-response to citalopram, escitalopram or duloxetine; in creased intra-ocular pressure or risk of acute narrow-angle glaucoma; taking psychotropic drugs, except z-drugs for insomnia, within 2 weeks of study or during study (5 weeks for</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS < 13</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean endpoint</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 151</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 143</p> <p>Escitalopram. Mean dose 20 mg/d - 10 mg/d weeks 1, 2, 25 and 26</p>	<p>SIGN: 1+; funding: Lundbeck; psychotropics not allowed during 2 weeks before entering trial</p>
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142

	<p>fluoxetine); ECT within 6 months.</p> <p>Baseline: HAMD-17 (SD) 22.7 (5)</p>	<p>Notes: Data given at week 8 and week 24; week 8 entered in acute phase comparisons and week 24 in continuation phase to match other studies; SDs calculated from p-values; MADRS used for remission/response at 24 weeks</p>		
YEVTUSHENKO2007				
<p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Outpatients; Russia (8 sites)</p> <p>Notes: RANDOMISATION: block randomisations</p>	<p>n= 330</p> <p>Age: Mean 35</p> <p>Sex: 134 males 188 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS score <25; no potential for benefit from treatment with study drug; met criteria for any bipolar or psychotic disorder, OCD, mental retardation or developmental disorder; eating disorder; dementia; drug or alcohol misuse in past 12 months; drug allergy; other serious illness; study drug treatment in past 60 days; inability to comply; study drugs considered not 'clinically relevant' (based on clinical judgement); oral antipsychotic or MAOI in past 2 weeks; depot antipsychotic preparation in past 6 months; SSRI, SNRI or TCA in past week; fluoxetine in past 5 weeks; treatment with anti-parkinsonian compound, barbiturate, chloral hydrate, lithium, anticonvulsant, hypnotic or anxiolytic (except benzodiazepines); pregnant or breastfeeding</p> <p>Notes: n=330 randomised; 322 'ITT'</p> <p>Claims that all (322) participants still in study at end of week 1 were maintained in study for remaining 5 weeks</p> <p>Baseline: MADRS: Escit 34.78 (3.53); Cit 10 mg 35.40 (3.29); Cit 20 mg 35.70 (3.85)</p>	<p>Data Used</p> <p>Remission: MADRS <= 10</p> <p>Remission: MADRS <= 12</p> <p>Response: 50% reduction in MADRS</p> <p>MADRS mean change</p> <p>Side effects reported</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>CGI - not relevant</p> <p>Notes: Citalopram 10 mg and 20 mg arms added for dichotomous data and 20 mg arm extracted for continuous data</p>	<p>Group 1 N= 109</p> <p>Escitalopram. Mean dose 10 mg/d</p> <p>Group 2 N= 111</p> <p>Citalopram. Mean dose 10 mg/d</p> <p>Group 3 N= 110</p> <p>Citalopram. Mean dose 20 mg/d</p>	<p>Funding: sponsored by OOO ARBACOM, Moscow, Federation of Russia</p>

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
10423	Study incomplete so data unavailable
10778	Unable to obtain clinical trial report from Lundbeck/Principle Investigator
11438A	Unable to obtain clinical trial report from Lundbeck/Principle Investigator
12104	Unable to obtain clinical trial report from Lundbeck/Principle Investigator
99812	Open label
ANDERS2008	Not RCT
AUQUIER2003	Review

7	Pooled analysis
BAUNE2007	Not RCT
BECH2006B	Pooled analysis
BERMAN2007	Escitalopram phase not rct
BOUFFARDposter	No relevant outcomes; no clinical trial report; not yet submitted for publication
BRETLAU2008	Not RCT; open label
BURKEposter	Open label

CHOKKA inpress	Open label
EINARSON 2004	Review
FANTINO 2007	Health economics
FERNANDEZ 2005	Health economics
GERGEL poster	Pooled analysis; safety study
GORMAN 2002	Pooled analysis
GUPTA poster	Not RCT
KARP 2008	Not RCT; open label
KASPER 2006	Not RCT
KASPER 2006A	Pooled analysis
KENNEDY 2006	Review
KHAN 2004	Not randomised; open label
KULP 2005	Health economics
LADER 2005	Pooled analysis
LAM 2006	Review
LAM 2008	Pooled analysis
LANCON 2006	Non randomised; 'naturalistic'
LANCON 2007	Review
LEINONEN 2007	Open label
LI 2006C	Foreign language
LLORCA 2005	Pooled analysis
LYDIARD poster	Anxiety; pooled analysis
MALLINCKRODT 2007	Review
MOHAMED 2006	Open label; comorbid anxiety
MOLLER 2007	Not rct
MONTGOMERY 2006	Review
MONTGOMERY posterA	Pooled trials from old guideline (Wade2002 and Burke2002)
MONTGOMERY posterB	Not depression
OLIE 2007	Open label
PAPAKOSTAS 2007C	Pooled analysis; not all escitalopram
PEC-S-08-00967	Health economics
PINTO 2007	Open label
RUSH 2005	Open label
SANCHEZ poster	Animals
SCHMITT 2006A	Open label
SCT-MD-24	Depression and chronic physical health problems guideline
SCT-MD-31	Generalised anxiety disorder
SCT-MD-35	Not therapeutic dose of escitalopram

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WADE2006E Not RCT

WAGNER2006 Children

WINKLER2007 Not RCT

References of Included Studies

- BALDWIN2006D** (Unpublished and Published Data)
 Lundbeck. A double-blind randomised multicentre study to evaluate the safety and efficacy of escitalopram (10 or 20 mg daily) versus paroxetine (20 or 40 mg daily) in the treatment of patients with major depressive disorder (99505). Report date: 3 February 2006.
 *Baldwin, D. S., Cooper, J. A., Huusom, A. K., & Hindmarch, I. (2006). A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. *International Clinical Psychopharmacology*, 21, 159-169.
- BIELSKI2004** (Unpublished and Published Data)
 Forest Research Institute. Double-blind fixed dose comparison of the safety and efficacy of 20 mg/day escitalopram and 225 mg/day venlafaxine xr in the treatment of major depressive disorder (SCT-MD-12). Report date: December 1, 2003.
 Bielski, R.J., Ventura, D. & Chang, C.C. A double-blind comparison of escitalopram with venlafaxine XR in the treatment of major depressive disorder. Poster presented at the 16th Congress of the European College of Neuropsychopharmacology, Prague, Czech Republic, September 20-24, 2003.
 *Bielski, R.J., Ventura, D. & Chang, C.C. (2004) A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. *Journal of Clinical Psychiatry*, 65, 1190-1196
- BOSE2008** (Unpublished and Published Data)
 See SCT-MD-13
 Bose, A., Li, D. & Gandhi, C. (2008) Escitalopram in the acute treatment of depressed patients aged 60 years or older. *American Journal of Geriatric Psychiatry*, 16, 14-20.
- BOULENGER2006** (Unpublished and Published Data)
 Lundbeck. A double-blind, randomised, multi-centre, fixed-dose study evaluating the efficacy and safety of escitalopram (2 mg daily) versus paroxetine (40 mg daily) in patients suffering from major depressive disorder (10351). Report date: 9 July 2007.
 Boulenger, J.P., Huusom, A.K.T., Florea, I., Baekdal, T. & Sarchiapone, M. A comparative study of the efficacy and tolerability of long-term treatment with escitalopram and paroxetine in severe major depression. Poster presented at the International Conference on Anxiety Disorders, 24-26 February 2006, Stellenbosch, South Africa.
 *Boulenger, J.P., Huusom, A.K.T., Florea, I., Baekdal, T. & Sarchiapone, M. (2006) A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. *Current Medical Research and Opinion*, 22, 1331-1341.
- CLAYTON2006C study1** (Published Data Only)
 Clayton, A.H., Croft, H.A., Horrigan, J.P., Wightman, D.S., Krishen, A., Richard, N.E. & Modell, J.G. (2006) Bupropion extended release compared with escitalopram. Effects on sexual functioning and antidepressant efficacy in 2 randomised, double-blind, placebo-controlled studies. *Journal of Clinical Psychiatry*, 67, 736-746.
- CLAYTON2006C study2** (Published Data Only)
 Clayton, A.H., Croft, H.A., Horrigan, J.P., Wightman, D.S., Krishen, A., Richard, N.E. & Modell, J.G. (2006) Bupropion extended release compared with escitalopram. Effects on sexual functioning and antidepressant efficacy in 2 randomised, double-blind, placebo-controlled studies. *Journal of Clinical Psychiatry*, 67, 736-746.
- COLONNA2005** (Unpublished and Published Data)
 Lundbeck. A double-blind, randomised, comparative trial evaluating the efficacy and safety of a 6-month treatment with Lu 26-054 (10 mg) and citalopram (20 mg) in outpatients with major depressive disorder (99022). Report date: 13 June 2002.
 *Colonna, L., Andersen, H.F. & Reines, E.H. (2005) A randomised, double-blind, 24 -week study of escitalopram (10 mg/day), versus citalopram (20 mg/day) in primary care patients with major depressive disorder. *Current Medical Research and Opinion*, 21, 1659-1668.
- KASPER2005** (Unpublished and Published Data)
 Lundbeck. A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of 10 mg lu 26-054 and 20 mg fluoxetine in elderly patients with major depressive disorder. Report date: 10 June 2002.
 *Kapser, S., Swart, H. & Andersen, H.F. (2005) Escitalopram in the treatment of depressed elderly patients. *American Journal of Geriatric Psychiatry*, 13, 884-891.
- KHAN2007B** (Unpublished and Published Data)
 Forest Research Institute. Double-blind study of escitalopram in adult patients with major depressive disorder/Tolerability and cost effectiveness of escitalopram in adult patients with major depressive

y 11, 2008.

Jonas, J., Bose, A., Alexopoulos, G., Gommoll, C., Li, D. & Gandhi, C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Poster presented at the 45th Annual Meeting of the American College of Neuropsychopharmacology. Hollywood, FL, US, 3-7 December 2006.

*Khan, A., Bose, A., Alexopoulos, G. S., Gommoll, C., Li, D., Gandhi, C. (2007) Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. *Clinical Drug Investigation*, 27, 481-492.

LEPOLA2003 (Unpublished and Published Data)

Montgomery, S.A., Loft, H., Sanchez, C., Reines, E.H. & Papp, M. (2001) Escitalopram (s-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. *Pharmacology and Toxicity*, 88, 282-286.

Montgomery, S.A., Loft, H. & Reines, E.H. Escitalopram 10 mg/day: effective antidepressant in primary care. Poster presented at the American Psychiatric Association annual meeting, 5-10 May, 2001.

Lundbeck. A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of lu 26-054 and citalopram in outpatients with major depressive disorder (99003). Report date: 17 January, 2001.

*Lepola, U.M., Loft, H. & Reines, H. (2003) Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *International Clinical Psychopharmacology*, 18, 211-217.

MAO2008 (Unpublished and Published Data)

Xian-Janssen Pharmaceutical LTD. A randomised, double-blind, fixed-dose study to compare the efficacy and safety of escitalopram and fluoxetine for the treatment of major depressive disorder (ESC-10123). Report date: 15 September 2004

*Mao, P.X., T., Y.L., Jiang, F., Shu, L., Gu, X., Li, M., Qian, M., Ma, C., Mitchell, P.B. & Cai, Z.J. (2008) Escitalopram in major depressive disorder: a multicentre, randomized, double-blind, fixed-dose, parallel trial in a Chinese population. *Depression and Anxiety*, 25, 46-54

MOORE2005 (Published Data Only)

Moore, N., Verdoux, H. & Fantino, B. (2005) Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *International Clinical Psychopharmacology*, 20, 131-137.

NIERENBERG2007B (Unpublished and Published Data)

Eli Lilly study F1J-US-HMCR, CT Registry ID# 7978. Duloxetine versus escitalopram and placebo in the treatment of patients with major depression. ClinicalTrialsResults.org [date site accessed 13.06.08].

Clayton, A., Kornstein, S., Prakash, A., Mallinckrodt, C., & Wohlreich, M. (2007). Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. *Journal of Sexual Medicine*, 4, 917-929.

Pigott, T. A., Prakash, A., Arnold, L. M., Aaronson, S. T., Mallinckrodt, C. H., & Wohlreich, M. M. (2007). Duloxetine versus escitalopram and placebo: An 8-month, double-blind trial in patients with major depressive disorder. *Current Medical Research and Opinion*, 23, 303-318.

*Nierenberg, A. A., Greist, J. H., Mallinckrodt, C. H., Prakash, A., Sambunaris, A., Tollefson, G. D. et al. (2007). Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Current Medical Research & Opinion*, 23, 401-416.

SCT-MD-02 (Unpublished Data Only)

Forest Laboratories Inc. Flexible dose comparison of the safety and efficacy of lu 26-054, citalopram, and placebo in the treatment of major depressive disorder (SCT-MD-02). Report date: December 5, 2000.

SCT-MD-09 (Unpublished Data Only)

Forest Research Institute. Double-blind comparison of the effects of lu 26-054 (escitalopram) and fluoxetine on sleep in depressed patients (SCT-MD-09). Report date: July 27, 2004.

SCT-MD-16 (Unpublished Data Only)

Forest Research Institute. Flexible dose comparison of the safety and efficacy of escitalopram and fluoxetine in the treatment of major depressive disorder (SCT-MD-16). Report date: July 26, 2004.

SCT-MD-26 (Unpublished Data Only)

Ninan, P.T., Ventura, D., Wang, J & Lenz, S. Escitalopram in the treatment of severe depression. Poster presented at the 13th World Congress of Psychiatry, September 10-15 2005, Cairo, Egypt.

*Forest Research Institute. Two-week double-blind placebo controlled study of escitalopram in the treatment of severe major depression. Report date: November 26, 2003.

SCT-MD-27 (Unpublished Data Only)

Alexopoulos, G., Gordon, J. & Zhang, D. A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder. Poster presented at the 43rd Annual Meeting of the American College of Neuropsychopharmacology, December 12-16, 2004, San Juan, Puerto Rico.

*Forest Research Institute. A double-blind flexible dose comparison of escitalopram sertraline and placebo in the treatment of major depressive disorder. Report date: February 7, 2005

VENTURA2007 (Unpublished and Published Data)

Forest Research Institute. Randomized, double-blind comparison of a fixed dose of escitalopram (10 mg/day) and an optimal dosing regimen of sertraline (50-200 mg/day) in the treatment of major depressive disorder (SCT-MD-18). Report date: November 14, 2003.

Alexopoulos, G.S., Privitera, W., Ventura, D., Bose, A. & Wang, Q. Double-blind comparison of escitalopram 10mg/day and optimally-dosed sertraline 50-200 mg/day in the treatment of major depressive disorder. Poster presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, December 7-11, 2003, San Juan, Puerto Rico.

*Ventura, D., Armstrong, E.P., Skrepnek, G.H. & Erder, M.H. (2007) Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. *Current Medical Research and Opinion*, 23, 245-250.

WADE2007 (Unpublished and Published Data)

Lundbeck. A double-blind, randomised, multi-centre, comparative study of escitalopram and duloxetine in outpatients with major depressive disorder (10990). Report date: 10 September 2007.

*Wade, A., Gembert, K., & Florea, I. (2007). A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. *Current Medical Research & Opinion*, 23, 1605-1614.

YEVTUSHENKO2007 (Published Data Only)

Yevtunshenko, V.Y., Belous, A.I., Yevtushenko, Y.G., Gusinin, S.E., Buzik, O.J. & Agibalova, T.V. (2007) Efficacy and tolerability of escitalopram versus citalopram in major depressive disorder: a 6-week, multicentre, prospective, randomized, double-blind, active-controlled study in adult outpatients. *Clinical Therapeutics*, 29, 2319-2332

References of Excluded Studies

10423 (Unpublished Data Only)

Casas. Effects of escitalopram versus reboxetine on somatic and visceral sensitivity in MDD patients: double-blind randomized, parallel, clinical trial. (Spain).

10778 (Unpublished Data Only)

Mendelwicz. A naturalistic study of the efficacy and safety of escitalopram in treatment resistant depression. (Belgium).

11438A (Unpublished Data Only)

Kennedy. Memory functioning and antidepressant treatment: a randomized controlled trial comparing escitalopram and bupropion XL. (Canada).

12104 (Unpublished Data Only)

Blier. Randomized controlled trial of monotherapy with escitalopram or bupropion versus combination therapy in MDD. (Canada).

99812 (Unpublished Data Only)

Lundbeck. An open, multicenter, prospective, randomised study assessing the impact of treatment information on treatment outcome and testing biochemical and symptom-related response predictors in depressed out-patients treated with CipraleX.

ANDERS2008 (Published Data Only)

Anders, M., Tuma, I. & Rösslerova, H. (2008) A surveillance study of escitalopram treatment of depressed patients. *Expert Opinion Pharmacotherapy*, 9, 1-6.

AUQUIER2003 (Published Data Only)

Auquier, P., Robitail, S., Llorca, P.M. & Rive, B. (2003) Comparison of escitalopram and citalopram efficacy: a meta-analysis. *International Journal of Psychiatry in Clinical Practice*, 7, 259-268

BANDELOW2007 (Published Data Only)

Bandelow, B., Andersen, H.F. & Dolberg, O.T. (2007) Escitalopram in the treatment of anxiety symptoms associated with depression. *Depression and Anxiety*, 24, 53-61

BAUNE2007 (Published Data Only)

Baune, B. T., Caliskan, S., & Todder, D. (2007). Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. *Human Psychopharmacology*, 22, 1-9.

BECH2006B (Published Data Only)

Bech, P., Andersen, H.F. & Wade A (2006) Effective dose of escitalopram in moderate versus severe DSM-IV major depression. *Pharmacopsychiatry*, 39, 128-134

BERMAN2007 (Published Data Only)

Berman, R. M., Marcus, R. N., Swanink, R., McQuade, R. D., Carson, W. H., Corey-Lisle, P. K. et al. (2007). The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*, 68, 843-853.

BOUFFARDposter (Published Data Only)

Bouffard, B., Kennedy, S.H., Ravindran, L., Styra, R & McIntyre, R.S. Memory impairment and antidepressant treatment: a randomized controlled trial comparing escitalopram & bupropion-XL preliminary report.

147

- BRETLAU2008** (Published Data Only)
Bretlau, L.G., Lunde, M., Lindberg, L., Unden, M., Dissing, S. & Bech, P. (2008) Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry*, 41, 41-47
- BURKEposter** (Published Data Only)
Burke, W.J., Bose, A., Wang, J. & Stahl, S.M. Switching depressed patients from citalopram to escitalopram is well tolerated and effective. Poster presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, Dec 7-11 2003, San Juan Puerto Rico.
- CHOKKAinpress** (Unpublished Data Only)
Lundbeck. An open multicentre prospective naturalistic phase iv investigation of the outcome of depressed patients treated with escitalopram in canada (99915). Report date: 10 December 2007.
*Chokka, P. & Legault, M. (2008) Escitalopram in the treatment of major depressive disorder in primary care settings: an open-label trial. *Depression & Anxiety*, 25, E173-E181.
- EINARSON2004** (Published Data Only)
Einarson, T.R. (2004) Evidence based review of escitalopram in treating major depressive disorder in primary care. *International Clinical Psychopharmacology*, 19, 305-310
- FANTINO2007** (Published Data Only)
Fantino, B., Moore, N., Verdoux, H. & Auray, J.P. (2007) Cost-effectiveness of escitalopram vs. citalopram in major depressive disorder, *International Clinical Psychopharmacology* 2007, 22, 107-115
- FERNANDEZ2005** (Published Data Only)
Fernandez, J.L., Montgomery, S. & Francois, C. (2005) Evaluation of the cost effectiveness of escitalopram versus venlafaxine xr in major depressive disorder. *Pharmacoeconomics*, 23, 155-167.
- GERGELposter** (Unpublished Data Only)
Gergel, I., Hakkarainen, H., Zornberg, G. & Korotzer, A. Escitalopram is a well tolerated SSRI. Poster presented at the 155th Annual Meeting of the American Psychiatric Association, May, 18-23 2002, Philadelphia, PA, US.
- GORMAN2002** (Published Data Only)
Gorman, J.M., Korotzer, A. & Su, G. (2002) Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectrums*, 7, 40-44
- GUPTAposter** (Unpublished Data Only)
Gupta, S. & Sanchez, C. Escitalopram, a new treatment for depression and anxiety. Poster presented at the 155th Annual Meeting of the American Psychiatric Association, May 18-23, 2002, Philadelphia, PA, US.
- KARP2008** (Published Data Only)
Karp, J.F., Whyte, E.M., Lenze, E.J., Dew, M.A., Begley, A., Miller, M.D. & Reynolds, C.F. (2008) Rescue pharmacotherapy with duloxetine for selective serotonin reuptake inhibitor nonresponders in late-life depression: outcome and tolerability. *Journal of Clinical Psychiatry*, 69, 457-463
- KASPER2006** (Unpublished and Published Data)
Kasper, S., Lemming, O.M. & Swart, H. de. (2006) Escitalopram in the long-term treatment of major depressive disorder in elderly patients. *Neuropsychobiology*, 54, 152-159.
Lundbeck. An open, long-term, safety extension study of lu 26-054 in the treatment of major depressive disorder in elderly patients (99258). Report date: 29 April 2005.
- KASPER2006A** (Published Data Only)
Kasper, A., Spadone, C., Verpillat, P & Angst, J. (2006) Onset of action of escitalopram compared with other antidepressants: results of a pooled analysis. *International Clinical Psychopharmacology*, 21, 105-110
- KENNEDY2006** (Published Data Only)
Kennedy, S.H., Andersen, H.F. & Lam, R.W. (2006a) Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *Journal of Psychiatry and Neuroscience*, 31, 122-131

- KHAN2004** (Published Data Only)
Khan, M.N.S. (2004) Comparison of escitalopram a new SSRI with TCA, clomipramine in major depressive disorder: a double blind study. *Pakistan Journal of Medical Science*, 20, 238-241
- KULP2005** (Published Data Only)
Kulp, W., von d., Greiner, W. (2005) Cost-effectiveness of outpatient treatment in depressive patients with escitalopram in Germany. *European Journal of Health Economics*, 6, 317-321.
- LADER2005** (Published Data Only)
Lader, M., Andersen, H.F. & Baekdal, T. (2005) The effect of escitalopram on sleep problems in depressed patients. *Human Psychopharmacology*, 20, 349-354.

148

- LAM2006** (Published Data Only)
Lam, R.W. & Andersen, H.F. (2006) The influence of baseline severity on efficacy of escitalopram and citalopram in the treatment of major depressive disorder: an extended analysis. *Pharmacopsychiatry*, 39, 180-184.
- LAM2008** (Published Data Only)
Lam, R.W., Andersen, H.F. & Wade, A.G. (2008) Escitalopram and duloxetine in the treatment of major depressive disorder: a pooled analysis of two trials. *International Clinical Psychopharmacology*, 23, 181-187.
- LANCON2006** (Published Data Only)
Lançon, C., Sapin, C., Note, I., & Fariße, J. (2006) Comparison of escitalopram and citalopram in outpatients with severe MDD: a prospective, naturalistic, eight-week study. *International Journal of Psychiatry in Clinical Practice*, 10, 131-137.
- LANCON2007** (Published Data Only)
Lancon, C., Verpillat, P., Annemans, L., Despiegel, N. & Francois, C. (2007) Escitalopram in major depressive disorder: clinical benefits and cost effectiveness versus citalopram. *International Journal of Psychiatry in Clinical Practice*, 11, 44-52.
- LEINONEN2007** (Unpublished and Published Data)
*Leinonen, E. & Niemi, H. (2007) The influence of educational information on depressed outpatients treated with escitalopram: a semi-naturalistic study. *Nordic Journal of Psychiatry*, 61, 109-114.
Lundbeck. An open, multicentre, prospective, randomised study assessing the impact of educational information on treatment outcome in depressed out-patients treated with CipraleX. Report date: 21 December 2004.
- LI2006C** (Published Data Only)
Li, J., Shen, W.W., Liu, Y., Xu, L., Liu, S.M., Kuang, W.H. (2006) The effectiveness and safety of escitalopram in the treatment of major depression: A randomized double-blind active-drug controlled trial. *Chinese Journal of Evidence-Based Medicine*, 6, 552-556.
- LLORCA2005** (Published Data Only)
Llorca, P.M., Azorin, J.M., Despiegel, N. & Verpillat, P. (2005) Efficacy of escitalopram in patients with severe depression: a pooled analysis. *International Journal of Clinical Practice*, 59, 268-275
- LYDIARDposter** (Unpublished Data Only)
Effects of escitalopram on anxiety symptoms in depression. Poster presented at the Annual Meeting of the American Psychiatric Association, May 5-10, 2001, New Orleans, LA, US.
- MALLINCKRODT2007** (Published Data Only)
Mallinckrodt, C.H., Prakash, A., Houston, J.P., Swindle, R., Detke, M.J. & Fava, M. (2007) Differential antidepressant symptom efficacy: placebo-controlled comparisons of duloxetine and SSRIs (fluoxetine, paroxetine, escitalopram). *Neuropsychobiology*, 56, 73-85.
- MOHAMED2006** (Published Data Only)
Mohamed, S., Osatuke, K., Aslam, M. & Kasckow, J. (2006) Escitalopram for comorbid depression and anxiety in elderly patients: a 12-week, open-label, flexible-dose, pilot trial. *American Journal of Geriatric Pharmacotherapy*, 4, 201-209.
- MOLLER2007** (Published Data Only)
Moller, H.J., Langer, S. & Schmauß, M. (2007) Escitalopram in clinical practice: results of an open-label trial in outpatients with depression in a naturalistic setting in Germany. *Pharmacopsychiatry*, 40, 53-57.
- MONTGOMERY2006** (Published Data Only)
Montgomery, S.A. & Andersen, H.F. (2006) Escitalopram versus venlafaxine XR in the treatment of depression. *International Clinical Psychopharmacology*, 21, 297-309.
- MONTGOMERYposterA** (Unpublished Data Only)
Escitalopram offers early separation from placebo in the treatment of depression. Presented at the 15th ECNP Congress, October 5-9 2002, Barcelona, Spain.
- MONTGOMERYposterB** (Unpublished Data Only)
Montgomery, S.A., Durr-Pal, N., Loft, H. & Nil, R. Escitalopram prevents relapse in patients suffering from social anxiety disorder (SAD). Poster presented at the 155th Annual Meeting of the

American Psychiatric Association, may 18-23 2002, Philadelphia, PA, US.

OLIE2007 (Unpublished and Published Data)

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

Lundbeck. An open multicentre prospective phase IV study assessing the efficacy and safety of Escitalopram in depressed patients with or without concomitant anxiety. Report date: 23 June 2005.

149

PAPAKOSTAS2007C (Published Data Only)

Papakostas, G.I., Montgomery, S.A., Thase, M.E., Katz, J.R., Krishen, A. & Tucker, V.L. (2007) Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *Journal of Clinical Psychiatry*, 68, 1907-1912.

PEC-S-08-00967 (Published Data Only)

A pharmacoeconomic comparison of escitalopram and duloxetine in the treatment of major depressive disorder using United Kingdom cost data. Report date: 30 January 2006.

PINTO2007 (Unpublished and Published Data)

Lundbeck. Open label Multicenter Study of Clinical Efficacy and Tolerability of Escitalopram in Indian Patients with Major Depressive Disorder (10083). Report date: August 2003

*Pinto, C., Trivedi, J.K., Vankar, G.K., Sharma, P.S.V.N. & Narasimha, V. (2007) An open-label multicentric study of the tolerability and response to escitalopram treatment in indian patients with major depressive disorder. *Journal of the Indian Medical Association*, 105, 364-369.

RUSH2005 (Unpublished and Published Data)

Forest Research Institute. Escitalopram Effects on Quality of Life (SCT-MD-25). Report date: February 22 2005.

*Rush, A.J. & Bose, A. (2005) Escitalopram in clinical practice: results of an open-label trial in a naturalistic setting. *Depression and Anxiety*, 21, 26-32.

SANCHEZposter (Unpublished Data Only)

Sanchez, C. & Owens, M. Effect of SSRI, Escitalopram, and non-selective 5-HT reuptake inhibitors in an animal model of pain. Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, Dec 7-11 2003, San Juan, Puerto Rico.

SCHMITT2006A (Unpublished and Published Data)

An open multicentre prospective study assessing the safety and efficacy of SeroplexB (escitalopram), 10 to 20 mg/day, as continuation treatment of SeropramB i.v. in patients suffering from Major Depressive Disorder (99863). Report date: September 2004.

*Schmitt, L., Tonnoir, B. & Arbus C. (2006) Safety and efficacy of oral escitalopram as continuation treatment of intravenous citalopram in patients with major depressive disorder. *Neuropsychobiology*, 54, 201-207.

SCT-MD-24 (Unpublished Data Only)

Forest Research Institute. A Double-blind Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Major Depressive Disorder in Diabetic Patients (SCT-MD-24). Report date: July 17, 2007.

SCT-MD-31 (Unpublished Data Only)

Forest Research Institute. A double-blind flexible dose comparison of escitalopram, venlafaxine, XR and placebo in the treatment of generalized anxiety disorder. Report date: June 24, 2005.

SCT-MD-35 (Unpublished Data Only)

Tsai, J., Tourkodimitris, S. & Bose, A. Low-dose combination of escitalopram and bupropion is an effective treatment for depression in adult outpatients. Poster presented at 161st Annual Meeting of the American Psychiatric Association, Washington DC, May 3-8, 2008.

*Forest Laboratories inc. Fixed-dose comparison of escitalopram combination in adult patients with major depressive disorder.

WADE2005 (Published Data Only)

Wade, A.G., Toumi, I. & Hemels, M.E. (2005) A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK. *Current Medical Research Opinion*, 21, 631-641.

WADE2005A (Published Data Only)

Wade, A.G., Toumi, I. & Hemels, M.E. (2005) A Pharmacoeconomic Evaluation of Escitalopram Versus Citalopram in the Treatment of Severe Depression in the United Kingdom. *Clinical Therapy*, 27, 486-496.

WADE2006E (Unpublished and Published Data)

Lundbeck. An open long-term safety follow-up study of Lu 26-054 in the treatment of Major Depressive Disorder (99002). Report date: 12 June 2002.

*Wade, A., Despiegel, N. & Reines, E.H. (2006) Escitalopram in the long-term treatment of major depressive disorder. *Annals of Clinical Psychiatry*, 18, 83-89.

WAGNER2006 (Published Data Only)

Wagner, K.D., Jonas, J., Findling, R.L., Ventura, D. & Saikali, K. (2006) A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 280-288.

WINKLER2007 (Published Data Only)

Winkler, D., Pjrek, E., Moser, U. & Kasper, S. (2007) Escitalopram in a working population: results from an observational study of 2378 outpatients in Austria. *Human Psychopharmacology*, 22, 245- 150 251.

Moclobemide - studies in previous guideline

Characteristics of included studies

	Duration: 4 weeks. Analysis: ITT	300.4. HRSD-24≥20. Mean baseline HRSD-24 score: moclobemide -41.7 placebo=36.3.	mean=297.2mg) 2. Placebo	3. Patients reporting side effects.	
Duarte1996 Y O I	Allocation: Random (no details). Duration: 6 weeks.	Outpatients.N=42,17 female. Age:21-60 Diagnosis: DSM-III-R major depressive episode & DSM-III-R dysthymia &	1. Moclobemide (300mg) 2. Fluoxetine (20mg)	1. HRSD-17 mean endpoint scores 2. Non-responders (≥50% decrease in HRSD-17)	B

	Analysis: ITT	HRSD-17 \geq 16. Mean HRSD-17 score=24		3. Patients reporting side effects.		
Gattaz1995 Y I C	Allocation: Random (no details). Analysis: Completer Duration: 4 weeks	Inclusion Criteria: DSM-III-R major depression, and HMD 18+. Age: 18-65. N=70, HMD analysis: N=52 Country: Germany. Setting: Inpatients.	1. Fluoxetine 2. Moclobemide (300mg, up to 600mg, mean=344mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
Geerts1994 Y M C	Allocation: Random (no details). Analysis: Completer Duration: 6 weeks	Inpatients & outpatients. Diagnosis: DSM-III-R major depression without psychotic features. HRSD-17 $>$ =17. Age: 18 - 70. N=49 (completers N=28).	Fluoxetine versus moclobemide (300mg, up to 600mg on day 22)	1. HRSD-17 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
Guelfi1992 Y I I	Allocation: Random (no details). Duration: 6 weeks (+ 3-15 day washout). Analysis: ITT	Inpatients. N=135 (ITT:N=129). Age:18-65, 89 female. Diagnosis: ICD-9 296.1 or 296.1, DSM-III major depressive episode + MADRS \geq 25. Mean HRSD-17 scores: moclobemide=27.3; clomipramine=27.7	1. Moclobemide (300-600mg, mean=462mg) 2. Clomipramine (100-200mg, mean=146mg)	1. HRSD mean change scores 2. Non- responders (\geq 50% decrease in MADRS + MADRS $<$ 20) 3. Leaving the study early 4. Leaving the study early due to side effects	7 patients taking adjunctive lithium (5 in mocl group and 2 & 2 in clomipramine)	B
Hebenstreit 90 Y M I	Allocation: Random (no details). Duration: 4 weeks. Analysis: ITT	Inpatients & outpatients. N=381. Age:18-80, 284 female. Diagnosis: DSM-III major depressive disorder + HRSD-21 \geq 17. Further diagnosis by ICD-09: endogenous unipolar depression (49.9%), endogenous bipolar depression(8.7%), neurotic/reactive depression(22.8%), organic symptomatic depression(15.5%), other depression (3.1%). Mean baseline HRSD: moclobemide=25, imipramine=24.3.	1. Moclobemide (300-600mg) 2. Imipramine (100-200mg)	1. Non- responders (patients not achieving \geq 50% decrease in HRSD)	Extracted data for n= 277 patients with endogenous unipolar depression or neurotic/reactive depression.	B
Hell1994 Y I C	Allocation: Random (no details). Duration: 4 weeks. Analysis: Completer	Inpatients. N=51. Age:18-70, mean=49.8 /48.2 Diagnosis: ICD-9 unipolar endogenous depression (60.8%), bipolar endogenous depression (3.9%), neurotic depression(17.7%), reactive depression (15.7%) or dysthymia (2%) & HRSD-21 \geq 21. Mean baseline HRSD: moclobemide=28.1, imipramine=27.2.	1. Moclobemide (minimum 450mg, mean=577.9mg) 2. Imipramine (75-150mg, mean=176.2mg)	1. HRSD mean endpoint scores	Extracted data for 33 patients with endogenous depression only.	B

Jouvent 1998 Y I I	Allocation: Random (no details). Duration: 4 weeks (+ 4-7 day washout). Analysis: ITT	Inpatients. N=124. Age: 18-65, mean = 44.5. Diagnosis: DSM-III major depressive episode + MADRS>25. Mean baseline MADRS scores: moclo- bemide=33.1, clomipramine=32.00	1. Moclobemide (450mg) 2. Clomipramine (150mg)	1. Leaving the study early	Efficacy data at endpoint/4 weeks not given.	B
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Koczkas 1989 Y M C	Allocation: Random (no details). Duration: 6 weeks. Analysis: Completer	In-/outpatients.N=62. Age:19-73, mean =49.5, 42 females. Diagnosis: DSM-III major depressive disorder + HRSD-17 >=15. Mean baseline HRSD-17 scores: moclobemide=22.3, clomipramine=22.8	1. Moclobemide (300mg) 2. Clomipramine (150mg)	1. Non-remitters (patients not achieving HRSD<=8) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B
KraghSoren- sen95 Y PI	Allocation: Random (no details).Duration : 6 weeks (+7 day washout). Analysis: ITT (LOCF)	Primary care patients. N=142. Age: 19-70. Diagnosis: DSM-III major depression and HRSD-17>=11 (for 46 patients 11=<HRSD<=15, for 96 patients HRSD>=16)	1. Moclobemide (400mg) 2. Clomipramine (150mg)	1. Non-remitters (patients not achieving HRSD<=8) 2. Leaving the study early 3. Leaving the study early due to side effects		B
Lapierre 1997 Y O I	Allocation: Random (no details). Duration: 6 weeks (+7 day washout). Analysis: ITT	Outpatients. N=128. Age: 18-64, mean=41.3/40.2, 95 female. Diagnosis: DSM-III major depressive disorder and HRSD-17>=18.	1. Moclobemide (200-600mg, mean=440mg) 2. Fluoxetine (20mg every other day - 40mg daily, mean=35mg daily)	1. Non-remitters (patients not achieving HRSD<10 and >=50% decrease in HRSD) 2. Non- responders (patients not achieving >=50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects		B
Larsen1989 Y M C	Allocation: Random (no details). Duration: 6 weeks. Analysis: Completer	In-/outpatients. N=60. Age: 25 -76, 40 female. Diagnosis: DSM-III major depressive disorder + HRSD-17>=15. Mean baseline HRSD scores: moclobemide = 17.5, clomipramine=17.8, placebo=18.3.	1. Moclobemide (300mg) 2. Clomipramine (150mg) 3. Placebo	1. Non-remitters (patients not achieving HRSD<=8) 2. Leaving the study early 3. Leaving the study early due to side effects		B
Lecrubier 1995 Y O I	Allocation: Random (no details). Duration :6 weeks Analysis: ITT	Outpatients. N=191. Age: 18-65, 116 female. Diagnosis: DSM-III major depressive episode and HRSD-17>=17. Mean baseline HRSD scores: moclobemide=23.7, clomipramine=24	1. Moclobemide (300-600mg, mean=488mg) 2. Clomipramine (75-150mg, mean=116mg)	1. Non- responders (patients not achieving HRSD<10 or >=50% decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects		B
Nair1995 E M I	Allocation: Random (no details). Duration: 7 weeks (+ 4-14 day washout). Analysis: ITT(LOCF)	In-/outpatients.N=109. Age:60 -90, 77 female. Diagnosis: DSM-III major depressive episode + HRSD-17>=18. Mean baseline HRSD scores: moclobemide = 23, nortriptyline=23.5, placebo=24.	1. Moclobemide (400mg) 2. Nortriptyline (75-100mg) 3. Placebo	1. Non-remitters (patients not achieving HRSD<10) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects		B

Newburn 1990 Y O C	Allocation: Random (no details). Duration: 6 weeks. Analysis: completer.	Inpatients (n=3) and outpatients. N=49. Age: 20-64, mean=37, 34 female. Diagnosis: DSM-III major depressive episode and HRSD>=17	1. Moclobemide (200- 400mg) 2. Amitriptyline (125- 150mg) 3. Placebo	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects		B
Ose1992 Y	Allocation: Random	Outpatients.N=68. Age:24-79, mean=59	1. Moclobemide (300	1. Leaving the study early		B

O I	(no details). Duration: 4 weeks. Analysis: ITT	/50, 39 female. Diagnosis: DSM-III major depressive episode. 26≥ HRSD-17≥15. Median HRSD scores=21.	500mg) 2. Placebo	2. Leaving the study early due to side effects 3. Patients reporting side effects		
Reynaert 1995 Y M C	Allocation: Random (no details). Analysis: Completer Duration: 6 weeks	Inpatients & outpatients. Diagnosis: DSM-III-R major depression, HRSD-17>=16. Age: mean=47. N=101, HAMD analysis: N=80. Country: Belgium	Fluoxetine versus moclobemide (300mg, up to 600mg on day 23)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	[Geddes2002]	B
Silverstone 94 Y ? ?	Allocation: Random (no details). Duration 6 weeks. Analysis: Evaluable patients (Undefined)	Setting unclear. N=249 (Evaluable patients N=207). Age: 18-65, 138 female. Diagnosis: DSM-III major depressive episode + HRSD-17≥16. Mean baseline HRSD scores: moclobemide =24.9, imipramine=25.4, placebo=24.4.	1. Moclobemide (450mg) 2. Imipramine (150mg) 3. Placebo	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving >=50% decrease on HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects		B
Tanghe1997 Y II	Allocation: Random (no details). Duration: 4 weeks Analysis: ITT	Inpatients. N=59. Age 18-69, mean = 43+12. Diagnosis: DSM-III-R major depressive episode and treatment resistance to >= 2 antidepressants.	1. Amitriptyline (up to 280mg) 2. Amitriptyline + moclobemide 3. Moclobemide (200-600mg)	1. MADRS mean endpoint scores	Only extracted data for 1 and 3.	B
Versiani 1989A	Allocation: Random (no details). Duration: 6 weeks Analysis: ITT (patients completing 7 days treatment)	Outpatients. N=490 (ITT: N=467). Age: 18-67, mean=44/42.373 female. Diagnosis: DSM-III major depressive episode + HRSD-21≥17. Mean baseline HRSD-17 scores: moclobemide=26, imipramine=25.5, placebo=25.4	1. Moclobemide (300-600mg, mean=509mg) 2. Imipramine (100-200mg, mean=159mg) 3. Placebo	1. HRSD-17 mean change scores 2. Non-responders (>=50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects		B
Williams 1993 Y M C	Allocation: Random (no details). Analysis: Completer (>=3 weeks treatment) Duration: 6 weeks	Inclusion Criteria: DSM-III-R major depression, 17+ on 21-item HAMD. Age: 20-86. N=122, HAMD analysis: N=92. Country: New Zealand. Setting: Not Clear.	Fluoxetine versus moclobemide (150?mg -> 300-600mg at day 15, mean at week 6 =505.1mg)	1. HRSD-21 mean endpoint scores* 2. Leaving the study early 3. Leaving the study early due to side effects	* Unpublished data. [Geddes2002]	B

Characteristics of excluded studies

Study	Reason for exclusion
Allain1992	No extractable data

Bocksberger1993	Some patients were receiving adjunctive lithium, numbers not specified [Geddes2002*]
Botte1992	Only 25% of patients were diagnosed with endogenous depression; other diagnoses: dysthymia (60%), 'others' (15%)

Casacchia1989	Only 75% patients were diagnosed with major depression (25% were diagnosed with dysthymia, 5% with bipolar disorder)
Cassano2000	Not a double blind RCT
Cattiez1990	Diagnostic inclusion criteria was DSM-III minor depression [Sub-typed as: unspecified (3%), neurotic (3%), reactive (3%), major depression (2%), anxious depression (3%), dysthymia (35%), endogenous (51%)]
Civeira1990	Only 66% patients were diagnosed with major depression [other diagnoses: depression unspecified, dysthymia and retarded depressive syndrome]
Classen1990	No mention of randomisation
Clunie2001	Abstract only; unable to find fully published details
DeVanna1990	No continuous data; number of patients allocated to each treatment group is not specified in either of the two studies described, therefore there is no interpretable dichotomous data either
Dierick1990	Inadequate diagnosis of depression
Dunningham1994	Criteria for entry included a diagnosis of bipolar disorder, number of patients with bipolar not specified
Evans1992	An unspecified number of patients were receiving supportive psychotherapy
Funke1990	Inadequate diagnosis of depression; not clear whether randomisation took place
Gabelic1990	Inadequate diagnosis of depression; unable to ascertain whether patients received an adequate dose of either moclobemide or desipramine
Gacgoud1992	Abstract only; unable to obtain full trial report
Gachoud1994	Most patients in the maprotiline group were receiving an inadequate dose (mean=84mg); an unspecified number of patients were receiving adjunctive lithium
Glue1993	Inadequate diagnosis of depression [inclusion criteria was HRSD-17 baseline score > 17 "corresponding to criteria of 'major depression'"]
Kok1995	30% patients were diagnosed with dysthymia; inadequate daily dose of imipramine: 75mg
Kragh-Sorensen1993	Not a full trial report; inadequate diagnosis of depression
Larsen1984	Only 58% patients diagnosed with DSM-III major depression [42% diagnosed with DSM-III atypical depression]; only 63% patients diagnosed with ICD-9 unipolar depression
Larsen1991	Only 60% patients were diagnosed with unipolar, major depression [other diagnoses: adjustment disorder (17%), atypical depression (10%), bipolar depression (6%), dysthymia (7%), atypical bipolar depression (<1%)]
Laux1989	22.5% patients were diagnosed with bipolar depression
Laux1990	No mention of randomisation or use of formal diagnostic criteria
Lingjaerde1995	Diagnosis of major depression did not form part of the study's inclusion criteria; diagnoses were performed post-randomisation, only 60-66% patients had major depression.
Lonnqvist1994	Only 60.76% patients had major depression; 17% diagnosed with dysthymia, 11% with adjustment disorder [Geddes2002*]
Macher1992	Inadequate diagnosis of depression

Philipp2000A	Not a double blind RCT
Radat1996	Irrelevant comparison for this review (moclobemide 300mg vs moclobemide 450mg vs moclobemide 600mg)
Rimon1993	Mean daily dose of imipramine was only 100mg (range: 25-175mg) during the last week of the study
Serra1992	Abstract only; inadequate description of diagnostic inclusion criteria
Shen1998	Only available in Chinese, unable to assess eligibility
Shi1999	Only available in Chinese, unable to assess eligibility
Sogaard1999	Only 66.3% patients received an adequate dose of sertraline; 33.7% received only 50mg daily; mean dose was 83.1mg
Steinmeyer1993	Some patients had comorbid psychiatric disorders: schizoid personality disorder, organic/ geriatric psychotic features, residual schizophrenia, chronic alcoholism and schizoaffective psychosis; three patients were receiving adjunctive lithium
Tiller1988	Abstract only, not full trial report; does not specify dose of either drug.
Tiller1990	Inadequate randomisation process; allocation was sequential using matched pairs
Ucha1990	Only 66.7% patients were diagnosed with ICD-9 endogenous depression (unipolar) or neurotic depression (other diagnoses: endogenous depression [bipolar](8.3%), reactive depression (11.1%), other (13.9%)).
Vaz-Serra1994	Only 17.5% patients were diagnosed with MDD (other: dysthymia 60%, adjustment disorder 13.75%, atypical depression 2.5%, no diagnosis 6.25%)
Zhang2001	Only available in Chinese, unable to assess eligibility
Zhao1997	Only available in Chinese, unable to assess eligibility

Older adults sub-analysis

Study	Source review
Alexopoulos00 E O C	Relapse prevention
Cohn1990 E O I	SSRI
Cook1986 E O C	Relapse prevention
Dorman1992 E O E	SSRI
Feighner1985a E O I	SSRI
Georgotas1989 E O C	Relapse prevention
Georgotas86 E O I	Phenelzine
Geretsegger95 E I E	SSRI
Guillibert89 E O ?	SSRI
Harrer99 E O I A	St John's wort

Hutchinson92 E P E	SSRI
Jensen1992 E I	Lithium augmentation

Klysner2002 E O C	Relapse prevention
La Pia1992 E M E	SSRI
Mahapatra97 E M I IR	Venlafaxine
Pelicier1993 E O I	SSRI
Phanjoo1991 E M E	SSRI
Rahman1991 E I E	SSRI
Schatzberg02 E O I	Mirtazapine
Smeraldi98 E M I IR	Venlafaxine
Wilson2003 E P	Relapse prevention

Phenelzine - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Davidson81 Y I C	Allocation: Random (no details) Duration: 3 weeks (+ 7 day placebo washout)	Inpatients. N=49. Diagnosis: Feighner criteria for definite depression, baseline scores: Imipramine - HRSD=26.4+-4.69, Phenelzine - HRSD=28 +-5.96	1. Phenelzine (mean=81+-3 S.E.) 2. Imipramine (mean =144+-6 S.E.)	1. Leaving the study early 2. HRSD mean endpoint scores 3. Leaving the study early due to side effects	Both primary depression and depression secondary to anxiety states were included.	B
Davidson87 Y O C	Allocation: Random (no details) Duration: 5 weeks	Outpatients. N=27, 24 female Diagnosis: RDC major depression	1. Phenelzine (median=75mg) 2. Imipramine (median=150mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Patients were recruited from a pain clinic, a psychosomatic clinic and a mental health clinic.	B
Georgotas86 E O PP	Allocation: Random (no details) Duration: 7 weeks (+7 day placebo washout) Analysis: Endpoint	Outpatients. N = 90, aged 55-76 mean = 65. Diagnosis: RDC Major depressive disorder, HRSD ≥ 16.	1. Phenelzine (15mg -> 30mg on day 4 -> 45mg on day 8, mean = 53.9mg) 2. Nortriptyline (25mg -> 50mg on day 4 -> 75mg on day 8, mean = 79mg 3. Placebo	1. Leaving the study early 2. Non-remitters (patients not achieving HRSD≤10) 3. Leaving the study early due to side effects 4. Patients reporting side effects	Paper used only 75 patients in efficacy analysis and did not include 15 exclu- ded patients in dropout data.	B

Pande1996 Y O I	Allocation: Random (no	Outpatients. N=40. Age: 18-65. Diagnosis: DSM-III-R major depressive	1. Phenelzine (45-90mg) 2. Fluoxetine (20-60mg)	1. Leaving the study early 2. Leaving the study early due to		B
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	details) Duration: 6 weeks (+7 day placebo washout) Analysis: ITT	disorder (38 patients), dysthymia or depressive disorder NOS, HRSD-17 \geq 10 and Columbia criteria for atypical depression		side effects 3. HRSD-17 mean change scores 4. Non-responders (patients not achieving \geq 50% decrease in HRSD) 5. Non-remitters (patients not achieving HRSD $<$ 5 and CGI-I 1 or 2)		
Quitkin1990 Y O I	Allocation: Random (no details) Duration: 6 weeks	Outpatients. N=285. Age: 18-65. Diagnosis: DSM-III or DSM-III-R major depressive disorder. 67.4% patients had atypical features.	1. Phenelzine (60mg up to 90mg) 2. Imipramine or Desipramine (150- 300mg)	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD $<$ 8) 3. HRSD mean endpoint scores	Sample comprises of a subset of the individual patient data supplied by author.	B
Raft1981 ? O ?	Allocation: Random (no details) Duration:5 weeks	Outpatients. N=29. Diagnosis: Definite primary depression according Feighner criteria.	1. Phenelzine (30mg ->90mg at day 12) 2. Amitriptyline (100mg -> 300mg at day 12) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	All patients were recruited from the N.C. Memorial Hospital Pain Clinic.	B
Robinson83 Y O C	Allocation: Random (no details) Duration: 6 weeks	Outpatients. N=130, aged: 19-67 years. Diagnosis: RDC major depressive (71.6%) disorder or probable major depressive disorder(16%) or DSM-III dysthymic disorder or atypical depression (12.4%).	1. Phenelzine (30mg -> 60mg on day 6) 2. Amitriptyline (75mg ->150mg on day 6)	1. HRSD mean change scores 2. Leaving the study early.		B
Swann1997 Y O I	Allocation: Random (no details) Duration: 6 weeks (+7 day placebo run-in)	Outpatients. N=39, 28 female, aged 18- 65. Diagnosis: DSM-III-R non-psychotic major depression, HRSD-21 \geq 20.	1. Phenelzine (mean=58+-15mg) 2. Desipramine (mean=167+-45mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects		B

Vallejo87A Melan YOC	Allocation: Random (no details) Duration: 6 weeks (+7 day placebo washout)	Outpatients. N=34, 24 female. Mean age=44.3+-10.3 Diagnosis: DSM-III major depressive episode with melancholia, HRSD≥16.	1. Phenelzine (30mg->75mg by week 4) 2. Imipramine (100mg ->250mg by week 4)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Published separately from Vallejo87A dysthymic in Spanish.	B
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Characteristics of excluded studies

Study	Reason for exclusion
Agosti1991	No useable data - combined data for 3 active drugs and compared to placebo; 31% patients diagnosed with dysthymia
Clunie2001	Abstract only; unable to find fully published details
Greenblatt1964	Inadequate diagnosis and exclusion criteria - 'All patients admitted with a symptomology of severe depression, regardless of dynamics or specific diagnostic criteria were included...psychoneurotics, manic-depressives, involuntions, schizophrenic reactions, schizoaffective type and a mixed category of character disorders with depression.'
Hamilton1982	Open trial; inadequate diagnosis - 'All the patients would conform to current diagnostic criteria, e.g. the St Louis criteria (Feighner et al, 1972), except that a few of the more seriously disturbed patients would have come for treatment after only 2 or 3 weeks of illness.'
Harrison1985	Sexual functioning analysis only, no useful data
Harrison1986	Sexual functioning analysis only, no useful data
Hutchinson1963	Inadequate diagnosis
Kay1973A	Inadequate diagnosis
Markowitz1985	Study of attrition rates only; inadequate definition of 'completer'; unclear description of RDC diagnoses of depressive disorders
Martin1963	Inadequate diagnosis
Medical Research1965	Inadequate diagnosis
Quitkin1979	Not an RCT
Raskin1972A	Not randomised and inadequate diagnosis
Rees1961	Inadequate diagnosis
Robinson1973	Inadequate diagnosis - 'presence of significant, persistent, and disabling depressive symptomatology'
Rowan1980	Unclear methods of diagnosing depression for inclusion criteria
Vallejo87A Dysth YOC	Patients diagnosed with dysthymia (not concurrent to major depression)
Young1979	Inadequate diagnosis

Acute-phase duloxetine - new studies in the guideline update

Comparisons Included in this Clinical Question

Duloxetine 120 mg vs placebo DETKE2004 ELI LILLY HMAQ GOLDSTEIN2002 PERAHIA2006B	Duloxetine 40 mg vs duloxetine 80 mg ELI LILLY HMAAT-A GOLDSTEIN2004	Duloxetine 40 mg vs placebo ELI LILLY HMAAT-A GOLDSTEIN2004	Duloxetine 60 mg vs duloxetine 120 mg WHITMYER2007
Duloxetine 60mg vs placebo BRANNAN2005A BRECHT2007 DETKE2002 DETKE2002A NIERENBERG2007B RASKIN2007	Duloxetine 80 mg vs duloxetine 120 mg DETKE2004 PERAHIA2006B	Duloxetine 80 mg vs placebo DETKE2004 ELI LILLY HMAAT-A GOLDSTEIN2004 PERAHIA2006B	Duloxetine vs escitalopram KHAN2007B WADE2007
Duloxetine vs fluoxetine ELI LILLY HMAQ GOLDSTEIN2002	Duloxetine vs paroxetine DETKE2004 ELI LILLY HMAAT-A GOLDSTEIN2004 LEE2007 PERAHIA2006B	Duloxetine vs venlafaxine 150 mg ELI LILLY HMBU ELI LILLY HMCQ	Duloxetine vs venlafaxine 75 mg ELI LILLY HMCQ

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BRANNAN2005A Study Type: RCT Type of Analysis: LOCF (at least one post-baseline evaluation) Blindness: Double blind Duration (days): Mean 63 Setting: Outpatients; US (25 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 411 patients screened; 129 did not meet entry criteria or declined	n= 282 Age: Mean 40 Range 18-79 Sex: 98 males 184 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 15; bipolar disorder, schizophrenia, other psychotic disorder; any anxiety disorder as a primary diagnosis within 6 months of study; current and primary Axis II disorder that could interfere with compliance; serious suicidal risk; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy or treatment-resistant depression; primary pain complaint with diagnosis such as arthritis, fibromyalgia, migraine headache or acute injury; >2 abdominal surgeries; serious medical illness; initiating, stopping or changing psychotherapy during study; history of substance misuse within 6 mths of study Notes: Pts had to have Brief Pain Inventory Average Pain score of >= 2 at 2nd visit (pain associated with depression); variable-duration placebo washout Baseline: HAMD-17 (SD) 23.4 (3.5) (dulox), 22.4 (3.4) (pbo) - significant difference	Data Used Leaving treatment early due to side effects Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change Leaving treatment early for any reason - Data not reported Leaving treatment early due to lack of efficacy Data Not Used Weight change - no variability measure Notes: Primary outcome related to pain; dropout data not reported in published paper so taken from report on clinicalstudyresults.org	Group 1 N= 141 Duloxetine. Mean dose 60 mg - 7 weeks active treatment + 2 weeks lead-out phase Group 2 N= 141 Placebo	SIGN: 1+; funding: Eli Lilly (Code HMCB); removed in some analyses as an outlier

<p>Study Type: RCT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; Belgium, Germany, France, Finland, Slovakia</p> <p>Notes: RANDOMISATION: randomised but not details</p> <p>Info on Screening Process: 393 patients screened, no further details</p>	<p>n= 327</p> <p>Age: Mean 50</p> <p>Sex: 86 males 241 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS < 20; Axis I disorder other than MDD, history of bipolar disorder, schizophrenia, other psychotic disorder; any anxiety disorder as a primary diagnosis within 6 mnths of study; current and primary Axis II disorder that could interfere with compliance; serious suicidal risk; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy or treatment-resistant depression; history of substance misuse within 12 mths of study; positive drug screen for drug misuse; no diagnosed pain syndrome</p> <p>Notes: Pts all had at least moderate pain based on BPI-SF score > = 3 on '24-hr average pain' item</p> <p>Baseline: MADRS (SD) 29.9 (4.5) (dul), 29.2 (4.5) (pbo); washout not mentioned</p>	<p>Data Used</p> <p>Number of people reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Weight change</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Data Not Used</p> <p>Response: 50% reduction in MADRS - N unclear</p> <p>Remission: MADRS < 13 - N unclear</p> <p>MADRS mean change - N unclear, no variability measure</p> <p>Notes: N in efficacy sample (taking >= 1 dose study meds and 1 post-baseline assessment) not given in published paper, so taken from clinicaltrialresults.org; primary outcome measure pain</p>	<p>Group 1 N= 162</p> <p>Duloxetine. Mean dose 60 mg - 8 weeks' treatment + 2 weeks' tapering</p> <p>Group 2 N= 165</p> <p>Placebo</p>	<p>SIGN 1+; funding Eli Lilly (code HMDH)</p>
<p>DETKE2002</p> <p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 63</p> <p>Setting: Outpatients; US 21 sites</p> <p>Notes: RANDOMISATION: randomised but no details</p> <p>Info on Screening Process: 367 people screened, 100 failed to meet inclusion criteria or declined</p>	<p>n= 267</p> <p>Age: Mean 41</p> <p>Sex: 83 males 184 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 15; Axis I disorder other than MDD; any anxiety disorder as a primary diagnosis within 6 months of study; current and primary Axis II disorder that could interfere with compliance; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy or treatment-resistant depression; initiating, stopping or changing psychotherapy during study; history of substance misuse within 12 months of study positive drug screen for drug misuse</p> <p>Baseline: HAMD-17 (SD) 20.33 (3.39) (dul), 20.46 (3.39) (pbo)</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Number with decreased libido</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Notes: Remission and response based on LOCF data</p>	<p>Group 1 N= 128</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 139</p> <p>Placebo</p>	<p>SIGN 1+; funding Eli Lilly (code HMBH-B); variable-duration placebo washout</p>
<p>DETKE2002A</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 63</p> <p>Setting: Outpatients; US 18 sites</p> <p>Notes: RANDOMISATION: randomised but no details</p> <p>Info on Screening Process: 341, 96 failed to meet entry criteria or declined to participate</p>	<p>n= 245</p> <p>Age: Mean 42</p> <p>Sex: 82 males 163 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 15; Axis I disorder other than MDD; any anxiety disorder as a primary diagnosis within 6 months of study; current and primary Axis II disorder that could interfere with compliance; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy or treatment-resistant depression; initiating, stopping or changing psychotherapy during study; history of substance misuse within 12 months of study positive drug screen for drug misuse</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change - no variability measure</p> <p>Leaving treatment early due to side effects</p> <p>Number with palpitation</p> <p>Number with decreased libido</p> <p>Number with chest pain</p> <p>Number with abnormal ejaculation</p> <p>Number of people reporting side effects</p> <p>Data Not Used</p> <p>Leaving treatment early for any reason - Not reported</p>	<p>Group 1 N= 123</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 122</p> <p>Placebo</p>	<p>SIGN 1+; funding Eli Lilly (code HMBH-A); variable-duration placebo washout; removed in some analyses as an outlier</p> <p style="text-align: right;">161</p>
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		Notes: No SDs for HAMD in published paper so used data from report on clinicaltrialsresults.org		
DETKE2004				
<p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Followup: 6-mth continuation phase</p> <p>Setting: Outpatients; country unclear (21 sites)</p> <p>Notes: RANDOMISATION: randomised not details</p> <p>Info on Screening Process: 440 people screened, 45 failed to meet entry criteria, 28 dropped out before randomisation due to adverse events (4), satisfactory response (1), lack of efficacy (2), personal conflict (14), physician decision (2), protocol violation (5)</p>	<p>n= 367</p> <p>Age: Mean 43</p> <p>Sex: 100 males 267 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 15; Axis I disorder other than MDD; any anxiety disorder as a primary diagnosis within 6 months of study; previous diagnosis of bipolar disorder, schizophrenia, other psychotic disorder; serious suicidal risk; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy; serious medical illness; history of substance misuse within 12 months of study</p> <p>Notes: Continuation phase entry criteria: >= 30% improvement in baseline HAMD-17 scores</p> <p>Baseline: HAMD-17 (SD) 19.9 (3.6) (pbo); 19.9 (3.6) (dul 80mg); 20.2 (3.4) (dul 120 mg); 20.3 (4.1) (parox)</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Number with palpitation</p> <p>Number with abnormal electrocardiogram T wave</p> <p>Notes: Only N leaving the study early due to side-effects and weight change from end of acute phase given for continuation phase; for overall dichotomous outcomes data for 12 0mg added to that for 80 mg</p>	<p>Group 1 N= 95</p> <p>Duloxetine. Mean dose 80 mg - 70 entered continuation phase - continued with same blinded treatment</p> <p>Group 2 N= 93</p> <p>Duloxetine. Mean dose 120 mg - 75 entered continuation phase - continued with same blinded treatment</p> <p>Group 3 N= 85</p> <p>Paroxetine. Mean dose 20 mg - 70 entered continuation phase - continued with same blinded treatment</p> <p>Group 4 N= 93</p> <p>Placebo - 58 entered continuation phase - continued with same blinded treatment</p>	<p>SIGN 1+; funding Eli Lilly (code HMAY-A); variable-duration placebo washout</p>
ELI LILLY HMAI				
<p>Study Type: RCT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Followup: 44-week extension for responders</p> <p>Setting: Outpatients; 13 countries (no details; 54 sites)</p> <p>Notes: RANDOMISATION: randomised not details</p> <p>Info on Screening Process: No details</p>	<p>n= 648</p> <p>Age: Mean 42</p> <p>Sex: 212 males 436 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: No details, but likely to be similar to other studies</p> <p>Notes: Entry criterion to extension phase > 50% reduction in baseline HAMD score and no longer meeting criteria for MDD (DSM-III-R)</p> <p>Baseline: HAMD-17 26 (3.7)</p>	<p>Data Used</p> <p>Number with hypertension</p> <p>Number with palpitation</p> <p>Number with postural hypotension</p> <p>Number with abnormal ejaculation</p> <p>Response: 50% reduction in HAMD-17</p> <p>Number of people reporting side effects</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>Remission: HAMD-17 < 7 - Not reported</p> <p>Notes: No efficacy data for extension phase</p>	<p>Group 1 N= 130</p> <p>Duloxetine. Mean dose 5 mg - 57 in extension phase</p> <p>Group 2 N= 129</p> <p>Duloxetine. Mean dose 10 mg - 71 in extension phase</p> <p>Group 3 N= 131</p> <p>Duloxetine. Mean dose 20 mg - 57 in extension phase</p> <p>Group 4 N= 132</p> <p>Clomipramine. Mean dose 150 mg - 64 in extension phase</p> <p>Group 5 N= 126</p> <p>Placebo - 59 in extension phase</p>	<p>SIGN 1+; funding Eli Lilly (code HMAI); variable-duration placebo washout. Data not used in final analyses because of low dosages.</p>

ELI LILLY HMAQ				
Study Type: RCT	n= 194	Data Used	Group 1 N= 82	SIGN: 1+; funding: Eli Lilly (Code HMAQ); 5-10 day no-drug screening phase
Type of Analysis: LOCF ITT data used	Age: Mean 40	Number with palpitation	Duloxetine. Mean dose 40 mg - 120 mg	
Blindness: Double blind	Sex: 65 males 129 females	Number with hypertension	Group 2 N= 37	
Duration (days): Mean 70	Diagnosis:	Number with decreased libido	Fluoxetine. Mean dose 20 mf	162
Setting: Outpatients; US (11 sites)	100% Major depressive disorder by DSM-IV	Weight change	Group 3 N= 75	
Notes: RANDOMISATION: randomised, no		Response: 50% reduction in HAMD-17	Placebo	
		Remission: HAMD-17 < 7		
		HAMD-17 mean change		

<p>details</p> <p>Info on Screening Process: 308 people screened, no further details</p>		<p>Number of people reporting side effects</p> <p>Leaving treatment early for any reason</p>		
<p>ELI LILLY HMAT-A</p> <p>Study Type: RCT</p> <p>Type of Analysis: MMRM</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US (22 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 354</p> <p>Age: Mean 44</p> <p>Sex: 136 males 218 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 15</p> <p>Baseline: HAMD-17 (SD) 17.79 (4.73) pbo; 17.47 (5.20) dul 40mg; 17.44 (5.16) dul 80 mg; 17.97 (5.87) parox</p>	<p>Data Used</p> <p>Number with abnormal ejaculation</p> <p>Number with palpitation</p> <p>Number with decreased libido</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p> <p>Notes: Duloxetine 80mg data used in comparisons with paroxetine</p>	<p>Group 1 N= 91</p> <p>Duloxetine. Mean dose 40 mg - Below licensed dose so not used except in comparison with 80 mg</p> <p>Group 2 N= 84</p> <p>Duloxetine. Mean dose 80 mg</p> <p>Group 3 N= 89</p> <p>Paroxetine. Mean dose 20 mg</p> <p>Group 4 N= 90</p> <p>Placebo</p>	<p>SIGN: 1+; funding: Eli Lilly (Code HMAT-A); 5-9 day no-drug screening phase</p>
<p>ELI LILLY HMBU</p> <p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Outpatients; Austria, Australia, Germany, France, Spain, Italy, US (34 sites)</p> <p>Notes: RANDOMISATION: randomised no details</p> <p>Info on Screening Process: No details</p>	<p>n= 332</p> <p>Age: Mean 44</p> <p>Sex: 98 males 234 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 18; no previous episode; Axis I disorder other than MDD including anxiety or dysthymia as primary diagnosis in past year; previous diagnosis of bipolar disorder, schizophrenia, other psychotic disorder; lack of response in current episode to >=2 adequate courses of antidepressant or treatment-resistant; history of lack of response to venlafaxine or SNRIs; serious suicide risk; history of substance misuse/dependence.</p> <p>Notes: Participants had >= 1 previous episode</p> <p>Baseline: HAMD-17 (SD) 23.10 (3.66)</p>	<p>Data Used</p> <p>Number of people reporting side effects</p> <p>Number with palpitation</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 166</p> <p>Duloxetine. Mean dose 60mg - 120 mg - 60 mg for first 6 weeks, allowed to increase to 120 mg in 2nd 6 weeks</p> <p>Group 2 N= 166</p> <p>Venlafaxine. Mean dose 150 mg - 225 mg - 150 mg for 1st 6 weeks, allowed to increase to 225 mg in 2nd 6 weeks</p>	<p>SIGN: 1+; funding Eli Lilly; Published paper is pooled analysis of this study and Eli Lilly HMCQ; washout period 3-9 days</p>
<p>ELI LILLY HMCQ</p>				

<p>Study Type: RCT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Outpatients; US, Canada (32 sites)</p> <p>Notes: RANDOMISATION: randomised no details</p> <p>Info on Screening Process: No details</p>	<p>n= 504</p> <p>Age: Mean 42</p> <p>Sex: 173 males 331 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 < 18; no previous episode; Axis I disorder other than MDD including anxiety or dysthymia as primary diagnosis in past year; previous diagnosis of bipolar disorder, schizophrenia, other psychotic disorder; lack of response in current episode to >=2 adequate courses of</p>	<p>Data Used</p> <p>Weight change</p> <p>Number with decreased libido</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>Number of people reporting side effects</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 164</p> <p>Duloxetine. Mean dose 60 mg - Dose increased to 120 mg in 2nd 6 weeks based on clinical response</p> <p>Group 2 N= 171</p> <p>Venlafaxine. Mean dose 150 mg - Dose increased to 225 mg in 2nd 6 weeks based on clinical response</p> <p>Group 3 N= 169</p> <p>Venlafaxine. Mean dose 75 mg - Dose increased to 150 mg in 2nd 6 weeks</p>	<p>SIGN: 1+; funding Eli Lilly; Published paper is pooled analysis of this study and Eli Lilly HMBU; washout period 3-9 days</p> <p style="text-align: right;">163</p>
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	antidepressant or treatment-resistant; history of lack of response to venlafaxine or SNRIs; serious suicide risk; history of substance misuse/dependence. Notes: Participants had >= 1 previous episode Baseline: HAMD-17 (SD) 22.32 (3.25)	Notes: Data from venlafaxine 150 mg used in comparisons		
GOLDSTEIN2002				
Study Type: RCT Type of Analysis: Mixed-effects likelihood-based repeated-measures Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; country unclear (8 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 173 Age: Mean 41 Sex: 62 males 111 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 <15; Axis I disorder other than MDD or anxiety disorder (other than specific phobias) in past year; history of substance misuse or dependence in past year; positive drug urine screen at study entry; failed >=2 adequate courses of antidepressants during current episode. Baseline: HAMD-17 (SD) 19.2 (5) (pbo); 18.4 (4) (dul); 17.9 (4.3) (fluox)	Data Used Weight change Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early for any reason Number with palpitation Number of people reporting side effects Data Not Used Leaving treatment early due to lack of efficacy - Ns not given just p-value Notes: LOCF analysis used for remission and response; SD for HAMD-17 mean change and weight for dulox and pbo groups not given in published report so taken from report on clinicaltrialsresults.org	Group 1 N= 70 Duloxetine. Mean dose 120 mg - Titrated in 1st 3 weeks from 40mg to 120mg (achieved by 75.7% patients) Group 2 N= 33 Fluoxetine. Mean dose 20 mg Group 3 N= 70 Placebo	Phase 2 trial; SIGN 1+; funding Eli Lilly (code HMAQ-A); variable-duration placebo washout
GOLDSTEIN2004				

<p>Study Type: RCT</p> <p>Type of Analysis: Mixed-effects likelihood-based repeated-measures</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US (19 psychiatric research sites)</p> <p>Notes: RANDOMISATION: randomised by computer-generated random table; used efficacy sample as ITT group</p> <p>Info on Screening Process: 527 people screened; 174 failed screening, no further details</p>	<p>n= 353</p> <p>Age: Mean 40</p> <p>Sex: 136 males 217 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 <15; Axis I disorder other than MDD or anxiety disorder (other than specific phobias) in past year; previous diagnosis of bipolar disorder, psychosis or schizoaffective disorder, or history of substance misuse or dependence in past year; positive drug urine screen at study entry; failed >=2 adequate courses of antidepressants during current episode.</p> <p>Baseline: HAMD-17 (SD) 17.2 (5.08) (pbo); 18.74 (5.97) (dul 40 mg); 17.86 (4.66) (dul 80 mg); 17.83 (5.19) (parox)</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Number with abnormal orgasmia</p> <p>Number with decreased libido</p> <p>Number of people reporting side effects</p> <p>Notes: HAMD-17 data not given in published report so taken from report on clinicaltrialsresults.org; 80 mg used in comparison with paroxetine</p>	<p>Group 1 N= 86</p> <p>Duloxetine. Mean dose 40 mg - Below licensed dose; data used only in comparison with higher dose</p> <p>Group 2 N= 91</p> <p>Duloxetine. Mean dose 80 mg</p> <p>Group 3 N= 87</p> <p>Paroxetine. Mean dose 20 mg</p> <p>Group 4 N= 89</p> <p>Placebo</p>	<p>SIGN 1++; funding Eli Lilly (code HMAT-B); variable-duration placebo washout</p>
<p>KHAN2007B</p> <p>Study Type: RCT</p> <p>Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p>	<p>n= 278</p> <p>Age: Mean 42</p> <p>Sex: 112 males 166 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 10</p> <p>MADRS mean change</p> <p>MADRS mean endpoint</p> <p>HAMD-17 mean endpoint</p>	<p>Group 1 N= 138</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 140</p> <p>Escitalopram. Mean dose 10 mg - 20 mg - Dose increased to 20 mg after 4 weeks if lack of response</p>	<p>SIGN: 1+; funding: National Institutes of Health Center and Forest Research Institute; 1-week no-drug screening phase 164</p>

<p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 382 people screened; 104 did not meet inclusion criteria</p>	<p>Exclusions: MADRS < 26; MADRS at baseline within 25% of score at screening; abnormal findings on physical exam, laboratory tests and 12-lead ECT; pregnant or breastfeeding; Axis I disorder other than MDD; mental retardation or pervasive developmental disorder or cognitive disorder; recent history or current diagnosis of drug or alcohol dependence; suicidal ideation or attempt within past year; history of psychotic disorder or psychotic features; personality disorder likely to interfere with study; history of seizure disorder or risk of seizure; history of narrow-angle glaucoma or inappropriate antidiuretic hormone secretion syndrome; current diagnosis or history of clinically significant medical illness unstable in last year; women not using adequate contraception</p> <p>Notes: 1 week placebo lead in and 16 week extension phase</p> <p>Baseline: HAMD-17 (SD) 21 (4)</p>	<p>Response: 50% reduction in HAMD-24</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early for any reason</p>		
<p>LEE2007</p> <p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; China, Korea, Taiwan, Brazil (20 sites)</p> <p>Notes: RANDOMISATION: randomised no details</p> <p>Info on Screening Process: 672 people screened, 194 did not meeting screening criteria</p>	<p>n= 478</p> <p>Age: Mean 38</p> <p>Sex: 145 males 333 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 <15; Axis I disorder other than MDD; previous diagnosis of psychotic disorder, dythymia in past 2 years, anxiety disorder as primary diagnosis in past year, axis II disorder that would interfere with protocol compliance, history of substance misuse; failed >=2 adequate courses of antidepressants during current episode; history of lack of response to adequate trial of paroxetine for depression, serious suicidal risk, serious medical illness, history of hepatic dysfunction, current jaundice, positive hepatitis B surface antigen or positive hepatitis C surface antibody, high alanine aminotransaminase level, ECT in last year, psychotherapy, started light therapy or phototherapy within 6 weeks of study entry, taking excluded medications or abnormal thyroid-stimulating hormone concentrations.</p> <p>Baseline: HAMD-17 (SD) 21.2 (4.12) (dul); 21.2 (4.04) (pbo)</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Number with viral myocarditis</p> <p>Number with palpitation</p> <p>Number with suicide attempt</p> <p>Number with decreased libido</p> <p>Number of people reporting side effects</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Notes: HAMD-17 SDs calculated from p-values</p>	<p>Group 1 N= 238</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 240</p> <p>Placebo</p>	<p>SIGN 1+; funding Eli Lilly (code HMCV); variable-duration placebo washout</p>
<p>NIERENBERG2007B</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: LOCF at least one post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Followup: 6-month continuation phase</p> <p>Setting: Outpatients; US (36 sites)</p> <p>Notes: RANDOMISATION: randomised using 'interactive voice response system'</p> <p>Info on Screening Process: 1049 people screened, 365 failed to meet entry criteria</p>	<p>n= 684</p> <p>Age: Mean 42 Range 18-79</p> <p>Sex: 238 males 446 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS < 22; abnormal physical exam, lab tests and ECT; pregnant or lactating; Axis I disorder other than MDD; previous diagnosis of bipolar disorder, schizophrenia or other psychotic disorder in past 2 years; axis II disorder that would interfere with protocol compliance; primary diagnosis of anxiety in past 6 months; history of substance dependence in last 6 months; failed >=2 adequate courses of antidepressants during current episode; history of lack of response to adequate trial of study drugs for depression; serious suicidal risk; serious medical illness likely to need intervention, hospitalisation or use of excluded medication during study, use of MAOI or fluoxetine with 30 days of 3rd</p>	<p>Data Used</p> <p>Number with palpitation</p> <p>Number with abnormal orgasmia</p> <p>Number with decreased libido</p> <p>Number with ventricular dysfunction</p> <p>Number with hypertension</p> <p>Number with suicidal depression</p> <p>Number with chronic airways disease exacerbated</p> <p>Number with cardiac failure congestive</p> <p>Number with arrhythmia</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Weight change</p>	<p>Group 1 N= 273</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 274</p> <p>Escitalopram. Mean dose 10 mg</p> <p>Group 3 N= 137</p> <p>Placebo</p>	<p>SIGN 1+++; funding Eli Lilly (code HMCR); variable-duration placebo washout; continuation phase data in Pigott2007 data not extracted as report incomplete - requested full report</p>
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	ECT or TMS in last year, initiating, stopping or changing psychotherapy frequency or modality after study entry Notes: placebo lead in Baseline: HAMD-17 17.6 (4.8) (dul); 17.8 (5.1) (esc); 17.7 (5.2) (pbo)	Notes: Not possible to calculate SDs for weight change Author emailed for n at randomisation 07/10/08		
PERAHIA2006B				
Study Type: RCT Type of Analysis: ITT LOCF Blindness: Double blind Duration (days): Mean 56 Followup: 6-mth continuation phase Setting: Outpatients; Bulgaria, Croatia, Hungary, Poland, Romania, Russia, Slovakia (22 sites in all) Notes: RANDOMISATION: randomised no further details Info on Screening Process: 480 people screened, no further details	n= 392 Age: Mean 45 Sex: 119 males 273 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 15; Axis I disorder other than MDD; any anxiety disorder as a primary diagnosis within 6 months of study; previous diagnosis of bipolar disorder, schizophrenia, other psychotic disorder; serious suicidal risk; lack of response of the current depressive episode to 2 or more adequate courses of AD therapy; serious medical illness; history of substance misuse within 12 months of study Notes: Continuation phase entry criteria: >= 30% improvement in baseline HAMD-17 scores Baseline: HAMD-17 (SD) 20.6 (3.7) (pbo); 21.3 (3) (dul 80mg); 21.4 (4.4) (dul 120 mg); 21 (3.4) (parox)	Data Used Number with tachycardia NOS Number of people reporting side effects Leaving treatment early due to lack of efficacy Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early for any reason Data Not Used Weight change - No variability measure; not given for all groups Notes: HAMD-17 mean change is least squares means; dropouts, dropouts due to side-effects or lack of efficacy, and mean HAMD-17 change scores give for continuation period	Group 1 N= 93 Duloxetine. Mean dose 80 mg - 71 entered continuation phase - continued with same blinded treatment Group 2 N= 103 Duloxetine. Mean dose 120 mg - 81 entered continuation phase - continued with same blinded treatment Group 3 N= 97 Paroxetine. Mean dose 20 mg - 70 entered continuation phase - continued with same blinded treatment Group 4 N= 99 Placebo - 71 entered continuation phase - continued with same blinded treatment	SIGN 1+; funding Eli Lilly (code HMA-Y-B); variable-duration placebo washout
RASKIN2007				

<p>Study Type: RCT</p> <p>Type of Analysis: LOCF (at least one post-baseline evaluation)</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Outpatients; US</p> <p>Notes: RANDOMISATION: randomised but no details</p> <p>Info on Screening Process: No details</p>	<p>n= 311</p> <p>Age: Mean 72 Range 65-90</p> <p>Sex: 126 males 185 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-17 <18, MMSE < 20 (i.e. moderate or severe dementia); Axis I disorder other than MDD; previous psychotic disorder; organic mental disorder; mental retardation; serious/unstable medical illness, psychological condition or clinically significant laboratory abnormality likely to compromise study or lead to hospitalisation; high alanine transaminase, aspartate transaminase, gamma glutamyl transferase levels</p> <p>Notes: All participants required to have had >= 1 previous episode i.e. recurrent depression</p> <p>Baseline: HAMD-17 (SD) 18.85 (6); N previous episodes (SD) 5(15) (dul), 6.3(13.6) pbo</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean change - no variability measure</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Number with suicide attempt</p> <p>Number with suicidal ideation</p> <p>Notes: SD for weight calculated from p-value; no SDs for HAMD in published paper, so taken from report on clinicaltrialresults.org; intentional overdose extracted as suicide attempt</p>	<p>Group 1 N= 207</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 104</p> <p>Placebo</p>	<p>SIGN: 1+; funding: Eli Lilly (Code HMBV); 1-week no-drug screening phase + 1-week placebo washout; analysis of data by medical comorbidity considered in Depression and chronic physical health problems guideline (WISE2007)</p>
WADE2007				
<p>Study Type: RCT</p> <p>Type of Analysis: LOCF (at least one post-baseline evaluation)</p> <p>Blindness: Double blind</p> <p>Duration (days):</p>	<p>n= 294</p> <p>Age: Mean 44</p> <p>Sex: 212 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV-TR</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS < 13</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 < 7</p> <p>HAMD-17 mean endpoint</p>	<p>Group 1 N= 151</p> <p>Duloxetine. Mean dose 60 mg</p> <p>Group 2 N= 143</p> <p>Escitalopram. Mean dose 20 mg/d - 10 mg/d weeks 1, 2, 25 and 26</p>	<p>SIGN: 1+; funding: Lundbeck; psychotropics not allowed during 2 weeks before entering trial 166</p>

<p>Setting: Outpatients and primary care; Belgium, Canada, Czech Republic, France, Germany, Italy, Spain, Sweden, UK (35 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>Exclusions: MADRS < 26; comorbid OCD, PTSD or panic disorder; bipolar disorder, psychotic disorder or fetures, current eating disorders, mental retardation, pervasive developmental disorder or cognitive disorder, alcohol or drug misuse-related disorders with 12 months of the study; serious suicide risk; receiving formal behaviour therapy, systematic psychotherapy, pregnant, breastfeeding, history of lactose intolerance; hypersensitivity or non-response to citalopram, escitalopram or duloxetine; in creased intra-ocular pressure or risk of acute narrow-angle glaucoma; taking psychotropic drugs, except z-drugs for insomnia, within 2 weeks of study or during study (5 weeks for fluoxetine); ECT within 6 months.</p> <p>Baseline: HAMD-17 (SD) 22.7 (5)</p>	<p>Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason</p> <p>Notes: Data given at week 8 and week 24; week 8 entered in acute phase comparisons and week 24 in continuation phase to match other studies; SDs calculated from p-values; MADRS used for remission/response at 24 weeks</p>		
<p>WHITMYER2007</p> <p>Study Type: RCT</p> <p>Study Description: H0P1; Patients randomised to acute phase trial (3 arms - dul 30mg, 30 mg twice a day, 60 mg once a day); non-responders randomised to 60 mg or 120 mg</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Followup: + 8 weeks APNR</p> <p>Setting: Outpatients; US (33 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 916 people screened, 269 failed to meet entry criteria or declined to participate</p>	<p>n= 647</p> <p>Age: Mean 43</p> <p>Sex: 232 males 415 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD0-17 < 16; Axis I disorder other than MDD, dysthymia or any anxiety disorder (apart from OCD); previous diagnosis of mania, BD, psychosis; serious suicidal risk; serious medical illness or clinically significant laboratory abnormalities likely to require intervention, hospitalisation or an excluded medication during the study period; lack of response during current episode to 2 or more adequate courses of ADs; history of lack of response to duloxetine; current axis II disorder that could interfere with compliance; history of substance misuse or dependence within past 6 months; positive drug urine screen ECT or TMS within past year; initiating, stopping or changing psychotherapy; MAOI within past 14 days or fluoxetine within 30 days.</p> <p>Notes: 441 in APNR phase (entry criterion HAMD-17 > 7 at end of acute phase); 62% women; mean age 45</p> <p>Baseline: HAMD-17 (SD) 21.6 (3.3) (dul 30 mg); 21.7 (3.7) (30 bid); 21.2 (3.9) (60 mg)</p>	<p>Data Used</p> <p>Number with palpitation Number with abnormal orgasmia Number with decreased libido Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 Weight change HAMD-17 mean change Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason Number with delayed ejaculation Number with abnormal ejaculation Number with sexual dysfunction</p> <p>Notes: Only leaving treatment early for any reason, lack of efficacy and AEs extracted for APNR extension study - other data given for all those taking 60 mg during extension which included those remitting</p>	<p>Group 1 N= 291 Duloxetine. Mean dose 30 mg - Dose less than licensed dose; used in comparison with 60mg only</p> <p>Group 2 N= 215 Duloxetine. Mean dose 60 mg</p> <p>Group 3 N= 213 Duloxetine. Mean dose 30 mg bid - Data not input as separate group; dichotomous data added to 60 mg group; continuous data not used</p> <p>Group 4 N= 131 Duloxetine. Mean dose 60 mg - Re-randomised acute-phase non-responders</p> <p>Group 5 N= 124 Duloxetine. Mean dose 120 mg - Re-randomised acute-phase non-responders</p>	<p>SIGN: 1+; funding: Eli Lilly (Code HMDR); 1-week no-drug screening phase</p>

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BADYAL2005	Open-label study (duloxetine vs venlafaxine)
ELI LILLY E001	No control group
ELI LILLY HMAG	Dose used (20 mg) is below licensed dose (duloxetine vs placebo)
ELI LILLY HMAH	Doses used (20 mg - 30 mg) are below licensed dose; re-randomised non-responders to 20 mg or 30 mg part-way through trial (duloxetine vs

ELI LILLY HMAI	placebo) Doses used (5 mg, 10 mg, 20 mg) are below licensed dose (duloxetine vs placebo)
ELI LILLY HMBY	No control group
ELI LILLY HMCX	Open-label, no comparator (duloxetine)
ELI LILLY HMCZ	Open-label study

GERETSEGGER2008 High proportion bipolar disorder (22%) (augmentation of paroxetine with pindolol vs placebo)

RASKIN2003 Non-comparative, open-label study (duloxetine)

References of Included Studies

BRANNAN2005A (Published Data Only)

Eli Lilly study F1J-MC-HMCB, CT Registry ID# 6365. Duloxetine once-daily dosing versus placebo in patients with major depression and pain. Clinicaltrialsresults.org [date site accessed 13.06.08].

Brannan, S. K., Mallinckrodt, C. H., Brown, E. B., Wohlreich, M. M., Watkin, J. G., & Schatzberg, A. F. (2005). Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. *Journal of Psychiatric Research*, 39, 43-53.

BRECHT2007 (Published Data Only)

Eli Lilly study F1J-MC-HMDH, CT Registry ID# 8605. A 10-week, randomized, double-blind study evaluating the efficacy of duloxetine 60 mg once daily versus placebo in outpatients with major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

Brecht, S., Courtecuise, C., Debieuvre, C., Croenlein, J., Desai, D., Raskin, J. et al. (2007). Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *Journal of Clinical Psychiatry*, 68, 1707-1716.

DETKE2002 (Published Data Only)

Eli Lilly study F1J-MC-HMBH-B, CT Registry ID# 4689. Duloxetine once-daily dosing versus placebo in the acute treatment of major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Detke, M. J., Lu, Y., Goldstein, D. J., McNamara, R. K., & Demitrack, M. A. (2002). Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *Journal of Psychiatric Research*, 36, 383-390.

DETKE2002A (Published Data Only)

Eli Lilly study F1J-MC-HMBH-A, CT Registry ID# 4689. Duloxetine once-daily dosing versus placebo in the acute treatment of major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Detke, M. J., Lu, Y., Goldstein, D. J., Hayes, J. R., & Demitrack, M. A. (2002). Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. [See comment]. *Journal of Clinical Psychiatry*, 63, 308-315.

DETKE2004 (Published Data Only)

Eli Lilly study F1J-MC-HMAY, CT Registry ID# 4298. Duloxetine versus placebo and paroxetine in the treatment of major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Detke, M. J., Wiltse, C. G., Mallinckrodt, C. H., McNamara, R. K., Demitrack, M. A., & Bitter, I. (2004). Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European Neuropsychopharmacology*, 14, 457-470.

ELI LILLY HMAI (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAI, CT Registry ID# 1126. A double-blind, placebo- and clomipramine-controlled study in duloxetine in patients with major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMAQ (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAQ, CT Registry ID# 7999. Duloxetine versus placebo in the treatment of major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMAT-A (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAT-A, CT Registry ID# 4091. Duloxetine versus placebo and paroxetine in the acute treatment of major depression. Study Group A. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMBU (Unpublished and Published Data)

not given in published report so taken from report on clinicaltrialsresults.org

*Eli Lilly study F1J-MC-HMBU, CT Registry ID# 6090. Duloxetine versus venlafaxine extended release in the treatment of major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMCQ (Unpublished and Published Data)

Eli Lilly study F1J-MC-HMCQ, CT Registry ID# 7999. Duloxetine versus venlafaxine extended release in the treatment of major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

GOLDSTEIN2002 (Published Data Only)

Eli Lilly study F1J-MC-HMAQ, CT Registry ID# 3327. Duloxetine versus placebo in the treatment of major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Goldstein, D. J., Mallinckrodt, C., Lu, Y., & Demitrack, M. A. (2002). Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *Journal of Clinical Psychiatry*, 63, 225-231.

168

GOLDSTEIN2004 (Published Data Only)

Eli Lilly study F1J-MC-HMAT-B, CT Registry ID# 4091. Duloxetine versus placebo and paroxetine in the acute treatment of major depression. Clinicaltrialresults.org [date site accessed 13.06.08].
Goldstein, D. J., Lu, Y., Detke, M. J., Wiltse, C., Mallinckrodt, C., & Demitrack, M. A. (2004). Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of Clinical Psychopharmacology*, 24, 389-399.

KHAN2007B (Unpublished and Published Data)

Forest Research Institute. Double-blind study of escitalopram in adult patients with major depressive disorder/Tolerability and cost effectiveness of escitalopram in adult patients with major depressive disorder (SCT-MD-23/23A). Report date: January 11, 2008.

Jonas, J., Bose, A., Alexopoulos, G., Gommoll, C., Li, D. & Gandhi, C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Poster presented at the 45th Annual Meeting of the American College of Neuropsychopharmacology. Hollywood, FL, US, 3-7 December 2006.

*Khan, A., Bose, A., Alexopoulos, G. S., Gommoll, C., Li, D., Gandhi, C. (2007) Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. *Clinical Drug Investigation*, 27, 481-492.

LEE2007 (Published Data Only)

Eli Lilly study F1J-AA-HMCV, CT Registry ID# 6937. Duloxetine versus paroxetine in the acute treatment of major depression. Clinicaltrialresults.org [date site accessed 13.06.08].

Lee, P., Shu, L., Xu, X., Wang, C. Y., Lee, M. S., Liu, C. Y. et al. (2007). Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. *Psychiatry & Clinical Neurosciences*, 61, 295-307.

NIERENBERG2007B (Unpublished and Published Data)

Eli Lilly study F1J-US-HMCR, CT Registry ID# 7978. Duloxetine versus escitalopram and placebo in the treatment of patients with major depression. Clinicaltrialresults.org [date site accessed 13.06.08].

Clayton, A., Kornstein, S., Prakash, A., Mallinckrodt, C., & Wohlreich, M. (2007). Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. *Journal of Sexual Medicine*, 4, 917-929.

Pigott, T. A., Prakash, A., Arnold, L. M., Aaronson, S. T., Mallinckrodt, C. H., & Wohlreich, M. M. (2007). Duloxetine versus escitalopram and placebo: An 8-month, double-blind trial in patients with major depressive disorder. *Current Medical Research and Opinion*, 23, 303-318.

*Nierenberg, A. A., Greist, J. H., Mallinckrodt, C. H., Prakash, A., Sambunaris, A., Tollefson, G. D. et al. (2007). Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Current Medical Research & Opinion*, 23, 401-416.

PERAHIA2006B (Published Data Only)

Eli Lilly study F1J-MC-HMAY, CT Registry ID# 4298. Duloxetine versus placebo and paroxetine in the treatment of major depression. Clinicaltrialresults.org [date site accessed 13.06.08].

Perahia, D. G., Wang, F., Mallinckrodt, C. H., Walker, D. J., & Detke, M. J. (2006). Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 21, 367-378.

RASKIN2007 (Published Data Only)

Eli Lilly study F1J-MC-HMBV, CT Registry ID# 6091. Duloxetine versus placebo in the treatment of elderly patients with major depressive disorder. Clinicaltrialresults.org [date site accessed 13.06.08].

Wise, T. N., Wiltse, C. G., Iosifescu, D. V., Sheridan, M., Xu, J. Y., & Raskin, J. (2007). The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. *International Journal of Clinical Practice*, 61, 1283-1293.

Raskin, J., Wiltse, C. G., Dinkel, J. J., Walker, D. J., Desai, D., & Katona, C. (2008). Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. *Journal of Clinical Psychopharmacology*, 28, 32-38.

*Raskin, J., Wiltse, C. G., Siegal, A., Sheikh, J., Xu, J., Dinkel, J. J. et al. (2007). Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *American Journal of Psychiatry*, 164, 900-909.

WADE2007 (Unpublished and Published Data)

Lundbeck. A double-blind, randomised, multi-centre, comparative study of escitalopram and duloxetine in outpatients with major depressive disorder (10990). Report date: 10 September 2007.

*Wade, A., Gembert, K., & Florea, I. (2007). A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. *Current Medical Research & Opinion*, 23, 1605-1614.

WHITMYER2007 (Unpublished and Published Data)

Kornstein, S. G., Dunner, D. L., Meyers, A. L., Whitmyer, V. G., Maillinckrodt, C. H., Wohlreich, M. M., Detke, M. J., Hollandbeck, M. S., Greist, J. H. (2008) A randomized, double-blind study of increasing or maintaining duloxetine dose in patients without remission of major depressive disorder after initial duloxetine therapy. *Journal of Clinical Psychiatry*, 69: 1383-1392.

Eli Lilly study F1J-MC-HMDR, CT Registry ID# 8950. A comparison of duloxetine dosing strategies in the treatment of patients with major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Whitmyer, V. G., Dunner, D. L., Kornstein, S. G., Meyers, A. L., Mallinckrodt, C. H., Wohlreich, M. M., Gonzales, J.S., Greist, J. H. (2007) A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *Journal of Clinical Psychiatry*, 68, 1921-1930.

References of Excluded Studies

BADYAL2005 (Published Data Only)

Badyal, D. K., Khosla, P. P., Deswal, R. S., & Matreja, P. S. (2005). Safety and efficacy of duloxetine versus venlafaxine in major depression in Indian patients. *JK Science*, 8, 95-99.

ELI LILLY E001 (Unpublished Data Only)

Eli Lilly study F1J-EW-E001, CT Registry ID# 1096. A pilot study in major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMAG (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAG, CT Registry ID# 1124. Duloxetine/placebo in major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMAH (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAH, CT Registry ID# 1125. Duloxetine 20/30 mg vs placebo in major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMAI (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAI, CT Registry ID# 1126. A double-blind, placebo- and clomipramine-controlled study in duloxetine in patients with major depressive disorder. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMBY (Unpublished Data Only)

Eli Lilly study F1J-US-HMBY, CT Registry ID# 6475. Dose Escalation, Double-Blind Treatment with Duloxetine Hydrochloride Once Daily Dosing for Evaluation of Safety in Major Depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMCX (Unpublished and Published Data)

Eli Lilly study F1J-MC-HMCM, CT Registry ID# 7442. Lilly's Emotional and Physical Symptoms of Depression Study (LEAPS). Clinicaltrialsresults.org [date site accessed 13.06.08].

Eli Lilly study F1J-MC-HMCY, CT Registry ID# 8300. Lilly's Emotional and Physical Symptoms of Depression Study (LEAPS). Clinicaltrialsresults.org [date site accessed 13.06.08].

*Eli Lilly study F1J-MC-HMCX, CT Registry ID# 8299. Lilly's Emotional and Physical Symptoms of Depression Study (LEAPS). Clinicaltrialsresults.org [date site accessed 13.06.08].

ELI LILLY HMCZ (Unpublished Data Only)

Eli Lilly study F1J-AY-HMCZ, CT Registry ID# 8163. Duloxetine in the treatment of melancholic depression: an 8-week open-label dose study. Clinicaltrialsresults.org [date site accessed 13.06.08].

GERETSEGGER2008 (Published Data Only)

Geretsegger, C., Bitterlich, W., Stelzig, R., Stuppaeck, C., Bondy, B., & Aichhorn, W. (2008). Paroxetine with pindolol augmentation: a double-blind, randomized, placebo-controlled study in depressed in-patients. *European Neuropsychopharmacology*, 18, 141-146.

RASKIN2003 (Unpublished and Published Data)

Eli Lilly study F1J-MC-HMAU, CT Registry ID# 4092. Long-term open-label treatment with duloxetine hydrochloride for evaluation of safety in major depression. Clinicaltrialsresults.org [date site accessed 13.06.08].

Raskin, J., Goldstein, D. J., Mallinckrodt, C. H., & Ferguson, M. B. (2003). Duloxetine in the long-term treatment of major depressive disorder. *Journal of Clinical Psychiatry*, 64, 1237-1244.

Mirtazapine - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Benkert 2000 Y M I	Allocation: random (no details) Double-blind 6-week trial	Primary care and outpatients. n=275, c.64% women, mean age: 47 years. Diagnosis: DSM-IV for major depressive episode, HRSD-17 \geq 18. Mean baseline HRSD score: Mirtazapine - 22.4+- 3.3, Paroxetine - 22.4+-3.2	1. Mirtazapine (mean 32.7 mg) 2. Paroxetine (mean 22.9 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (Patients not achieving \geq 50% reduction on HRSD) 4. Non-remitters (Patients not achieving HRSD \leq 7) 5. HRSD mean endpoint scores 6. Patients reporting side effects	Setting: Germany	B

Bremner	Allocation: random	Outpatients. n=150, age: 18+, mean = 38	1. Mirtazapine	1. Leaving the study early	Setting: US	B
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1995 Y O I	(no details) Double-blind 6-week trial.	Diagnosis: DSM-III moderate to severe major depression, HRSD-17 \geq 18. Mean baseline HRSD score: Mirtazapine = 28.3, amitriptyline = 27.3, placebo = 26.6.	(mean 22mg) 2. Amitriptyline (mean 168.4mg/day) 3. Placebo	2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores		
Bruijn1996 Y I I	Allocation: random (no details). Double-blind. 4 weeks on study drug at dosage to achieve pre-defined blood levels, plus time to achieve this level (mean time for mirtazapine 10.9 days, imipramine 13.6 days)	Inpatients. N=107, 23 women. Mean age: 45-47 years. Diagnosis: DSM-III-R for major depressive episode (including 6 with bipolar disorder). Mean baseline HRSD score: mirtazapine - 26.1+4.5 (19-37), imipramine - 26.5+5.0 (18-37).	1. Mirtazapine (mean 76.2mg) 2. Imipramine (235.5mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores	Setting: Holland	B
Guelfi2001 Y I I	Allocation: random (no details) Double-blind 8-week trial	Inpatients. N=157, 103 women, mean age: mirtazapine group = 45, venlafaxine group = 44.5 years (+10.8). Diagnosis: DSM-IV for severe depressive episode with melancholic features, HRSD-17 \geq 25. Mean baseline HRSD score: mirtazapine = 29.5+3.0, venlafaxine = 29.2+2.9.	1. Mirtazapine (mean 49.5+8.3 mg) 2. Venlafaxine (mean 255+59.8mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects 4. HRSD mean change scores 5. Non-responders (Patients not achieving \geq 50% decrease in HRSD) 6. Non-remitters	Setting: France, Belgium, Denmark and Holland	B
Halikas1995 Y O I	Allocation: random (no details) Double-blind 6-week trial ITT analysis	Outpatients. N=150, 80 women, mean age 62 (range 55-81). Diagnosis: DSM-III major depressive episode, \geq 18 on HRSD. Mean baseline HRSD score: mirtazapine = 24.6, trazodone = 24.6, placebo = 23.5.	1. Mirtazapine (mean 28.7+8.5mg by week 6) 2. Trazodone (mean 219.5+57.4 mg by week 6) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores 5. Patients reporting side effects	Setting: US	B

Leinonen 1999 Y O I	Allocation: random (centrally prepared randomisation list) Double-blind 8-week trial	Outpatients (97.4%). N=270, 62% women, mean age mirtazapine group: 42.1 (+12.3), citalopram group 41.1 (+10.8). Diagnosis: DSM-IV major depressive episode, MADRS≥ 22. Mean baseline MADRS score: mirtazapine - 29.6+4.9, citalopram - 29.1+4.5.	1. Mirtazapine (mean 35.9 mg) 2. Citalopram (mean 36.6 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving ≥50% reduction on MADRS) 4. MADRS mean endpoint scores 5. Patients reporting side effects	Setting: Finland, Denmark, Norway and Sweden	A
Marttila	Allocation: random	Inpatients and outpatients. N=163, 98 women,	1. Mirtazapine	1. Leaving the study early	Setting: Finland	B

172

1995 Y M I	(no details) Double-blind 6-week trial	mean age: mirtazapine group = 41.3 years (+-10), doxepin group = 41.2 years (+-11.8). Diagnosis: DSM-III and RDC for major depressive episode, HRSD-17 \geq 18. Mean baseline HRSD score: mirtazapine = 22.0+3.9, doxepin - 22.4+3.8.	(mean 37 mg) 2. Doxepin (mean 189 mg)	2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores		
Mullin1996 Y M I	Allocation: random (no details) Double-blind 5-week trial	Inpatients and outpatients. N=156, 116 women, mean age: mirtazapine group = 45.4 years (+-11.8); amitriptyline group = 44.2 years (+-10.3). Diagnosis: DSM-III and RDC for major depressive episode, HRSD-21 \geq 18. Mean baseline HRSD score: mirtazapine - 22.5+3.9, amitriptyline = 22.6+4.0.	1. Mirtazapine (modal 40mg by weeks 4-5) 2. Amitriptyline (modal 150 mg by weeks 4-5)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores	Setting: UK	B
Richou1995 Y I I	Allocation: random (no details) Double-blind 6-week trial	Inpatients. N=174, 116 women, mean age: mirtazapine group = 51.8 years (+-12.0); clomipramine group = 49.5 years (+-12.7). Diagnosis: DSM-III and RDC for major depressive episode, HRSD-21 \geq 18. Mean baseline HRSD score: mirtazapine - 27.7+5.7, clomipramine - 26.7+5.4	1. Mirtazapine (mean 47.3 mg) 2. Clomipramine (mean 113.7 mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving \geq 50% reduction on HRSD) 4. HRSD mean endpoint scores	Setting: France	B
Schatzberg 2002 E O I	Allocation: random (no details) Double-blind 8-week acute phase followed by 16-week extension phase	Outpatients. N = 254, age: 65+. Diagnosis: DSM-IV major depressive episode, HRSD-17 \geq 18. Mean baseline HRSD score: mirtazapine = 22.2+3.5, paroxetine = 22.4+3.5.	1. Mirtazapine (mean = 25.7+-6.7mg) 2. Paroxetine (mean = 26.5 +- 5.5mg)	1. HRSD mean endpoint scores 2. Patients reporting side effects 3. Non-responders (patients not achieving \geq 50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD \leq 7) 5. Leaving the study early 6. Leaving the study early due to side effects	Setting: US	B
Smith1990 Y O I	Allocation: random (no details) Double-blind 6-week trial	Outpatients. N=150, 57% women, mean age 43 years. Diagnosis: DSM-III for major depressive illness, HRSD-17 \geq 18. Mean baseline HRSD score: mirtazapine = 23.4, amitriptyline = 23.7, placebo = 23.3.	1. Mirtazapine (mean 18 mg) 2. Amitriptyline (mean 111mg) 3. Placebo	1. Leaving the study early due to side effects 2. Leaving the study early 3. HRSD mean endpoint scores 4. Non-responders (patients not achieving \geq 50% reduction in HRSD)	Setting: US	B
VanMoffaert 1995 Y I I	Allocation: random (no details) Double-blind 6-week trial	Inpatients. N=200, 140 women, mean age: mirtazapine group=46.1 years (+-10.8); trazodone group = 46.3 years (+-12.6). Diagnosis: DSM-III for major depressive illness, HRSD-17 score 18 or higher. Mean baseline HRSD score: mirt=29.2, traz=27.5.	1. Mirtazapine (24-72 mg) 2. Trazodone (range :50-450 mg)	1. Leaving the study early due to adverse events 2. Leaving the study early 3. Non-responders (patients not achieving \geq 50% reduction in HRSD) 4. HRSD mean endpoint scores	Setting: Belgium	B
Wade2003	Allocation: Random	Primary care patients. N=197 (ITT=177), 130	1. Mirtazapine	1. Leaving the study early	Setting: UK	B

Y P I	(no details). Double blind. 24 week trial.	female, age: 18+, mean=40. Diagnosis: DSM-IV major depressive disorder, HRSD-17>18. Baseline HRSD-17: mirtazapine=23.8+-3.76, paroxetine=24.4+-3.51	(30mg-45mg, mean=34.6+-5.7mg) 2. Paroxetine (20-30mg, mean=23.9+-3.96mg)	2. Leaving the study early due to side effects 3. Patients reporting side effects		
Wheatley 1998 Y O I	Allocation: random (centrally prepared randomisation list) Double-blind 6-week trial	Inpatients (15.4%) and outpatients. N=133, 70 women in 'ITT' sample, mean age ('ITT' sample): mirtazapine group - 47.2 years (+-15.3), fluoxetine group - 47.5 years (+-14.8) Diagnosis: DSM-III-R major depressive episode, HRSD-17 ≥ 21. Mean baseline HRSD score: mirtazapine - 26.0+-4.4, fluoxetine - 26.1+-4.3. ITT sample comprised patients receiving at least 1 dose and 1 assessment (n=60 in mirtazapine group n=63 in fluoxetine group)	1. Mirtazapine (mean* 39.8 mg) 2. Fluoxetine (mean* 23.8 mg) * 'ITT' groups	1. Leaving the study early 2. Leaving the study early due to adverse events 3. HRSD mean endpoint scores 4. Non-responders (patients not achieving >50% decrease in HRSD) 5. Non-remitters	Setting: UK, Belgium, Holland	A
Zivkov 1995 Y I E	Allocation: random (no details) Double-blind 6-week trial	Inpatients. N=251, 174 women (in 'efficacy' sample n=224), mean age: mirtazapine group = 46.8 years (+-10.9); amitriptyline group = 46.9 years (+-10.5). Diagnosis: DSM-III and RDC for major depressive episode, HRSD-21 ≥20. Mean baseline HRSD score - mirtazapine = 28+-4.9, amitriptyline = 27.6+-4.8.	1. Mirtazapine (mean 19.9+-0.9 mg to 52.8+-1.2 mg) 2. Amitriptyline (mean 74.6+-3.8 mg to 196.9 +-45mg - completers only)	1. Leaving the study early due to side effects 2. Leaving the study early 3. HRSD mean endpoint scores 4. Non-responders (patients not achieving ≥50% reduction in HRSD)	Setting: Yugoslavia 'Efficacy' sample - all patients completing at least 14 days of treatment	B

Characteristics of excluded studies

Study	Reason for exclusion
Bremner1996 Y O I	Maintenance phase trial
Carpenter2002 Y O I	Augmentation trial not acute phase RCT
Catterson1996	Abstract only; unable to find full publication
Claghorn1987 Y O I	Placebo controlled trial - no comparator antidepressant arm
Debonnel2000	Abstract only; unable to find full publication
Hoyberg1996	Comparator drug (amitriptyline) dose sub-therapeutic
Kasper1997	Abstract only; unable to find full publication
Montgomery1998 YO I	Maintenance phase trial
Sitsen1994	No recognised diagnosis of depression

Thase2001 Y O E	Maintenance phase trial
Vartiainen1994 YII	Placebo controlled trial - no comparator antidepressant arm

Reboxetine - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Andreoli 2002 Y M	Allocation: Random (no details) Duration: 8 weeks (+4-28 day washout). Analysis: ITT	Inpatients and outpatients. N=381. Age: 18-65. Diagnosis: DSM-III-R major depression without psychotic features, HRSD \geq 22. Baseline HRSD: reboxetine=26.8 +3.4, fluoxetine=26.9 +3.6, placebo=27.4 +3.6.	1. Reboxetine (8mg up to 10mg after 4 weeks) 2. Fluoxetine (20mg up to 40mg after 4 weeks) 3. Placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD \leq 10) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted in 33 centres in 6 countries.	B
Ban1998 Y I	Allocation: Random (no details). Duration: 4 weeks (+7 day washout). Analysis: ITT.	Inpatients. N=258. Age: 18-65. Diagnosis: DSM-III-R major depression, HRSD-17 \geq 16. Mean baseline HRSD: reboxetine = 26.89, placebo = 25.43.	1. Reboxetine(4mg->8mg) 2. Desipramine (100mg->200mg on day 7) 3. Placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Leaving the study early due to side effects	Conducted in at 10 centres in 6 countries.	B
Berzewski 1997 Y M	Allocation: Random (no details). Duration: 6 weeks (+4-14 day washout). Analysis: ITT (patients with \geq 1 assessment post-baseline).	Inpatients and outpatients. N=256. Age: 18-65. Diagnosis: DSM-III-R major depressive episode, HRSD \geq 22. Mean baseline HRSD: reboxetine - 28.8 +4.8, imipramine - 28 +5.2	1. Reboxetine (8mg up to 10mg) 2. Imipramine (150mg up to 200mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Non-responders (patients not achieving \geq 50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD \leq 10) 5. Leaving the study early due to side effects 6. Patients reporting side effects	Conducted in 22 centres in Germany, Belgium and South Africa.	B

Katona 1999 E M	Allocation: Random (no details). Duration:8	Inpatients and outpatients. N=347. Age: 65+. Diagnosis: DSM-III-R major	1 Reboxetine (4mg up to 6mg)	1 HRSD mean endpoint scores 2 Leaving the study early due to side effects	Conducted in 46 centres in 7	B
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	weeks (+ up to 28 day washout) Analysis: ITT	depressive disorder (N=218) or dysthymia (N=129) without psychotic features, HRSD-21 \geq 18, MMSE \geq 22. Mean baseline HRSD: reboxetine =27+4.9, imipramine - 26.9 +5.4.	2. Imipramine (75mg up to 100mg)	3. Non-responders (patients not achieving \geq 50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD \leq 10) 5. Patients reporting side effects	European countries. Extracted data for 218 patients with MDD only.	
Massana 1999 Y M	Allocation: Random (no details). Duration:8 weeks (up to 28 day washout).Analysis: ITT	Inpatients and outpatients. N=168. Age: 18-65. Diagnosis: DSM-III-R acute major depressive episodes not accompanied by psychotic features, HRSD-21 \geq 22. Mean baseline HRSD: reboxetine = 28.6 +-5.3, fluoxetine=27.4 +-4.1.	1. Reboxetine (8mg up to 10mg) 2. Fluoxetine (20mg up to 40mg)	1. HRSD-21 mean endpoint scores 2. Non-responders (patients not achieving \geq 50% decrease in HRSD) 3. Non-remitters (patients not achieving HRSD \leq 10) 4. Leaving the study early 5. Leaving the study early due to side effects 6. Patients reporting side effects	Conducted at 16 centres in four countries.	B
Versiani 2000B Y I	Allocation: Random (no details) Duration: 6 weeks (+ 7-14 day placebo washout) Analysis: ITT	Inpatients. N=56. Age: 18-65. Diagnosis: DSM-III-R major depression, HRSD-21 \geq 20. Mean baseline HRSD: 35.7, placebo = 35.1.	1. Reboxetine (6mg- >10mg) 2. Placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Conducted in three centres in Canada and Brazil.	B

Characteristics of excluded studies

Study	Reason for exclusion
Farina2002	Not an RCT
Versiani99 Cont Y M	Not an acute phase trial

Venlafaxine - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
014Nemeroff Y O I IR	Allocation: Random (no details). Duration: 6 weeks (+ 7 day placebo). Analysis: ITT - LOCF	Outpatients. N = 308. Around 65% female. Age: 18+, mean = 40. Diagnosis: DSM-IV major depression, HRSD-21 \geq 20.	1. Venlafaxine IR (75mg up to 225mg) 2. Fluoxetine (20mg up to 60mg) 3. Placebo	1. Non-remitters (patients not achieving HRSD \leq 7)# 2. Leaving the study early due to side effects	Unpublished study. Baseline HRSD-21 scores: venlafaxine=23.5, fluoxetine=23.6, placebo=23.7	B
015Schatzberg E O I IR	Allocation: Random (no details). Duration: 8 weeks (+ 7 day placebo). Analysis: ITT - LOCF	Outpatients. N = 300. Around 50% female. Age: 65+, mean=71. Diagnosis: DSM-IV Major Depression, HRSD-21 \geq 20	1. Venlafaxine IR (75mg up to 225mg) 2. Fluoxetine (20mg up to 60mg) 3. Placebo	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD \leq 7)# 3. Leaving the study early due to side effects 4. Patients reporting side effects	Unpublished study. Baseline HRSD-21 scores: venlafaxine=23.7, fluoxetine=23.9, placebo=23.5	B

102Tsai Y O I XR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT - LOCF	Setting unclear. N = 66, age: 18+. Diagnosis: DSM-IV major depressive episode, HRSD-21 ≥ 18	1. Venlafaxine XR (75mg) 2. Fluoxetine (20mg)	1. Non-remitters (patients not achieving HRSD≤7)# 2. Non-responders (patients not achieving: ≥ 50% decrease in HRSD or MADRS and CGI-I 'much improved' or 'very much improved') 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Unpublished study.	B
332Rickels	Allocation: Random	Outpatients. N = 51,	1. Venlafaxine IR (150	1. Non-remitters (patients not achieving HRSD≤7)#	Unpublished study.	B

Y O I IR	(no details). Duration: 6 weeks (+ 7 day placebo). Analysis: ITT - LOCF	38 female, mean age = 36/39. Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 20	225mg, mean = 154mg) 2. Fluoxetine (20-40mg, mean=39mg)	2. Leaving the study early due to side effects 3. Patients reporting side effects	Baseline HRSD-21 scores: venlafaxine=23.6, fluoxetine=23	
349Wyeth ? O I IR	Allocation: Random (no details). Duration: 8 weeks (+ 7 day placebo). Analysis: ITT - LOCF	Outpatients. N = 167, around 66% female, age unclear. Diagnosis: DSM-III-R major depression	1. Venlafaxine IR (75mg up to 150mg) 2. Paroxetine (20mg up to 40mg)	1. Non-remitters (patients not achieving HRSD≤7)# 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting side effects	Unpublished study.	B
428Casabona Y O I XR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT - LOCF	Outpatients. N = 114, 88 female, age: 18+. Diagnosis: DSM-IV major depressive disorder, MADRS≥19	1. Venlafaxine XR (75mg) 2. Paroxetine (20mg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥ 50% decrease in HRSD) 3. Non-remitters (patients not achieving HRSD≤7) 4. Patients reporting side effects	Unpublished study. Baseline HRSD scores: venlafaxine=27.9, paroxetine=28	B
626Kornaat Y O I IR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT - LOCF	Outpatients. N = 156, 100 female, age: 18-70. Diagnosis: DSM-IV major depression, 25≥HRSD-21≥18	1. Venlafaxine (75-225mg) 2. Fluoxetine (20-40mg)	1. Non-remitters (patients not achieving HRSD≤8) 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects	Unpublished study. Baseline HRSD-21 scores: venlafaxine=22, fluoxetine=22	D
671Lenox-Smith Y ? I XR	Allocation: Random (no details). Duration: 12 weeks. Analysis: ITT - LOCF	Setting unclear. N = 406. around 66% female, age: 18-65. Diagnosis: DSM-IV Major depressive disorder. not responded to ≥8 weeks of SSRI treatment (not citalopram). HRSD-21≥20	1. Venlafaxine XR (75mg - 300mg) 2. Citalopram (20-60mg)	1. Leaving study early due to side effects 2. Patients reporting side effects	Unpublished study. Baseline HRSD-21 scores: venlafaxine=28.6, citalopram = 28.8	B

Alves1999 Y O I IR	Allocation: Random (using a balanced randomisation from randomly permuted blocks. Duration: 12 weeks. Analysis: ITT - LOCF	Outpatients. N = 87, 80 female, age: 18-68. Diagnosis: DSM-IV Major Depression, HRSD-21 \geq 20	1. Venlafaxine IR (75mg up to 150mg) 2. Fluoxetine (20mg up to 40mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD-17 mean endpoint scores# 4. Non-responders (patients not achieving: \geq 50% decrease in HRSD or MADRS and a CGI-I of 1 or 2 persisting to the end of the study, lasting \geq 2 weeks) 5. Patients reporting side effects 6. Non-remitters (patients not achieving HRSD \leq 8)	Conducted at 3 clinical sites in Portugal. Baseline HRSD-21 scores: venlafaxine: 27.9 (+-5.2), fluoxetine: 26.9 (+-3.9)	A
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Benkert1996 Y I I IR	Allocation: Random (no details). Duration: 6 weeks (+ 4 day placebo washout). Analysis: ITT - LOCF	Inpatients. N=167 (ITT=164), 114 female. Age: 19-70. Diagnosis: DSM-III-R major depression and melancholia, MADRS ≥ 30	1. Venlafaxine IR (75mg - >375mg by day 5 then decreased to 150mg on day 14) 2. Imipramine (50mg -> 200mg by day 5)	1. Leaving the study early 2. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 3. Leaving the study early due to side effects 4. HRSD mean endpoint scores 5. Patients reporting side effects	Conducted at 20 study centres in Europe. Baseline HRSD-21 scores: venlafaxine: 30.6(+6.3), imipramine: 28.8(+6.6)	B
Bielski2003 Y ? I XR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT	Setting unclear. N=198. Age: 18-65, mean=37. Diagnosis: DSM-IV major depressive disorder, HRSD-17 ≥ 20	1. Escitalopram (20mg) 2. Venlafaxine (225mg)	1. HRSD mean change scores 2. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 3. Non-remitters (patients not achieving HRSD ≤ 7) 4. Leaving the study early 5. Leaving the study early due to side effects	Baseline scores: escitalopram: HRSD-17=28.6, venlafaxine: MADRS=28.9+4.6, HRSD=27.4	B
Clerc1994 Y I I IR	Allocation: Random (no details). Duration: 6 weeks (+ 4 day placebo washout). Analysis: ITT - LOCF	Inpatients. N=68 (ITT sample = 67), 46 female. Age: 18+. Diagnosis: DSM-III-R major depression with melancholia, MADRS ≥ 25	1. Venlafaxine IR (200mg) 2. Fluoxetine (40mg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects 6. Non-remitters (patients not achieving HRSD ≤ 7)#	Conducted at sites in France and Belgium. Baseline HRSD-21 scores: venlafaxine: 29.1(+5.2), fluoxetine: 29.7(+4.2)	B
Costa 1998 Y O I IR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT - LOCF	Outpatients. N=382, 301 female. Age: 18-60. Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 20	1. Venlafaxine IR (75mg up to 150mg [dose increased in 22% patients]) 2. Fluoxetine (20mg up to 40mg [dose increased in 29% patients])	1. Leaving the study early 2. HRSD-17 mean endpoint scores# 3. Non-responders (patients not achieving: $\geq 50\%$ decrease in HRSD or MADRS and a CGI-I of 1 or 2) 4. Leaving the study early due to side effects 5. Non-remitters (patients not achieving HRSD ≤ 8) 6. Patients reporting side effects	Conducted at clinical sites in South America. Baseline HRSD-21 scores: venlafaxine: 30.4 (+6.2) or fluoxetine: 29.7 (+5.3)	B
Cunningham 1994 Y O I IR	Allocation: Random (no details). Duration: 6 weeks (+ 4-10 day placebo washout). Analysis: ITT - LOCF/ observed case	Inpatients and outpatients. N=227. Age: 18+, mean = 40.7 years old. Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 20	1. Venlafaxine IR (75-200mg, mean=156-160mg) 2. Trazodone (150-400mg, mean=294-300mg) 3. Placebo	1. Leaving the study early 2. Leaving the study early due to side effects	Conducted at 6 sites in the US Baseline HRSD-21 scores: venlafaxine: 25.02, trazodone: 24.66, placebo: 24.41	B
Dierick1996 Y O I IR	Allocation: Random (no details). Duration: 8 weeks. Analysis: ITT - LOCF (≥ 1 dose of	Outpatients N=314, 205 female. Age: 18-83. Diagnosis: DSM-III-R major depressive episode,	1. Venlafaxine IR (75mg up to 150mg) 2. Fluoxetine (20mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 4. Leaving the study early due to side effects	Baseline HRSD-21 scores: Venlafaxine: 27(+4.2), fluoxetine: 26.6(+4.1)	B

	treatment and ≥ 1 assessment)	HRSD-21 ≥ 20		5. Patients reporting side effects 6. Non-remitters (patients not achieving HRSD ≤ 7)#		
Guelfi2001 Y I I IR	Allocation: random, centrally pre-prepared randomisation list. Duration: 8 weeks (+3-7 day placebo washout). Analysis: ITT-LOCF (≥ 1 dose of treatment and ≥ 1 assessment)	Inpatients. N=157 (ITT=152), 103 female, mean age 45.2 (+/- ~10). Diagnosis: DSM-IV severe depressive episode with melancholic features; HRSD-17 ≥ 25	1 Venlafaxine IR (150mg increasing to 225mg/day by day 6 - then to increase to 375mg/day if necessary, mean=255mg) 2 Mirtazapine (15mg -> 45mg by day 6 - then to 60mg if necessary, mean=49.5mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. HRSD mean change scores 4. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 5. Non-remitters (patients not achieving HRSD ≤ 7) 6. Patients reporting side effects	Conducted in 33 centres in Europe. Baseline HRSD-17 scores: venlafaxine: 29.2(+2.9), mirtazapine: 29.5(+3)	A
Hackett1996 Y O I XR	Allocation: random (no details). Duration: 8 weeks. Analysis: ITT - LOCF	Outpatients. N=332. Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 20	1. Venlafaxine XR(75mg) 2. Venlafaxine XR (150mg) 3. Paroxetine (20mg) 4. Placebo Combined data for 1 & 2	1. HRSD-21 mean endpoint scores	Conducted at 35 centres in Europe. Unable to extract dichotomous data. Baseline HRSD-21 scores: 26.6	B
Lecrubier1997 Y PC I IR	Allocation: Random (no details). Duration: 13 weeks (+ 7-10 placebo washout). Analysis: ITT - LOCF (at least 1 dose of treatment and at least 1 assessment)	Primary care patients. N=229 (ITT=222), 106 female, mean age 39.8. Diagnosis: RDC major (79%), minor (14%) or intermittent (7%) depression	1. Venlafaxine IR (25mg -> 50mg on day 2 -> 75mg on day 5 up to 150mg by day 15, mean by week 2 = 104mg) 2. Imipramine (dose as above, mean by week 2 = 107mg) 3. Placebo	1. MADRS mean endpoint scores 2. Non-responders (patients not achieving $\geq 50\%$ decrease in MADRS) 3. Leaving the study early due to side effects 4. Leaving the study early 5. Patients reporting side effects	Includes unpublished data. Patients recruited or referred by GP, assessment conducted in 24 GP sites and 1 psychiatrist. Baseline MADRS scores: venlafaxine: 24.9, imipramine: 24.4, placebo: 24.2	B
Mahapatra 1997 E M I IR	Allocation: Random (no details). Duration: 6 weeks (+ 4-10 placebo washout). Analysis: ITT - LOCF	Inpatients and outpatients. N=92 (ITT=89), 64 female, Age: 64-87, mean age 74. Diagnosis: DSM-III-R major depression, HRSD-21 ≥ 18	1. Venlafaxine IR (25mg-> 75mg on day 2 up to 150mg by day 15) 2. Dosulepin/dothiepin (dose as above)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted at 9 sites in the UK and the Netherlands. Baseline HRSD-21 scores: venlafaxine: 29(+6), dosulepin/ dothiepin: 27(+5)	B

McPartlin 1998 YPC I IR	Allocation: Random (no details). Duration: 12 weeks. Analysis: ITT	Primary care patients. N=361 (ITT=336), 114 female. Age: 18-83.	1. Venlafaxine IR (75mg) 2. Paroxetine (20mg)	1. HRSD-17 mean endpoint scores# 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving: ≥50%)	Conducted at general practice sites in the UK. Baseline HRSD-17 scores: 23(+4).	B
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		Diagnosis: DSM-IV major depression, MADRS \geq 19		decrease on HRSD or MADRS and CGI-I 1 or 2) 5. Non-remitters (patients not achieving HRSD<7)		
Montgomery 2002 Y P I XR	Allocation: Random (no details). Duration: 8 weeks Analysis: responder and remission data given for observed cases only (data extracted as ITT for this review).	Primary care patients. N=293. Age: 18-85. Diagnosis: DSM-IV major depressive disorder, MADRS \geq 18.	1. Escitalopram (10mg-20mg, mean = 12.1mg, 22% patients received 20mg) 2. Venlafaxine (75-150mg, mean=95.2mg)	1. Non-responders (patients not achieving \geq 50% decrease in MADRS) 2. Non-remitters (patients not achieving MADRS \leq 12) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Baseline scores: escitalopram - MADRS = 28.7, venlafaxine - MADRS = 29	B
Poirier1999 Y M I IR	Allocation: Random (in blocks of 4). Duration: 4 weeks. Analysis: ITT - LOCF	Treatment resistant inpatients and outpatients. N=123 (ITT=122). 88 female. Age: 21-62. Diagnosis: DSM-III-R major depression, HRSD-17 \geq 18	1. Venlafaxine IR (75mg- > 200mg-300mg. mean = 269 +- 46.7) 2. Paroxetine (20mg up to 30-40mg. mean = 36.3mg +- 4.9)	1. HRSD-17 mean endpoint scores 2. Non-responders (patients not achieving: \geq 50% decrease in HRSD and a CGI-I of 1 or 2) 3. Leaving the study early due to side effects 4. Leaving the study early 5. Non-remitters (patients not achieving HRSD<10) 6. Patients reporting side effects	Baseline HRSD-17 scores: venlafaxine: 24.6(+3.9), 18-35. paroxetine: 24.5(+4.1), 18-34.	B
Rudolph1999 Y O I XR	Allocation: Random (in blocks of 6 using a table of random numbers). Duration: 8 weeks (+ 4-10 day placebo washout). Analysis: ITT - LOCF or observed case	Outpatients. N=301 (ITT=295). Age: 18-80, mean age 40. Diagnosis: DSM-IV major depressive disorder, HRSD-21 \geq 20	1. Venlafaxine XR (75-225mg, mean = 175mg) 2. Fluoxetine (20-60mg, mean = 47mg) 3. Placebo	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-remitters (patients not achieving: HRSD \leq 7) 5. Non-responders (patients not achieving: \geq 50% decrease in HRSD)	Conducted at 12 outpatient psychiatric clinics and private psychiatric practices in the US. Baseline HRSD-21 scores: venlafaxine: 25 (20-38), fluoxetine: 26 (19-38), placebo: 25 (20-34)	B
Samuelian 1998 Y O I IR	Allocation: Random (no details). Duration: 6 weeks (+4-10 day placebo washout). Analysis: ITT - LOCF	Outpatients. N=102 (ITT=97), 53 female. Age: 18-79, mean age=47. Diagnosis: DSM-III-R major depression, MADRS \geq 24	1. Venlafaxine IR (50mg - > 100mg by day 7 up to 150mg, mean = 105mg) 2. Clomipramine (as above)	1. HRSD-21 mean endpoint scores 2. Leaving the study early 3. Non-responders (patients not achieving \geq 50% decrease in HRSD) 4. Leaving the study early due to side effects 5. Patients reporting side effects	Conducted at 3 clinical sites in Portugal. Baseline HRSD-21 scores: 28 (+7)	B

Schweizer 1994 Y O I IR	Allocation: Random (no details). Duration: 6 weeks (+ 4-10 day placebo	Outpatients. N = 224 (ITT=213). Diagnosis: DSM-III-R major depression, HRSD-21	1 Venlafaxine IR (75mg up to 225mg, mean at week 6 = 179 +- 52) 2. Imipramine (75mg up	1. HRSD mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving $\geq 50\%$	Baseline HRSD-21 scores: venlafaxine: 25.5 (+3.4), imipramine: 24.2 (+2.9) or placebo: 24.6 (+2.9)	B
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181

	washout). Analysis: ITT - LOCF (at least 3 days of treatment)	≥ 20	to 225mg, mean at week 6= 170+60mg) 3. Placebo	decrease in HRSD)		
Silverstone 1999 Y O I X R	Allocation: Random (no details). Duration: 12 weeks (+ 7-10 day placebo washout). Analysis: ITT - LOCF	Outpatients. N= 368 (ITT=359), 217 female. Age: 18-71. Diagnosis: DSM-IV major depressive disorder, HRSD-17 ≥ 20	1. Venlafaxine XR (75mg-225mg, mean = 111.2mg in week 4) 2. Fluoxetine (20mg-60mg, mean = 30.7 in week 4) 3. Placebo	1. HRSD mean endpoint scores 2. Leaving the study early 3. Non-responders (patients not achieving ≥ 50% decrease in HRSD) 4. Leaving the study early due to side effects 5. Patients reporting side effects 6. Non-remitters (patients not achieving HRSD≤7)	All patients had concomitant anxiety. Includes unpublished data. Baseline HRSD-21 scores: venlafaxine: 27.6(+5.1), fluoxetine: 27(+4.6), placebo: 27.1(+4.5)	B
Smeraldi1998 E M I I R	Allocation: Random (no details). Duration: 6 weeks (+ 7 day placebo washout). Analysis: ITT - LOCF	Inpatients, outpatients and day hospital patients. N=170, 127 female. Age: 65+. Diagnosis: DSM-III-R major depression, MADRS ≥ 24	1. Venlafaxine IR (37.5mg -> 75mg up to 150mg, mean = 83.2) 2. Clomipramine (25mg-> 50mg up to 100mg, mean = 61.5mg) 3. Trazodone (50mg -> 150mg, mean = 180) Extracted data from 1 and 2 only	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving: ≥ 50% decrease in HRSD or MADRS) 5. Patients reporting side effects	Baseline HRSD scores: venlafaxine: 28.2 (+5.7), clomipramine: 28.2 (+5.2), trazodone: 27.5 (+5.9)	B
Tylee1997 Y P C I I R	Allocation: Random (by the permuted blocks method). Duration: 12 weeks. Analysis: ITT	Primary care patients. N = 341, 97 female. Age: 18-85. Diagnosis: DSM-IV major depression, MADRS ≥ 19	1. Venlafaxine IR (75mg) 2. Fluoxetine (20mg)	1. HRSD mean endpoint scores# 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving: ≥ 50% decrease in HRSD or MADRS and a CGI-I of 1 or 2, final on therapy results) 5. Non-remitters (patients not achieving MADRS≤6) 6. Patients reporting side effects	Patients recruited through 34 general practices in the UK. Baseline HRSD scores: venlafaxine: 22.4 (+5), fluoxetine: 22.5 (+4.4)	B
Tzanakaki 2000 Y M I I R	Allocation: Random (no details). Duration: 6 weeks (+ 7 day placebo). Analysis: ITT - LOCF	Inpatients and outpatients. N=109, 86 female. Age: 18-64. Diagnosis: DSM-IV major depression with melancholia, MADRS ≥ 25	1. Venlafaxine IR (75mg -> 150mg->225mg) 2. Fluoxetine (20mg -> 40mg-> 60mg)	1. HRSD-17 mean endpoint scores# 2. Leaving the study early 3. Leaving the study early due to side effects 4. Non-responders (patients not achieving: ≥ 50% decrease in HRSD or MADRS and a CGI-I of 1 or 2) 5. Non-remitters (patients not achieving HRSD<7) 6. Patients reporting side effects	Baseline HRSD-21 scores: venlafaxine: 27.8 (+5.6), fluoxetine: 27.1 (+5.6)	B

Data supplied by manufacturers (Wyeth Laboratories).

Characteristics of excluded studies

Study	Reason for exclusion
016Cantillon	Unable to confirm, from trial report, that diagnosis was made using formal criteria
347 Hackett2000	Number of patients in trial is unclear; study report states that 92 patients were randomised but COMPARE study gives ITT sample as 111
372 Calabrese1998	Unable to confirm that venlafaxine was administered to patients at a therapeutic dose
632 Andersson1998	Unable to confirm, from trial report, that diagnosis was made using formal criteria
654 Stevens1997	Unable to ascertain how many patients were enrolled or how many were randomised to each treatment group
Amsterdam1998 (US)	Not relevant comparison for this review (once versus twice-daily venlafaxine)
Ballus2000 Y O I IR	Inclusion criteria were ICD-10 mild-moderate depression or dysthymia, number of patients diagnosed with dysthymia not given
Cunningham1997 (US)	Not relevant comparison for this review (extended release versus immediate release)
Dallal1998 (Can)	Not an RCT
de Montigny99 (Can)	Not an RCT
De Nayer2002	Inadequate diagnosis of depression
Diaz-Martinez1998	Open-label study/not double blind
Entsuah1996 (US)	Not relevant comparison for this review (venlafaxine versus placebo)
Entsuah1997 (US)	Not relevant comparison for this review (extended release versus immediate release)
Entsuah2001 (US)	Not an RCT (pooled analysis of 8 RCTs already included in the review)
Fava1997 (US)	Not relevant comparison for this review (investigation of discontinuation effects in venlafaxine versus placebo)
Geerts1999	Abstract only; full publication of results in DeNayer2002
Gentil2000 (Brazil)	Average dosage of comparator drug is < 105% of the therapeutic level; mean dose of amitriptyline between days 15 and 36 = 103.1mg; 50% patients were receiving only 75mg amitriptyline
Guelfi1995 (Fr)	Not relevant comparison for this review (venlafaxine versus placebo)
Mehtonen2000 (Fin)	< 75% of patients were on \geq 100mg of comparator drug; 64% patients were given 100mg sertraline, 36% were given 50mg
Mendels1993 (US)	Not relevant comparison for this review (dosage effects in venlafaxine versus placebo)
Michelson1999 (US)	Not an RCT
Morton1995 (US)	Not an RCT (analysis of RCTs already included in this review)
Ravindran1998 (Can)	Not relevant comparison for this review (all patients received venlafaxine)
Rudolph1998	Not relevant comparison for this review (dose response, placebo controlled trial)
Schweizer1991 (US)	Not relevant comparison for this review (dosage investigation of venlafaxine versus placebo)
Shrivastava94 (US)	Presence of comorbid mental illness; 4% of patients with substance misuse, 1% of patients with panic disorder
Smith1996	Not relevant comparison for this review (venlafaxine versus placebo)
Stanley1998	Inadequate diagnosis of depression; no useable data
Taylor1996	Not relevant comparison for this review (extended release versus immediate release)
Thase1997 (US)	Not relevant comparison for this review (venlafaxine versus placebo)
Wyeth600 XR	Inadequate diagnosis of depression

Zanardi2000 (Italy)

> 15% of patients were diagnosed with bipolar disorder; 6/28 patients had bipolar disorder = 21.4%

von Bardeleben1989	There were only 2/14 patients in the placebo arm
Wade2002 E Y P I	No citalopram arm - escitalopram versus placebo
Wakelin 1986	Sub-analysis of elderly patients from Amin1984, Itil1983 and Block1983
White1990	Reports results of crossover from desipramine to fluvoxamine in desipramine non-responders; unable to locate publication of acute phase trial

Gender effects on antidepressant efficacy - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Quitkin 1990 Y O I	Allocation: Random (no details) Duration: 6 weeks	Outpatients. N=285. Age: 18-65. Diagnosis: DSM-III or DSM-III-R major depressive disorder. 67.4% patients had atypical features.	1. Phenelzine (60mg up to 90mg) 2. Imipramine or desipramine (150-300mg)	1. Non-responders (patients not achieving ≥50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD<8) 3. HRSD mean endpoint scores	Sample comprises of a sub-set of the individual patient data supplied by author	B

Characteristics of excluded studies

There were no excluded studies.

Psychotic depression - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Anton 1990 Y I I	Allocation: Random (no details). Duration: 4 weeks. Analysis: ITT	Inpatients. Age: 18-65, mean= 44-46. N=46. Diagnosis: DSM-III major depression with psychotic features, HRSD-17 \geq 18 (between 13 and 17.4% patients diagnosed with	1. Amitriptyline (150-250mg) + perphenazine (24-40mg) 2. Amoxapine (300-400mg)	1. Non-responders (patients not achieving \geq 50% decrease in HRSD) 2. HRSD mean endpoint scores		B

189

		bipolar disorder)		3. leaving the study early		
Bellini 1994 Y I I	Allocation: Random (no details). Duration: 6 weeks (+7 day washout). Analysis: ITT	Inpatients. N=48. Age: 18-65. Diagnosis: DSM-III-R major depressive episode with congruent or incongruent psychotic features (25% patients diagnosed with bipolar disorder)	1. Desipramine + haloperidol 2. Desipramine + placebo 3. Fluvoxamine + haloperidol 4. Fluvoxamine + placebo	1. Non-responders (patients not achieving $\geq 50\%$ decrease in HRSD)	Included in ' $\leq 25\%$ bipolar' analysis only	B
Mulsant 2001 E I I	Allocation: Random (no details). Duration: 2-16 weeks, mean=8.4. Analysis: ITT (≥ 2 weeks treatment)	Inpatients. N=36. Age: 50+, mean = 71-74. Diagnosis: DSM-III-R major depressive episode with psychotic features	1. Nortriptyline + perphenazine (4-24mg) 2. Nortriptyline + placebo	1. Non-remitters (patients not achieving HRSD ≤ 10) 2. HRSD mean endpoint scores		B
Spiker 1985 Y I C	Allocation: Random (no details). Duration: 5 weeks. Analysis: Completer	Inpatients. N=58. Age: 18-65, mean=44.1 (data extracted for 41 patients in interventions 1 and 2). Diagnosis: RDC primary major depressive disorder, psychotic subtype, HRSD-17 ≥ 15 (14.6% of 41 patients used in analysis diagnosed with bipolar disorder)	1. Amitriptyline (mean=170mg) + perphenazine (mean = 54.2mg) 2. Amitriptyline (mean=217.6mg) 3. Perphenazine	1. Non-remitters (patients not achieving HRSD ≤ 6) 2. HRSD mean endpoint scores 3. Leaving the study early	Extracted data for interventions 1 and 2 only.	B
Zanardi 1996 Y I I	Allocation: Random (no details). Duration: 6 weeks. Analysis: ITT	Inpatients. N=46. Age: mean = 52-60. Diagnosis: DSM-III-R major depressive episode with mood congruent or mood incongruent psychotic features (14 patients diagnosed with bipolar)	1. Sertraline (150mg) 2. Paroxetine (50mg)	1. Non-remitters (patients not achieving HRSD ≤ 8) 2. Leaving the study early 3. Leaving the study early due to side effects	Extracted data for 32 unipolar patients only	B
Zanardi 2000 Y I I	Allocation: Random (no details). Duration: 6 weeks. Analysis: ITT	Inpatients. Age: 18-65. N= 28. Diagnosis: DSM-IV severe major depression with psychotic features (21.4% patients diagnosed with bipolar disorder)	1. Fluvoxamine (300mg) 2 Venlafaxine (300mg)	1. Non-remitters (patients not achieving HRSD ≤ 8) 2. Leaving the study early 3. Leaving the study early due to side effects	Included in ' $\leq 25\%$ bipolar' analysis only.	B

Characteristics of excluded studies

Braus2000	Two case studies not an RC 1
Casacchia1984	Only 56% of patients were diagnosed with unipolar psychotic depression, 44% were diagnosed with neurotic depression
Davidson1982	Inadequate diagnosis of depression; N=6
Friedman1966	Inadequate diagnosis of depression
Furlong1977	Inadequate description of diagnosis and randomisation method
Hackett1969	Inadequate diagnosis of depression

Kocsis1990	Not a relevant comparison so no useable data; study compared psychotic patients with non-psychotic patients rather than two treatments
McClure1973	Inadequate diagnosis of depression
Roy1973	Inadequate diagnosis of depression
Sacchetti1997	Letter not full publication of trial; does not give number of patients randomised to each group or mention whether the study was double blind; further publications could not be found
Smeraldi1998	30% of patients were diagnosed with bipolar depression
Vinar1971	Inadequate diagnosis of depression
Zanardi1998	30% of patients were diagnosed with bipolar depression
Zanardi2001	30% of patients were diagnosed with bipolar depression

Low dose tricyclics - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Burch 1988 Y I C	Allocation: Random (no details) Duration: 6 weeks Analysis: completer	Inpatients. N=71. Age: 18-65. Diagnosis: Primary depressive illness according to Feighner criteria	1. Amitriptyline (mean=40 mg, range: 28-70 mg) 2. Amitriptyline (mean=109mg, range 55-180mg) 3. Amitriptyline (mean=202 mg, range: 136-280 mg)	1. MADRS mean endpoint scores 2. Non-remitters (patients not achieving MADRS≤9) 3. Leaving the study early	Extracted low (1) and high (3) dose data only as some patients in medium dose group (2) were on as low as 55mg/d	B
Danish 1999 Y M I	Allocation: Random (no details) Duration: 6 weeks. Analysis: LOCF	Outpatients and inpatients. N=151. Age: 18-70, mean=43 years old. Diagnosis: DSM-III-R major depression, HRSD≥18	1. Clomipramine 25 mg 2. Clomipramine 50 mg 3. Clomipramine 75 mg 4. Clomipramine 125 mg 5. Clomipramine 200 mg	1. Non-remitters (patients not achieving HRSD ≤7) 2. Leaving the study early 3. Leaving the study early due to side effects	Dichotomous data: Added together 25mg, 50mg &75mg for low dose and 125mg & 200mg for high dose	B
Rouillon	Allocation: Random	Outpatients. N=181. Age: 18-65.	1. Clomipramine (75mg up to	1. MADRS mean endpoint scores	177 patients included	B

1994 Y O I	(no details) Duration: 8 weeks Analysis: ITT (patients completing 2 weeks treatment.)	Diagnosis: DSM-III-R major depressive episode in partial remission, 15=<MADRS≤25, resistant to 2 antidepressants at adequate doses.	150mg - 30% received increased dose, mean = 97.5mg) 2. Placebo	2 Non-remitters (patients not achieving MADRS≤10)	in tolerability analyses, no details of 4 patients who dropped out after randomisation	
Simpson 1988 Y O C	Allocation: Random (no details).Duration: 6 weeks. Analysis: completer	Outpatients. N=34. Age: 22-60, mean =40 years. Diagnosis: RDC endogenous major depression.	1. Trimipramine (75 mg) 2. Trimipramine (150 mg)	1. HRSD-21 mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD or HRSD ≤10) 3. Non-remitters (patients not achieving HRSD≤7)	Completer data only, no details given on 14 dropouts.	B
WHO 1986 Y M I	Allocation: Random (no details).Duration: 4 weeks. Analysis: ITT	Outpatients and inpatients. N=186. Age: 18-60. Diagnosis: ICD 9: major depression, bipolar depression, reactive depressive psychosis, neurotic depression, adjustment disorder.	1. Amitriptyline or imipramine (37.5-75mg) 2. Amitriptyline or imipramine (75-150mg)	1. Non-responders (patients not achieving ≥50% decrease in HRSD)		B

Characteristics of excluded studies

Study	Reason for exclusion
Ahmed1988	Patients not diagnosed with depression
Blashki1971	Inadequate diagnosis; no mention of randomisation
Brick1962	Inadequate diagnosis
Couch1979	Patients being treated for migraine, no diagnosis of depression
Diamond1971	Patients being treated for chronic tension headache, no diagnosis of depression
Fryer1963	Inadequate diagnosis
Goldberg1972	Inadequate diagnosis; patient diagnosed with anxiety neurosis
Goldberg 1980	Inadequate diagnosis
Hollanda1970	Unable to obtain a full report; probably ineligible according to details given in Furukawa included table; methods: '.....depression according to traditional criteria, mainly adult (range 17-58)'; outcomes: 'Noticeable to moderate change on overall global improvement'
Hormazabal1985	55% of amitriptyline and placebo patients diagnosed with prolonged adjustment reaction
Houston1983	Inadequate diagnosis
Jacobson1978	Inadequate diagnosis
Jenkins1976	Patients being treated for low back pain, no diagnosis of depression

Kerr1970	Inadequate diagnosis
Laederach1999	Patients were described as 'obese binge eaters'

Lecrubier1997	Patients in imipramine group all received 100mg, which is an acceptable, therapeutic, dose
Macfarlane1986	Patients were being treated for rheumatoid arthritis, no diagnosis of depression
Morakinyo1970	Inadequate diagnosis
Murphy1976	Inadequate diagnosis
Nandi1976	Inadequate diagnosis
Petracca1996	Patients were diagnosed as having 'probably Alzheimer's disease'
Philipp1999	Patients in imipramine group all received 100mg, which is an acceptable, therapeutic dose
Rampello1995	Bipolar depression formed part of inclusion criteria, numbers not given
Reifler1989	All patients were diagnosed with Alzheimer's disease.
Rickels1970A	Inadequate diagnosis
Rickels1974	Inadequate diagnosis
Robertson127	Patients were being treated for epilepsy
Schweizer1998	Patients were aged 65-89; mean dose imipramine was 89mg which is a therapeutic dose for the elderly
Tan1994	Inadequate diagnosis; patients were over 65 years old and being treated with 70mg lofepramine
Tetreault1966	Inadequate diagnosis
Thompson1989	Inadequate diagnosis
Tyrer1988	Patients were diagnosed with generalised anxiety disorder (71), panic disorder (74) or dysthymic disorder (65)
Weissman1992	Patients were aged 60-85; mean dose imipramine was 97.5mg which is a therapeutic dose for the elderly; in addition all patients received inter-personal therapy as well as pharmacotherapy

Switching strategies - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Thase 2002a Y O 1	Allocation: Random (no details) double-blind. Duration: 12 weeks. Analysis: ITT	Outpatients. N=168, 112 female. Age: 21-65. Diagnosis: DSM-III-R major depressive disorder, HRSD-24 \geq 18. No response to 12 weeks randomised, double-blind treatment with sertraline or imipramine.	1. Patients previously on imipramine switched to sertraline (mean=163+-48mg) 2. Patients previously on sertraline switched to imipramine (mean=221+-84mg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving \geq 50% decrease in HRSD + HRSD \leq 15 + CGI-I 1 or 2 + CGI-S \leq 3) 3. Leaving the study early		B

Characteristics of excluded studies

There were no excluded studies.

Treatment-resistant depression - studies in previous guideline

Characteristics of excluded studies

Study	Reason for exclusion
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Amsterdam1987	No extractable data
Amsterdam1997	Naturalistic open trial - not an RCT

Arnheim2003	Not an RCT
Bauer2000	Patients did not have treatment resistant depression
Bell1998	Not an RCT - case report of 1 patient
Braus2000	Case studies, not an RCT
Charney1986	No useable data
Clunie2001	Abstract only, unable to locate full written report
Dabkowska1993	Not an RCT
Davidson1978	No useable data
Delgado1988	Not an RCT
Dinan1989	27% patients diagnosed with bipolar disorder
Dinan1996	Not an RCT
Dube2002	Abstract only; unable to find full publication
Dursun2001	Case studies; not an RCT
Ebert1995	Matched pairs - not an RCT
Feet1985	No useable data
Gonul1999	Abstract only, unable to obtain full publication
Heninger1983	Inadequate randomisation method: 'the 1st 3 to enter the study received lithium, the 2nd 3 placebo, and thereafter patients were assigned in alternating order to placebo or lithium while we attempted to balance as near possible the placebo and lithium within AD drug treatment groups' (N=15, patients were receiving a variety of ADs).
Inoue1996	Not an RCT
Kantor1986	Inadequate description of randomisation; 6/13 patients were removed from the analyses for 'methodologic contamination'
Katona1995	Sample included patients diagnosed with bipolar depression, numbers not given
Kramlinger1989	Not an RCT
Landen1998	Patients with bipolar disorder enrolled as part of the inclusion criteria; number of patients in study with bipolar disorder not specified
Maes1999	Only 65% patients had treatment resistant depression
McGrath1987	Less than 80% patients diagnosed with major depression
McGrath1993	Less than 80% patients diagnosed with major depression
Moreno1997	Once patients with comorbid personality disorder had been removed from sample there were only 5 patients left; in 2 of these patients presence of comorbid axis I disorder was unknown; patients only received each treatment (pindolol or placebo) for 2 weeks before being crossed over to the other
Nolen1993	20% patients diagnosed with bipolar disorder

Peet2002	Inadequate diagnosis
Rolighed1997	Not an RCT

Rosan1995	Unable to obtain report to ascertain eligibility
Rybakowski1999	30% patients were diagnosed with bipolar disorder
Sackeim2001 1	Patients did not have treatment resistant depression
Schopf1989	33.3% patients were diagnosed with bipolar disorder
Sethna1974	Inadequate diagnosis of depression
Sunderland1994	Crossover trial, unable to extract any useable data
Thase2002	Review not an RCT
Vinar1996	Not an RCT
White1990	Crossover/switch strategy trial from fluvoxamine to desipramine and vice versa; only patients switched from fluvoxamine to desipramine described therefore there is no comparator arm

Augmentation with a second antidepressant - studies in previous guideline

Characteristics of included studies

	Duration: 4 weeks Analysis:	disorder, HRSD-17 ≥ 16	Non-responders ($\leq 50\%$ decrease in HRSD and HRSD ≥ 10) randomised to phase 2: 1. Fluoxetine (40-60mg) 2. Fluoxetine (20mg) + lithium (300-600mg) 3. Fluoxetine (20mg) + desipramine	achieving HRSD ≤ 7 3. Leaving the study early due to side effects 4. Leaving the study early		
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218

Fava2002 Y O	Allocation: Random (no details) Duration: 4 weeks	Outpatients. N=101. Age: 18-65. Diagnosis: DSM-III-R major depressive disorder, HRSD-17 \geq 16	Phase 1: Patients treated openly with fluoxetine (20mg) for 8 weeks. Non-responders (\leq 50% decrease in HRSD and HRSD \geq 10) randomised to phase 2: 1. Fluoxetine (40-60mg) 2. Fluoxetine (20mg) + lithium (300-600mg) 3. Fluoxetine (20mg) + desipramine	1. HRSD mean endpoint scores 2. Non-remitters (patients not achieving HRSD \leq 7) 3. Leaving the study early	Same protocol as Fava1994 but different patient sample.	B
Ferreri2001 Y M	Allocation: Random (no details). Duration 6 weeks (following 6 weeks treatment with fluoxetine (20mg)) Analysis: LOCF	Inpatients and outpatients. N=104. Age: 18+. Diagnosis: DSM-III-R major depression, HRSD \geq 25	Phase 1: 6 weeks' fluoxetine (20mg) patients with HRSD \geq 25 randomised to phase 2: 1. Fluoxetine (20mg) 2. Fluoxetine (20mg) + mianserin (60mg) 3. Mianserin (60mg)	1. HRSD mean change scores 2. Non-responders (patients not achieving \geq 50% decrease in HRSD) 3. Non-remitters (patients not achieving HRSD \leq 8) 4. Leaving the study early 5. Patients reporting side effects 6. Leaving the study early due to side effects		B
Licht2002 Y O	Allocation: Random (no details). Duration: 5 weeks (following 6 weeks treatment with sertraline). Analysis: LOCF	Outpatients. N=295, aged: 18-65. Diagnosis: DSM-IV Major depressive disorder without psychosis	Phase 1: All patients received open treatment of 50mg sertraline for 4 weeks, those who did not respond went onto phase 2: further 2 weeks of sertraline at 100mg. Those who did not respond randomised to phase 3: 1. 100mg sertraline + placebo 2. 100 mg sertraline + 30mg mianserin 3. 200mg sertraline	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving \geq 50% decrease in HRSD) 3. Non-remitters 4. Leaving the study early 5. Leaving the study early due to side effects 6. Patients reporting side effects		B
Maes1999 Y I	Allocation: Random (no details). Duration: 5 weeks (+ 10 day washout) Analysis: LOCF	Inpatients. N=34. Age: 25-70. Diagnosis: DSM-III-R major depression, HRSD \geq 16. 22 patients with treatment resistant depression (Thase and Rush stage 1).	1. Fluoxetine (20mg) 2. Fluoxetine (20mg) + pindolol (7.5mg) 3. Fluoxetine (20mg) + mianserin (30mg)	1. HRSD-17 mean change scores 2. Non-responders (patients not achieving \geq 50% decrease in HRSD-17)	Conducted on a treatment resistant depression ward in a Belgian hospital	B

Tanghe1997 Y I	Allocation: Random (no details). Duration:	Inpatients. N=59. Age 18-69, mean = 43+- 12. Diagnosis: DSM-III-R major	1. Amitriptyline (up to 280mg) 2. Amitriptyline (up to 280mg) +	1.MADRS mean endpoint scores		B
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	4 weeks	depressive episode and treatment resistance to ≥ 2 antidepressants	moclobemide (200-600mg) 3. Moclobemide (200-600mg)			
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Characteristics of excluded studies

Study	Reason for exclusion
Amsterdam1997	Naturalistic open trial - not an RCT
Ebert1995	Matched pairs - not an RCT
Lafon1986	Unable to confirm randomisation method
Lauritzen1992	Unclear diagnoses of ITT sample
Maes1996	Dose of trazodone below therapeutic level
Murphy1977	Inadequate diagnosis of depression
Sethna1974	Inadequate diagnosis of depression
Young1979	Inadequate diagnosis of depression

Augmentation with antipsychotics - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Shelton2001 3	Allocation: Random (no details). Duration: 8 weeks. Analysis: LOCF	Outpatients. N=28, mean age = 42 +-11. Diagnosis: DSM-IV recurrent major depression without psychotic features, resistant to conventional antidepressant treatment (failure to respond to 2 antidepressants (one of which was not an SSRI) after 4 weeks at a therapeutic dose, HRSD-21 \geq 20	6 weeks open label treatment with fluoxetine, non-responders randomised to: 1. Fluoxetine (20-60mg) + olanzapine (5-20mg) 2. Fluoxetine (20-60mg)+ placebo 3. Olanzapine (5-20-mg) +placebo	1. Non-responders (patients not achieving \geq 50% decrease in MADRS) 2. Leaving the study early		B

Characteristics of excluded studies

There were no excluded studies.

Augmentation with benzodiazepines - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Feet 1985 Y O	Allocation: Random (no details) Duration: 8 weeks	Outpatients. N= 63. Age: 20-64, mean=45 Diagnosis: Feighner-Robins-Guze criteria for primary depression. All patients were previously treated in general practice without success.	1. Imipramine (100-200mg, mean = 200mg) + diazepam (10mg) 2. Imipramine (100-200mg, mean=175mg) + placebo 3. Imipramine (100-200mg, mean = 150mg) + dixyrazine (50mg)	1. Leaving the study early 2. Leaving the study early due to side effects		B
Nolen 1993 Y I	Allocation: Random (no details) Duration: 30 days (+ 8 day washout) Analysis: ITT -LOCF (except patients who dropped out before day 16 who were excluded from analysis)	Inpatients. N= 53. Age: 20-65 Diagnosis: DSM-III-R major depression, HRSD≥18. 32 patients had recurrent major depression, 31 Pts had pre-morbid personality disorder, 4 patients had bipolar depression.	1. Maprotiline or nortriptyline (100mg->150mg) + flunitrazepam(2mg) 2. Maprotiline or nortriptyline (100mg->150mg) + lormetazepam(2mg) 3. Maprotiline or nortriptyline (100mg->150mg) + placebo	1. Non-responders (patients not achieving ≥50% decrease on HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects		B
Scharf 1986 Y M	Allocation: Random (no details) Duration: 8 weeks (+ 2 week placebo washout) Analysis: Completer	Inpatients and outpatients. N= 20. Age: mean=34.8 Diagnosis: DSM-III clinically depressed, HRSD≥20 and insomnia.	1. Amitriptyline (50mg->150mg, mean=110mg) + chlordiazepoxide (20mg->60mg, mean=44mg) 2. Amitriptyline (50mg->150mg, mean=122.5mg)	1. Leaving the study early 2. Leaving the study early due to side effects 3. Patients reporting side effects		B
Smith 1998 Y O	Allocation: Random (no details) Duration: 3 weeks (+ 5 weeks discontinuation study) Analysis: ITT -LOCF	Outpatients. N= 81. Age: 18+ Diagnosis: DSM-IV non-psychotic major depressive disorder, HRSD≥18	1. Fluoxetine (20mg) + clonazepam (0.5mg up to 1mg) 2. Fluoxetine (20mg) + placebo	1. Non-responders (patients not achieving ≥50% decrease on HRSD) 2. Leaving the study early	1. Patient dropped out on day 4 and was replaced. This patient was included in safety analysis but not efficacy.	B

Smith 2002 Y O	Allocation: Random (no details) Duration: 12 weeks (+ 6 weeks taper) Analysis: LOCF	Outpatients. N=52. Age: 18-65 Diagnosis: DSM-IV major depression, 18≤HRSD≤26	1. Fluoxetine (20mg up to 40mg) + clonazepam (0.5mg up to 1mg) 2. Fluoxetine (20mg up to 40mg) + placebo	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease on HRSD) 3. Non-remitters (patients not achieving HRSD ≤8)	2 patients failed to provide data at day 7 and were excluded from efficacy analysis. Replication of Smith 1998	B
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Characteristics of excluded studies

Study	Reason for exclusion
Calcedo1992	Open label design - not double blind
Dominguez1984 Y O	No interpretable data
Fawcett1987	22% (17/79) of patients were diagnosed with bipolar depression according to RDC criteria.
Feighner1979	Only 42% patients were diagnosed with unipolar depression, 10% had bipolar depression whilst 48% had a history that was insufficient for further classification (according to Feighner criteria)
Yamaoka1994	Paper is in Japanese, unable to translate in order to assess eligibility.

Augmentation with Buspirone - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Appelberg 2001 Y M 1	Allocation: Random (no details) Double blind. Duration: 6 weeks (+ 2wk placebo washout) Analysis: ITT	Outpatients. N=108. Age: 18+. Diagnosis: DSM-IV major depressive disorder. Treated with fluoxetine or paroxetine for ≥6 weeks with no improvement.	1. (Fluoxetine (≥30mg) or citalopram(≥40mg)) + buspirone (20-60mg) 2. (fluoxetine(≥30mg) or citalopram(≥40mg)) + placebo	1. Leaving study early 2. Leaving study early due to side effects		B

Characteristics of excluded studies

There were no excluded studies.

Augmentation with lithium - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
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Baumann 1996 Y I AN	Allocation: Random (no details) Duration: (1 week washout + 4 weeks open treatment) 1 week of randomised treatment (+ 1 week open treatment)	Inpatients. N=24. Aged: 18-65. Diagnosis: DSM-III single episode depressive disorder, recurrent depressive disorder, bipolar: depressed (1 patient) or dysthymic disorder (1 patient)	Phase 1: Citalopram (40mg up to 60mg) for 4 weeks. Non- responders through to phase 2. Randomisation to: 1. Lithium 800mg 2. Placebo for 1 week Phase 3: All patients received	1. HRSD mean endpoint scores 2. Non-responders (Patients not achieving ≥50% decrease in HRSD)	Planned plasma levels: 0.5- 0.8mmol/L. Mean on day 1= 0.75+- 0.22mmol/L, mean on day 7 =0.5+-	B
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	Analysis: ITT		lithium for 1 week.		0.24mmol/L	
Bloch1997 Y O	Allocation: Random (no details) Duration: 5 weeks (+ 1 week washout) Analysis: ITT	Outpatients. N=31. Age: 26-75. Diagnosis: DSM-III-R non-psychotic major depression, non treatment-resistant, HRSD≥18. (6% patients diagnosed with bipolar disorder.)	1. Desipramine (150-300mg, median=200mg) + lithium (600mg up to 900 mg, median = 900mg) 2. Desipramine (dose as above) + placebo	1. HRSD mean endpoint scores 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving ≥50% decrease in HRSD and HRSD≤16 and 'much' or 'markedly' improved on CGI) 4 Non-remitters (patients not achieving HRSD≤10) 5. Leaving the study early	Planned plasma level: 0.7-1.0mEq/L. Mean = 0.77+-0.28mEq/L	B
Cappiello 1998 Y M	Allocation: Random (no details) Duration: 5 weeks (+ 2 weeks' placebo lead in). Analysis: LOCF (≥2 weeks treatment)	Inpatients and outpatients. N=31. Age: 23-64. mean=39.8. Diagnosis: DSM-III-R major depression, HRSD≥18. (14% patients diagnosed with bipolar disorder). 62% previously failed ≥ 1 antidepressant treatment.	1. Desipramine (median=200mg) + lithium (900mg) 2. Desipramine (as above) + placebo	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥ 50% decrease in HRSD & HRSD =10) 3. Leaving the study early 4. Leaving the study early due to side effects	Planned plasma level: 0.50-1.00mmol/L. Mean = 0.67+-0.19mmol/L, range = 0.34-0.92mmol/L	B
Januel2002 Y I	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Inpatients. N=149. Age: 18-65. Diagnosis: DSM-IV major depression, MADRS ≥25	1. Clomipramine (150mg) + lithium (750mg) 2. Clomipramine (150mg) + placebo	1. MADRS mean endpoint scores 2. Non-remitters (patients not achieving MADRS<10) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Lithium plasma level: mean = 0.5+-0.18mmol/L. Includes unpublished data.	B
Jensen1992 E I	Allocation: Random (no details) Duration: 6 weeks (+ 1 wk washout) Analysis: LOCF	Inpatients. N=44 Age: 65+. Diagnosis: DSM-III major depressive disorder, HRSD≥15	1. Nortriptyline (25-100mg, median=75mg) + lithium (300-600, median=450mg) 2. Nortriptyline (50-100mg, median =75mg) + placebo	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-remitters (patients not achieving HRSD≤8)	12-hour standard serum level: median = 0.6mmol/L, range:0.5-0.7mmol/L	B
Joffe1993a Y O AN	Allocation: Random (no details) Duration: 2 weeks	Outpatients.N=51.Age: mean=37.4 Diagnosis: RDC unipolar, non-psychotic, major depression. HRSD ≥16 after 5 weeks of desipramine (N=46) or imipramine (N=5)	1. TCA + lithium (900mg) 2. TCA + placebo 3. TCA + T3 (37.5µg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD & HRSD ≤10)	Target plasma level: ≥0.55nmol/L. Mean = 0.68 nmol/L, range: 0.56-0.93nmol/L	B
Nierenberg 2003 Y O I TR	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=35. 16 female. Age: 18-70. Diagnosis: DSM-III-R major depressive disorder, HRSD-17≥18. Failed at least 1 but less than 5 adequate medication trials of at least 6 weeks duration each.	6 weeks open treatment with nortriptyline (100mg) non-responders randomised to: 1. Nortriptyline (100mg) + Lithium 2. Nortriptyline (100mg) + placebo	1. Non-responders (patients not achieving ≥50% decrease in HRSD-17) 2. Leaving the study early	Mean blood level at week 2 = 0.63 (range: 0.3-1.4)	B

		Mean number of failed trials = lithium: 1.9+-1.2, placebo: 2.5+-1.6				
Shahal1996 Y I	Allocation: Random (no details) Duration: 5 weeks Analysis: completer	Inpatients. N= 22. Age: mean =53 +-16 years. Diagnosis: DSM-III-R major depression without psychotic features.	1. Imipramine (150-175mg) + lithium (mean=630mg) 2. Imipramine (150-175mg) + placebo	1. Leaving the study early	Target plasma level: 0.7-0.9mEq/L Mean = 0.8+-0.2mEq/L	B
Stein1993 Y ? AN	Allocation: Random (no details) Duration: 3 weeks Analysis: completer (no dropouts)	N= 34. Aged: 18-65. Diagnosis: RDC major depressive disorder, failure to respond to at least 3 weeks of TCA treatment, HRSD≥18	1. Lithium (250mg) 2. Placebo Phase 2 (weeks 4-6): 1. Lithium (750mg) 2. Lithium (250mg) Phase 3 (weeks 7-9): 1. Lithium (750mg) 2. Lithium (750mg) Only extracted data from phase 1.	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Mean plasma level = 0.76+-0.45mmol/l	B
Zusky1988 Y ? AN	Allocation: Random (no details) Duration: 3 weeks Analysis: LOCF	N= 18. Age: 18-80. Diagnosis: DSM-III major depressive disorder without psychosis, treatment resistant (HRSD ≥12 after least 4 weeks of adequate antidepressant treatment)	1. Antidepressant + lithium (300 mg up to 900mg) 2. Antidepressant + placebo	1. HRSD mean endpoint scores 2. Non-remitters (patients not achieving HRSD≤7) 3. Leaving the study early 4. Non-responders (patients not achieving ≥50% decrease on HRSD)	Mean plasma level = 0.57+-0.18	B

Characteristics of excluded studies

Study	Reason for exclusion
Bauer1999	Not relevant comparison: lithium + amitriptyline versus lithium + paroxetine
Bauer2000	Not relevant comparison: patients who did not respond to various ADs treated with lithium, remitters randomised to continue on or switch to pbo
Browne1990	3/17 (17.65%) patients were diagnosed with bipolar depression
Bruijn1998	Not relevant comparison: lithium + imipramine versus lithium + mirtazapine
Dinan1989	Not relevant comparison: lithium + TCAs versus ECT
Fava1994 Y ? TR	Mean lithium level=0.21+-0.11meq/litre
Fava2002 Y O TR	Mean lithium level=0.37+-0.15mEq/L
Hardy1997	Not relevant comparison: patients in remission after treatment with antidepressant + lithium randomised to continue with antidepressant + lithium or switch to antidepressant + placebo
Heninger1983	Inadequate randomisation method: 'the 1st 3 to enter the study received lithium, the 2nd 3 placebo, and thereafter patients were assigned in alternating order to placebo or lithium while we attempted to balance as near possible the placebo and lithium within AD drug treatment groups'

Hoencamp1994	Not relevant comparison: lithium + maprotiline versus brofaromine + maprotiline.
Kantor1986	Inadequate description of randomisation; 6/13 patients were removed from the analyses for 'methodologic contamination'

Katona1995	Sample included patients diagnosed with bipolar depression, numbers not given
Lingjaerde1974	Inadequate diagnosis
Milijkovic1997 Y I	Not carried out under double-blind conditions
Nick1976	Inadequate diagnosis.
Reynolds1996	Not an RCT
Rybakowski1999	Not a relevant comparison: AD + lithium versus AD + carbamazepine
Schopf1989	33.3% patients were diagnosed with bipolar disorder

Augmentation with pindolol - studies in previous guideline

Characteristics of included studies

1	RANLab programme in a VAX system). Duration 6 weeks (+ 1 week placebo wash-out). Analysis: LOCF	unipolar major depression, HRSD-17 \geq 18. Median baseline HRSD=21, range=18-35	2. Fluoxetine (20mg) + placebo	3. Non-responders at last assessment (patients not achieving \geq 50% decrease in HRSD) 4. Non-remitters at late assessment (patients not achieving HRSD \leq 8) 5. Leaving the study early due to side effects	the affective disorders unit of the Sant Pau Hospital, Barcelona.	
Perez 1999 Y O	Allocation: Random (using computer	Outpatients & 2 outpatients. N=80, aged:18-65 . Diagnosis:	All patients received fluoxetine (40mg),	1. HRSD-17 mean endpoint scores at early assessment 2. Non-responders at early assessment (patients not	Conducted by 4 psychiatrists in	B

229

I	generated random numbers, carried out by an independent researcher). Duration 6 weeks SSRI treatment + 10 days trial treatment (+ 5 day run-in). Analysis: LOCF	DSM-IV major depressive disorder, HRSD ≥ 16 following at least 6 weeks of antidepressant treatment. Median level of TRD = 2, range 1-4, according to Thase and Rush criteria. Mean baseline HRSD=20	Fluvoxamine (200mg), Paroxetine (40mg) or Clomipramine (150mg) for at least 6 weeks before randomisation: 1. SRI + Pindolol (7.5mg) 2. SRI + placebo	achieving $\geq 50\%$ decrease in HRSD) 3. Non-remitters at early assessment (patients not achieving HRSD ≤ 8)	the affective disorders unit of the San Pau Hospital, Barcelona.	
Tome 1997 Y O I	Allocation: Random (no details). Duration 6 weeks. Analysis: ITT	Outpatients. N=80. Age: 18-65. Diagnosis: ICD-10 mild, moderate or severe unipolar depression, MADRS ≥ 18 . Mean baseline MADRS=32, range: 22-45.	1. Paroxetine (20mg) + pindolol (7.5mg) 2. Paroxetine (20mg) + placebo	1. MADRS mean endpoint scores at early assessment 2. MADRS mean endpoint scores at late assessment 3. Leaving the study early 4. Non-responders at early assessment (patients not achieving $\geq 50\%$ decrease in HRSD) 5. Non-responders at late assessment (patients not achieving $\geq 50\%$ decrease in HRSD) 6. Leaving the study early due to side effects	Conducted at 2 centres in London.	B
Zanardi 1997 Y I I	Allocation: Random (no details). Duration 4 weeks (+ 1 week placebo washout) Analysis: ITT	Inpatients. N=63, 42 female. Age: 18-65, mean=47.2+-10.5 years. Diagnosis: DSM-IV recurrent major depression, HRSD-17 ≥ 18 . Mean baseline HRSD=22.	1. Paroxetine (20mg) + pindolol (7.5mg) 2. Paroxetine (20mg) + placebo 3. Paroxetine (20mg) + [pindolol (7.5mg) for 1 week -> placebo for 3 weeks]	1. Leaving the study early 2. Non-remitters at early assessment (patients not achieving HRSD ≤ 8) 3. Non-remitters at late assessment (patients not achieving HRSD ≤ 8) 4. Leaving the study early due to side effects	Conducted at the San Raffaele Hospital, Milan.	B

Characteristics of excluded studies

Study	Reason for exclusion
Artigas1994	Not an RCT; not a relevant comparison - all patients received pindolol
Bakish1997	Not an RCT; not a relevant comparison - all patients received pindolol and nefazodone
Bell1998	Not an RCT - case report of 1 patient
Berman1999	Some patients with comorbid psychiatric disorders (OCD:N=2, social phobia:N=11,panic disorder:N=2) + 6/86(7%) patients with bipolar depression
Blier1995	Not an RCT; not a relevant comparison - all patients received pindolol
Blier1997	Not an RCT; not a relevant comparison - all patients received pindolol
Dinan1996	Not an RCT; not a relevant comparison - all patients received pindolol
Dursun2001	Not an RCT; not a relevant comparison - all patients received pindolol

Gonul1999	Not a relevant comparison - patients randomised to treatment with pindolol or buspirone
Maes1996 Y I E	Trazodone administered below therapeutic dose

Moreno1997	Once patients with comorbid personality disorder had been removed from sample there were only 5 patients left; in 2 of these patients presence of comorbid axis I disorder was unknown; patients only received each treatment (pindolol or placebo) for 2 weeks before being crossed over
Serretti2001a	Pooled sample of patients from Smeraldi1998 and Zanardi 2001; 36% patients diagnosed with bipolar depression
Serretti2001b	28% of patients were diagnosed with bipolar depression.
Shiah2000	Not a relevant comparison - (ECT + pindolol) versus (ECT + placebo)
Smeraldi1998	30% of patients were diagnosed with bipolar depression
Vinar1996	Not an RCT; not a relevant comparison - all patients received pindolol
Zanardi1998	30% of patients were diagnosed with bipolar depression
Zanardi2001	30% of patients were diagnosed with bipolar depression

Augmentation with triiodothyronine (T3) - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Joffe1993 A Y O AN	Allocation: Random (no details). Duration: 2 weeks	Outpatients. N=51. Age: mean=37.4 . Diagnosis: RDC unipolar, non-psychotic, major depression. HRSD≥16 after 5 weeks of desipramine (N=46) or imipramine (N=5) treatment	1. TCA + Lithium (900mg) 2. TCA + placebo 3. TCA + T3 (37.5µg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD & HRSD ≤10)	Target plasma level: ≥0.55nmol/L. Mean = 0.68nmol/L, range: 0.56-0.93nmol/L	B

Characteristics of excluded studies

There were no excluded studies.

Next-step treatments - new studies in the guideline update

Comparisons Included in this Clinical Question

AD + aripiprazole vs AD + placebo BERMAN2007 MARCUS2008	AD + atemoxetine vs AD + placebo MICHELSON2007	AD + lamotrigine vs AD + lithium	AD + lithium vs AD + T3
AD + quetiapine vs AD + placebo MCINTYRE2007B	AD + risperidone vs AD + placebo KEITNER2009 MAHMOUD2007 SONG2007	Bilateral ECT vs unilateral ECT ESCHWEILER2007 HEIKMAN2002B MCCALL2002 RANJKESH2005 SACKEIM1993 SACKEIM2000 SACKEIM2008 SIENAERT2009 STOPPE2006 TEW2002	CBT vs (bupropion or buspirone)
Duloxetine 60 mg vs duloxetine 120 mg WHITMYER2007	Escitalopram vs fluoxetine	Fluoxetine + desipramine vs desipramine vs fluoxetine	Fluoxetine + olanzapine vs fluoxetine CORYA2006 SHELTON2005 THASE2007D
Fluoxetine + olanzapine vs olanzapine CORYA2006 SHELTON2005 THASE2007D	Fluoxetine + olanzapine vs placebo (low-dose drugs) CORYA2006	Fluoxetine + olanzapine vs venlafaxine CORYA2006	Fluoxetine vs nortriptyline SHELTON2005
Olanzapine + fluoxetine vs nortriptyline SHELTON2005	Olanzapine vs fluoxetine CORYA2006 SHELTON2005 THASE2007D	Olanzapine vs nortriptyline SHELTON2005	Olanzapine vs venlafaxine CORYA2006
Tranlycypromine vs venlafaxine + mirtazepine	Venlafaxine vs citalopram LENOXSMITH2008	Venlafaxine vs sertraline	

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BERMAN2007 Study Type: RCT Study Description: H2P1; 8-week single blind treatment phase for those with MDD range of SSRIs or venlafaxine based on clinical factors; then RCT if inadequate response	n= 362 Age: Mean 45 Sex: 133 males 255 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR	Data Used Weight change Leaving treatment early due to lack of efficacy Response: 50% reduction in MADRS Remission: MADRS <=10 + response Leaving treatment early due to side effects	Group 1 N= 181 AD + aripiprazole - AD as treatment phase + 5mg rising to 15 mg (for those on fluoxetine or paroxetine) or 20 mg (other drugs)	SIGN 1+; funding Bristol Myers-Squibb; 7-28-day screening phase, then 8-weeks prospective treatment before randomisation 228

<p>Blindness: Double blind Duration (days): Mean 42</p> <p>Setting: Outpatients ; US (24 sites)</p> <p>Notes: RANDOMISATION: based on permuted block design with fixed blocks of 4, stratified by centre, no further details</p> <p>Info on Screening Process: 1044 patients screened, 781 eligible, 159 discontinued during treatment phase, 42% of remaining 622 met criteria for response so ineligible for RCT</p>	<p>Exclusions: HAMD-17 < 18 for inclusion into acute phase; HAMD-17 > 50% reduction for inclusion into treatment phase; <18 or > 65 years old; current Axis I delirium, dementia, amnesic/cognitive disorder, schizophrenia, psychotic disorder, BD I or II, eating disorder, OCD, panic disorder, PTSD, clinically significant Axis II disorder, psychotic symptoms in current episode, substance use disorder in past 12 months; known intolerance to study drugs; received adjunctive antipsychotics (> 3 weeks) or ECT for current episode; inadequate response to previous ECT; suicide risk; MAOI in past 2 weeks; inpatient care in past 4 weeks</p> <p>Notes: Inadequate response = <50% reduction in symptoms after >= 8 weeks' AD treatment (up to 3 ADs >6 weeks each)</p>	<p>Leaving treatment early for any reason</p>	<p>Group 2 N= 172</p> <p>AD + placebo - AD as treatment phase + placebo</p>	
<p>CORYA2006</p> <p>Study Type: RCT</p> <p>Study Description: H1P1; Open-label treatment for 7 weeks (venlafaxine 75-375 mg), then RCT for non-responders</p> <p>Blindness: Double blind Duration (days): Mean 84</p> <p>Setting: Unclear; 16 countries (40 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p>	<p>n= 483 Age: Mean 46 Sex: 133 males 350 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >1 AD + failed prospective trial</p> <p>Exclusions: Age < 18 years; CGI-Severity < 4; psychotic features; no documented history of failure to 6-weeks' SSRI at therapeutic dose</p> <p>Notes: Prospective trial failure: <30% improvement in MADRS during 7-week open-label venlafaxine treatment</p> <p>Baseline: MADRS (SD) 30 (6.8); 51% > 3 lifetime MDD episodes; 22% > 2 lifetime MDD episodes</p>	<p>Data Used</p> <p>Weight change MADRS mean change Remission: MADRS <= 8 Response: 50% reduction in MADRS Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason</p>	<p>Group 1 N= 243</p> <p>Olanzapine + fluoxetine - 4 dose combinations: olz 6 mg/flu 25 mg; olz 6 mg/flu 50 mg; olz 12 mg/flu 25 mg; olz 12 mg/flu 50 mg - dose-finding study planned but too low power, so these groups combined</p> <p>Group 2 N= 62</p> <p>Olanzapine</p> <p>Group 3 N= 60</p> <p>Fluoxetine</p> <p>Group 4 N= 59</p> <p>Venlafaxine</p> <p>Group 5 N= 59</p> <p>Placebo (low-dose drugs) - Olz 1 mg/flu 5 mg</p>	<p>SIGN 1+; funding Eli Lilly; 2-7-day screening phase</p>
<p>ESCHWEILER2007</p>				

<p>Study Type: RCT</p> <p>Study Description: H3P0</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 21</p> <p>Setting: Inpatients; Germany and Austria (4 sites)</p> <p>Notes: RANDOMISATION: code prepared by statistician before study, stored in sealed envelopes</p> <p>Info on Screening Process: 207 screened; 115 excluded; 92 randomised</p>	<p>n= 92</p> <p>Age: Mean 54</p> <p>Sex: 39 males 53 females</p> <p>Diagnosis: 100% Major depressive disorder by ICD-10</p> <p>Additional specifier: Failed >= 2 ADs at adequate dose</p> <p>Exclusions: left-handed; HAMD-21 < 15; < 2 months in index episode; pregnancy; stroke within past 3 months; brain surgery or severe head trauma; ECT in past 6 months; prior study participation; drug or alcohol dependence within past 2 years; non-German speaking; clinically leading symptoms of PD; co-medication with > 3 mg lorazepam; antiepileptic drugs or mood stabilisers except lithium (as long as serum levels < 0.4 mmol/l during ECT procedures).</p> <p>Notes: 13% bipolar disorder; 'failed' AD = no response over 3-week period</p> <p>Baseline: HAMD-21 bilateral 27.6; unilateral 28; >3= previous episodes; duration of current episode bilateral 40 months, unilateral 33 months; mean number of antidepressants failed bilateral 3 (2-8), unilateral 3 (2-13)</p>	<p>Data Used</p> <p>Remission: HAMD-21 <= 8</p> <p>Response: 50% reduction in HRSD21</p> <p>Data Not Used</p> <p>BDI mean endpoint - no variability measure</p> <p>HRSD 21 mean endpoint - no variability measure</p>	<p>Group 1 N= 46</p> <p>Unilateral ECT - 6 treatments: 0.5 to 1 ms pulse width; 0.9 Amps, 30-70 Hz; seizure threshold titrated with subsequent treatments administered at 2.5 times the seizure threshold (150%)</p> <p>Group 2 N= 46</p> <p>Bilateral ECT - 6 treatments: 0.5 to 1 ms pulse width; 0.9 Amps, 30-70 Hz; seizure threshold titrated with subsequent treatments administered at 1.5 times the seizure threshold (50%)</p>	<p>SIGN: 1++; funding Tuebingen University Medical School</p>
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<p>HEIKMAN2002B</p> <p>Study Type: RCT</p> <p>Study Description: H0P0</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Inpatients referred for ECT; Finland</p> <p>Notes: RANDOMISATION: randomised in blocks of 6, no further details</p> <p>Info on Screening Process: Screened 81 consecutive patients referred for ECT, 24 met inclusion criteria</p>	<p>n= 24</p> <p>Age: Mean 57</p> <p>Sex: 9 males 13 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Psychotic features</p> <p>Exclusions: HAMD-17 <= 16; ECT during past 3 months; alcohol misuse in past year; schizophrenia, schizoaffective disorder, another psychotic disorder no part of the mood disorder, rapid-cycling bipolar disorder, neurologic illness or severe medical illness</p> <p>Notes: Demographics are for completers; age is estimated median; 21% bipolar disorder; 21% psychotic features; 79% had previous AD treatment for current episode (median 2)</p> <p>Baseline: HAMD-17 median (range) Bilateral 27 (16-29); unilateral high-dose 29 (20-40); unilateral low-dose 27 (22-37)</p>	<p>Data Used</p> <p>Response: HAMD-17 < 10</p>	<p>Group 1 N= 7</p> <p>Bilateral ECT - Just above seizure threshold</p> <p>Group 2 N= 15</p> <p>Unilateral ECT - Combined high-dose (400%) and low-dose (150%)</p>	<p>SIGN: 1+; funding Clinical Research Institute of Helsinki University Central Hospital</p>
<p>KEITNER2009</p> <p>Study Type: RCT</p> <p>Study Description: Hvp1; Open-label AD (clinician's choice) for 5 weeks (some entered into RCT if clear documentation of failed AD), then RCT if failed to respond</p> <p>Type of Analysis: 'ITT' for those with >1 dose drugs + 1 assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 28</p> <p>Setting: Outpatients; US</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 246 screened; 147 entered open-label phase; 43 enrolled into RCT; 54 enrolled into RCT as had clear documented history of failed AD</p>	<p>n= 97</p> <p>Age: Mean 45</p> <p>Sex: 42 males 55 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: MADRS <15; not able to read and write English; bipolar I or II disorder; psychotic features; suicide risk; substance dependence or abuse in past 3 months; concurrent medical illness or seizures contraindicating study medication; receiving ECT; pregnant or breastfeeding; taking herbal medicines (eg St John's wort).</p> <p>Notes: 95 in 'ITT' group</p> <p>Baseline: HAMD-17 (SD) risperidone 19.5 (4.7); placebo 18.6 (4.3); ADs escitalopram 26%, citalopram 9.4%, sertraline 18.8%, fluoxetine 11.5%, bupropion 12.5%, venlafaxine 10.4%, paroxetine 7.3%, nefazadone 2.1%, mirtazepin 1%, imipramine 1%</p>	<p>Data Used</p> <p>Weight change</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 <= 7</p> <p>Number of people reporting side effects</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Notes: MADRS available but HAMD-17 extracted weight change given in lbs but converted to kgs</p>	<p>Group 1 N= 64</p> <p>AD + risperidone. Mean dose 1.6 mg (0.73) - Range of ADs</p> <p>Group 2 N= 33</p> <p>AD + placebo - Range of ADs</p>	<p>SIGN 1+; funding Janssen Pharmaceuticals</p>
<p>LENOXSMITH2008</p>				

<p>Study Type: RCT</p> <p>Study Description: H1P0</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 84</p> <p>Setting: Inpatients and outpatients; Belgium, France, Germany, Greece, Hungary, Italy, Netherlands, Spain, Sweden, Switzerland, Australia</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 406</p> <p>Age: Mean 42</p> <p>Sex: 136 males 170 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Inadequate response to AD</p> <p>Exclusions: History or presence of seizure disorder; any mental disorder due to a general medical condition; bipolar, mania or psychotic illness; suicidal, history of drug or alcohol dependence or misuse with 1 year of baseline; previous unsuccessful treatment with, or hypersensitivity to, study drugs; taken MAOIs within 14 days; received ECT, sumatriptan, or any investigational or antipsychotic within 30 days; taken any anxiolytic or sedative/hypnotic drugs, or other psychotropic drug or substance within 7 days; taken</p>	<p>Data Used</p> <p>Response: 50% reduction in HRSD21</p> <p>Remission: HAMD-17 <= 8 - no data</p> <p>HRSD 21 mean endpoint - no variability measure</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 200</p> <p>Venlafaxine ER. Mean dose 191 mg</p> <p>Group 2 N= 206</p> <p>Citalopram. Mean dose 51 mg</p>	<p>SIGN: 1+; funding Wyeth Research, US</p>
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230

	<p>within 7 days unless maintained at stable dose for \geq 1 month before baseline; MI within 6 months; uncontrolled hypertension, history or presence of clinically important medical conditions, clinically significant abnormal findings on lab tests or physical exam; pregnancy or lactation; not using adequate contraception</p> <p>Notes: Inadequate response = HAMD-21 \geq 20 after 8 weeks' monotherapy</p> <p>Baseline: HAMD-21 (SD) venlafaxine 28.6 (5.7); citalopram 28.8 (5.4)</p>			
MAHMOUD2007				
<p>Study Type: RCT</p> <p>Study Description: H0P1 ;4-week open prospective phase (current AD standard dose), then RCT if inadequate response</p> <p>Type of Analysis: Mixed model repeated measures</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Mix of primary care, outpatients, plus some patients recruited via media; US (75 sites)</p> <p>Notes: RANDOMISATION: random code generator accessed via telephone interactive voice response system, stratified by AD class (SSRI/non-SSRI) & site</p> <p>Info on Screening Process: 463 entered open-label phase; 101 prematurely discontinued; 362 completed open-label phase with 274 eligible for randomisation</p>	<p>n= 274</p> <p>Age: Mean 46</p> <p>Sex: 71 males 197 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Failed prospective trial of 1 AD</p> <p>Exclusions: Pregnant; serious suicidal risk or serious medical or neurologic illness; active substance or alcohol use disorders; currently treatment with TCA, MAOI, mood stabilizer, anti-epileptic , or centrally acting gent for ADHD or narcolepsy</p> <p>Notes: Failed trial = still met criteria for MDD</p> <p>Baseline: HAMD-17 (SD) risperidone 24.2 (0.5); placebo 24.4 (0.51); SSRIs 81%; SNRI 31%; Other24%</p>	<p>Data Used</p> <p>Number of people reporting side effects</p> <p>Response: 50% reduction in HAMD-17</p> <p>Remission: HAMD-17 \leq 7</p> <p>HAMD-17 mean endpoint</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 141</p> <p>AD + risperidone - 1 mg</p> <p>Group 2 N= 133</p> <p>AD + placebo</p>	<p>SIGN: 1++; funding Ortho-McNeil Janssen Scientific Affairs</p>
MARCUS2008				

<p>Study Type: RCT</p> <p>Study Description: H1P1; 8-week single blind treatment phase for those with MDD range of SSRIs or venlafaxine based on clinical factors; then RCT if inadequate response</p> <p>Type of Analysis: ITT LOCF for those with ≥ 1 dose + 1 assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Unclear; US (36 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 1151 patients screened, 830 eligible, 651 completed treatment phase, 266 responded to treatment so not eligible for RCT, 385 eligible</p>	<p>n= 381</p> <p>Age: Mean 44</p> <p>Sex: 127 males 254 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV-TR</p> <p>Additional specifier: Failed ≥ 1 AD + failed prospective trial</p> <p>Exclusions: HAMD-17 < 18 for inclusion into acute phase; HAMD-17 > 50% reduction for inclusion into treatment phase; <18 or > 65 years old; current Axis I delirium, dementia, amnesic/cognitive disorder, schizophrenia, psychotic disorder, BD I or II, eating disorder, OCD, panic disorder, PTSD, clinically significant Axis II disorder, psychotic symptoms in current episode, substance use disorder in past 12 months; known intolerance to study drugs; received adjunctive antipsychotics (>3 weeks) or ECT for current episode; inadequate response to previous ECT; suicide risk; MAOI in past 2 weeks; inpatient care in past 4 weeks</p> <p>Notes: Failure = < 50% reduction in HAMD scores + HAMD-17 ≥ 14 or CGI-I ≥ 3</p> <p>Baseline: MADRS (SD) placebo: 27 (5.5); aripiprazole 25.2 (6.2)</p>	<p>Data Used</p> <p>Remission: MADRS ≤ 10</p> <p>Response: 50% reduction in MADRS</p> <p>MADRS mean change</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 191</p> <p>AD + aripiprazole. Mean dose 11 mg - AD as treatment phase + 5 mg rising to 15 mg (for those on fluoxetine or paroxetine) or 20 mg (other drugs)</p> <p>Group 2 N= 190</p> <p>AD + placebo - AD as treatment phase</p>	<p>SIGN 1+; funding Bristol Myers-Squibb; 7-28-day screening phase, then 8-weeks prospective treatment before randomisation</p>
<p>MCCALL2002</p>				<p>224</p>

<p>Study Type: RCT</p> <p>Study Description: H1P0 (based on 81% received adequate treatment for index episode)</p> <p>Type of Analysis: ITT</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Unclear; US</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: No details</p>	<p>n= 77</p> <p>Age: Mean 57</p> <p>Sex: 28 males 49 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-III-R</p> <p>Exclusions: HAMD-21 < 20; history of schizophrenia, schizoaffective disorder, active substance misuse, mental retardation, or neurologic illness; ECT within past 4 months</p> <p>Notes: 81% received adequate treatment before ECT for index episode; no details about psychotic symptoms</p> <p>Baseline: HAMD-21 (SD) bilateral 28.6 (4.6); unilateral 29.2 (5.3); mean length of current episode bilateral 26.2(20); unilateral 24 (20.9)</p>	<p>Data Used</p> <p>Response: 60% decrease in HAMD-21</p> <p>BDI mean endpoint</p> <p>HRSD 21 mean endpoint</p> <p>Notes: Additional criteria for response: endpoint score < 12</p>	<p>Group 1 N= 37</p> <p>Bilateral ECT - 50% seizure threshold; mean 5.8 sessions</p> <p>Group 2 N= 40</p> <p>Unilateral ECT - 700% seizure threshold - right unilateral; mean 5.8 sessions</p>	<p>SIGN: 1+; funding NIMH</p>
<p>MCINTYRE2007B</p> <p>Study Type: RCT</p> <p>Study Description: H1P0</p> <p>Type of Analysis: ITT LOCF for those with >=1 dose</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Mixed primary care and outpatients; Canada</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 73 patients screened, no further details</p>	<p>n= 58</p> <p>Age: Mean 44</p> <p>Sex: 21 males 37 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Inadequate response to AD</p> <p>Exclusions: DSM-IV substance misuse or dependence in last 6 months; receiving an antipsychotic or benzodiazepine 7 days before study; receiving potent cytochrome P450 inhibitor or induce 14 days before study; pregnant or breastfeeding; risk of suicide</p> <p>Notes: Inadequate response - still had HAMD-17 >= 18 after 6 weeks on SSRI or venlafaxine; all had comorbid anxiety</p> <p>Baseline: HAMD-17 (sd) quetiapine 23.4 (3); placebo 23.2 (2.2)</p>	<p>Data Used</p> <p>Remission: HAMD-17 <= 7</p> <p>Response: 50% reduction in HAMD-17</p> <p>HAMD-17 mean change</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Data Not Used</p> <p>HAMD-17 mean endpoint - Mean change scores used</p>	<p>Group 1 N= 29</p> <p>AD + quetiapine. Mean dose 182 mg - AD is SSRI or venlafaxine</p> <p>Group 2 N= 29</p> <p>AD + placebo - AD is SSRI or venlafaxine</p>	<p>SIGN 1+; funding AstraZeneca Pharmaceuticals</p>
<p>MICHELSON2007</p>				

<p>Study Type: RCT</p> <p>Study Description: H0P1; 8-weeks' sertraline treatment (100-200 mg); those with inadequate response entered into RCT</p> <p>Type of Analysis: ITT >= baseline + post-baseline assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Unclear; US (15 sites)</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: 276 met entry criteria for open-label phase; 227 completed treatment; 157 were nonresponders or partial responders; 146 continued into RCT</p>	<p>n= 146</p> <p>Age: Mean 45</p> <p>Sex: 50 males 46 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Inadequate response to AD</p> <p>Exclusions: Age <18 years; <1 prior episode; HAMD-17 < 18; serious medical illness, BD or ADHD, or treatment-resistant depression (>3 trials of ADs)</p> <p>Notes: Inadequate response = >4 on Maier & Philipp core mood severity subscale of HAMD-17 (MPS)</p> <p>Baseline: HAMD-17 (SD) 23 (4) (entry to study); 15.5 (5.5) entry to RCT</p>	<p>Data Used</p> <p>HAMD-17 mean endpoint</p> <p>Remission: MPS<=4 + no single HAMD items > 1</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Notes: MPS = Maier & Philipp core mood severity subscale of HAMD-17</p>	<p>Group 1 N= 72</p> <p>Atemoxetine. Mean dose 66 - sertraline [mean dose (SD) 146mg (27)] + atemoxetine (66 mg (30))</p> <p>Group 2 N= 74</p> <p>Placebo - sertraline [mean dose (SD) 144 (30)]</p>	<p>SIGN 1+; funding Eli Lilly</p>
<p>RANJKESH2005</p> <p>Study Type: RCT</p> <p>Study Description: H?P0</p> <p>Type of Analysis: Completer (>= 8 sessions)</p>	<p>n= 45</p> <p>Age: Mean 35</p> <p>Sex: 18 males 27 females</p>	<p>Data Used</p> <p>HRDS 24 mean endpoint</p>	<p>Group 1 N= 15</p> <p>Unilateral ECT - 'high dose' 400% above seizure threshold</p>	<p>SIGN 1+; funding no details 232</p>

<p>Blindness: Double blind Duration (days):</p> <p>Setting: Iran; referrals for ECT</p> <p>Notes: RANDOMISATION: randomised, no details</p> <p>Info on Screening Process: All referrals for ECT (n=45) were randomised</p>	<p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Exclusions: HAMD-24 < 16; history of ECT in previous 3 months; taking non-BZD anticonvulsants, lidocaine, theophylline, or lithium; psychotic symptoms, history of schizophrenia, schizoaffective disorder, another psychotic disorder not part of a mood disorder, rapid-cycling bipolar disorder, neurologic illness, severe medical illness.</p> <p>Notes: Participants excluded from study if did not receive >= 8 treatments</p> <p>Baseline: HAMD-24 (SD) 33.2 (5.4)</p>	<p>Notes: Outcomes taken just after 8th sessions (used Persian version of HDRS)</p>	<p>Group 2 N= 15 Bilateral ECT - 'moderate dose' 50% above seizure threshold</p> <p>Group 3 N= 15 Bilateral ECT - 'low dose' just above seizure threshold (data not used)</p>	
<p>SACKEIM1993</p> <p>Study Type: RCT</p> <p>Blindness: Double blind Duration (days):</p> <p>Setting: Inpatients; US</p> <p>Notes: RANDOMISATION: in block of 20, no further details</p> <p>Info on Screening Process: No details</p>	<p>n= 100 Age: Mean 57 Sex: 41 males 59 females</p> <p>Diagnosis: 100% Major depressive disorder by Research Diagnostic criteria</p> <p>Exclusions: HAMD-24 < 18; schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar disorder, neurological illness or insult, alcohol and other drug misuse in pat year; ECT in past 6 months; severe medical illness</p> <p>Notes: 4 patients dropped out, not included in data, allocation not given so added 1 to each group</p> <p>Baseline: HAMD-24 (SD): bilateral low dose 34 (9), high 47 (8); unilateral low dose 36 (9), high 32 (8)</p>	<p>Data Used Response: 60% decrease in HAMD-24</p> <p>Notes: Additional criterion for response: HAMD-24 < 17</p>	<p>Group 1 N= 24 Bilateral ECT - 0% ST 3x per week; up to 10 treatments</p> <p>Group 2 N= 28 Bilateral ECT - 250% ST 3x per week; up to 10 treatments</p> <p>Group 3 N= 24 Unilateral ECT - 0% ST 3x per week; up to 10 treatments</p> <p>Group 4 N= 24 Unilateral ECT - 250% ST 3x per week; up to 10 treatments</p>	<p>SIGN: 1+; funding NIMH; sourced from Geddes et al. 2003 and added because it is used in dose analysis</p>
<p>SACKEIM2000</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: Completer</p> <p>Blindness: Double blind</p> <p>Duration (days):</p> <p>Setting: Inpatients (except 3 outpatients); US</p> <p>Notes: RANDOMISATION: stratified by adequate ADs in index episode, permuted block procedures, used sealed envelopes</p> <p>Info on Screening Process: No details</p>	<p>n= 84</p> <p>Age: Mean 57</p> <p>Sex: 33 males 51 females</p> <p>Diagnosis:</p> <p>100% Major depressive disorder by Research Diagnostic criteria</p> <p>Additional specifier: Psychotic features</p> <p>31% Bipolar disorder (depressed phase) by Research Diagnostic criteria</p> <p>Exclusions: HAMD-24 < 18; schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar disorder, neurological illness or insult, alcohol and other drug misuse in pat year; ECT in past 6 months; severe medical illness</p> <p>Notes: 29 with psychotic symptoms; 4 drop-outs not included in data analyses, allocation not given so added 1 to each group</p> <p>Baseline: HAMD-24 (SD) bilateral: 29.2 (7.4); unilateral 0% 32.4 (7.9); 150% 29.6 (6.2); 500% 32.6 (7.8)</p>	<p>Data Used</p> <p>Response: 60% decrease in HAMD-24</p> <p>Remission: HAMD-24 <= 10</p> <p>Leaving treatment early for any reason</p> <p>Notes: Additional criteria for outcomes: response - endpoint HAMD-24 < 17; remission - met criteria for response</p>	<p>Group 1 N= 21</p> <p>Bilateral ECT - 150% ST; 3x per week; >=5 treatments</p> <p>Group 2 N= 21</p> <p>Unilateral ECT - 0% ST; 3x per week; >=5 treatments</p> <p>Group 3 N= 21</p> <p>Unilateral ECT - 150% ST; 3x per week; >=5 treatments</p> <p>Group 4 N= 21</p> <p>Unilateral ECT - 500% ST; 3x per week; >=5 treatments</p>	<p>SIGN: 1++; funding NIMH; sourced from Geddes et al. 2003 and added because it is used in dose analysis</p>
<p>SACKEIM2008</p> <p>Study Type: RCT</p> <p>Type of Analysis: ITT</p>	<p>n= 90</p> <p>Age: Mean 50</p> <p>Sex: 39 males 51 females</p>	<p>Data Used</p> <p>Leaving treatment early for any reason</p> <p>Response: 50% reduction in HAMD-24</p> <p>Remission: HAMD-24 <= 10</p>	<p>Group 1 N= 23</p> <p>Bilateral ECT - Ultrabrief ECT; 150% above ST; mean 8.7 sessions</p>	<p>Emailed author for data by diagnosis as BD population > 15% (21/1/9)</p>

<p>Blindness: Single blind Duration (days): Followup: 1 week after last session Setting: Inpatients; US Notes: RANDOMISATION: randomised no details; used permuted blocks of 12 Info on Screening Process: 459 consecutive referrals for ECT screened; 104 offered and consented to protocol participant; 14 left before randomisation - no reasons given</p>	<p>Diagnosis: 70% Major depressive disorder by DSM-IV 30% Bipolar disorder (depressed phase) by DSM-IV Exclusions: HAMD-24 <18; no clinical indication for ECT; history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling BD, neurologic illness or insult, alcohol, or other drug misuse within past year, ECT in past 6 months, severe medical illness</p>	<p>Notes: Outcomes taken 1 week after last session</p>	<p>Group 2 N= 23 Bilateral ECT - Brief ECT; 150% above ST; mean 8.9 sessions Group 3 N= 22 Unilateral ECT - Ultrabrief ECT; 500% above ST; mean 8.5 sessions Group 4 N= 22 Unilateral ECT - Ultrabrief ECT; 500% above ST; mean 6,2 sessions</p>	
<p>SHELTON2005 Study Type: RCT Study Description: RCT for non-responders to 7-week open-label nortriptyline Blindness: Double blind Duration (days): Mean 56 Setting: Unclear; US and Canada (71 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 946 patients entered the study, 446 discontinued during lead-in phase</p>	<p>n= 500 Age: Mean 42 Sex: 160 males 340 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >=1 AD + failed prospective trial Exclusions: MADRS < 20; psychotic symptoms during lead-in phase; pregnant or lactating; ECT within 1 month; likely to require ECT during study Notes: Treatment failure defined as < 30% improvement in MADRS scores Baseline: MADRS (SD) olanzapine + fluoxetine 28.5 (7.5); fluoxetine 28.4 (7.3); olanzapine 28.4 (7.3); nortriptyline 28.8 (6.5)</p>	<p>Data Used Remission: MADRS <= 8 Response: 50% reduction in MADRS MADRS mean change Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason Notes: Remission defined as scoring <= 8 on 2 consecutive occasions</p>	<p>Group 1 N= 144 Olanzapine. Mean dose 8.3 mg Group 2 N= 142 Fluoxetine. Mean dose 35.8 mg Group 3 N= 68 Nortriptyline. Mean dose 103.5 mg Group 4 N= 146 Olanzapine + fluoxetine. Mean dose 8.3 mg/35.6 mg</p>	<p>SIGN 1+; funding Eli Lilly</p>
<p>SIENAERT2009 Study Type: RCT Study Description: H0P0 Type of Analysis: Completer Blindness: Single blind Duration (days): Setting: Unclear; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: No information given</p>	<p>n= 81 Age: Mean 55 Sex: 39 males 42 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 18; schizophrenia; neurological illness; cognitive disorder; substance abuse or dependence in past year; ECT in past 6 months. Notes: 20% with bipolar disorder; 27% with psychotic features Baseline: HAMD-17 (SD) bilateral 30.25 (6.46); unilateral 29.03 (5.18)</p>	<p>Data Used Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 Leaving treatment early for any reason</p>	<p>Group 1 N= 40 Bilateral ECT - 1.5 times ST; bifrontal Group 2 N= 41 Unilateral ECT - 6 times ST</p>	<p>SIGN 1+; funding 'study performed without external funding sources'</p>
<p>SONG2007</p>				

<p>Study Type: RCT</p> <p>Type of Analysis: ITT</p> <p>Blindness: Single blind</p> <p>Duration (days): Mean 42</p> <p>Setting: Inpatients and outpatients; China</p> <p>Notes: RANDOMISATION: randomised, no details</p>	<p>n= 100</p> <p>Age: Mean 44</p> <p>Sex: 50 males 50 females</p> <p>Diagnosis: 100% depression by Chinese Classification & Diagnostic Criteria</p> <p>Additional specifier: Failed >= 2 ADs at adequate dose</p> <p>Exclusions: Other mental/neurological disorders; severe liver or renal disease: pregnant or breastfeeding</p>	<p>Data Used</p> <p>HAMD-17 mean change</p> <p>Remission: >=75% reduction in HAMD</p> <p>Response: 50-74% reduction in HAMD</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p>	<p>Group 1 N= 50</p> <p>AD + risperidone. Mean dose Not stated - Venlafaxine 50 mg at start increased over 1st week based on response to maximum of 250 mg; risperidone 0.5 mg to 2 mg</p> <p>Group 2 N= 50</p> <p>Venlafaxine. Mean dose Not stated - Venlafaxine 50 mg at start increased over 1st week based on response to maximum of 250 mg</p>	<p>Sign 1+; funding not stated; paper in Chinese (Mandarin), data extracted by native speaker</p> <p style="text-align: right;">234</p>
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	Notes: Definition of treatment failure: >=6 weeks' treatment at sufficient dose with <=30% reduction in HAMD scores Baseline: HAMD (SD) augmentation group 28 (5.42); control 28 (4.75)	Notes: Assumed HAMD-17 as version not stated or referenced		
STOPPE2006				
Study Type: RCT Study Description: H2P0 Blindness: Double blind Duration (days): Setting: Inpatients; Brazil Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 39 Age: Mean 75 Sex: 17 males 22 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Additional specifier2: Failed >=2 ADs or 1 AD if severely ill Exclusions: left-handed; MADRS < 20; history of schizophrenia, other functional psychosis, alzheimer disease, other dementia, alcohol or drug misuse in past year; ECT in past 6 months; high anaesthesia risk Notes: 33% psychotic features; also included if poor pharmacological response and good response to previous ECT Baseline: MADRS (SD) bilateral. 38.05 (6.61), unilateral 32.76 (7.99)	Data Used Remission: MADRS <= 10 Notes: Outcomes taken 1 month after last treatment	Group 1 N= 22 Bilateral ECT - 'fixed high dose'; Pulse width 1ms, 0.8 Amps, max charge 1152 mC, frequency 60-120 Hz. Between 4 and 16 treatments (mean [SD] 10 [3.46]) Group 2 N= 17 Unilateral ECT - 'fixed high dose'; Pulse width 1ms, 0.8 Amps, max charge 1152 mC, frequency 60-120 Hz. Between 4 and 16 treatments (mean [SD] 10 [3.46])	SIGN: 1+; funding unclear
TEW2002				
Study Type: RCT Study Description: H0P1; RCT for non-responders to 5-8 moderate charge unilateral ECT (150% above seizure threshold) Blindness: Double blind Duration (days): Setting: Unclear; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 24 Age: Mean 67 Range 50-81 Sex: Diagnosis: 100% Major depressive disorder by DSM-III-R Additional specifier: Psychotic features Exclusions: < 50 years old; no distinction between left- and right-handedness; no other exclusion criteria Notes: % psychotic symptoms not given; gender not given; response defined as HAMD-24 >= 20 or < 33% reduction in baseline score Baseline: HAMD-24 (SD) unilateral 30.4 (6.6); bilateral 30.8 (12)	Data Used Remission: HAMD-24 <= 10 Response: 50% reduction in HAMD-24 HRDS 24 mean endpoint Notes: Outcomes taken 1 to 3 days after last treatment	Group 1 N= 11 Bilateral ECT - >= 3 treatments, time period unclear; 150% above seizure threshold Group 2 N= 13 Unilateral ECT - >= 3 treatments; time period unclear; high-charge right unilateral ECT; 450% above seizure threshold	SIGN 1+; funding US Public Health Service and NIMH
THASE2007D				

<p>Study Type: RCT</p> <p>Study Description: RCT for non-responders to 8-week fluoxetine treatment. Paper reports data from 2 studies in the same paper.</p> <p>Type of Analysis: LOCF (MMRM data available) >= 1 dose/assessment</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 56</p> <p>Setting: Unclear; US (33 sites)</p> <p>Notes: RANDOMISATION: no details of method, patients randomised and sites randomised to one of 2 concurrent identical</p>	<p>n= 605</p> <p>Age: Mean 44</p> <p>Sex: 221 males 383 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Failed >1 AD + failed prospective trial</p> <p>Exclusions: Aged < 18 or > 65 years; HAMD-17 < 22; psychotic features; schizophrenia; schizoaffective disorder; other psychotic disorder; bipolar disorder; PTSD; dissociative disorder; pregnant or breastfeeding; current postpartum depression; MDD with atypical features or</p>	<p>Data Used</p> <p>Response: 50% reduction in MADRS</p> <p>Remission: MADRS <= 10</p> <p>MADRS mean change</p> <p>Leaving treatment early due to lack of efficacy</p> <p>Leaving treatment early due to side effects</p> <p>Leaving treatment early for any reason</p> <p>Notes: Some data given by study and some pooled</p>	<p>Group 1 N= 200</p> <p>Olanzapine + fluoxetine. Mean dose 8.6 mg/48.8 mg</p> <p>Group 2 N= 206</p> <p>Fluoxetine. Mean dose 49.5 mg</p> <p>Group 3 N= 199</p> <p>Olanzapine. Mean dose 8.7 mg</p>	<p>SIGN: 1+; funding Eli Lilly</p> <p style="text-align: right;">235</p>
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studies Info on Screening Process: 1313 patients enrolled; 708 discontinued	illness; concomitant medication with primary CNS activity Notes: Treatment failure: < 25% decrease in HAMD-17 scores or HAMD-17 > 18 or < 15% decrease between week 7 and 8 of lead-in phase Baseline: HAMD-17 (SD) at 26.2 (5.4)			
WHITMYER2007				
Study Type: RCT Study Description: H0P1; Patients randomised to acute phase trial (3 arms - dul 30mg, 30 mg twice a day, 60 mg once a day); non-responders randomised to 60 mg or 120 mg Blindness: Double blind Duration (days): Mean 42 Followup: + 8 weeks APNR Setting: Outpatients; US (33 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 916 people screened, 269 failed to meet entry criteria or declined to participate	n= 647 Age: Mean 43 Sex: 232 males 415 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD0-17 < 16; Axis I disorder other than MDD, dysthymia or any anxiety disorder (apart from OCD); previous diagnosis of mania, BD, psychosis; serious suicidal risk; serious medical illness or clinically significant laboratory abnormalities likely to require intervention, hospitalisation or an excluded medication during the study period; lack of response during current episode to 2 or more adequate courses of ADs; history of lack of response to duloxetine; current axis II disorder that could interfere with compliance; history of substance misuse or dependence within past 6 months; positive drug urine screen ECT or TMS within past year; initiating, stopping or changing psychotherapy; MAOI within past 14 days or fluoxetine within 30 days. Notes: 441 in APNR phase (entry criterion HAMD-17 > 7 at end of acute phase); 62% women; mean age 45 Baseline: HAMD-17 (SD) 21.6 (3.3) (dul 30 mg); 21.7 (3.7) (30 bid); 21.2 (3.9) (60 mg)	Data Used Number with palpitation Number with abnormal orgasmia Number with decreased libido Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 Weight change HAMD-17 mean change Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason Number with delayed ejaculation Number with abnormal ejaculation Number with sexual dysfunction Notes: Only leaving treatment early for any reason, lack of efficacy and AEs extracted for APNR extension study - other data given for all those taking 60 mg during extension which included those remitting	Group 1 N= 291 Duloxetine. Mean dose 30 mg - Dose less than licensed dose; used in comparison with 60mg only Group 2 N= 215 Duloxetine. Mean dose 60 mg Group 3 N= 213 Duloxetine. Mean dose 30 mg bid - Data not input as separate group: dichotomous data added to 60 mg group; continuous data not used Group 4 N= 131 Duloxetine. Mean dose 60 mg - Re-randomised acute-phase non-responders Group 5 N= 124 Duloxetine. Mean dose 120 mg - Re-randomised acute-phase non-responders	SIGN: 1+; funding: Eli Lilly (Code HMDR); 1-week no-drug screening phase

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BALDOMERO2005	open-label; mixed diagnoses (16% dysthymia; 8.7% minor depression) (venlafaxine vs other antidepressants) (narrative description of study used in full guideline)
BARBOSA2003	High proportion of bipolar II disorder (8/23) (augmentation of fluoxetine with lamotrigine vs placebo)
BAUNE2007	Not RCT (augmentation with quetiapine vs placebo)
COOPERKAZAZ2007	Participants not selected because of treatment-resistance (T3 augmentation vs placebo)
JOFFE2006	No extractable data; 3 groups contained < 10 people (augmentation with lithium vs T3 vs combo vs placebo)
MAZEH2007	Single blind; inadequate randomisation (also, no SDs for mean endpoint data, and small study in elderly [n=30]) (venlafaxine vs paroxetine)

N

ention of how participants diagnosed (eg DSM-IV); not all sample
treatment resistant (n=16, so 5 or 6 in each group only); unclear from
which group dropout (n=1) occurred

NORMANN2002

Patients not recruited specifically because of past treatment failure

PERRY2004

No extractable data (augmentation with pindolol vs placebo)

POSTERNAK2008

Participants not selected because of treatment-resistance (T3
augmentation vs placebo)

ROGOZ2007	No mention of how treatment allocation undertaken, therefore assumed not randomised (AD+amantadine vs AD alone)
SCHINDLER2007	Open label study (AD + lamotrigine vs AD + lithium) (narrative review of study used in full guideline)
SCT-MD-11B	Open label
SCT-MD-11C	Open label
SCT-MD-21	Inadequate trial of acute-phase antidepressant (3 weeks) (escitalopram vs fluoxetine)
SHAPIRA2006	Too few people in each arm; inclusion criteria non-response to 3 weeks SSRI treatment (augmentation with phenytoin vs placebo)
STAR-D level 2	Open-label (bupropion vs cognitive therapy vs sertraline vs venlafaxine vs citalopram + bupropion vs citalopram + buspirone vs citalopram + cognitive therapy) (study described narratively in full guideline)
STAR-D level 3	Open-label (mirtazepine vs nortriptyline vs lithium augmentation vs T3 augmentation vs sertraline augmentation vs venlafaxine augmentation (study described narratively in full guideline)
STAR-D level 4	Open-label (tranylcypromine vs mirtazepine augmentation (study described narratively in full guideline)
WHYTE2004	Not an RCT; post-hoc analysis of earlier trial (sequenced augmentation of bupropion, nortriptyline and lithium)
ZARATE2006	Trial has too few participants (< 10 per arm; total n=18); crossover trial (N-methyl-D-aspartate vs placebo)

References of Included Studies

BERMAN2007 (Published Data Only)

Berman, R. M., Marcus, R. N., Swanink, R., McQuade, R. D., Carson, W. H., Corey-Lisle, P. K. et al. (2007). The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*, 68, 843-853.

CORYA2006 (Published Data Only)

Corya, S. A., Williamson, D., Sanger, T. M., Briggs, S. D., Case, M., & Tollefson, G. (2006). A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depression & Anxiety*, 23, 364-372.

ESCHWEILER2007 (Published Data Only)

Eschweiler, G. W., Vonthein, R., Bode, R., Huell, M., Conca, A., Peters, O. et al. (2007). Clinical efficacy and cognitive side effects of bifrontal versus right unilateral electroconvulsive therapy (ECT): a short-term randomised controlled trial in pharmaco-resistant major depression. *Journal of Affective Disorders*, 101, 149-157.

HEIKMAN2002B (Published Data Only)

Heikman, P., Kalska, H., Katila, H., Sarna, S., Tuunainen, A., & Kuoppasalmi, K. (2002). Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: a preliminary study.[see comment]. *Journal of ECT*, 18, 26-30.

KEITNER2009 (Published Data Only)

Keitner, G. I., Garlow, S. J., Ryan, C. E., Ninan, P. T., Solomon, D. A., Nemeroff, C. B., & Keller, M. B. (2009). A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. *Journal of Psychiatric Research*, 43, 204-214.

LENOXSMITH2008 (Unpublished and Published Data)

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Jiang, Q. (2008). Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. *International Clinical Psychopharmacology*, 23, 113-119.

MAHMOUD2007 (Published Data Only)

Mahmoud, R. A., Pandina, G. J., Turkoz, I., Kosik-Gonzalez, C., Canuso, C. M., Kujawa, M. J. et al. (2007). Risperidone for treatment-refractory major depressive disorder: a randomized trial.[summary for patients in *Ann Intern Med*. 2007 Nov 6;147(9):I34; PMID: 17975178]. *Annals of Internal Medicine*, 147, 593-602.

- MARCUS2008** (Published Data Only)
 Clinical Study Report CN138163 A multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of aripiprazole as adjunctive therapy in the treatment of patients with major depressive disorder. www.clinicaltrials.gov site accessed 22 July 2008.
 Marcus, R. N., McQuade, R. D., Carson, W. H., Hennicken, D., Fava, M., Simon, J. S. et al. (2008). The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology*, 28, 156-165.
- MCCALL2002** (Published Data Only)
 McCall, W. V.; Dunn, A.; Rosenquist, P. B.; Hughes, D. (2002) Markedly suprathreshold right unilateral ECT versus minimally suprathreshold bilateral ECT: antidepressant and memory effects. *Journal of ECT*, 18, 126-129.
- MCINTYRE2007B** (Published Data Only)
 McIntyre, A., Gendron, A., & McIntyre, A. (2007). Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depression & Anxiety*, 24, 487-494.
- MICHELSON2007** (Published Data Only)
 Michelson, D., Adler, L. A., Amsterdam, J. D., Dunner, D. L., Nierenberg, A. A., Reimherr, F. W. et al. (2007). Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*, 68, 582-587.
- RANJKESH2005** (Published Data Only)
 Ranjkesh, F., Barekatin, M., & Akuchakian, S. (2005) Bifrontal versus right unilateral and bitemporal electroconvulsive therapy in major depressive disorder. *Journal of ECT*, 21, 207-210.
- SACKEIM1993** (Published Data Only)
 Sackeim, H. A., Prudic, J., Devanand, D. P., Kiersky, J. E., Fitzsimons, L., Moody, B. J., McElhiney, M. C., Coleman, E. A., Settembrino, J. M. (1993) Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New England Journal of Medicine*, 328, 839-846.
- SACKEIM2000** (Published Data Only)
 Sackeim, H. A., Prudic, J., Devanand, D. P., Nobler, M. S., Lisanby, S. H., Peyser, S., Fitzsimons, L., Moody, B. J., & Clark, J. (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Archives of General Psychiatry*, 57, 425-434.
- SACKEIM2008** (Published Data Only)
 Sackeim, H. A., Prudic, J., Nobler, M. S., Fitzsimons, L., Lisanby, S. H., Payne, N., Berman, R. M., Brakemeier, E-L., Perera, T. P. & Devanand, D. P. (2008). Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation*, 2008, 71-83.
- SHELTON2005** (Published Data Only)
 Shelton, R. C., Williamson, D. J., Corya, S. A., Sanger, T. M., Van, C., Case, M. et al. (2005). Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. [See comment]. *Journal of Clinical Psychiatry*, 66, 1289-1297.
- SIENAERT2009** (Published Data Only)
 Sienaert, P., Vansteelandt, K., Demyttenaere, K., & Peuskens, J. (2009). Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: Clinical efficacy. *Journal of Affective Disorders*, 122, 60-67.
- SONG2007** (Published Data Only)
 Song, Z. W., Liu, X. B., & Li, Y. D. (2007). Venlafaxine combined with low-dose risperidone for treatment-resistant depression. [Chinese]. *Journal of Clinical Rehabilitative Tissue Engineering Research*, 11.
- STOPPE2006** (Published Data Only)
 Stoppe, A., Louza, M., Rosa, M., Gil, G., & Rigonatti, S. (2006). Fixed high-dose electroconvulsive therapy in the elderly with depression: a double-blind, randomized comparison of efficacy and tolerability between unilateral and bilateral electrode placement. *Journal of ECT*, 22, 92-99.
- TEW2002** (Published Data Only)

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, Dolata, D., Hixson, L., & Mann, J. J. (2002). A randomized comparison of high-charge right unilateral electroconvulsive therapy and bilateral electroconvulsive therapy in older depressed patients who failed to respond to 5 to 8 moderate-charge right unilateral treatments. *Journal of Clinical Psychiatry*, 63, 1102-1105.

THASE2007D (Published Data Only)

Study 2: Thase, M. E., Corya, S. A., Osuntokun, O., Case, M., Henley, D. B., Sanger, T. M. et al. (2007). A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*, 68, 224-236.

Study 1: Thase, M. E., Corya, S. A., Osuntokun, O., Case, M., Henley, D. B., Sanger, T. M. et al. (2007). A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*, 68, 224-236.

WHITMYER2007 (Unpublished and Published Data)

Kornstein, S. G., Dunner, D. L., Meyers, A. L., Whitmyer, V. G., Maillinckrodt, C. H., Wohlreich, M. M., Detke, M. J., Hollandbeck, M. S., Greist, J. H. (2008) A randomized, double-blind study of increasing or maintaining duloxetine dose in patients without remission of major depressive disorder after initial duloxetine therapy. *Journal of Clinical Psychiatry*, 69: 1383-1392.

Eli Lilly study F1J-MC-HMDR, CT Registry ID# 8950. A comparison of duloxetine dosing strategies in the treatment of patients with major depression. Clinicaltrialresults.org [date site accessed 13.06.08].

Whitmyer, V. G., Dunner, D. L., Kornstein, S. G., Meyers, A. L., Mallinckrodt, C. H., Wohlreich, M. M., Gonzales, J.S., Greist, J. H. (2007) A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *Journal of Clinical Psychiatry*, 68, 1921-1930.

References of Excluded Studies

BALDOMERO2005 (Published Data Only)

Baldomero, E. B., Ubago, J. G., Cercos, C. L., Ruiloba, J. V., Calvo, C. G., & Lopez, R. P. (2005). Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depression & Anxiety*, 22, 68-76.

BARBOSA2003 (Published Data Only)

Barbosa, L., Berk, M., & Vorster, M. (2003). A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *Journal of Clinical Psychiatry*, 64, 403-407.

BAUNE2007 (Published Data Only)

Baune, B. T., Caliskan, S., & Todder, D. (2007). Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. *Human Psychopharmacology*, 22, 1-9.

COOPERKAZAZ2007 (Published Data Only)

Cooper-Kazaz, R., Apter, J. T., Cohen, R., Karagichev, L., Muhammed-Moussa, S., Grupper, D. et al. (2007). Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. *Archives of General Psychiatry*, 64, 679-688.

JOFFE2006

Joffe, R., Sokolov, S., & Levitt, A. (2006). Lithium and triiodothyronine augmentation of antidepressants. [References]. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*, 51, 791-793.

MAZEH2007 (Published Data Only)

Mazeh, D., Shahal, B., Aviv, A., Zemishlani, H., & Barak, Y. (2007). A randomized, single-blind, comparison of venlafaxine with paroxetine in elderly patients suffering from resistant depression. *International Clinical Psychopharmacology*, 22, 371-375.

NELSON2004 (Published Data Only)

Nelson, J.C.; Mazure, C.M.; Jatlow, P.I.; Bowers, M.B.J.; Price, L.H. (2004) Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biological Psychiatry*, 55, 296-300.

NORMANN2002 (Published Data Only)

Normann, C., Hummel, B., Scharer, L. O., Horn, M., Grunze, H., & Walden, J. (2002). Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *Journal of Clinical Psychiatry*, 63, 337-344.

PERRY2004 (Published Data Only)

Perry, E. B., Berman, R. M., Sanacora, G., Anand, A., Lynch-Colonese, K., & Charney, D. S. (2004). Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. *Journal of Clinical Psychiatry*, 65, 238-243.

POSTERNAK2008 (Published Data Only)

Posternak, M., Novak, S., Stern, R., Hennessey, J., Joffe, R., Prange, A. J. et al. (2008). A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. *International Journal of Neuropsychopharmacology*, 11, 15-25.

ROGOZ2007 (Published Data Only)

Rogoz, Z., Skuza, G., Daniel, W. A., Wojcikowski, J., Dudek, D., & Wrobel, A. (2007). Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. *Pharmacological Reports*, 59, 778-784.

SCHINDLER2007 (Published Data Only)

Schindler, F. & Anghelescu, I. G. (2007). Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. *International Clinical Psychopharmacology*, 22, 179-182.

239

- SCT-MD-11B** (Unpublished Data Only)
Forest Research Institute. Evaluation of the safety and efficacy of escitalopram in the prevention of depression recurrence (SCT-MD-11B).
- SCT-MD-11C** (Unpublished Data Only)
Forest Research Institute. Evaluation of the safety and efficacy of escitalopram in the prevention of depression recurrence (SCT-MD-11C).
- SCT-MD-21** (Unpublished Data Only)
Forest Research Institute. Double-blind comparison of the safety and efficacy of escitalopram and fluoxetine in the treatment of fluoxetine nonresponders (SCT-MD-21). Report date: March 26 2004.
- SHAPIRA2006** (Published Data Only)
Shapira, B., Nemets, B., Trachtenberg, A., & Belmaker, R. H. (2006). Phenytoin as an augmentation for SSRI failures: A small controlled study. [References]. *Journal of Affective Disorders*, 96, 123-126.
- STAR-D level 2** (Published Data Only)
Thase, M. E., Friedman, E. S., Biggs, M. M., Wisniewski, S. R., Trivedi, M. H., Luther, J. F. et al. (2007). Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *American Journal of Psychiatry*, 164, 739-752.
Trivedi, M. H., Fava, M., Wisniewski, S. R., Thase, M. E., Quitkin, F., Warden, D. et al. (2006). Medication augmentation after the failure of SSRIs for depression. *New England Journal of Medicine*, 354, 1243-1252.
*Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Stewart, J. W., Nierenberg, A. A., Thase, M. E. et al. (2006). Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *New England Journal of Medicine*, 354, 1231-1242.
- STAR-D level 3** (Published Data Only)
Fava, M., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Alpert, J. E., McGrath, P. J. et al. (2006). A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. [See comment]. *American Journal of Psychiatry*, 163, 1161-1172.
Nierenberg, A. A., Fava, M., Trivedi, M. H., Wisniewski, S. R., Thase, M. E., McGrath, P. J. et al. (2006). A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. [See comment]. *American Journal of Psychiatry*, 163, 1519-1530.
- STAR-D level 4** (Published Data Only)
McGrath, P. J., Stewart, J. W., Fava, M., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A. et al. (2006). Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. [See comment]. *American Journal of Psychiatry*, 163, 1531-1541.
- WHYTE2004** (Published Data Only)
Whyte, E. M., Basinski, J., Farhi, P., Dew, M. A., Begley, A., Mulsant, B. H. et al. (2004). Geriatric depression treatment in nonresponders to selective serotonin reuptake inhibitors. *Journal of Clinical Psychiatry*, 65, 1634-1641.
- ZARATE2006** (Published Data Only)
Zarate, C. A. J., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A. et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. [See comment]. *Archives of General Psychiatry*, 63, 856-864.

Relapse prevention - studies in previous guideline

Characteristics of included studies

Cook1986	RDC unipolar depression	Age: mean=63.2. N=15, all male. Outpatients.	At least 1 year's treatment with various TCAs.	At least 1 year without a reoccurrence of depressive symptoms.	7 months on: 1. Desipramine (75-250mg), amitriptyline (75-200mg), doxepin (100-200mg),	Reoccurrence (HRSD \geq 18)	Paper gives HRSD baseline and endpoint scores for individual papers so we can use our
Kupfer1992	RDC major depressive disorder	N=20. Age: 21-65 (completers from Frank1990)	3 years of treatment with 1. IPT + imipramine or 2. Imipramine (+ medication clinic visits) see Frank990	In remission (not meeting RDC major depressive episode)	2 years of: 1. Imipramine (mean=236mg) or Placebo	Recurrence (meeting RCD criteria for major depressive disorder and HRSD \geq 15)	The 13 patients receiving IPT before randomisation continued to do so afterwards - 6
Montgomery 1988	DSM-III major depression and HRSD>18	N=220.	6 weeks treatment with Fluoxetine (40-80mg). Responders(HRSD<12) continued on fluoxetine (40mg) for further 18 weeks.	HRSD \leq 8	1 year on: 1. Fluoxetine (40mg) 2. Placebo	Recurrence (HRSD>18)	Recurrence rate give for completers only. Does not specify whether any dropouts suffered

Relapse prevention - new studies in the guideline update

Comparisons Included in this Clinical Question

Nortriptyline vs ECT + nortriptyline - NAVARRO 2008

Characteristics of Included Studies

<p>NAVARRO2008</p> <p>Study Type: RCT</p> <p>Study Description: RCT for remitters to acute-phase ECT</p> <p>Blindness: Double blind</p> <p>Duration (days): Mean 730</p> <p>Setting: Spain; inpatient and outpatient referrals for ECT</p> <p>Notes: RANDOMISATION: computer-generated</p> <p>Info on Screening Process: 38 in phase I, 33 remitted and randomised</p>	<p>n= 33</p> <p>Age: Mean 70</p> <p>Sex: 12 males 21 females</p> <p>Diagnosis: 100% Major depressive disorder by DSM-IV</p> <p>Additional specifier: Psychotic features</p> <p>Exclusions: HAMD-17 < 21; Neurological disorders affecting CNS; uncontrolled medical illness; contraindications to study treatments; history of mania, hypomania or nonaffective psychosis; current substance dependence; demential (MMSE <= 25)</p> <p>Notes: 100% psychotic symptoms; remission defined as HAMD-17 <8 and no psychotic symptoms</p> <p>Baseline: HAMD-17 (SD) acute phase: nortriptyline 35.82 (5.17); nortriptyline + ECT 35.31 (2.8); continuation phase: nortriptyline 2.88 (1.32); nortriptyline + ECT 3.19 (1.33)</p>	<p>Data Used</p> <p>Recurrence</p> <p>Relapse</p> <p>Notes: Relapse = reemergence of depressive symptoms within 6 months of remission; recurrence = new episode of depression after at least 6 months without relapse</p>	<p>Group 1 N= 17</p> <p>Nortriptyline - Maximum dose 100 mg adjusted to achieve 80 to 120 ng/mL + risperidone 2 mg/day for 6 weeks withdrawn by tapering for 4 weeks</p> <p>Group 2 N= 16</p> <p>Nortriptyline - Maximum dose 100 mg adjusted to achieve 80 to 120 ng/mL</p> <p>ECT - Weekly for first month, every 2 weeks for next month, then monthly (used bilateral ECT)</p>	<p>SIGN 1++; funding unclear</p>
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NAVARRO2008 (Published Data Only)

Navarro, V., Gasto, C., Torres, X., Masana, G., Penades, R., Guarch, J. et al. (2008). Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. *American Journal of Geriatric Psychiatry*, 16, 498-505.