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

Contents

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: H*nn* 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:
*nn*mg->*nn*mg indicates that all patients started on *nn*mg and increased to *nn*mg

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

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

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

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 ffects		B
Claghorn92A Y OC 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 ffects	* 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 ≥50% reduction in HRSD) 2. Leaving the study early 3. Leaving the study early due to side ffects	Undertaken in 11 centres.	B

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≥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 (≥1 dose of medication and ≥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 buproprion - not extracted) (sertraline: mean 121 mg/day)	1. Non-responders (patients not achieving ≥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≥14 and ≤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 ≥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≥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≥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		B

	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≥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 OE 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≥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≥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

	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 efects	‡ 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 ffects	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

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≥17	Fluoxetine (20mg) placebo	1. Non-responders (patients not achieving ≥ 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD≤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 (≥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 ≥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≥20, Raskin≥8.	1. Fluoxetine (20-80mg) 2. Placebo	1. Non-responders (patients not achieving ≥ 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 ≥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

		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 ffects		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 ffects	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 a 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 Y O I	Allocation: Random (no details) Duration: 6 weeks	Outpatients. Age: 18-65, mean=39.8. N=356 (HRSD analysis: N=345). Diagnosis: DSM-III unipolar major depressive disorder, HRSD≥20,	1. Fluoxetine (20mg) 2. Fluoxetine (40mg) 3. Fluoxetine (60mg) 4. Placebo	1. HRSD mean change scores (20mg only) 2. Non-responders (patients not achieving ≥50% decrease in HRSD)	Dichotomous data is combined for 20, 40 and 60mg groups.	B

		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 ≥100mg)
Thompson1994 Y P I	Sertraline given at sub-therapeutic dose - 76% patients on 50mg
Tollefson93 E O? H17	Some participants on HRT
Vanelle1997	All patients were diagnosed with dysthymia (not concurrent with major depression)

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
AMSTERDAM2003A Study Type: RCT Study Description: 3-arm study; zimeldine vs amitriptyline vs placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 158 Age: Mean 41 Range 21-67 Sex: 95 males 63 females Diagnosis: 100% Major depressive disorder by RDC 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. Notes: amitriptyline (55) + placebo (54) = 109 participants. amitriptyline (38M: 17F) and placebo (31M: 19F). Baseline: Zimeldine Amitriptyline Placebo Total HRSD-21 25.1 (5.8) 24.5 (4.2) 23.4 (4.9) 24.3 (5.0)	**Data Used** Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-21 mean endpoint	**Group 1 N= 55** Amitriptyline. Mean dose 182mg/day - Days 1-3: 100mg/day. Days 4-7: 200mg/day. From thereon, could be increased to 300mg/day. **Group 2 N= 54** Placebo - No details.	Funding; part-pharma (Astra Phamaceutical).
BAKISH1992B Study Type: RCT Study Description: 3-arm study; moclobemide vs amitriptyline vs placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; Canada. Notes: Participants had to weigh within 20% of the 1983 standard weight established by the Metropolitan Life Insurance Company. Info on Screening Process: Unknown	n= 55 Age: Mean 39 Range 20-63 Sex: 23 males 32 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Women in their childbearing years who were not using an effective form of contraception, were pregnant or lactating, or were at risk of commiting suicide. Patients who had a major depressive episode associated with mood-incongruent psychotic features, bipolar disorder in manic phase, acute confusional states, epileptic or seizure	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change	**Group 1 N= 19** Amitriptyline. Mean dose 132mg/day - 50-150mg/day. Increased incrementally by 25mg up until the 4th week. **Group 2 N= 18** Placebo - No details.	Funding; unknown.

	disorders, mental retardation, narrow angle glaucoma, or increased intraocular pressure, had a history of urinary retention or a renal, cardiovascular, respiratory, gastointestinal, 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. Notes: amitriptyline (19) + placebo (18) = 37 participants. amitriptyline (14F:5M) and placebo (8F:10M). Baseline: Amitriptyline Moclobemide Placebo HAM-D (17) 22.37 22.94 23.35			
BAKISH1992C Study Type: RCT Study Description: 3-arm study; moclobemide vs amitriptyline vs placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 49 Setting: Outpatients; multicentre, Canada. Notes: 4 participants excluded from analysis because they failed to return after baseline. 173 participants were initially randomised. Info on Screening Process: Unknown.	n= 169 Age: Mean 43 Range 19-64 Sex: 95 males 74 females Diagnosis: 98% Major depressive disorder by DSM-III-R 1% Depression by Bipolar disorder 1% Dysthymia by DSM-III-R 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. Notes: Amitriptyline (57) + Placebo (55) = 112 participants. Amitriptyline (28F:29M) and Placebo (20F:35M). Baseline: Moclobemide Amitriptyline Placebo HAM-D (17) 23.79 22.81 23.04	**Data Used** Weight mean change (kg) Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 58** 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. **Group 2 N= 55** Placebo - 2 capsules 3 times/day. Doses were individually titrated up to an optimum over a period of 2 weeks, depending on tolerability.	Funding; unknown.
BARGESCHAAPVELD2002 Study Type: RCT Study Description: 2-arm study; imipramine vs placebo Type of Analysis: Completers (completed 1st week) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multiple primary care settings, the Netherlands. 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	n= 63 Age: Mean 43 Range 25-59 Sex: 17 males 46 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Current use of psychotropic medications and major medical disorders. Notes: Imipramine (32) + Placebo (31) = 63 participants. MDD also diagnosed by DSM-IV. Baseline: Imipramine Placebo HAM-D (17) 24.0 (3.5) 23.5 (2.6)	**Data Used** Leaving treatment early for any reason HRSD-17 mean endpoint	**Group 1 N= 29** Imipramine - 50-200mg/day in the first week. Could be reduced to 100mg/day if poorly tolerated. **Group 2 N= 30** Placebo - 1-4 capsules/day in week 1.	Funding; part-pharma (Solvay Pharmaceuticals).

out in the first week.				
BEASLEY1991B Study Type: RCT Study Description: 3-arm study; fluoxetine vs imipramine vs placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Notes: Patients were given chloral hydrate or flurazepam for sleep. 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.	n= 706 Age: Mean 41 Sex: 244 males 462 females Diagnosis: 100% Major depressive disorder by DSM-II Exclusions: Patients with bipolar illness, psychosis or active substance misuse. 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. Baseline: HAM-D (21): 27.3	**Data Used** Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects Non-response 50% reduction in HRSD HRSD-21 mean endpoint Notes: 2 Fluox, 5 Imip and 3 Pbo participants discontinued prior to completing 1 visit - excluded from efficacy data	**Group 1 N= 238** 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. **Group 2 N= 225** Placebo - No details.	Funding; part-pharma (Eli Lilly, Lilly Research Laboratories). Participants received =>4 weeks of treatment
BOYER1996A Study Type: RCT Study Description: 3-arm study; imipramine vs amisulpride vs placebo Type of Analysis: Both Blindness: Double blind Duration (days): Mean 168 Setting: Outpatients, multicentre; France. Info on Screening Process: Unknown.	n= 219 Age: Mean 43 Sex: 99 males 120 females Diagnosis: 100% Dysthymia by DSM-III 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 wtihin 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. 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. Baseline: MADRS: 17.9 (.26)	**Data Used** MADRS mean change	**Group 1 N= 73** Imipramine. Mean dose 100mg/day - No details. **Group 2 N= 73** Placebo - No details.	Funding; unclear.
BREMNER1995 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. Info on Screening Process: Unknown.	n= 150 Age: Mean 38 Range 18-93 Sex: 48 males 102 females Diagnosis: 100% Major depressive disorder by DSM-III 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 hypertrophy, seizure disorders, drug allergy or other	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects **Data Not Used** MADRS mean endpoint - no data HRSD-17 mean endpoint - no data	**Group 1 N= 50** Amitriptyline - Week 1: 40-80mg/day, week 2: 40-160mg/day and weeks 3-6: 40-280mg/day. **Group 2 N= 50** Placebo - Week 1: 1-2 capsules/day, week 2: 1-4 capsules/day, and weeks 3-6: 1-7 capsules/day.	Funding; pharma (Organon, Inc.).

	hypersensitivity reaction to TCAs or related compounds, hyperthyroidism, and clinicaly 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. Notes: Amitriptyline (50) + Placebo (50) = 100 participants. Amitriptyline (37F:13M) and Placebo (35F:15M). Baseline: Amitriptyline Org 3770 Placebo HAM-D (17) 27.3 28.3 26.6 MADRS 36.4 37.7 36.6			
BYERLEY1988 Study Type: RCT Study Description: 3-arm study; Fluoxetine vs. Imipramine vs. Placebo Type of Analysis: Completers (had to have had 2 weeks treatment) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US Notes: Randomisation was carried out using a table of randomised numbers. Info on Screening Process: 103 participants entered; 6 excluded. 5 improved significantly during the washout period whilst 1 had an abnormal ECG.	n= 97 Age: Mean 39 Sex: 33 males 64 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Patients with psychotic symptoms, bipolar illness, schizophrenia, active drug or alcohol misuse, or significant medical illnesses. Notes: Imipramine (34) + Placebo (29) = 63 participants. Imipramine (21F:13M) and Placebo (18F:11M). Baseline: Imipramine Fluoxetine Placebo HAM-D (21) 28.3 (4.2) 27.2 (4.9) 27.3 (4.6)	**Data Used** Leaving treatment early for any reason Weight mean change (kg) HRSD-21 mean endpoint	**Group 1 N= 34** 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. **Group 2 N= 29** Placebo - Patients took capsules three times a day for up to 6 weeks.	Funding; pharma (Eli Lilly, Inc.) and research.
CASSANO1986 Study Type: RCT Study Description: 3-arm study; Imipramine vs. Fluvoxamine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Mixed; multicentre, US, Canada, England, Italy and France. Notes: 481 participants entered study. 448 included in analysis because had at least 2 evaluations. Info on Screening Process: Unknown.	n= 448 Age: Mean 42 Sex: 162 males 286 females Diagnosis: 100% Major depressive disorder by No details 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, depedence 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. Notes: Imipramine (153) + Placebo (149) = 302 participants. Imipramine (92F: 61M) and Placebo (95F: 54M). Baseline: Fluvoxamine Imipramine Placebo HAM-D 25.61 25.92 25.60	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint	**Group 1 N= 153** 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. **Group 2 N= 149** 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.	Funding; unknown.
CASSANO1996				

Study Type: RCT Study Description: 3-arm study; Tianeptine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients; Belgium, Italy, Mexico, Portugal, Spain and Switzerland. Notes: Benzodiazepines allowed as associated treatment. 186 participants in ITT population. Parallel group design. Info on Screening Process: Unknown.	n= 187 Age: Mean 47 Sex: 82 males 105 females Diagnosis: 25% Major depressive disorder by DSM-III-R 67% Depression by DSM-III-R 9% Double depression by DSM-III-R 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. 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. Baseline: Tianeptine Imipramine Placebo MADRS (SE) 31.2 (0.6) 31.4 (0.6) 31.0 (0.5)	**Data Used** Leaving treatment early due to side effects Number reporting side effects Suicide Leaving treatment early for any reason MADRS mean endpoint **Data Not Used** Non-response 50% reduction in MADRS - no data	**Group 1 N= 75** 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. **Group 2 N= 76** 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.	Funding; unclear.
CLAGHORN1983 Study Type: RCT Study Description: 3-arm study; Zimeldine vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Unclear; multicentre, US. 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.	n= 263 Age: Mean 39 Range 19-65 Sex: 124 males 139 females Diagnosis: 4% Depression by RDC 96% Major depressive disorder by RDC Exclusions: Females of childbearing potential, patients with somatic illness, pre-existing conditions, and alcohol or drug dependence. Lactating and pregnant women. Notes: AMI (85) + PLA (87) = 172 participants. MDD = definite. Depression = probable. Baseline: Unknown.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects Weight mean change (kg)	**Group 1 N= 85** 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. **Group 2 N= 87** Placebo. Mean dose 230mg/day - No details.	Funding; unknown.
CLAGHORN1983B Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Zimelidine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; multicentre, US. Notes: Presented data as completer data - I have calculated ITT values. Info on Screening Process: 393 participants screened; 130 excluded. 90 participants did not return for treatment after entry or after washout	n= 263 Age: Mean 39 Sex: 113 males 150 females Diagnosis: 100% Major depressive disorder by RDC 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. Notes: Amitriptyline (91) + Placebo (87) = 178 participants. Endogenous depression (72%), primary depression (98%)	**Data Used** Leaving treatment early for any reason Non-response 50% reduction in HRSD **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 91** Amitriptyline. Mean dose 180mg/day - 75-300mg/day. Dosage increased to 300mg/day over the first wo weeks. Investigators were encouraged to titrate the patients to the maximum tolerable dose as rapidly as possible. **Group 2 N= 87** Placebo. Mean dose 230mg/day - Initital dosage was 1 capsule 3 times/day. Dosage was increase to 4 capsules 3 times/day over the first 2 weeks.	Funding; unknown.

period. 22 participants responded to placebo durnig the washout period. 10 participants didn't meed inclusion criteria.	and unipolar depression (91%). Baseline: HDS (21): 27 (for all completers, ie. N=229).			
CLAGHORN1996A 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.	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	**Data Used** HRSD-21 mean change	**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.	Funding; pharma (Solvay Pharmaceuticals).
COHN1984 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.	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	**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	**Group 1 N= 21** Imipramine. Mean dose 137.5mg/day - 5.5 capsules (25mg each)/day. **Group 2 N= 21** Placebo	Funding; unknown.
COHN1985 Study Type: RCT Study Description: 3-arm study; Fluoxetine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: Parallel groups design. Info on Screening Process: Unknown.	n= 166 Age: Mean 43 Range 20-64 Sex: 68 males 98 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Concomitant physical conditions or histories of conditions that would interfere with therapy or evaluation. Notes: Imipramine (54) + Placebo (58) = 112 participants. Imipramine (23M:31F) and Placebo (30M:28F). Baseline: Fluoxetine Imipramine Placebo HAM-D (21) 25.75 25.90 25.14	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-21 mean endpoint	**Group 1 N= 54** 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. **Group 2 N= 58** Placebo - No details.	Funding; unknown.
COHN1990A				

Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo. Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: 120 entered; 102 completed.	n= 120 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (40) + Placebo (40) = 80 participants. Baseline: Unknown.	**Data Used** Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 31** Imipramine - 65-275mg/day. Received medication in the morning and at bedtime. **Group 2 N= 36** Placebo - No details.	Funding; unknown.
COHN1992 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; 128 excluded from analysis. Main reason was use of prohibited concomitant medication. Info on Screening Process: Unknown.	n= 102 Age: Mean 42 Sex: 42 males 60 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (31) + Placebo (36) = 67 participants. Imipramine (12M:19F) and Placebo (19M:17F). Baseline: Paroxetine Imipramine Placebo HAM-D (17) 24.9 (0.72) 24.5 (0.71) 25.6 (0.71)	**Data Not Used** Leaving treatment early for any reason - no data MADRS mean endpoint - no data HRSD-17 mean endpoint - no data	**Group 1 N= 31** Imipramine. Mean dose 144.9mg/day - 65-275mg/day. Treatment started with 80mg/day. **Group 2 N= 36** Placebo - No details.	Funding; unclear.
COHN1996 Study Type: RCT Study Description: 3-arm study; Nefazodone vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US. Notes: Parallel group design. 128 participants entered study; 119 included in ITT analyses. Info on Screening Process: Unknown.	n= 119 Age: Mean 39 Sex: 33 males 86 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Imipramine (38) + Placebo (42) = 80 participants. Imipramine (29F:9M) and Placebo (27F:15M). Baseline: Nefazadone Imipramine Placebo HAM-D (17) 22.8 23.6 23.4	**Data Used** HRSD-17 mean change	**Group 1 N= 38** Imipramine. Mean dose 126mg/day - 100-300mg/day. **Group 2 N= 42** Placebo - No details.	Funding; part-pharma (Bristol-Myers Squibb U.S. Pharmaceuticals).
DOMINGUEZ1981 Study Type: RCT Study Description: 3-arm study; Amoxapine vs. Imipramine vs. Placebo Type of Analysis: Unsure Blindness: Double blind Duration (days): Mean 42	n= 97 Age: Mean 41 Range 21-64 Sex: 38 males 59 females Diagnosis: 100% Depression by No details Exclusions: Treatment with any psychoactive drug within 7	**Data Used** Number reporting side effects Leaving treatment early for any reason **Data Not Used** HRSD-21 mean change - no data	**Group 1 N= 38** 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.	Funding; unknown.

Setting: Outpatients; US. Notes: 46 participants completed 6 weeks of treatment. Info on Screening Process: Unknown.	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. 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. Baseline: Amoxapine Imipramine Placebo HAM-D (21) 33.4 32.0 32.3	Notes: Unsure which HRSD version.	**Group 2 N= 20** 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.	
DOMINGUEZ1985 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US Notes: Excluded data from 7 participants who didn't complete 4 weeks. Only 16 of the 17 HRSD items used (excluded loss of weight). Info on Screening Process: 124 participants screened; 13 excluded from entering study.	n= 101 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (35) + Placebo (31) = 66 participants. Baseline: Fluvoxamine Imipramine Placebo HAM-D 17 20.4 22.0 20.9	**Data Used** 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	**Group 1 N= 35** 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. **Group 2 N= 31** Placebo - No details.	Funding; unclear.
DUNBAR1991 Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Notes: Main reasons for exclusions from efficacy analyses were concomitant use of medication with potential CNS activity. Info on Screening Process: Unknown.	n= 717 Age: Mean 40 Sex: 390 males 327 females Diagnosis: 100% Major depressive disorder by DSM-II Exclusions: Patients who had a reduction of over 20% in HRSD score in the washout period. Notes: Imipramine (237) + Placebo (240) = 477 participants. Imipramine (101M:109F) and Placebo (115M:106F). Baseline: Paroxetine Imipramine Placebo HAM-D (17) 26.5 26.2 26.6	**Data Used** Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects MADRS mean change HRSD-17 mean change	**Group 1 N= 237** 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. **Group 2 N= 240** Placebo - No details.	Funding; unclear.
ELKIN1989 Study Type: RCT Study Description: 4-arm study; CBT vs. IPT vs. PLA-CM vs. ICM Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 84 Setting: Outpatients; US. Info on Screening Process: 556 participants screened. The primary reason for rejection was failure to meet the MDD and/or HRSD inclusion	n= 239 Age: Mean 35 Sex: 71 males 168 females Diagnosis: 100% Major depressive disorder by RDC 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,	**Data Used** Leaving treatment early for any reason Non-response 50% reduction in HRSD Non-remission HRSD-17 < 7 BDI mean endpoint HRSD-17 mean endpoint Notes: <6 for remission.	**Group 1 N= 57** Imipramine - Average for first two weeks 185mg/day. **Group 2 N= 62** Placebo - No details.	Funding; research (NIMH).

criteria either at screening or at rescreening.	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. Notes: Imipramine (57) + Placebo (62) = 119 participants. 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)			
ENTSUAH1994 Study Type: RCT Study Description: 3-arm study; Imipramine vs. Venlafaxine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 213 Age: Mean 42 Sex: 71 males 142 females Diagnosis: 100% Major depressive disorder by No details Exclusions: Unknown. Notes: Imipramine (71) + Placebo (78) = 149 participants. Baseline: Unknown.	**Data Used** MADRS mean change HRSD-21 mean change Notes: Cumulative mean changes given.	**Group 1 N= 71** Imipramine - No details. **Group 2 N= 78** Placebo - No details.	Funding; unclear. Work for Clinical Biostatics, Wyeth-Ayerst Research.
ESCOBAR1980 Study Type: RCT Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Inpatients; Colombia. Info on Screening Process: Unknown.	n= 40 Age: Mean 45 Range 25-66 Sex: Diagnosis: 85% Depression by RDC 15% Double depression by RDC Exclusions: No history of other psychiatric disorder or major physical illness. Notes: Imipramine (15) + Placebo (12) = 27 participants. Imipramine (8F:7M) and Placebo (8F:4M). Double depression = bipolar. Baseline: Trazodone Imipramine Placebo HAM-D (21) 30.8 31.3 30.9	**Data Used** Non-response 50% reduction in HRSD	**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. **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.	Funding; unclear.
FABRE1980 Study Type: RCT Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo Type of Analysis: Completer Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 154 Age: Sex: Diagnosis: 100% Depression by No details Exclusions: Not suffering primarily from primary depression, were psychopathic, sociopathic or psychotic, were suffering from bipolar, involutional 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 sympathicomimetic amines, were receiving guanethidine,	**Data Used** Leaving treatment early for any reason	**Group 1 N= 52** Imipramine. Mean dose 128.4mg/day - No details. **Group 2 N= 51** Placebo - No details.	Funding; unknown.

	propranolol, a methyldopa or thyroid medications, or could not read of understand the symptoms check list. Notes: Imipramine (52) + Placebo (51) = 103 participants. Baseline: Unknown.			
FABRE1992 Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 120 participants entered the study. 111 included in efficacy analyses. Info on Screening Process: Unknown.	n= 111 Age: Mean 36 Sex: 42 males 69 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (37) + Placebo (36) = 73 participants. Imipramine (12M:25F) and Placebo (13M:23F). Baseline: Paroxetine Imipramine Placebo HAM-D (21) 29.7 (0.64) 27.8 (0.65) 28.8 (0.66)	**Data Used** MADRS mean change HRSD-21 mean change **Data Not Used** Leaving treatment early for any reason - no data Notes: SDs for mean HRSD very small and gave high heterogeneity - convered to Ses and now no heterogeneity - assume error in labelling in the paper	**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. **Group 2 N= 36** Placebo - No details.	Funding; unknown.
FABRE1996 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: F (46), I (48) and P (44) in ITT sample. Info on Screening Process: 235 participants screened; 150 entered (50 participants/group).	n= 150 Age: Sex: 33 males 105 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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. Notes: Imipramine (48) + Placebo (44) = 92 participants. Imipramine (8M:40F) and Placebo (14M:30F) in ITT sample. Baseline: Fluvoxamine Imipramine Placebo HAM-D (21) 27.7 26.5 26.0 MADRS 30.6 30.6 29.5	**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	**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. **Group 2 N= 44** Placebo - No details.	Funding; pharma (Solvay Pharmaceuticals).
FEIGER1996A Study Type: RCT Study Description: 3-arm study; Imipramine vs. Geripone vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US Info on Screening Process: Unknown.	n= 123 Age: Mean 40 Sex: 36 males 45 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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 azaperones or tricyclic antidepressants, significant suicide	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects Number reporting side effects MADRS mean endpoint **Data Not Used** HRSD-21 mean endpoint - no data HRSD-17 mean endpoint - no data Notes: HAM-D 28 used where 21 denoted.	**Group 1 N= 41** Imipramine - Days 1-2: 50mg/day, days 3-7: 100mg/day and 50-300mg/day thereafter. **Group 2 N= 40** Placebo - Days 1-2: 1 capsule/day, days 3-7: 2 capsules/day and up to 6 capsules/day thereafter.	Funding; unclear.

	risk, electroconvulsive therapy within 6 months of the study, and a history of glaucoma, urinary retention, or seizure disorders. 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). Baseline: Gepirone Imipramine Placebo MADRS 26.98 28.26 26.88			
FEIGHNER1979 Study Type: RCT Study Description: 4-arm study; Amitriptyline vs. Limbitrol (Amitriptyline + Chlordiazepoxide) vs. Chlordiazepoxide vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; multicentre, US. Notes: Randomisation was in blocks of 7 participants (2-2-2-1). 58 participants excluded from efficacy analysis. Info on Screening Process: Unknown.	n= 337 Age: Mean 40 Sex: 102 males 235 females Diagnosis: 100% Depression by Feighner criteria 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. Notes: Amitriptyline (93) + Placebo (50) = 143 participants. Amitriptyline (40M:53F) and Placebo (17M:33F). 143 unipolar and 33 bipolar depressives. Baseline: Limb Amit Chlord Pbo HRSD-24 34.3 36.0 35.0 34.7 BDI 19.0 19.4 18.9 19.2	**Data Used** Number reporting side effects Leaving treatment early for any reason Leaving treatment early due to side effects BDI mean endpoint HRSD-24 mean endpoint **Data Not Used** Non-response 50% reduction in HRSD - no data	**Group 1 N= 93** 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. **Group 2 N= 50** Placebo. Mean dose 130mg/day - No details.	Funding; unknown.
FEIGHNER1980 Study Type: RCT Study Description: 3-arm study; Imipramine vs. Trazodone vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Inpatients; US Info on Screening Process: 50 participants admitted; 1 had pre-treatment HRSD <18, and 4 withdrew.	n= 45 Age: Sex: 12 males 33 females Diagnosis: 100% Depression by Feighner criteria 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. Notes: Imipramine (18) + Placebo (10) = 28 participants. Imipramine (2M:16F) and Placebo (4M:6F). Baseline: Trazodone Imipramine Placebo HAMD (21) 35.4 36.6 36.0	**Data Used** Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 18** Imipramine - Started with 100mg/day. This could be increased by 25mg every 3-4 days up to a maximum of 300mg/day. **Group 2 N= 10** Placebo. Mean dose 157.5mg/day - 6.37 capsules/day.	Funding; pharma.
FEIGHNER1982 Study Type: RCT Study Description: 3-arm study; Lofepramine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Info on Screening Process: Unknown.	n= 139 Age: Sex: 40 males 99 females Diagnosis: 100% Depression by DSM-III 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	**Data Used** Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-21 mean endpoint Notes: Non-response = 40% reduction in HRSD.	**Group 1 N= 45** Placebo - No details. **Group 2 N= 48** Imipramine. Mean dose 150mg/day - Week 1: 75mg/day. From thereon could be increased to 150mg/day.	Funding; unknown.

	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. Notes: Imipramine (48) + Placebo (45) = 93 participants. Imipramine (13M:35F) and Placebo (11M:34F). Baseline: Lofepramine Imipramine Placebo HAM-D 26.98 (0.59) 26.94 (0.64) 27.36 (0.59)			
FEIGHNER1983A Study Type: RCT Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Multicentre; US. Info on Screening Process: Unclear. 906 participants enrolled at start.	n= 723 Age: Mean 38 Sex: 208 males 515 females Diagnosis: 100% Major depressive disorder by Feighner criteria 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. Notes: Imipramine (244) + Placebo (243) = 487 participants. Imipramine (78M:166F) and Placebo (64M:179F). Baseline: HDRS: 26.06 (5.11)	**Data Used** Number reporting side effects **Data Not Used** HRSD-17 mean endpoint - no data Notes: Unclear which HRDS version was used. Need to check how scores were added.	**Group 1 N= 244** Imipramine - Started at 50mg daily. At 3 days, went up to 75mg. Maximum dosage 225mg. **Group 2 N= 243** Placebo - No details.	Funding; pharma (The Upjohn Company).
FEIGHNER1983B Study Type: RCT Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 129 Age: Mean 39 Sex: 24 males 105 females Diagnosis: 100% Major depressive disorder by Feighner criteria 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 chlorohydrate. Notes: Imipramine (43) + Placebo (45) = 88 ppts. Imipramine (9M:34F) and Placebo (3M:42F). Baseline: Alprazolam Imipramine Placebo HAM-D 30.5 30.4 30.0	**Data Used** Leaving treatment early for any reason **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 43** 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. **Group 2 N= 45** 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. Ths investigators further increased the dose at 1 week intervals for patients for optimum clinical effect to a maximum of 2 capules 3 times/day.	Funding; research (The Feighner Research Institute).
FEIGHNER1989				

Study Type: RCT Study Description: 3-arm study; Nefazodone vs. Imipramine vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US Info on Screening Process: Unknown.	n= 45 Age: Mean 45 Range 27-64 Sex: 23 males 22 females Diagnosis: 100% Depression by RDC Exclusions: Unknown. 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. Baseline: Unknown.	**Data Used** Leaving treatment early for any reason **Data Not Used** Leaving treatment early due to side effects HRSD-17 mean endpoint - no data	**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. **Group 2 N= 15** Placebo - Started at 2 capsules/day.	Funding; unknown.
FEIGHNER1989A Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo. Type of Analysis: Completers (at least 4 days of treatment) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US Info on Screening Process: Unknown.	n= 120 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (40) + Placebo (37) = 77 participants. Baseline: Unknown.	**Data Used** Leaving treatment early due to side effects Leaving treatment early for any reason Non-response 50% reduction in HRSD - no data **Data Not Used** MADRS mean endpoint - no data	**Group 1 N= 40** Imipramine - Maximum dose: 275mg/day. **Group 2 N= 37** Placebo - No details.	Funding; unknown.
FEIGHNER1989B Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients; US. 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. Info on Screening Process: Unknown.	n= 86 Age: Mean 41 Range 18-71 Sex: 13 males 73 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Imipramine (36) + Placebo (19) = 55 participants. Imipramine (32F:4M) and Placebo (17F:2M). Baseline: Unknown.	**Data Used** Leaving treatment early due to side effects	**Group 1 N= 36** Imipramine - 150-300mg/day. **Group 2 N= 19** Placebo - No details.	Funding; unclear.
FEIGHNER1989C Study Type: RCT Study Description: 3-arm study; Imipramine vs. Fluoxetine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 145 participants completed at least 2	n= 145 Age: Mean 42 Sex: 37 males 108 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Pregnant, not practicing medically acceptable contraception, or if they posed a serious suicide risk. Organic brain syndrome, schizophrenia, a history of	**Data Used** HRSD-21 mean endpoint Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 45** Imipramine - Maximum dose: 150mg/day. **Group 2 N= 48** Placebo - No details.	Funding; unclear.

weeks of treatment. Info on Screening Process: 198 enrolled. 178 entered double-blind treatment phase. Reasons for exclusion unknown.	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. Notes: Imipramine (45) + Placebo (48) = 93. Imipramine (34F:11M) and Placebo (38F:10M). Baseline: Fluoxetine Imipramine Placebo HAM-D (21) 25.60 25.96 25.90			
FEIGHNER1992B 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 the study. Info on Screening Process: Unknown.	n= 116 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (40) + Placebo (37) = 77 participants. Baseline: HAMD (21): Approx. 25 (graphical data).	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 40** Imipramine. Mean dose 111.3mg/day - 65mg/day-275mg/day. **Group 2 N= 37** Placebo. Mean dose 5.46 capsules - No details.	Funding; research.
FEIGHNER1993 Study Type: RCT Study Description: 3-arm study; Paroxetine vs. Imipramine vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Notes: Parallel groups. Info on Screening Process: Unknown.	n= 717 Age: Mean 40 Sex: 347 males 370 females Diagnosis: 100% Major depressive disorder by DSM-II 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 lactacting were excluded. Notes: Imipramine (237) + Placebo (240) = 477 participants. Imipramine (112M:125F) and Placebo (122M:118F). Baseline: Paroxetine Imipramine Placebo HAM-D 26.4 26.2 26.6	**Data Used** Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason Non-remission HRSD-17 < 10 HRSD-21 mean change	**Group 1 N= 237** 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. **Group 2 N= 240** Placebo - No details.	Funding; unclear.
FERGUSON1994B Study Type: RCT Study Description: 3-arm study; Dothiepin vs. Doxepin vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 70 Setting: Outpatients; multicentre, US. Notes: 25 participants excluded from analyses; 23 didn't return after baseline and 2 withdrew consent.	n= 579 Age: Mean 40 Sex: 214 males 340 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change Weight mean change (kg)	**Group 1 N= 194** Dosulepin (dothiepin). Mean dose 140.7mg/day - 50mg/day days 1-3, 100mg/day days 4-7, and from thereafter up to 150mg/day. **Group 2 N= 192** Placebo - Unknown.	Funding; pharma (Boots Pharmaceuticals, Inc.).

Info on Screening Process: 765 participants screened; 186 excluded. Reasons unknown.	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. Notes: Participant demographics based on efficacy analyses. Dothiepin (194) + Placebo (192) = 386 participants. Dothiepin (118F:66M) and Placebo (112F:74M). 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)			
FONTAINE1994 Study Type: RCT Study Description: 4-arm study; Nefazodone (high dose) vs. Nefazodone (low dose) vs. Imipramine vs. Placebo. Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; Canada. Info on Screening Process: Unknown.	n= 180 Age: Mean 42 Range 20-65 Sex: 68 males 112 females Diagnosis: 100% Major depressive disorder by RDC 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. Notes: Imipramine (45) + Placebo (45) = 90 participants. Imipramine (15M:30F) and Placebo (23M:22F). Baseline: HAMD (21): Nefazadone (50-250mg/day) = 25.2, Nefazadone (100-500mg/day) = 25.6, Imipramine = 25.8, Placebo = 25.9	**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 HRSD-21 mean change	**Group 1 N= 45** Imipramine - 50-250mg/day. By day 8, patients were receiving 150mg/day. **Group 2 N= 45** Placebo - No details.	Funding; pharma (Bristol-Myers Squibb Pharmaceutical Research Institute).
GELENBERG1990 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Clovoxamine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: Parallel groups design. Info on Screening Process: Unknown.	n= 62 Age: Range 21-62 Sex: 19 males 43 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Amitriptyline (19) + Placebo (22) = 41 participants. Baseline: Unknown.	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects **Data Not Used** HRSD-17 mean endpoint - no data Notes: Unsure of HAMD version.	**Group 1 N= 19** 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. **Group 2 N= 22** Placebo. Mean dose 152mg/day - No details.	Funding; unknown.
GELENBERG2002				

Study Type: RCT Study Description: 3-arm study; Tyrosine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US Info on Screening Process: Unknown.	n= 65 Age: Mean 40 Range 21-60 Sex: 46 males 19 females Diagnosis: 100% Major depressive disorder by RDC 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. Notes: Imipramine (22) + Placebo (22) = 44 participants. Imipramine (16M:6F) and Placebo (14M:8F). Baseline: Tyrosine Imipramine Placebo HAMD (21) 24.3 24.3 24.5	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 22** 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. **Group 2 N= 22** Placebo - No details.	Funding; unclear.
GEORGOTAS1982A Study Type: RCT Study Description: 3-arm study; Zimeldine vs. Amitriptyline vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Unclear; US. Notes: 60 participants completed at least 2 weeks' treatment. Assumed 20 participants per treatment arm. Info on Screening Process: Unknown.	n= 52 Age: Mean 40 Sex: 31 males 21 females Diagnosis: 100% Major depressive disorder by RDC Exclusions: Intercurrent medical illness, childbearing potential, and the need to take other medications. Notes: AMI (15) + PLA (18) = 33 participants. Amitriptyline (12M:3F) and Placebo (10M:8F). Baseline: Zimelidine Amitriptyline Placebo HAM-D 21 (SE) 29.9 (1.1) 28.5 (1.5) 28.6 (1.3)	**Data Used** Leaving treatment early for any reason BDI mean endpoint HRSD-21 mean endpoint	**Group 1 N= 18** Placebo. Mean dose 223mg/day - No details. **Group 2 N= 15** Amitriptyline. Mean dose 206mg/day - 150mg/day by the end of week 1 and 300mg/day by the end of week 2.	Funding; unknown.
GEORGOTAS1986A Study Type: RCT Study Description: 3-arm study; Nortriptyline vs. Phenelzine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 49 Setting: Outpatients; US. Notes: RANDOMISATION: randomised, no details Info on Screening Process: 295 screened; 137 met inclusion criteria; 126 entered washout period; 90 in double-blind study	n= 58 Age: Mean 65 Range 55-76 Sex: 22 males 36 females Diagnosis: 100% Major depressive disorder by RDC 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. Notes: Ns do not include phenelzine group; No M/F based on % M/F in ITT sample Baseline: Placebo Nortriptyline Phenelzine HAM-D 21 23.07 23.58 22.14	**Data Used** Non-remission HRSD-21 < 10 Number reporting side effects Leaving treatment early for any reason **Data Not Used** HRSD-21 mean endpoint - no variablility measure Notes: Remission reported as 'response' but definition closer to that for remission on other studies	**Group 1 N= 28** 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. **Group 2 N= 30** 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.	SIGN 1+; funding partly NIMH grant, no further details
GERNER1980B Study Type: RCT Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo Type of Analysis: ITT	n= 60 Age: Mean 68 Range 60-90 Sex: 23 males 37 females Diagnosis: 100% Depression by RDC	**Data Used** Non-remission HRSD-17 < 10 Non-response 50% reduction in HRSD Leaving treatment early for any reason **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 20** Imipramine. Mean dose 145mg/day - 50-200mg/day. **Group 2 N= 20** Placebo - Equivalent of 50-200mg/day.	Funding; part-pharma (Mead Johnson Pharmaceuticals).

Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Notes: Assume 20 participants per treatment arm. Info on Screening Process: Unknown.	Exclusions: Unknown. Notes: Depression = unipolar depression. Imiprimine (20) + Placebo (20) = 40 participants. Baseline: Unknown.	BDI mean endpoint - no data Notes: 30% rather than 50% reduction in HAMD used to define responders.		
GOLDBERG1980 Study Type: RCT Study Description: 3-arm study; Trazodone vs. Amitriptyline vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 184 participants entered study. Efficacy evaluated in 127 participants. Remaining 57 participants evaluated for safety only. Info on Screening Process: Unknown.	n= 127 Age: Mean 37 Range 18-60 Sex: 34 males 93 females Diagnosis: 100% Depression by Details below Exclusions: Unknown. 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. Baseline: Unknown.	**Data Used** Non-response 50% reduction in HRSD Number reporting side effects Leaving treatment early due to side effects	**Group 1 N= 60** Amitriptyline - 75-200mg/day. Increased every 3-4 days. **Group 2 N= 62** Placebo - No details.	Funding; unclear. Suspect pharma.
HAYES1983 Study Type: RCT Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 60 Age: Mean 68 Sex: 23 males 37 females Diagnosis: 100% Depression by RDC Exclusions: Unknown. Notes: Imipramine (19) + Placebo (15) = 34 participants. Baseline: Unknown.	**Data Used** Leaving treatment early for any reason	**Group 1 N= 19** 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. **Group 2 N= 15** 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.	Funding; unknown.
HICKS1988 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Adinazolam vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: Participants admitted as inpatients and kept in the centre for 10-14 days. Info on Screening Process: Unknown.	n= 48 Age: Mean 42 Sex: 15 males 33 females Diagnosis: 100% Major depressive disorder by DSM-III 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. 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. Baseline: Amitriptyline Adinazolam Placebo HAMD 30.8 31.6 29.4	**Data Used** Weight mean change (kg) Leaving treatment early for any reason **Data Not Used** HRSD-17 mean endpoint - no data Notes: Unsure of HAMD version.	**Group 1 N= 16** Amitriptyline. Mean dose 142mg/day - 25-300mg/day. **Group 2 N= 15** Placebo - No details.	Funding; part-pharma (Upjohn Company).
HOLLYMAN1988				

Study Type: RCT Study Description: 2-arm study; Amitriptyline vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; UK. Info on Screening Process: 290 participants identified by GPs for study inclusion; 112 excluded. 53 ineligible and 59 declined to enter.	n= 141 Age: Range 18-64 Sex: 24 males 117 females Diagnosis: 28% Minor depression by RDC 71% Major depressive disorder by RDC 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. Notes: Amitriptyline (54F:13M) and Placebo (63F:11M). Minor depression = minor OR intermittent depression. Baseline: HRDS (17): 14.75 (3.65) (ALL)	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change	**Group 1 N= 67** Amitriptyline - 25-75mg/day by the end of week1, 100mg/day by the end of week 2 and 125-175mg/day thereafter. **Group 2 N= 74** Placebo - Unknown.	Funding; pharma (Parke-Davis).
HORMAZABAL1985 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Cianopramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Mixed; unclear. Notes: Parallel groups design. Info on Screening Process: Unknown.	n= 60 Age: Mean 44 Range 20-93 Sex: 9 males 51 females Diagnosis: 100% Depression by DSM-III Exclusions: Uncontrolled organic disease, pregnancy or puerperium. Notes: Amitriptyline (20) + Placebo (20) = 40 participants. Depression = depressive episodes. Amitriptyline (3M:17F) and Placebo (4M:16F). Baseline: Cianopramine Amitriptyline Placebo HAMD (21) 38.3 (6.3) 36.7 (6.8) 35.8 (8.1)	**Data Used** Leaving treatment early for any reason Notes: 7 participants in amitriptyline group and 2 participants in placebo group were treated concomitantly with benzodiazepines. 1 amitriptyline participant received phenobarbital.	**Group 1 N= 20** Amitriptyline. Mean dose 86.4mg/day - Initial dose was 1 capsule/day (25mg) which could be increased depending on efficacy and side-effects. **Group 2 N= 20** Placebo. Mean dose 4 capsules/day - Initial dose was 1 capsule/day (25mg) which could be increased depending on efficacy and side-effects.	Funding; unknown.
HOSCHL1989 Study Type: RCT Study Description: 4-arm study; Verapamil vs. Amitriptyline vs. State-adjusted treatment vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 35 Setting: Inpatients; Czech Republic Notes: Amitriptyline (24F:2M) and Placebo (10F:1M). Info on Screening Process: Unknown.	n= 86 Age: Mean 45 Sex: 7 males 79 females Diagnosis: 14% Dysthymia by Bipolar disorder 12% Major depressive disorder by DSM-III 15% Depression by DSM-III 5% Affective disorder by DSM-III 2% Double depression by DSM-III 2% Minor depression by DSM-III 1% Chronic depression by DSM-III Exclusions: Unknown.	**Data Used** Leaving treatment early for any reason Non-response 50% reduction in HRSD HRSD-17 mean endpoint Notes: HRSD 16. Response was <= 10 on HRSD 16.	**Group 1 N= 19** Amitriptyline. Mean dose 113mg/day - 75-175mg/day. Dosage depended on the individual. **Group 2 N= 11** Placebo - No details.	Funding; part-pharma (Knoll Pharmaceuticals).

	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. Baseline: Verapamil Amitriptyline Placebo HAMD (16) 20.3 (8.7) 24.4 (6.1) 22.2 (8.1)			
ITIL1983A Study Type: RCT Study Description: 3 arm study; fluvoxamine vs. imipramine vs. placebo. Type of Analysis: ITT (included if received >2 weeks' medication) Blindness: Double blind Duration (days): Setting: Outpatients; US. Info on Screening Process: Not known.	n= 69 Age: Mean 41 Range 21-68 Sex: 39 males 39 females Diagnosis: 100% Depression by RDC 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. 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. Baseline: Placebo Imipramine Fluvoxamine HDRS-16 19.7 (2.7) 21.9 (4.2) 20.3 (3.0)	**Data Used** Suicide Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint Notes: HRSD-16 used.	**Group 1 N= 25** Imipramine. Mean dose 127 - 50-210mg/daily. Initial dose was 50mg, then increased according to participant response. **Group 2 N= 22** Placebo. Mean dose 173 - 50-750mg. Initial dose of 50mg, increased according to participant response.	Funding; unclear.
ITIL1993 Study Type: RCT Study Description: 3-arm study; Dothiepin vs. Doxepin vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 63 Setting: Unclear; US. Notes: Parallel groups. Info on Screening Process: 62 participants screened; 25 participants excluded. Did not meet eligibility criteria.	n= 37 Age: Mean 37 Range 18-74 Sex: Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Unknown. Notes: MDD without psychotic features. Dothiepin (13) + Placebo (10) = 23 participants. 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)	**Data Used** MADRS mean endpoint Leaving treatment early due to side effects HRSD-17 mean endpoint **Data Not Used** Non-response 50% reduction in HRSD - no data Notes: Unsure of HRSD version.	**Group 1 N= 13** Dosulepin (dothiepin) - 50-150mg/day. **Group 2 N= 10** Placebo - No details.	Funding; pharma (Boots Pharmaceuticals, Inc.).
KASPER1995B Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 28 Setting: Mixed; multicentre, US and Canada. Info on Screening Process: Unclear.	n= 338 Age: Mean 42 Sex: 148 males 194 females Diagnosis: 86% Major depressive disorder by DSM-III 14% Depression by Bipolar disorder 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, wer epregnant or were not using adequate concentration.	**Data Used** Suicide Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-17 mean endpoint Notes: 16 item HRSD.	**Group 1 N= 113** Imipramine. Mean dose 151mg/day - Day 1-3: 50mg/day, then adjusted between 50-300mg/day according to response. **Group 2 N= 109** Placebo - 1-6 capsules/day.	Funding; unknown.

	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 Study Type: RCT Study Description: 2-arm study; Nortiptyline vs. Placebo Type of Analysis: Completer Blindness: Double blind Duration (days): Mean 49 Setting: Community (nursing home or congregate housing residents); US. Notes: RANDOMISATION: randomised, no details 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	n= 30 Age: Mean 84 Sex: 2 males 28 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: HAM-D-24 < 18; not medically stable; contraindications to nortripytline 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 Baseline: Placebo Nortriptyline HAM-D 24 23.7 (4.1) 24.7 (2.5)	**Data Used** Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-24 mean endpoint Notes: HAMD-24 modified to exclude item on genital symptoms	**Group 1 N= 18** 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. **Group 2 N= 12** Placebo - Comparable dose increments to those in the nortriptyline group were implemented.	SIGN 1+; funding NIMH
KELLAMS1979 Study Type: RCT Study Description: 3-arm study; Trazodone vs. Imipramine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 28 Setting: Inpatients; US. Info on Screening Process: Unknown.	n= 28 Age: Sex: Diagnosis: 100% Depression by No details 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. Notes: Imipramine (10) + Placebo (9) = 19 participants. Approximately equal number of each sex per treatment arm. Baseline: Trazadone Imipramine Placebo HAM-D (21) 23.5 25.1 26.9	**Data Used** Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 10** 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. **Group 2 N= 9** 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.	Funding; unknown.
KLIESER1988 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Trazodone vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 21 Setting: Unclear; Germany. Info on Screening Process: Unknown.	n= 37 Age: Mean 41 Sex: 12 males 25 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Amitriptyline (12) + Placebo (14) = 26 participants. Amitriptyline (9F:3M) and Placebo (9F:5M). Baseline: Trazodone Amitriptyline Placebo HAMD 31 (6.8) 34 (8.6) 31 (7.5)	**Data Used** Leaving treatment early for any reason HRSD-17 mean endpoint Notes: Unclear which HAMD version.	**Group 1 N= 12** Amitriptyline - 150mg/day **Group 2 N= 14** Placebo - 4 capsules/day.	Funding; unknown.
LAAKMAN1995				

Study Type: RCT Study Description: 4-arm study; Alprazolam vs. Amitriptyline vs. Lorazepam vs. Placebo Type of Analysis: ITT (all participated for at least 1 week) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; Germany. 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.	n= 282 Age: Mean 47 Range 19-75 Sex: 82 males 200 females Diagnosis: 100% Depression by ICD-9 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. Notes: Depression = mild to moderate depression. Amitriptyline (72) + Placebo (74) = 146 participants. Baseline: Lorazepam Alprazolam Amitriptyline Placebo HAMD 19.6 (4.5) 20.2 (4.5) 19.7 (4.5) 19.2 (3.7)	**Data Used** Leaving treatment early due to side effects HRSD-17 mean change Leaving treatment early for any reason Non-response 50% reduction in HRSD Notes: Unsure of HRSD version.	**Group 1 N= 72** Amitriptyline. Mean dose 102mg/day - 50-200mg/day. **Group 2 N= 74** Placebo. Mean dose 2.79 tablets/day - No details.	Funding; unknown.
LAIRD1993 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Info on Screening Process: Unknown.	n= 54 Age: Mean 47 Sex: 17 males 37 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Imipramine (14) + Placebo (16) = 20 participants. Baseline: Unknown.		**Group 1 N= 14** Imipramine. Mean dose 180mg/day - No details. **Group 2 N= 16** Placebo. Mean dose 240mg/day - No details.	Funding; pharma.
LAPIERRE1987 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients; Canada. Info on Screening Process: Unknown.	n= 63 Age: Mean 45 Sex: 26 males 37 females Diagnosis: 100% Major depressive disorder by DSM-III 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 depenendt 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. Notes: Imipramine (21) + Placebo (20) = 41 participants. Imipramine (12F:9M) and Placebo (12F:8M). Baseline: None.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 21** Imipramine - No details. **Group 2 N= 20** Placebo - No details.	Funding; unknown.
LAPIERRE1991 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Sertraline vs. Placebo Type of Analysis: Completers	n= 448 Age: Sex:	**Data Used** Non-response 50% reduction in HRSD **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 123** Amitriptyline. Mean dose 111mg/day - Weeks 1-3: 50-150mg/day. Maintained at 150mg/day thereafter.	Funding; unknown.

Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; Canada and US. Notes: There is a H2H study also written up in this article that may be of use. Info on Screening Process: Unknown.	Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Amitriptyline (123) + Placebo (130) = 253 participants. Bipolar = 11 participants. MD single episode = 203 participants. MD recurrent = 234 participants. Baseline: Unknown. HAM-D (17) data displayed graphically.		**Group 2 N= 130** Placebo - No details.	
LARSEN1989 Study Type: RCT Study Description: 3-arm study; Clomipramine vs. Moclobemide vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients and outpatients; Denmark. Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 38 Age: Mean 50 Range 25-76 Sex: 13 males 25 females Diagnosis: 100% Major depressive disorder by DSM-III 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 Baseline: Placebo Moclobemide Clomipramine HAMD 17 18.3 (15-27) 17.5 (14-24) 17.8 (15-27)	**Data Used** Non-remission HRSD-17 < 9 Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** HRSD-17 mean endpoint - Data in graph; no SDs	**Group 1 N= 20** Clomipramine. Mean dose 150 mg - Day 1: 75mg/day, increased by 25mg/day up to 50mg three times per day (ie. 150mg/day). **Group 2 N= 18** Placebo - 1 capsule 3 times per day. Increased by 1 capsule daily up to 2 capsules 3 times per day (ie. 6 capsules/day).	SIGN: 1+; funding no details. Baseline statistics are median (range)
LECRUBIER1997B Study Type: RCT Study Description: 3-arm study; Imipramine vs. Venlafaxine vs. Placebo Type of Analysis: ITT; LOCF method Blindness: Double blind Duration (days): Mean 91 Setting: Outpatients; France, Italy and UK. Info on Screening Process: Unknown.	n= 229 Age: Mean 40 Sex: 75 males 154 females Diagnosis: 14% Minor depression by RDC 79% Major depressive disorder by RDC 7% Depression by RDC 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. Notes: 7% intermittent depression. Imipramine (75) + Placebo (76) = 151 ppts. Imipramine (51F:24M) and Placebo (48F:28M). Baseline: Venlafaxine Imipramine Placebo MADRS 24.9 24.4 24.2	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects Non-response 50% reduction in MADRS	**Group 1 N= 75** Imipramine - Day 1: 50mg/day, days 5-7: 75mg/day and days 8-15: 150mg/day. This dose maintained thereafter. **Group 2 N= 76** Placebo - No details.	Funding; unclear.
LIPMAN1986				

Study Type: RCT Study Description: 3-arm study; Imipramine vs. Placebo vs. Chlordiazepoxide Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 387 Age: Mean 38 Sex: 158 males 229 females Diagnosis: 75% Major depressive disorder by DSM-III 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. Notes: Imipramine (116) + Placebo (139) = 255 participants. Imipramine (69F:47M) and Placebo (80F:59M). Baseline: Unknown.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 116** 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. **Group 2 N= 139** 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.	Funding; pharma and research (Hoffman, La Roche and NIMH).
LYDIARD1989 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo. Type of Analysis: Completers (at least 2 weeks of treatment) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; part of multicentre study, USA. Notes: 54 entered; 45 completed. Info on Screening Process: Unknown.	n= 54 Age: Mean 47 Range 23-81 Sex: Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (18) + Placebo (17) = 35 participants. Baseline: Fluvoxamine Imipramine Placebo HRSD 24.5 26.4 26.0	**Data Used** Number reporting side effects Leaving treatment early due to side effects Non-response 50% reduction in HRSD HRSD-17 mean endpoint	**Group 1 N= 18** Imipramine. Mean dose 180mg/day - 100-300mg/day. **Group 2 N= 17** Placebo. Mean dose 240mg/day - No details.	Funding; pharma.
LYDIARD1997 Study Type: RCT Study Description: 3-arm study; Sertraline vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; multicentre, US. Info on Screening Process: 473 participants screened; 81 excluded. Reasons unknown.	n= 392 Age: Mean 40 Sex: 131 males 261 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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 3 weeks of baseline. Patients with	**Data Used** Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects BDI mean endpoint HRSD-17 mean endpoint	**Group 1 N= 131** 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. **Group 2 N= 129** Placebo - No details.	Funding; pharma.

	significant laboratory or ECG abnormalities. Notes: Amitriptyline (131) + Placebo (129) = 260 participants. Amitriptyline (90F:41M) and Placebo (86F:43M). MDD Single = 128 participants. MDD Recurrent = 264 participants. Baseline: Amitriptyline Sertraline Placebo (Note: SE in brackets) HAM-D 22.1 (0.26) 21.5 (0.24) 22.1 (0.25) BDI 15.0 (0.56) 14.6 (0.56) 14.3 (0.57)			
MARCH1990 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US Notes: 54 participants entered study. 40 completed. Info on Screening Process: Unknown.	n= 54 Age: Mean 39 Sex: 17 males 37 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (15) + Placebo (12) = 27 participants. Baseline: Unknown.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects **Data Not Used** MADRS mean endpoint - no data HRSD-17 mean endpoint - no data	**Group 1 N= 15** 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. **Group 2 N= 12** 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.	Funding; part-pharma (Kali-Duphar Laboratories).
MARKOWITZ1985 Study Type: RCT Study Description: 3-arm study; Phenelzine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Unclear; US. Info on Screening Process: Unknown.	n= 238 Age: Sex: Diagnosis: 100% Depression by DSM-III Exclusions: Unknown. Notes: Imipramine (80) + Placebo (77) = 157 participants. Baseline: Unknown.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 80** Imipramine - At least 200mg. **Group 2 N= 77** Placebo - No details.	Funding; unknown.
MENDELS1986 Study Type: RCT Study Description: 3-arm study; Alprazolam vs. Imipramine vs. Placebo Type of Analysis: ITT: LOCF (at least 1 week of treatment) Blindness: Double blind Duration (days): Mean 42	n= 98 Age: Mean 37 Sex: 53 males 45 females Diagnosis: 100% Major depressive disorder by No details Exclusions: Pregnant women and those who could become	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects Non-response 50% reduction in HRSD **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 34** Imipramine. Mean dose 167mg/day - No details. **Group 2 N= 34** Placebo. Mean dose 3.7 capsules/day - No details.	Funding; unknown.

Setting: Outpatients; US. Notes: 107 participants entered the study. Info on Screening Process: Unknown.	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.			
MERIDETH1983 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.	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	**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 variablility 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	**Group 1 N= 46** Imipramine - Between 100-300mg/day. **Group 2 N= 47** Placebo - No details.	Funding; unclear.
MINDHAM1991 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.	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	**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.	**Group 1 N= 17** Dosulepin (dothiepin). Mean dose 150mg/day - 50mg 3 times a day (150mg/day). **Group 2 N= 20** Placebo - No details.	Funding; pharma (The Boots Company).
MYNORSWALLIS1995 Study Type: RCT Study Description: 3-arm study; Problem solving therapy vs. Amitriptyline vs. Placebo Type of Analysis: ITT (at least 4 sessions completed) Blindness: Double blind Duration (days): Mean 42	n= 91 Age: Mean 37 Range 18-65 Sex: 21 males 70 females Diagnosis: 100% Major depressive disorder by RDC Exclusions: Another psychiatric disorder before the onset of the depression, receiving current psychological or	**Data Used** Non-remission HRSD-17 < 7 BDI mean endpoint HRSD-17 mean endpoint	**Group 1 N= 31** Amitriptyline. Mean dose 139mg/day - Days 1-2: 50mg/day, followed by an increase of 25mg every third night until 150mg/day taken. **Group 2 N= 30** Placebo - No details.	Funding; part-pharma (Warner-Lambert).

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. Info on Screening Process: 173 participants referred; 66 excluded because didn't meet entry criteria. 91 agreed to take part.	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. Notes: Amitriptyline (31) + Placebo (30) = 60 participants. Amitriptyline (7M:24F) and Placebo (9M:21F). 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)			
MYNORSWALLIS1997 Study Type: RCT Study Description: 3-arm study; Problem-solving therapy vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 84 Setting: Primary care; UK. Info on Screening Process: Unknown.	n= 91 Age: Mean 37 Sex: 21 males 70 females Diagnosis: 100% Major depressive disorder by RDC Exclusions: Unknown. Notes: Amitriptyline (31) + Placebo (30) = 61 participants. Baseline: Unknown.	**Data Used** Non-remission HRSD-17 < 10	**Group 1 N= 31** Amitriptyline - No details. **Group 2 N= 30** Placebo - No details.	Funding; research.
NAIR1995 Study Type: RCT Study Description: 3-arm study; Moclobemide vs. Nortriptyline vs. Placebo Type of Analysis: ITT (for those completing >3 wks) Blindness: Double blind Duration (days): Mean 49 Setting: Outpatients; Canada, Denmark, England. Notes: RANDOMISATION: randomised, no details Info on Screening Process: 115 screened	n= 73 Age: Mean 71 Sex: 21 males 52 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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. Notes: Ns don't include moclobemide group Baseline: Placebo Nortriptyline HAM-D 17 24.0 (18-31) 23.5 (18-32)	**Data Used** Non-remission HRSD-17 < 10 Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** HRSD-17 mean change - Data given as medians	**Group 1 N= 38** 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. **Group 2 N= 35** Placebo - Received 2 pills in the morning, afternon and evening.	SIGN 1+; funding Roche International. For baseline statistics scores refer to median (range)
NANDI1976 Study Type: RCT Study Description: 3-arm study; Imipramine vs. Placebo vs. Natural Process Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 28 Setting: Rural outpatients; India Info on Screening Process: Unknown.	n= 41 Age: Sex: Diagnosis: 100% Depression by No details Exclusions: Free from any physical illness. Notes: Imipramine + Placebo = 27 participants. Baseline: Placebo Imipramine HDRS 57.0 (7.0) 60.8 (11.0)	**Data Used** HRSD-17 mean endpoint	**Group 1 N= 17** Imipramine - 25mg twice a day for two days, then 50mg twice a day. **Group 2 N= 10** Placebo - No details.	Funding; unclear.
NORTON1984 Study Type: RCT Study Description: 3-arm study; Fluvoxamine vs. Imipramine vs. Placebo Type of Analysis: ITT	n= 91 Age: Mean 38 Sex: 21 males 70 females	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint	**Group 1 N= 30** Imipramine. Mean dose 153.3mg/day - Treatment was started at 50mg/day for 4 days, rising to 100mg/day for the	Funding; unknown.

Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; UK. Info on Screening Process: Unknown.	Diagnosis: 100% Major depressive disorder by RDC Exclusions: Younger than 18 and older than 65, had depressive symptoms which were manifestations of another current psychaitric 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. Notes: Imipramine (30) + Placebo (25) = 55 participants. Imipramine (23F:7M) and Placebo (21F:4M). Baseline: Fluvoxamine Imipramine Placebo HRSD-17 19.5 19.6 19.9		remainder of the first week of treatment. Thereafter the dosage was adjusted according to clinical situation. **Group 2 N= 25** 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.	
PECKNOLD1976B Study Type: RCT Study Description: 2-arm study; Clomipramine vs. Placebo Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 42 Setting: Inpatients and outpatients; Canada Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 20 Age: Mean 41 Range 20-63 Sex: 5 males 15 females Diagnosis: 100% Depression by No details Exclusions: No details Baseline: No details	**Data Used** Number reporting side effects **Data Not Used** HRSD-17 mean endpoint - No data given Notes: Results of statistical tests given but no data	**Group 1 N= 10** Clomipramine. Mean dose 140 mg - Week 1: 75mg/day, week 2: 100mg/day, week 3: 150mg/day and weeks 4-6: 200mg/day. **Group 2 N= 10** Placebo - Week 1: 75mg/day, week 2: 100mg/day, week 3: 150mg/day and weeks 4-6: 200mg/day.	SIGN 1+; funding unclear
PEDERSEN2002 Study Type: RCT Study Description: 3-arm study: Imipramine vs. Venlafaxine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Setting: Outpatients; US Notes: No details of randomisation given. Info on Screening Process: No details given.	n= 459 Age: Mean 41 Sex: 148 males 311 females Diagnosis: 100% Depression by No details by No details Exclusions: No details given. Notes: Placebo + Imipramine = 307 participants. Placebo = 39M/81F completers, 52M/106F in total. Imipramine = 33M/62F completers, 52M/98F in total. Baseline: Placebo Venlafaxine Imipramine HAM-D 17 22.0 22.0 22.5	**Data Used** Leaving treatment early for any reason MADRS mean endpoint HRSD-17 mean endpoint	**Group 1 N= 158** Placebo - No details. **Group 2 N= 149** Imipramine - No details.	Funding; Wyeth-Ayerst Research (not stated explicitly).
PESELOW1989 Study Type: RCT Study Description: 3-arm study: Placebo vs. Paroxetine vs. Imipramine. Type of Analysis: Completers	n= 105 Age: Mean 45 Sex: 67 males 38 females	**Data Used** Non-response 50% reduction in HRSD **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 32** Imipramine - Dose ranged between 65-275 mg/day.	Funding; no details.

Blindness: Double blind Duration (days): Setting: Inpatients; US Notes: No details of randomisation. Info on Screening Process: 137 screened; 32 excluded. 15 did not meet criteria after single-blind phase. Unclear why remaining 17 did not enter.	Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Hamilton score dropped below 18 or more than 20% from pre-single blind phase. Notes: No baseline or final HAM-D scores given. Imipramine + Placebo = 72 participants. Imipramine (32). Placbeo (39). Imipramine = 22M/10F. Placebo = 24M/15F. Baseline: Placebo (HAM-D 21): 26.93		**Group 2 N= 39** Placebo - No details.	
PESELOW1989B 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 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 122 Age: Sex: Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Imipramine (40) + Placebo (42) = 82 participants. Baseline: Unknown.	**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	**Group 1 N= 40** Imipramine - 65-275mg/day. **Group 2 N= 42** Placebo - No details.	Funding; unclear.
PHILIPP1999 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): Setting: Unclear; Germany. Info on Screening Process: No details.	n= 263 Age: Mean 47 Sex: 66 males 197 females Diagnosis: 100% Depression by No details 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. Notes: Placebo + Imipramine = 157 participants. Placebo = 9M/38F. Imipramine = 31M/79F. Mean age = 45.5. Baseline: Placebo Imipramine Hypericum HDRS-17 22.7 (4.0) 22.2 (4.2) 22.7 (4.2)	**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	**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.	Funding; Steiner Arzneimittel, Berlin, Germany.
QUITKIN1989 Study Type: RCT Study Description: 3-arm study; Phenelzine vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Unclear; US. Notes: Could be seen as atypical depression. May need to be excluded. Info on Screening Process: Unknown.	n= 60 Age: Mean 38 Sex: 26 males 34 females Diagnosis: 61% Major depressive disorder by RDC 16% Minor depression by RDC 40% Affective disorder by RDC 9% Depression by Bipolar disorder Exclusions: Unknown	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint	**Group 1 N= 19** Imipramine - No details. **Group 2 N= 20** Placebo - No details.	Funding; unclear.

	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 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Sertraline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; multicentre, US. Notes: Parallel groups. 20.8% AMI and 14.7% PLA had concurrent medical diseases. Info on Screening Process: Unknown.	n= 448 Age: Mean 39 Range 18-64 Sex: 207 males 241 females Diagnosis: 2% Depression by Bipolar disorder 45% Major depressive disorder by DSM-III 52% Double depression by DSM-III 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 wtihin 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. Notes: Depression = bipolar disorder. MDD = single episode. Double depression = recurrent depression. Amitriptyline (149) + Placebo (150) = 299 participants. Amitriptyline (65M:84F) and placebo (72M:78F). Baseline: Amitriptyline Sertraline Placebo HAM-D (17) 23.18 (3.63) 23.28 (3.65) 23.43 (3.73)	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean change	**Group 1 N= 149** Amitriptyline - 50, 100 or 150mg/day. **Group 2 N= 150** Placebo - No details.	Funding; unknown.
RICKELS1981 Study Type: RCT Study Description: 3-arm study; Amoxapine vs. Imipramine vs. Placebo Type of Analysis: Completers (at least 4 weeks' treatment)	n= 158 Age: Mean 38 Range 25-57 Sex: 58 males 100 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Pregnant, lactating, or planned to become	**Data Used** HRSD-21 mean endpoint	**Group 1 N= 43** Imipramine - 75-200mg/day. Initial dosge was 75mg/day for the first week. Thereafter, dosage could be adjusted individually according to therapeutic response. Maximum dosage was 200mg/day.	Funding; research (NIMH) .

Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 96 participants were volunteers with symptoms of depression. Info on Screening Process: Unknown.	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. Notes: Imipramine (43) + Placebo (27) = 70 participants. Baseline: HAM-D (21): 23.8		**Group 2 N= 27** Placebo - Up to 8 capsules/day. Started at 3 capsules/day in the first week.	
RICKELS1982A Study Type: RCT Study Description: 3-arm study; Lofepramine vs. Imipramine vs. Placebo Type of Analysis: ITT? Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 158 Age: Mean 43 Range 30-56 Sex: 54 males 104 females Diagnosis: 100% Major depressive disorder by DSM-III 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. 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. Baseline: HAM-D (21): 25.9 (5.7)	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-21 mean endpoint	**Group 1 N= 52** Imipramine - 105-210mg/day. **Group 2 N= 52** Placebo - No details.	Funding; part-pharma (EM Industries).
RICKELS1982D Study Type: RCT Study Description: 3-arm study; Trazodone vs. Amitriptyline vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: HRSD-21 scores all seem very small. Bring up in discussion. Info on Screening Process: Unknown.	n= 202 Age: Mean 40 Sex: 69 males 133 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: 45% endogenous depression. 55% reactive subtype. Amitriptyline (68) + placebo (68) = 136 participants. Baseline: HRSD (21): 1.26 (ALL)	**Data Used** Leaving treatment early for any reason Number reporting side effects HRSD-21 mean endpoint	**Group 1 N= 68** Amitriptyline. Mean dose 123.75mg/day - 100mg/day by the end of week 1. Up to 200mg/day. **Group 2 N= 68** Placebo. Mean dose 135mg/day - No details.	Funding; part-research.
RICKELS1985 Study Type: RCT Study Description: 4-arm study; Alprazolam vs. Doxepin vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; multicentre, US. Notes: Participants had at least 2 weeks of efficacy data. 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	n= 504 Age: Mean 39 Sex: 171 males 333 females Diagnosis: 100% Major depressive disorder by Feighner criteria 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 retention, paralytic ileus, and convulsive disorders. Patients	**Data Used** HRSD-21 mean endpoint Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** Non-response 50% reduction in HRSD - no data	**Group 1 N= 124** Amitriptyline. Mean dose 148mg/day - 50mg to start, increasing to 75mg/day by day 3. From then on could increase to 225mg/day. **Group 2 N= 130** Placebo - No details.	Funding; unknown.

unavailable for follow-up.	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. Notes: Amitriptyline (124) + placebo (130) = 254 participants. Baseline: HAM-D (21): 26.6 (5.4) (ALL)			
RICKELS1987 Study Type: RCT Study Description: 4-arm study; Diazepam vs. Alprazolam vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: Unknown.	n= 241 Age: Mean 39 Sex: 92 males 149 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Psychopathy or psychosis, bipolar, involutional, 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, propanolol, methyldopa, or thyroid medications. Notes: Imipramine (63) + Placebo (61) = 124 participants. Baseline: Alprazolam Imipramine Placebo Diazepam HRSD-21 23.2 24.4 24.5 23.7	**Data Used** Number reporting side effects Leaving treatment early for any reason Non-response 50% reduction in HRSD HRSD-21 mean endpoint	**Group 1 N= 63** 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. **Group 2 N= 61** 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.	Funding; unclear.
RICKELS1991 Study Type: RCT Study Description: 4-arm study; Imipramine vs. Adinazolam vs. Diazepam vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: Between-participants design. Info on Screening Process: Unknown.	n= 259 Age: Mean 42 Sex: 114 males 145 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Patients with other psychiatric disorders, history of convulsive disorder, significant uncontrolled medical condiotions, 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. Notes: Imipramine (64) + placebo (67) = 131 participants. Baseline: Unknown.	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects **Data Not Used** HRSD-21 mean endpoint - no data Notes: Response rates correspond to patients who completed at least 2 weeks' medication only.	**Group 1 N= 64** Imipramine - 25-150mg/day by the end of week 1. **Group 2 N= 67** Placebo - No details.	Funding; Upjohn company.
ROFFMAN1982 Study Type: RCT Study Description: 3-arm study; Oxaprotiline vs. Amitriptyline vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; USA. Notes: Parallel groups.	n= 278 Age: Mean 44 Range 18-65 Sex: 152 males 126 females Diagnosis: 100% Major depressive disorder by DSM-II Exclusions: History or evidence of clinically significant renal disease, BUN or creatinine elevations, hepatic disease, SGOT, SGPT, or alkaline phosphatase elevations,	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects HRSD-17 mean endpoint	**Group 1 N= 94** Placebo - No details. **Group 2 N= 95** Amitriptyline - 75mg at start - could be increased to 150mg/day at visit three.	Funding; unknown.

Info on Screening Process: 358 participants entered single-blind washout period; 50 excluded. 30 not included because of violations of protocol.	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. Notes: No details of which DSM version. Amitriptyline (95) + Placebo (94) = 189 participants. Amitriptyline (53M:42F) and Placebo (54M:40F). Baseline: Amitriptyline Oxaprotiline Placebo HAM-D (SE) 24.2 (0.52) 24.8 (0.50) 24.5 (0.43)	Notes: Unsure of HRSD version.		
ROWAN1982 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Phenelzine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; UK. Notes: Randomised using minimisation. Info on Screening Process: Unknown.	n= 131 Age: Mean 37 Sex: 38 males 93 females Diagnosis: 100% Depression by RDC 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. Notes: Included participants with depression or depression and anxiety. Amitriptyline (44) + Placebo (45) = 89 participants. Amitriptyline (31F:13M) and Placebo (33F:12M). Baseline: Unknown.	**Data Used** Leaving treatment early for any reason Leaving treatment early due to side effects	**Group 1 N= 44** 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. **Group 2 N= 45** Placebo - No details.	Funding; part-pharma (Warner-Lambert).
SCHWEIZER1994 Study Type: RCT Study Description: 3-arm study; Venlafaxine vs. Imipramine vs. Placebo Type of Analysis: ITT; LOCF method Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Info on Screening Process: 224 participants entered study. 213 completed.	n= 224 Age: Mean 42 Sex: 75 males 149 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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. Notes: Imipramine (73) + Placebo (78) = 151 participants. Imipramine (28M:45F) and Placbeo (26M:52F). Baseline: HAM-D (21): 24.77 (3.07)	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects MADRS mean change HRSD-21 mean change	**Group 1 N= 73** 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. **Group 2 N= 78** 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.	Funding; pharma (Wyeth-Ayerst Laboratories).
SCHWEIZER1998 Study Type: RCT Study Description: 3-arm study; Buspirone vs. Imipramine vs. Placebo Type of Analysis: ITT; LOCF	n= 177 Age: Mean 72 Range 65-89 Sex: 83 males 94 females Diagnosis:	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects Number reporting side effects	**Group 1 N= 60** Imipramine - Week 1: 25mg/day, week 2: 100mg/day and thereafter could be increased to 150mg/day.	Funding; pharma (Bristol Myers Squibb Pharmaceuticals).

Blindness: Double blind Duration (days): Mean 56 Setting: Unclear; US. Info on Screening Process: Unknown.	100% Major depressive disorder by DSM-III-R 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. Notes: Imipramine (60) + Placebo (60) = 120 participants. Baseline: Imipramine Buspirone Placebo HAM-D 17 23.9 (4.0) 24.1 (3.9) 24.1 (4.2)	HRSD-17 mean change	**Group 2 N= 60** Placebo - Week 1: 1 capsule/day, week 2: 2 capsules/day and from thereon up to 3 capsules/day.	
SHRIVASTAVA1992 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.	n= 107 Age: Mean 35 Sex: 65 males 42 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (38) + Placebo (36) = 74 participants. Imipramine (21M:17F) and Placebo (22M:14F). Baseline: Paroxetine Imipramine Placebo HAM-D (17) 27.6 (0.64) 26.3 (0.60) 26.7 (0.62)	**Data Used** Number reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-17 mean change	**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. **Group 2 N= 36** Placebo - No details.	Funding; pharma (SmithKline Pharmaceuticals).
SILVERSTONE1994 Study Type: RCT Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Multicentre; UK. Info on Screening Process: Unclear.	n= 249 Age: Sex: 111 males 138 females Diagnosis: 100% Major depressive disorder by DSM-III-R 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. Notes: 89 participants withdrew; data is from 160 participants? Imipramine (50) + Placebo (54) = 104 participants. Baseline: HDRS 17: 24.9 (4.9)	**Data Used** Suicide Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-17 mean endpoint	**Group 1 N= 50** Imipramine - Started on 25mg. 75mg for week 1. 150mg thereafter. **Group 2 N= 54** Placebo - No details.	Funding; unclear.
SMALL1981 Study Type: RCT Study Description: 4-arm study; ECT vs. Trazodone vs. Imipramine vs. Placebo Type of Analysis: ITT? Blindness: Double blind Duration (days): Mean 28	n= 263 Age: Sex: Diagnosis: 100% Major depressive disorder by RDC	**Data Used** Non-response 50% reduction in HRSD Leaving treatment early for any reason **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 100** Imipramine - No details. **Group 2 N= 72** Placebo - No details.	Funding; unknown.

Setting: Unclear; multicentre, US. Info on Screening Process: Unknown.	Exclusions: Unknown. Notes: Imipramine (100) + Placebo (72) = 172 participants. Baseline: Unknown.			
SMITH1990 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.	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	**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	**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.	Funding; unknown but suspect pharma.
SPRING1992 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.	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)	**Data Used** HRSD-21 mean endpoint	**Group 1 N= 10** Amitriptyline. Mean dose 114 mg/day - 50-350 mg/day. **Group 2 N= 15** Placebo - No details.	Funding; unknown.
STASSEN1993 Study Type: RCT Study Description: 3-arm study; Amitriptyline vs. Oxaprotiline vs. Placebo Type of Analysis: ITT; LOCF Blindness: Double blind Duration (days): Mean 40 Setting: Unclear; multicentre, US. Notes: Says it is a meta-analysis. Appears to be a secondary analysis of an earlier study. Info on Screening Process: Unknown.	n= 429 Age: Range 17-73 Sex: 154 males 275 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Unknown. Notes: Amitriptyline (120) + Placebo (189) = 309 participants. Baseline: Unknown.	**Data Used** Leaving treatment early due to side effects Non-response 50% reduction in HRSD **Data Not Used** HRSD-21 mean endpoint - no data	**Group 1 N= 189** Placebo - No details. **Group 2 N= 120** Amitriptyline - Weeks 1 and 2: 75-225mg/day. Kept at 225mg/day thereafter. **Group 3 N=**	Funding; unclear.
THOMPSON2001B				

Study Type: RCT Study Description: 2-arm study; Dothiepin vs. Placebo Type of Analysis: ITT; LVCF (included those who returned at 2-weeks Blindness: Double blind Duration (days): Mean 28 Setting: Unclear; UK. Notes: This study should not be read as a clinical tiral of the efficacy of dothiepin. GPs administered all tests after receiving training. Sex ratio only. 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.	n= 52 Age: Sex: Diagnosis: 58% Major depressive disorder by RDC 27% Depression by RDC 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. 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. Baseline: Unknown. Used HRSD-17.	**Data Used** Leaving treatment early for any reason Number reporting side effects **Data Not Used** HRSD-17 mean endpoint - no data	**Group 1 N= 25** Dosulepin (dothiepin). Mean dose 75mg/day - 75mg/day. **Group 2 N= 27** Placebo - No details.	Funding; part-pharma (Boots Company PLC).
UCHA1990 Study Type: RCT Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo Type of Analysis: ITT? Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; Argentina. Info on Screening Process: Unknown.	n= 72 Age: Mean 43 Range 19-66 Sex: 18 males 44 females Diagnosis: Exclusions: Unknown. Notes: Very little data provided. Summarised. May need to be excluded. Baseline: Unknown.	**Data Used** Number reporting side effects **Data Not Used** HRSD-17 mean change - no data	**Group 1 N= 24** Imipramine - 33.3mg-200mg/day. **Group 2 N= 24** Placebo - No details.	Funding; unclear.
VERSIANI1989 Study Type: RCT Study Description: 3-arm study; Moclobemide vs. Imipramine vs. Placebo Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; South America. Notes: 1 M patient and 2 I patients were receiving lithium on entry and continued to be treated with it throughout the study. Info on Screening Process: Unknown.	n= 490 Age: Mean 42 Range 18-69 Sex: 117 males 373 females Diagnosis: 100% Major depressive disorder by DSM-III 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. Notes: Imipramine (164) + Placebo (162) = 326 participants. Imipramine (38M:126F) and Placebo (39M:123F). Monopolar = 51.8%. Bipolar = 6.8%. Baseline: Moclobemide Imipramine Placebo HRSD-17 26 (5.4) 25.5 (5.1) 25.4 (5.0)	**Data Used** Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early due to side effects Leaving treatment early for any reason HRSD-17 mean endpoint	**Group 1 N= 164** 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. **Group 2 N= 162** Placebo - No details.	Funding; unknown.
VERSIANI1990 Study Type: RCT Study Description: 3-arm study; Imipramine vs. Moclobemide vs. Placebo. Type of Analysis: Unclear	n= 75 Age: Sex: 25 males 50 females		**Group 1 N= 25** Imipramine. Mean dose 200mg/day - No details.	Funding; unknown.

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: randomsed, 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; uriary retention; hyperthyroidsm; 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 Study Type: RCT Study Description: 3-arm study; Placebo vs. Mianserin vs. Amitriptyline Type of Analysis: ITT (at least 1 evaluable visit 2wks post-base) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; US. Notes: 10 participants excluded from ITT analyses because there were no post-baseline data available. Info on Screening Process: 217 enrolled; 68 excluded. Reasons unknown.	n= 149 Age: Mean 41 Sex: 76 males 73 females Diagnosis: 100% Major depressive disorder by DSM-III Exclusions: Clinically significant renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease, narrow-angle glaucoma, clinicalyl 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. Notes: Amitriptyline (50) + Placebo (49) = 99 participants. Amitriptyline (26M:24F) and Placebo (26M:23F). 58 participants = recurrent depression. 91 participants = single	**Data Used** HRSD-21 mean endpoint Number reporting side effects Non-response 50% reduction in HRSD Leaving treatment early for any reason Leaving treatment early due to side effects MADRS mean endpoint Weight mean change (kg)	**Group 1 N= 50** Amitriptyline. Mean dose 121.8mg/day - Week 1: 120mg/day and weeks 2-6: 300mg/day. **Group 2 N= 49** Placebo. Mean dose 3.1 capsules/day - 2-5 capsules/day.	Funding; pharma (Organon, Inc.).

	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 Amitrityline, 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. (Imipramive 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
BUYSSE1996	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).
KROGMEYER1984	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

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. Chloropromazine 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. Napthylamine 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)

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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: 2458	1. Amoxapine (150 mg300	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 ≥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 ≥ 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 ≥ 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 ≥ 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 I I	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

		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
Montgom-ery80 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

	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 ≥18	2. Amitriptyline (modal 150 mg/day by weeks 4-5)	side effects 3. Non-responders (Patients not achieving ≥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 ≥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≥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

					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 ≥ 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

			3. Placebo	achieving ≥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 ≥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 ≥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 ≥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 ≥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

				achieving ≥50% decrease in HRSD)	least 14 days of treatment	

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 YOE	* Dosage below therapeutic level for amitriptyline
Delaunay1978 YOI	* 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 YOI	* Patients not diagnosed against recognised classification system
Dorn1980	* No formal depression diagnostic assessment conducted
Elwan1976	No efficacy/safety data available
Feighner1983 YOI	* 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 YOI	* Patients not diagnosed against recognised classification system
Goldberg1980 YOI	* Dosage below therapeutic level for amitriptyline and trazodone
Goldstein1969 YOI	* 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 YOI	* Dosage below therapeutic level for amitriptyline
Hackett1967	No efficacy/safety data available
Harding1973 YOI	* 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 YOE	* 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
Berzewski1997 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 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

	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

	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 ≥ 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

	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

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

	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	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). Diagnosis: DSM-III for major depression, HRSD >20.	1. Fluoxetine (40 mg starting - 80 mg) 2. Amitriptyline (150 mg starting - 250 mg)	1. Leaving the study early 2. Leaving the study early due to side effects	Setting: Canada. [Geddes2002]	B

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 d epression, 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

	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 PC I	Double Blind RCT Concealment of Allocation: Unclear Analysis: Intention	Inclusion Criteria: DSM-IV major depression, MADRS ≥ 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

	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	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

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

	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 I I	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

Stark1985 Y O I	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. 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: ITT (≥ 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

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 epidose, 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				

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*]
Ansseau1994	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 ≥100mg) [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 ≥ 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 ≥100mg, mean=148.75mg)	1. Non-responders (patients not achieving ≥50% decrease in MADRS) 2. Non-remitters (patients not achieving MADRS≤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

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

Escitalopram10mg v escitalopram 20 mg v citalopram 40 mg v placebo

Escitaloram v duloxetine
KHAN2007B
NIERENBERG2007B
WADE2007

Escitaloram v duloxetine v placebo

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BALDWIN2006D Study Type: RCT Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Followup: 19 week continuation phase Setting: Primary care; multinational (36 sites) Notes: RANDOMISATION: no details (1:1)	n= 325 Age: Mean 45 Sex: 87 males 238 females Diagnosis: 100% Current episode of major depressive disorder by DSM-IV 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 antcoagulants, sildenafil citrate, cimetidine, type 1c anti-arrhythmics, cardiac glycosides, narcotic analgesics, invesitgational drug in past 3 months; formal psychotherapy Notes: 1 week placebo lead in Continuation data not extracted because contains treatment interruption n= 325 randomised; 323 'ITT' Baseline: MADRS: Escit 29.6 (4.2); Prx 29.7 (4.1)	**Data Used** 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 **Data Not Used** DESS - not relevant ASEX - not relevant Notes: Data avaliable 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	**Group 1 N= 166** Escitalopram. Mean dose 10-20 mg/d - mean 13.9 mg/d **Group 2 N= 159** Paroxetine. Mean dose 20-40 mg/d - mean 26.3 mg/g	Funding: sponsored by Lundbeck
BIELSKI2004 Study Type: RCT Study Description: Was BIELSKI2003 in original guideline (based on conference	n= 198 Age: Mean 37 Sex: 83 males 115 females	**Data Used** Remission: MADRS <= 12 MADRS mean change	**Group 1 N= 98** Escitalopram. Mean dose 20 mg/d - Titrated as per US label instructions	Funding: unclear - two authors from Forest Laboratories Inc

abstract) Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: Unclear Notes: RANDOMISATION: no details	Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 <20 No other exclusion criteria reported Notes: n= 198 randomised; 195 'ITT' Baseline: HAMD-17: Escit 28.6; Vfx 27.4	HAMD-17 mean change Response: 50% reduction in MADRS Remission: HAMD-17 <= 7 Response: 50% reduction in HAMD-17 Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 2 N= 100** Venlafaxine XR. Mean dose 225 mg/d - Titrated as per US label instructions	
BOSE2008 Study Type: RCT Type of Analysis: 'ITT': min 1 dose and 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 84 Setting: Outpatients; US Notes: RANDOMISATION: computer generated schedule	n= 267 Age: Mean 68 Sex: 107 males 156 females Diagnosis: 100% MDD with ongoing episode of at least 4 weeks by DSM-IV 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) Notes: 1 week placebo lead in n=267 randomised; 264 'safety'; 263 'ITT' Baseline: MADRS: Escit 29.4 (4.1); Plb 28.4 (3.6) HAMD-17: Escit 20.3 (4.3); Plb 19.6 (3.9)	**Data Used** Number of people reporting side effects MADRS mean change Leaving treatment early due to side effects CGI HAMD-24 mean change Remission: MADRS <= 10 Response: 50% reduction in MADRS HAMD-17 mean change Leaving treatment early for any reason **Data Not Used** QoL - not relevant Hamilton Anxiety Scale - not relevant Geriatric Depression Scale - not relevant Mini-Mental State Examination - not relevant	**Group 1 N= 132** Escitalopram. Mean dose 10 mg/d - Adjustable after week 4 up to 20 mg/d **Group 2 N= 135** Placebo	Funding: funded by Forest Laboratories
BOULENGER2006 Study Type: RCT Type of Analysis: 'ITT': LOCF (not all randomised; criteria unclear) Blindness: Double blind Duration (days): Mean 168 Setting: Outpatients; 6 countries (49 centres) Notes: RANDOMISATION: no details (1:1)	n= 459 Age: Mean 44 Sex: 143 males 311 females Diagnosis: 100% Major depressive disorder with current episode by DSM-IV-TR 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 developemental 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. Notes: 2 week taper period at end n= 459 randomised; 454 treated; 451 'ITT' Baseline: MADRS: Escit 35.2 (3.7); Prx 34.8 (3.8) HAMD-17: Escit 24.7 (4.8); Prx 24.3 (5.0)	**Data Used** 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 **Data Not Used** Hamilton Anxiety Scale - not relevant CGI - not relevant	**Group 1 N= 232** Escitalopram. Mean dose 10-20 mg/d - 10 mg/d 1st week then increased **Group 2 N= 227** Paroxetine. Mean dose 20-40 mg/d - 20 mg/d 1st week, 30 mg/d 2nd week, then increased	Funding: sponsored by Lundbeck

CLAYTON2006C study1 Study Type: RCT Type of Analysis: 'ITT':LOCF 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Unclear Notes: RANDOMISATION: no details (1:1:1)	n= 420 Age: Mean 36 Sex: 164 males 256 females Diagnosis: 100% MDD with current episode =>12 weeks and =<12 years by DSM-IV 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, suizure 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. Notes: 1 week screening n= 425 randomised; 420 'safety'; 397 'ITT' Baseline: HAMD-17: Escit 23.3 (0.3); Bpn 23.9 (0.3); Plb 23.3 (0.2)	**Data Used** Leaving treatment early for any reason HAMD-17 mean change Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 Leaving treatment early due to side effects **Data Not Used** Hospital Anxiety and Depression Scale - not relevant CGI - not relevant CSFQ - not relevant	**Group 1 N= 142** Escitalopram. Mean dose 10-20 mg/d - mean (sd) 13 mg/d (2.6) **Group 2 N= 142** Bupropion XL. Mean dose 150-450 mg/d - mean (sd) 323 mg/d (59.4) **Group 3 N= 141** Placebo	Funding: supported by GlaxoSmithKline
CLAYTON2006C study2 Study Type: RCT Type of Analysis: 'ITT':LOCF 1 dose&no orgasm dysfnctn&postbln evltn Blindness: Double blind Duration (days): Mean 56 Setting: Unclear Notes: RANDOMISATION: no details (1:1:1)	n= 424 Age: Mean 37 Sex: 180 males 230 females Diagnosis: 100% MDD with current episode =>12 weeks and =<12 years by DSM-IV 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. Notes: 1 week screening n= 424 randomised; 410 'safety'; 388 'ITT' Baseline: HAMD-17: Escit 23.3 (0.3); Bpn 23.2 (0.3); Plb 23.3 (0.3)	**Data Used** HAMD-17 mean change Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** Hospital Anxiety and Depression Scale - not relevant CGI - not relevant CSFQ - not relevant	**Group 1 N= 149** Escitalopram. Mean dose 10-20 mg/d - mean (sd) 13 mg/d (3.2) **Group 2 N= 138** Bupropion XL. Mean dose 150-450 mg/d - mean (sd) 309 mg/d (58.3) **Group 3 N= 137** Placebo	Funding: supported by GlaxoSmithKline
COLONNA2005 Study Type: RCT Type of Analysis: 'ITT':LOCF min 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 168 Setting: Outpatients; multi-national (6 sites) Notes: RANDOMISATION: computer-generated randomisation list (1:1)	n= 357 Age: Mean 46 Sex: 92 males 265 females Diagnosis: 100% Major depressive disorder with current episode by DSM-IV 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 in past month, history of schizophrenia, psychotic disorder or	**Data Used** MADRS mean change MADRS mean endpoint Remission: MADRS <= 12 Response: 50% reduction in MADRS Leaving treatment early due to side effects Side effects reported Leaving treatment early for any reason **Data Not Used** CGI - not relevant	**Group 1 N= 175** Escitalopram. Mean dose 10 mg/d **Group 2 N= 182** Citalopram. Mean dose 20 mg/d	Funding: sponsored by Lundbeck

	drug misuse; drug hypersensitivity or allergy; lack of repsonse to more than one AD treatment. Notes: 1 week placebo lead in Baseline: MADRS: Esct 29.5 (4.3); Cital 30.2 (4.7)			
KASPER2005 Study Type: RCT Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Primary Care and Specialist; 11 countries Notes: RANDOMISATION: no details	n= 518 Age: Mean 75 Sex: 125 males 393 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS <22 or >40; MMSE <22; mania or any bipolar disorder; shizophrenia or any psychotic disorder; OCD; eating disorder; mental retardation or cognitive disorder; MADRS <5 on item 10; trreatment 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 Notes: 1 week placebo lead in n= 518 randomised; 517 treated Baseline: MADRS: Escit 28.2 (3.8); Fluox 28.5 (3.8); Plb 28.6 (4.2)	**Data Used** MADRS mean endpoint Response: 50% reduction in MADRS Remission: MADRS <= 12 Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** CGI - not relevant	**Group 1 N= 174** Escitalopram. Mean dose 10 mg/d **Group 2 N= 164** Fluoxetine. Mean dose 20 mg/d **Group 3 N= 180** Placebo	Funding: unclear - two authors are full-time employees of Lundbeck and third author has received pharmaceutical funding for past research (and this trial?)
KHAN2007B Study Type: RCT Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US (12 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 382 people screened; 104 did not meet inclusion criteria	n= 278 Age: Mean 42 Sex: 112 males 166 females Diagnosis: 100% Major depressive disorder by DSM-IV 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 adequete contraception Notes: 1 week placebo lead in and 16 week extension phase Baseline: HAMD-17 (SD) 21 (4)	**Data Used** Response: 50% reduction in MADRS Remission: MADRS <= 10 MADRS mean change MADRS mean endpoint HAMD-17 mean endpoint Response: 50% reduction in HAMD-24 Remission: HAMD-17 < 7 HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason	**Group 1 N= 138** Duloxetine. Mean dose 60 mg **Group 2 N= 140** Escitalopram. Mean dose 10 mg - 20 mg - Dose increased to 20 mg after 4 weeks if lack of response	SIGN: 1+; funding: National Institutes of Health Center and Forest Research Institute; 1-week no-drug screening phase
LEPOLA2003 Study Type: RCT Study Description: Was MONTGOMERY2001 in original guideline (based on conference abstract)	n= 471 Age: Mean 43 Sex: 133 males 338 females	**Data Used** Remission: MADRS <= 12 Side effects reported Leaving treatment early due to side effects	**Group 1 N= 156** Escitalopram. Mean dose 10 mg/d (min) - Dose could be doubled at week 4 or 6	Funding: sponsored by Lundbeck

Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Primary Care; multinational Notes: RANDOMISATION: no details (1:1:1)	Diagnosis: 100% Major depressive disorder by DSM-IV 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, hypnitics, anxiolytics, barbiturates, chloral hydrate or other 5-hydroxytryptamine receptor agonists, ECT, behaviour therapy or psychotherapy Notes: 1 week placebo lead in n=471 randomised; 468 'ITT' Baseline: MADRS: Plb 28.7; Escit 29.0; Cital 29.2	Leaving treatment early for any reason Response: 50% reduction in MADRS MADRS mean change MADRS mean endpoint **Data Not Used** CGI - not relevant	**Group 2 N= 161** Citalopram. Mean dose 20 mg/d (min) - Dose could be doubled at week 4 or 6 **Group 3 N= 154** Placebo	
MAO2008 Study Type: RCT Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients and inpatients; China (6 sites) Notes: RANDOMISATION: no details (1:1)	n= 240 Age: Mean 39 Sex: 105 males 135 females Diagnosis: 100% Major depressive disorder by DSM-IV 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. Notes: 2 week washout period n= 240 randomised; 231 'ITT' Baseline: MADRS: Escit 30.1 (5.4); Fluox 31.2 (5.1) HAMD-17: Escit 24.7 (5.4); Fluox 24.1 (4.5)	**Data Used** MADRS mean change MADRS mean endpoint HAMD-17 mean change HAMD-17 mean endpoint Response: 50% reduction in MADRS Response: 50% reduction in HAMD-17 Remission: MADRS <= 12 Remission: HAMD-17 <= 7 Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 123** Escitalopram. Mean dose 10 mg/d - + placebo fluoxetine **Group 2 N= 117** Fluoxetine. Mean dose 20 mg/d - + placebo escitalopram	Funding: Contract grant sponsor - Xian-Janssen Pharmaceutical Company
MOORE2005 Study Type: RCT Type of Analysis: 'ITT': LOCF min 1 dose & 1 post-baseline evaluatio Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; France (multicentre) Notes: RANDOMISATION: block randomisation	n= 294 Age: Mean 45 Sex: 97 males 197 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS <30; any other axis I disorder; mania or any bipolar disorder; shizophrenia 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. Notes: n= 294 randomised; 294 'safety'; 280 'ITT' Baseline: MADRS: Escit 36.3 (4.8); Cit 35.7 (4.4)	**Data Used** Response: 50% reduction in MADRS Remission: MADRS <= 12 Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason MADRS mean endpoint **Data Not Used** MADRS-S endpoint - no variablility measure CGI - not relevant Notes: 'Adjusted' means reported	**Group 1 N= 142** Escitalopram. Mean dose 10-20 mg/d - 10 mg/d week 1 then increased **Group 2 N= 152** Citalopram. Mean dose 20-40 mg/d - 20 mg/d week 1 then increased	Funding: funded by Lundbeck
NIERENBERG2007B Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 56 Followup: 6-month continuation phase	n= 684 Age: Mean 42 Range 18-79 Sex: 238 males 446 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS < 22; abnormal physical exam, lab tests	**Data Used** Number with palpitation Number with abnormal orgasmia Number with decreased libido Number with ventricular dysfunction Number with hypertension Number with suicidal depression	**Group 1 N= 273** Duloxetine. Mean dose 60 mg **Group 2 N= 274** Escitalopram. Mean dose 10 mg **Group 3 N= 137** Placebo	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

Setting: Outpatients; US (36 sites) Notes: RANDOMISATION: randomised using 'interactive voice response system' Info on Screening Process: 1049 people screened, 365 failed to meet entry criteria	and ECT; pregnant or lactacting; Axis I disorder other than MDD; previous diagnosis of bipolar disroder, 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 meciation during study, use of MAOI or fluoxetine with 30 days of 3nd 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 Notes: placebo lead in Baseline: HAMD-17 17.6 (4.8) (dul); 17.8 (5.1) (esc); 17.7 (5.2) (pbo)	Number with chronic airways disease exacerbated Number with cardiac failure congestive Number with arrhythmia 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 Weight change Notes: Not possible to calculate SDs for weight change Author emailed for n at randomisation 07/10/08		
SCT-MD-02 Study Type: RCT Type of Analysis: 'ITT': min 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US (22 sites) Notes: RANDOMISATION: no details	n= 386 Age: Mean 42 Sex: 176 males 199 females Diagnosis: 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 signigicant medical condition; abnormal blood pressure; treatment wth 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 to respond to SSRI or two other antidepressants; ECT current or past 6 months; pschotherapy or behaviour therapy in past 3 months; unable to follow protocol; not suitable for study (investigator opinion) Notes: 1 week placebo lead in Baseline: MADRS: Escit 28.7 (4.3); Cit 28.3 (5.0); Plb 28.8 (5.0) HAMD: Escit 24.8 (5.4); Cit 25.0 (5.5); Plb 25.0(5.3)	**Data Used** MADRS mean endpoint Response: 50% reduction in MADRS MADRS mean change Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** CGI - not relevant	**Group 1 N= 129** Escitalopram. Mean dose 10-20 mg/d **Group 2 N= 128** Citalopram. Mean dose 20-40 mg/d **Group 3 N= 129** Placebo	Funding: Forest Laboratories Inc
SCT-MD-09 Study Type: RCT Type of Analysis: Completers (and no prohibited meds) Blindness: Double blind Duration (days): Mean 35 Setting: Outpatients; US Notes: RANDOMISATION: no details	n= 30 Age: Mean 39 Sex: 4 males 26 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD score <18 or sleep disturbance scale score <1 No other criteria reported - need appendices from Lundbeck Notes: n= (original n randomised unlcear); 30 'safety' (received at least one dose of double blind medication); 27 completers; 24 'evaulable' (no prohibited meds) Baseline: MADRS: Escit 24.4 (2.36); Fluox 25.3 (3.74)	**Data Used** Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason HAMD-17 mean change MADRS mean change **Data Not Used** CGI - not relevant Hamilton Anxiety Scale - not relevant	**Group 1 N= 16** Escitalopram. Mean dose 10-20 mg/d - Lower dose for initial 7 days then increased to max dose **Group 2 N= 14** Fluoxetine. Mean dose 20-40 mg/d - Lower dose for initial 7 days then increased to max dose	Funding: Sponsored by Forest Research Institute

	HAMD: Escit 21.5 (3.10); Fluox 21.5 (2.70)			
SCT-MD-16 Study Type: RCT Type of Analysis: 'ITT': LOCF 1 dose & 1 post-basline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US (9 sites) Notes: RANDOMISATION: no details	n= 205 Age: Mean 37 Sex: 69 males 128 females Diagnosis: Major depressive disorder by DSM-IV Exclusions: MADRS score <22 No other criteria reported Notes: 1 week placbo lead in 8 patients unaccounted for between randomisation and treatment - need to email Lundbeck for details Baseline: MADRS: Escit 30.4 (4.31); Fluox 30.2 (5.15) HAMD-24: Escit 25.9 (5); Fluox 26.5 (5.74)	**Data Used** Remission: MADRS <= 10 Response: 50% reduction in MADRS HAMD-24 mean change MADRS mean endpoint MADRS mean change Leaving treatment early due to side effects **Data Not Used** CES-D - not relevant QoL - not relevant CGI - not relevant Hamilton Anxiety Scale - not relevant Notes: HAMD response and remission data also reported but exact definition unclear	**Group 1 N= 98** Escitalopram. Mean dose 10-20 mg/d - Started on minimum dose and raised to maximum dose after 3 weeks **Group 2 N= 99** Fluoxetine. Mean dose 20-40 mg/d - Started on minimum dose and raised to maximum dose after 3 weeks	Funding: Sponsored by Forest Research Institute
SCT-MD-26 Study Type: RCT Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 14 Followup: 6 week continuation phase Setting: Unclear; US (20 sites) Notes: RANDOMISATION: no details	n= 309 Age: Mean 39 Sex: 117 males 183 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: Not reported 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' Baseline: MADRS: Escit 30.4 (4.0); Plb 30.5 (4.13) HAMD: Escit 30.4 (4.1); Plb 29.7 (3.61)	**Data Used** Remission: HAMD-17 <= 7 Response: 50% reduction in MADRS Response: 50% reduction in HAMD-17 HAMD-17 mean change HAMD-17 mean endpoint MADRS-S endpoint MADRS mean change Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** Remission: MADRS <= 10 - 'sustained' remission QoL - not relevant CES-D - not relevant CGI - not relevant Hamilton Anxiety Scale - not relevant 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	**Group 1 N= 147** Escitalopram. Mean dose 10-20 mg/d - Started at 10 mg and possibly increased after 1 week **Group 2 N= 153** Placebo	Funding: supported by Lundbeck
SCT-MD-27 Study Type: RCT Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56	n= 409 Age: Mean 40 Sex: 179 males 224 females Diagnosis: 100% Major depressive disorder by DSM-IV	**Data Used** HAMD-17 mean change MADRS mean change Response: 50% reduction in MADRS Remission: MADRS <= 10 Side effects reported	**Group 1 N= 136** 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)	Fundiing: Sponsored by Forest Research Institute

Setting: Outpatients; US (24 sites) Notes: RANDOMISATION: no details	Exclusions: None reported Notes: 1 week placebo lead in n= 409 randomised; 403 'safety'; 398 'ITT' Baseline: MADRS: Escit 30.4 (4.58); Stl 30.1 (4.65); Plb 30.7 (4.6) HAMD baseline data also available	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	**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	
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)	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); Srtl 29.0 (4.02) HAMD-24: Escit 26.8 (4.74; Srtl 26.8 (4.51)	**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 clarfication or dosing regime and on version of HAMD that was used (discrepancy between published article and ctr)	**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	Funding: funded by Forest Laboratories
WADE2007 Study Type: RCT Type of Analysis: LOCF (at least one post-baseline evaluation) Blindness: Double blind Duration (days): Setting: Outpatients and primary care; Belgium, Canada, Czech Republic, France, Germany, Italy, Spain, Sweden, UK (35 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 294 Age: Mean 44 Sex: 212 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR Exclusions: MADRS < 26; comorbid OCD, PTSD or panic disorder; bipolar disorder, psychotic disorder or fetaures, 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	**Data Used** Response: 50% reduction in MADRS Remission: MADRS < 13 Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean endpoint Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason	**Group 1 N= 151** Duloxetine. Mean dose 60 mg **Group 2 N= 143** Escitalopram. Mean dose 20 mg/d - 10 mg/d weeks 1, 2, 25 and 26	SIGN: 1+; funding: Lundbeck; psychotropics not allowed during 2 weeks before entering trial

	fluoxetine); ECT within 6 months. Baseline: HAMD-17 (SD) 22.7 (5)	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		
YEVTUSHENKO2007 Study Type: RCT Type of Analysis: 'ITT': LOCF 1 dose & 1 post-baseline evauation Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients; Russia (8 sites) Notes: RANDOMISATION: block randomisations	n= 330 Age: Mean 35 Sex: 134 males 188 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS score <25; no potential for benefit from treatment with study drug; met crteria 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 treatmnet 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-parkinsonion compound, barbiturate, chloral hydrate, lithium, anticonvulsant, hypnotic or anxiolytic (except benzodiazepines); pregnant or breastfeeding Notes: n=330 randomised; 322 'ITT' Claims that all (322) participants still in study at end of week 1 were maintained in study for remaining 5 weeks Baseline: MADRS: Escit 34.78 (3.53); Cit 10 mg 35.40 (3.29); Cit 20 mg 35.70 (3.85)	**Data Used** Remission: MADRS <= 10 Remission: MADRS <= 12 Response: 50% reduction in MADRS MADRS mean change Side effects reported Leaving treatment early for any reason **Data Not Used** CGI - not relevant Notes: Citalopram 10 mg and 20 mg arms added for dichotomous data and 20 mg arm extracted for continuous data	**Group 1 N= 109** Escitalopram. Mean dose 10 mg/d **Group 2 N= 111** Citalopram. Mean dose 10 mg/d **Group 3 N= 110** Citalopram. Mean dose 20 mg/d	Funding: sponsored by OOO ARBACOM, Moscow, Federation of Russia

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
10423	Study incomplete so data unavailable
10778	Unable to obtain clincal trial report from Lundbeck/Principle Investigator
11438A	Unable to obtain clincal trial report from Lundbeck/Principle Investigator
12104	Unable to obtain clincal trial report from Lundbeck/Principle Investigator
99812	Open label
ANDERS2008	Not RCT
AUQUIER2003	Review
BANDELOW2007	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

CHOKKAinpress	Open label
EINARSON2004	Review
FANTINO2007	Health economics
FERNANDEZ2005	Health economics
GERGELposter	Pooled analysis; safety study
GORMAN2002	Pooled analysis
GUPTAposter	Not RCT
KARP2008	Not RCT; open label
KASPER2006	Not RCT
KASPER2006A	Pooled analysis
KENNEDY2006	Review
KHAN2004	Not randomised; open label
KULP2005	Health economics
LADER2005	Pooled analysis
LAM2006	Review
LAM2008	Pooled analysis
LANCON2006	Non randomised; 'naturalistic'
LANCON2007	Review
LEINONEN2007	Open label
LI2006C	Foreign language
LLORCA2005	Pooled analysis
LYDIARDposter	Anxiety; pooled analysis
MALLINCKRODT2007	Review
MOHAMED2006	Open label; comorbid anxiety
MOLLER2007	Not rct
MONTGOMERY2006	Review
MONTGOMERYposterA	Pooled trials from old guideline (Wade2002 and Burke2002)
MONTGOMERYposterB	Not depression
OLIE2007	Open label
PAPAKOSTAS2007C	Pooled analysis; not all escitalopram
PEC-S-08-00967	Health economics
PINTO2007	Open label
RUSH2005	Open label
SANCHEZposter	Animals
SCHMITT2006A	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
WADE2005	Health economics
WADE2005A	Health economics
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 dperessive 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 evaluatiing 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)

Lundebeck. 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 disorder (SCT-MD-23/23A). Report date: January 11, 2008.

Jonas, J., Bose, A., Alexpoulos, 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 onet 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 fluroxine 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) Esciatlopram 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. 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.

SCT-MD-02 (Unpublished Data Only)

Forest Laboratories Inc. Flexible dose comparison of the saftey 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)

Alexpoulos, G., Gordon, J. & Zhang, D. A placbo-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)

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11438A (Unpublished Data Only)

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12104 (Unpublished Data Only)

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LAM2008 (Published Data Only)

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Moclobemide - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Bakish1992 Y O I	Allocation: Random (no details). Duration: 6 weeks (+ 1week placebo run-in). Analysis: ITT	Outpatients. N=173. Age: mean= 42/44. 74 female. Diagnosis: DSM-III-R major depressive episode and HRSD-17>=18. Mean baseline HRSD-17 score: moclobemide=23.79, amitriptyline= 22.81 placebo=23.04	1. Moclobemide (200-600mg) 2. Amitriptyline (50-150mg,mean=112mg) 3. Placebo	1. Non- responders (patients not achieving >=50% decrease in HRSD) 2. Leaving the study early 3. Patients reporting side effects. 4. Leaving the study early due to side effects		B
Beckers1990 Y I I	Allocation: Random (no details). Duration: 6 weeks. Analysis: ITT	Inpatients. N=27. Age: 18-60. Diagnosis: DSM-III-R major depression and HRSD-17>=13.	1. Moclobemide (300-600mg) 2. Amitriptyline (105-210mg)	1. HRSD mean endpoint scores 2. Leaving the study early 3. Patients reporting side effects. 4. Leaving the study early due to side effects	Extracted data for Study 2 only. Study 1 patients had minor depression.	B
Barrelet 1991 Y M C	Allocation: Random (no details). Duration: 4 weeks. Analysis: completer	Inpatients & outpatients.N=61, HRSD analysis: N=51. Age: mean 54 years Diagnosis: DSM III Major Depression, HRSD>=18. Country: Switzerland.	1. Fluvoxamine 2. 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
Beaumont 1993 Y P C	Allocation: Random (no details). Duration: 6 weeks. Analysis: Completer	Primary care. N=345 (Completers: N= 265).Age:18-65, mean=43.6, 71% female. Diagnosis: DSM-III-R major depressive disorder + HRSD-17≥13. Mean HRSD-17 score: moclobemide=21.4, dosulepin/ dothiepin=21.2.	1. Moclobemide (450mg) 2. Amitriptyline (75mg increased to 150mg after 14 days)	1. Non- responders (patients not achieving >=50% decrease in HRSD) 2. Leaving the study early 3. Patients reporting side effects. 4. Leaving the study early due to side effects	Paper did not report no. patients in each group so ITT data was not extractable.	B
Bougerol 1992 Y M I	Allocation: Random (no details). Analysis: ITT. Active Treatment: 4 weeks	Inpatients & outpatients. Diagnosis: DSM-III-R, major depression, HRSD>= 17. Age:18+. N=130 (ITT: N=126). Country: Switzerland & France	1. Fluvoxamine 2. Moclobemide (300, up to 450mg on day 8, mean = 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
Casacchia 1984 Y I I	Allocation: Random (no details). Duration: 4 weeks. Analysis: ITT	Inpatients. N=34. Age: mean=49/49.5, 19 female. Diagnosis: ICD-9 296.1 or 300.4. HRSD-24≥20. Mean baseline HRSD-24 score: moclobemide -41.7 placebo=36.3.	1. Moclobemide (150-450mg, mean=297.2mg) 2. Placebo	1. HRSD-24 mean endpoint scores 2. Leaving the study early 3. Patients reporting side effects.		B
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≥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 d epression, 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≥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 (>=50% decrease in MADRS + MADRS <20) 3. Leaving the study early 4. Leaving the study early due to side effects	7 patients taking adj-unctive 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>=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 >=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≥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:1 8-65, mean = 44.5. Diagnosis: DSM-III major depressive episode + MADRS>25. Mean baseline MADRS scores: moclobemide=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

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 I I	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-III0R 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); un 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
Norman1985	Inadequate randomisation process; inadequate diagnosis of depression
Orsel1995	Not a double blind RCT
Pancheri1994	20% patients were diagnosed with bipolar disorder
Philipp1993	No mention that allocation to treatment group was randomised

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 excluded 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

	details) Duration: 6 weeks (+7 day placebo washout) Analysis: ITT	disorder (38 patients), dysthymia or depressive disorder NOS, HRSD-17≥10 and Columbia criteria for atypical depression		side effects 3. HRSD-17 mean change scores 4. Non-responders (patients not achieving ≥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 ≥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≥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

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, involutionals, 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 HMAT-A
GOLDSTEIN2004

Duloxetine 40 mg vs placebo
ELI LILLY HMAT-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 HMAT-A
GOLDSTEIN2004
PERAHIA2006B

Duloxetine vs escitalopram
KHAN2007B
WADE2007

Duloxetine vs fluoxetine
ELI LILLY HMAQ
GOLDSTEIN2002

Duloxetine vs paroxetine
DETKE2004
ELI LILLY HMAT-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, fibroymalgia, 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 variablility 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
BRECHT2007				

Study Type: RCT Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; Belgium, Germany, France, Finland, Slovakia Notes: RANDOMISATION: randomised but not details Info on Screening Process: 393 patients screened, no further details	n= 327 Age: Mean 50 Sex: 86 males 241 females Diagnosis: 100% Major depressive disorder by DSM-IV 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 Notes: Pts all had at least moderate pain based on BPI-SF score > = 3 on '24-hr average pain' item Baseline: MADRS (SD) 29.9 (4.5) (dul), 29.2 (4.5) (pbo); washout not mentioned	**Data Used** Number of people reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason Weight change Leaving treatment early due to lack of efficacy **Data Not Used** Response: 50% reduction in MADRS - N unclear Remission: MADRS < 13 - N unclear MADRS mean change - N unclear, no variability measure 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	**Group 1 N= 162** Duloxetine. Mean dose 60 mg - 8 weeks' treatment + 2 weeks' tapering **Group 2 N= 165** Placebo	SIGN 1+; funding Eli Lilly (code HMDH)
DETKE2002 Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 63 Setting: Outpatients; US 21 sites Notes: RANDOMISATION: randomised but no details Info on Screening Process: 367 people screened, 100 failed to meet inclusion criteria or declined	n= 267 Age: Mean 41 Sex: 83 males 184 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; 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 Baseline: HAMD-17 (SD) 20.33 (3.39) (dul), 20.46 (3.39) (pbo)	**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 decreased libido Leaving treatment early due to lack of efficacy Notes: Remission and response based on LOCF data	**Group 1 N= 128** Duloxetine. Mean dose 60 mg **Group 2 N= 139** Placebo	SIGN 1+; funding Eli Lilly (code HMBH-B); variable-duration placebo washout
DETKE2002A Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 63 Setting: Outpatients; US 18 sites Notes: RANDOMISATION: randomised but no details Info on Screening Process: 341, 96 failed to meet entry criteria or declined to participate	n= 245 Age: Mean 42 Sex: 82 males 163 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; 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 Baseline: HAMD-17 21.42 (dul), 21.14 (pbo)	**Data Used** Weight change Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change - no variablility measure Leaving treatment early due to side effects Number with palpitation Number with decreased libido Number with chest pain Number with abnormal ejaculation Number of people reporting side effects **Data Not Used** Leaving treatment early for any reason - Not reported	**Group 1 N= 123** Duloxetine. Mean dose 60 mg **Group 2 N= 122** Placebo	SIGN 1+; funding Eli Lilly (code HMBH-A); variable-duration placebo washout; removed in some analyses as an outlier

		Notes: No SDs for HAMD in published paper so used data from report on clinicaltrialresults.org		
DETKE2004 Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 56 Followup: 6-mth continuation phase Setting: Outpatients; country unclear (21 sites) Notes: RANDOMISATION: randomised not details 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)	n= 367 Age: Mean 43 Sex: 100 males 267 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) 19.9 (3.6) (pbo); 19.9 (3.6) (dul 80mg); 20.2 (3.4) (dul 120 mg); 20.3 (4.1) (parox)	**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 with abnormal electrocardiogram T wave 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	**Group 1 N= 95** Duloxetine. Mean dose 80 mg - 70 entered continuation phase - continued with same blinded treatment **Group 2 N= 93** Duloxetine. Mean dose 120 mg - 75 entered continuation phase - continued with same blinded treatment **Group 3 N= 85** Paroxetine. Mean dose 20 mg - 70 entered continuation phase - continued with same blinded treatment **Group 4 N= 93** Placebo - 58 entered continuation phase - continued with same blinded treatment	SIGN 1+; funding Eli Lilly (code HMAY-A); variable-duration placebo washout
ELI LILLY HMAI Study Type: RCT Blindness: Double blind Duration (days): Mean 56 Followup: 44-week extension for responders Setting: Outpatients; 13 countries (no details; 54 sites) Notes: RANDOMISATION: randomised not details Info on Screening Process: No details	n= 648 Age: Mean 42 Sex: 212 males 436 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: No details, but likely to be similar to other studies Notes: Entry criterion to extension phase > 50% reduction in baseline HAMD score and no longer meeting criteria for MDD (DSM-III-R) Baseline: HAMD-17 26 (3.7)	**Data Used** Number with hypertension Number with palpitation Number with postural hypotension Number with abnormal ejaculation Response: 50% reduction in HAMD-17 Number of people reporting side effects HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason **Data Not Used** Remission: HAMD-17 < 7 - Not reported Notes: No efficacy data for extension phase	**Group 1 N= 130** Duloxetine. Mean dose 5 mg - 57 in extension phase **Group 2 N= 129** Duloxetine. Mean dose 10 mg - 71 in extension phase **Group 3 N= 131** Duloxetine. Mean dose 20 mg - 57 in extension phase **Group 4 N= 132** Clomipramine. Mean dose 150 mg - 64 in extension phase **Group 5 N= 126** Placebo - 59 in extension phase	SIGN 1+; funding Eli Lilly (code HMAI); variable-duration placebo washout. Data not used in final anslyses because of low dosages.
ELI LILLY HMAQ Study Type: RCT Type of Analysis: LOCF ITT data used Blindness: Double blind Duration (days): Mean 70 Setting: Outpatients; US (11 sites) Notes: RANDOMISATION: randomised, no	n= 194 Age: Mean 40 Sex: 65 males 129 females Diagnosis: 100% Major depressive disorder by DSM-IV	**Data Used** Number with palpitation Number with hypertension Number with decreased libido Weight change Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change	**Group 1 N= 82** Duloxetine. Mean dose 40 mg - 120 mg **Group 2 N= 37** Fluoxetine. Mean dose 20 mf **Group 3 N= 75** Placebo	SIGN: 1+; funding: Eli Lilly (Code HMAQ); 5-10 day no-drug screening phase

details Info on Screening Process: 308 people screened, no further details		Number of people reporting side effects Leaving treatment early for any reason		
ELI LILLY HMAT-A Study Type: RCT Type of Analysis: MMRM Blindness: Double blind Duration (days): Mean 56 Setting: Oupatients; US (22 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 354 Age: Mean 44 Sex: 136 males 218 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 15 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	**Data Used** Number with abnormal ejaculation Number with palpitation Number with decreased libido 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 due to lack of efficacy Leaving treatment early for any reason Notes: Duloxetine 80mg data used in comparisons with paroxetine	**Group 1 N= 91** Duloxetine. Mean dose 40 mg - Below licensed dose so not used except in comparison with 80 mg **Group 2 N= 84** Duloxetine. Mean dose 80 mg **Group 3 N= 89** Paroxetine. Mean dose 20 mg **Group 4 N= 90** Placebo	SIGN: 1+; funding: Eli Lilly (Code HMAT-A); 5-9 day no-drug screening phase
ELI LILLY HMBU Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 84 Setting: Outpatients; Austria, Australia, Germany, France, Spain, Italy, US (34 sites) Notes: RANDOMISATION: randomised no details Info on Screening Process: No details	n= 332 Age: Mean 44 Sex: 98 males 234 females Diagnosis: 100% Major depressive disorder by DSM-IV 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. Notes: Participants had >= 1 previous episode Baseline: HAMD-17 (SD) 23.10 (3.66)	**Data Used** Number of people reporting side effects Number with palpitation Leaving treatment early due to lack of efficacy 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	**Group 1 N= 166** Duloxetine. Mean dose 60mg - 120 mg - 60 mg for first 6 weeks, allowed to increase to 120 mg in 2nd 6 weeks **Group 2 N= 166** Venlafaxine. Mean dose 150 mg - 225 mg - 150 mg for 1st 6 weeks, allowed to increase to 225 mg in 2nd 6 weeks	SIGN: 1+; funding Eli Lilly; Published paper is pooled analysis of this study and Eli Lilly HMCQ; washout period 3-9 days
ELI LILLY HMCQ Study Type: RCT Blindness: Double blind Duration (days): Mean 84 Setting: Outpatients; US, Canada (32 sites) Notes: RANDOMISATION: randomised no details Info on Screening Process: No details	n= 504 Age: Mean 42 Sex: 173 males 331 females Diagnosis: 100% Major depressive disorder by DSM-IV 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	**Data Used** Weight change Number with decreased libido Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 Number of people reporting side effects HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason	**Group 1 N= 164** Duloxetine. Mean dose 60 mg - Dose increased to 120 mg in 2nd 6 weeks based on clinical response **Group 2 N= 171** Venlafaxine. Mean dose 150 mg - Dose increased to 225 mg in 2nd 6 weeks based on clinical response **Group 3 N= 169** Venlafaxine. Mean dose 75 mg - Dose increased to 150 mg in 2nd 6 weeks based on clinical response	SIGN: 1+; funding Eli Lilly; Published paper is pooled analysis of this study and Eli Lilly HMBU; washout period 3-9 days

	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 Study Type: RCT Type of Analysis: Mixed-effects likelihood-based repeated-measures Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US (19 psychiatric research sites) Notes: RANDOMISATION: randomised by computer-generated random table; used efficacy sample as ITT group Info on Screening Process: 527 people screened; 174 failed screening, no further details	n= 353 Age: Mean 40 Sex: 136 males 217 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; 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. 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)	**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 abnormal orgasmia Number with decreased libido Number of people reporting side effects Notes: HAMD-17 data not given in published report so taken from report on clinicaltrialsresults.org; 80 mg used in comparison with paroxetine	**Group 1 N= 86** Duloxetine. Mean dose 40 mg - Below licensed dose; data used only in comparison with higher dose **Group 2 N= 91** Duloxetine. Mean dose 80 mg **Group 3 N= 87** Paroxetine. Mean dose 20 mg **Group 4 N= 89** Placebo	SIGN 1++; funding Eli Lilly (code HMAT-B); variable-duration placebo washout
KHAN2007B Study Type: RCT Type of Analysis: 'ITT': minimum 1 dose & 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56	n= 278 Age: Mean 42 Sex: 112 males 166 females Diagnosis: 100% Major depressive disorder by DSM-IV	**Data Used** Response: 50% reduction in MADRS Remission: MADRS <= 10 MADRS mean change MADRS mean endpoint HAMD-17 mean endpoint	**Group 1 N= 138** Duloxetine. Mean dose 60 mg **Group 2 N= 140** Escitalopram. Mean dose 10 mg - 20 mg - Dose increased to 20 mg after 4 weeks if lack of response	SIGN: 1+; funding: National Institutes of Health Center and Forest Research Institute; 1-week no-drug screening phase

Notes: RANDOMISATION: randomised, no details Info on Screening Process: 382 people screened; 104 did not meet inclusion criteria	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 adequete contraception Notes: 1 week placebo lead in and 16 week extension phase Baseline: HAMD-17 (SD) 21 (4)	Response: 50% reduction in HAMD-24 Remission: HAMD-17 < 7 HAMD-17 mean change Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason		
LEE2007 Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; China, Korea, Taiwan, Brazil (20 sites) Notes: RANDOMISATION: randomised no details Info on Screening Process: 672 people screened, 194 did not meeting screening criteria	n= 478 Age: Mean 38 Sex: 145 males 333 females Diagnosis: 100% Major depressive disorder by DSM-IV 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 adequat trial of paroxetine for depression, serious suicidal risk, serious medical illness, history of hepatic dysfunction, current jaundice, postivie 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. Baseline: HAMD-17 (SD) 21.2 (4.12) (dul); 21.2 (4.04) (pbo)	**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 viral myacarditis Number with palpitation Number with suicide attempt Number with decreased libido Number of people reporting side effects Leaving treatment early due to lack of efficacy Notes: HAMD-17 SDs calculated from p-values	**Group 1 N= 238** Duloxetine. Mean dose 60 mg **Group 2 N= 240** Placebo	SIGN 1+; funding Eli Lilly (code HMCV); variable-duration placebo washout
NIERENBERG2007B Study Type: RCT Type of Analysis: LOCF at least one post-baseline assessment Blindness: Double blind Duration (days): Mean 56 Followup: 6-month continuation phase Setting: Outpatients; US (36 sites) Notes: RANDOMISATION: randomised using 'interactive voice response system' Info on Screening Process: 1049 people screened, 365 failed to meet entry criteria	n= 684 Age: Mean 42 Range 18-79 Sex: 238 males 446 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: MADRS < 22; abnormal physical exam, lab tests and ECT; pregnant or lactacting; Axis I disorder other than MDD; previous diagnosis of bipolar disroder, 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 meciation during study, use of MAOI or fluoxetine with 30 days of 3nd visit; positive drug urine screen for substances of misuse,	**Data Used** Number with palpitation Number with abnormal orgasmia Number with decreased libido Number with ventricular dysfunction Number with hypertension Number with suicidal depression Number with chronic airways disease exacerbated Number with cardiac failure congestive Number with arrhythmia 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 Weight change	**Group 1 N= 273** Duloxetine. Mean dose 60 mg **Group 2 N= 274** Escitalopram. Mean dose 10 mg **Group 3 N= 137** Placebo	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

	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 variablility 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 HMAY-B); variable-duration placebo washout
RASKIN2007 Study Type: RCT Type of Analysis: LOCF (at least one post-baseline evaluation) Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; US Notes: RANDOMISATION: randomised but no details Info on Screening Process: No details	n= 311 Age: Mean 72 Range 65-90 Sex: 126 males 185 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 <18, MMSE < 20 (i.e. moderate or severe dementia); Axis I disorder other than MDD; previous psychotic disorer; organic mental disorder; mental retardation; serious/unstable medical illness, psychological condition or clinically significant laboratory abnormailty likely to compromise study or lead to hospitalisation; high alanine transaminase, aspartate transaminase, gamma glutamyl tansferase levels Notes: All participants required to have had >= 1 previous episode i.e. recurrent depression Baseline: HAMD-17 (SD) 18.85 (6); N previous episodes (SD) 5(15) (dul), 6.3(13.6) pbo	**Data Used** Weight change Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean change - no variablility measure Leaving treatment early due to side effects Leaving treatment early for any reason Leaving treatment early due to lack of efficacy Number with suicide attempt Number with suicidal ideation 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	**Group 1 N= 207** Duloxetine. Mean dose 60 mg **Group 2 N= 104** Placebo	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)
WADE2007 Study Type: RCT Type of Analysis: LOCF (at least one post-baseline evaluation) Blindness: Double blind Duration (days):	n= 294 Age: Mean 44 Sex: 212 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR	**Data Used** Response: 50% reduction in MADRS Remission: MADRS < 13 Response: 50% reduction in HAMD-17 Remission: HAMD-17 < 7 HAMD-17 mean endpoint	**Group 1 N= 151** Duloxetine. Mean dose 60 mg **Group 2 N= 143** Escitalopram. Mean dose 20 mg/d - 10 mg/d weeks 1, 2, 25 and 26	SIGN: 1+; funding: Lundbeck; psychotropics not allowed during 2 weeks before entering trial

Setting: Outpatients and primary care; Belgium, Canada, Czech Republic, France, Germany, Italy, Spain, Sweden, UK (35 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	Exclusions: MADRS < 26; comorbid OCD, PTSD or panic disorder; bipolar disorder, psychotic disorder or fetaures, 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. Baseline: HAMD-17 (SD) 22.7 (5)	Leaving treatment early due to side effects Leaving treatment early due to lack of efficacy Leaving treatment early for any reason 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		
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, dysthmia 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
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 placebo)
ELI LILLY HMAI	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. Clinicaltrialresults.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 evaluationg the efficacy of duloxetine 60 mg once daily versus placebo in outpatients with major depressive disorder. Clinicaltrialresults.org [date site accessed 13.06.08].

Brecht, S., Courtecuisse, C., Debieuvre, C., Croenlein, J., Desaiah, 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. Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.org [date site accessed 13.06.08].

ELI LILLY HMAQ (Unpublished Data Only)

Eli Lilly study F1J-MC-HMAQ, CT Registry ID# 7999. Duloxetine vesus placebo in the tretament of major depressive disorder. Clinicaltrialresults.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. Clinicaltrialresults.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 vesus venlafaxine extended release in the tretament of major depressive disorder. Clinicaltrialresults.org [date site accessed 13.06.08].

ELI LILLY HMCQ (Unpublished and Published Data)

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GOLDSTEIN2002 (Published Data Only)

Eli Lilly study F1J-MC-HMAQ, CT Registry ID# 3327. Duloxetine versus placebo in the treatment of major depression. Clinicaltrialresults.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.

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].

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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., Alexpoulos, 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.

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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.

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

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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 Pychiatry, 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.

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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. Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.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). Clinicaltrialresults.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). Clinicaltrialresults.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). Clinicaltrialresults.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. Clinicaltrialresults.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. Clinicaltrialresults.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 ≥ 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 ≥50% reduction on HRSD) 4. Non-remitters (Patients not achieving HRSD ≤ 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

1995 Y O I	(no details) Double-blind 6-week trial.	Diagnosis: DSM-III moderate to severe major depression, HRSD-17 ≥ 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 ≥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 ≥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 ≥ 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 ≥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, ≥ 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 ≥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

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 epidose,HRSD-17 ≥ 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 ≥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 ≥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 ≥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 ≥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 ≥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≥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 ≥ 50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD≤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 ≥ 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 ≥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: mirtaz-apine 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 ≥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 epidose, 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 YOI	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≥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 ≥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
Ban1998 Y I	Allocation: Random (no details).Duration: 4 weeks (+7 day wash-out). Analysis: ITT.	Inpatients. N=258. Age: 18-65. Diagnosis: DSM-III-R major depression, HRSD-17≥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 ≥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 ≥ 1 assessment post-baseline).	Inpatients and outpatients. N=256. Age: 18-65. Diagnosis: DSM-III-R major depressive episode, HRSD≥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 ≥50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD≤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

	weeks (+ up to 28 day washout) Analysis: ITT	depressive disorder (N=218) or dysthymia (N=129) without psychotic features, HRSD-21≥18, MMSE≥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 ≥50% decrease in HRSD) 4. Non-remitters (patients not achieving HRSD≤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≥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 ≥50% decrease in HRSD) 3. Non-remitters (patients not achieving HRSD≤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≥20. Mean baseline HRSD: 35.7, placebo = 35.1.	1. Reboxetine (6mg->10mg) 2. Placebo	1. Non-responders (patients not achieving ≥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 ≥ 20.	1. Venlafaxine IR (75mg up to 225mg) 2. Fluoxetine (20mg up to 60mg) 3. Placebo	1. Non-remitters (patients not achieving HRSD≤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 OI 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 ≥ 20	1. Venlafaxine IR (75mg up to 225mg) 2. Fluoxetine (20mg up to 60mg) 3. Placebo	1. Non-responders (patients not achieving ≥ 50% decrease in HRSD) 2. Non-remitters (patients not achieving HRSD≤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 ≥ 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: ≥ 50% decrease in HRSD or MADRS and a CGI-I of 1 or 2 persisting to the end of the study, lasting ≥ 2 weeks) 5. Patients reporting side effects 6. Non-remitters (patients not achieving HRSD≤8)	Conducted at 3 clinical sites in Portugal. Baseline HRSD-21 scores: venlafaxine: 27.9 (+-5.2), fluoxetine: 26.9 (+-3.9)	A

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 ≥ 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 ≥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 ≥ 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: ≥ 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 ≥ 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 ≥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.VenlafaxineXR (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 ≥ 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 depres-sion, 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 ≥ 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

		Diagnosis: DSM-IV major depression, MADRS ≥ 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 ≥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 ≥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	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≥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: ≥ 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 ≥ 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≤7) 5. Non-responders (patients not achieving: ≥ 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 ≥ 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 ≥ 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 ≥ 50%	Baseline HRSD-21 scores: venlafaxine: 25.5 (+-3.4), imipramine: 24.2 (+-2.9) or placebo: 24.6 (+-2.9)	B

	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 XR	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 IR	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 PC I IR	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 IR	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 ≥ 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

St John's Wort - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Behnke2002 Y M C A	Allocation: Random (no details) Duration: 6 weeks Analysis: completer	Inpatients and outpatients. Age: 18-73. N=70. Diagnosis: ICD-10 Depression (F32), HRSD≥16 and ≤24. Mean baseline HRSD: SJW - 20 +-3.2, Fluoxetine - 20.7 +-2.9.	1. St John's wort (300mg = 2 x 150mg Hypericum perforatum: 0.450-0.495mg total hypericin per tablet) 2. Fluoxetine (40mg)	1. HRSD-17 mean change scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving the study early 4. Patients reporting adverse effects		B
Bergmann93 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. Age: 25-83. N= 80. Diagnosis: ICD-10 mild-moderate depressive episode. Mean baseline HRSD: SJW - 15.82 +-0.70, amitriptyline - 15.26 +-0.74	1. St John's wort 2. Amitriptyline	1. HRSD-17 mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting adverse effects 5. Non-responders (patients not achieving ≥50% decrease in HRSD)		B
Brenner00 Y O I A/L	Allocation: Random (no details) Duration: 7 weeks Analysis: ITT	Outpatients. Age: 18-65. N=30. Diagnosis: DSM-IV major depression recurrent (21 patients) or single episode (9 patients) and HRSD≥17, baseline HRSD=21.5+-3.1	1. St John's wort (600mg -> 900mg LI 160) 2. Sertraline (50mg -> 75mg)	1. HRSD-17 mean endpoint 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	Dose of sertraline was below the therapeutic level.	B
Davidson02 YOI A/L P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT - LOCF	Outpatients. Age: 18+. N=340. Diagnosis: DSM-IV major depressive disorder and HRSD-17≥20, baseline = 22.5-23.1	1. St John's wort (900 up to 1500mg LI 160: standardised to 0.12-0.28% hypericin) 2. Sertraline (50mg up to 100mg) 3. Placebo	1. HRSD-17 mean change scores 2. Non-responders (patients not achieving ≥50 decrease in HRSD and 12≥HRSD≥9) 3. Non-remitters (patients not achieving HRSD ≤ 8) 4. Leaving the study early 5. Leaving the study early due to side effects	Dose of sertraline was below the therapeutic level	B
Hansgen1996	Allocation: Random	Outpatients and primary care	1. St John's wort (900mg =	1. HRSD mean endpoint scores		B

Y M C P	(no details) Duration: 4 weeks Analysis: completer	patients. N=108. Age: 18-70. Diagnosis: DSM-III-R major depression, HRSD≥16.	3x300mg LI 160) 2. Placebo	2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving the study early 4. Patients reporting adverse effects		
Harrer94 Y O C A/L	Allocation: Random (no details) Duration: 4 weeks Analysis: Completers	Outpatients. N=102. Age: 24-65. Diagnosis: ICD-10 Moderate depressive episode, HRSD-17≥16. Mean baseline HRSD: SJW - 20.5, maprotiline - 21.5	1. St John's wort (900mg = 3x 300mg LI 160) 2. Maprotiline (75mg)	1. HRSD-17 mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD or HRSD≤10) 3. Leaving the study early due to side effects 4. Leaving the study early 5. Patients reporting adverse effects	Dose of maprotiline was below the therapeutic level	B
Harrer99 E O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. N=161. Age: 60-80. Diagnosis: ICD-10 mild-moderate depressive episode, baseline HRSD 16.6-17.18	1. St John's wort (800mg = 4 x 200mg LoHyp-57: drug extract ratio 5-7:1) 2. Fluoxetine (20mg)	1. HRSD-17 mean endpoint scores 2. Non-responders (patients not achieving HRSD≤10 or >=50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting adverse effects	ITT sample=149.	B
Kalb2001 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=72. Age: 18-65. Diagnosis: DSM-IV mild-moderate major depression and HRSD≥16. Mean baseline HRSD: SJW - 19.7 +-3.4, range 16-34; placebo - 20.1 +-2.6, range 16-26.	1. St John's wort (900mg = 3 x 300mg WS5572: drug extract ratio 2.5-5:1, 5% hyperforin) 2. Placebo	1. HRSD-17 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 adverse effects		B
Laakmann98 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: LOCF	Outpatients. N=147. Age: 18-65. Diagnosis: DSM-IV mild or moderate depression and HRSD-17≥17. Mean baseline HRSD: SJW - 20.9 +-3.1, placebo - 21.2 +-3.3	1. St John's wort (900mg = 3 x 300mg WS5572: 5% hyperforin) 2. St John's wort (900mg = 3 x 300mg WS5573: 0.5% hyperforin) 3. Placebo	1. HRSD-17 mean change score 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 adverse effects	Data extracted for higher dose SJW (1) and placebo (3).	B
Lecrubier02 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. Age: 18-66. N=375. Diagnosis: DSM-IV mild - moderate depression and 25=>HRSD≥18, baseline = 21.9 +-1.7, range: 18-27	1 St John's wort (900mg = 3 x 300mg WS5570: 0.12-0.28% hypericin) 2. Placebo	1. HRSD-17 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. Non-remitters (patients not achieving HRSD≤6) 6. Patients reporting adverse effects		B
Philipp99 Y O I A P	Allocation: Random (no details)	Primary care patients(?). N=263. Age: 18-65, mean=47.	1. St John's wort (1050mg = 3 x 350mg STEI 300: 0.2-	1. HRSD-17 mean change scores 2. Non-responders (patients not achieving		B

	Duration: 8 weeks Analysis: ITT - LOCF	Diagnosis: ICD-10 moderate depressive episode and HRSD-17 ≥18, baseline=22.6 +-4.1	0.3% hypericin, 2-3% hyperforin) 2. Imipramine (50mg -> 100mg) 3. Placebo	≥50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting adverse effects		
Schrader00 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. N=240. Age: 18+, mean = 56.5. N=240. Diagnosis: mild - moderate depressive episode, 24≥HRSD≥16, mean HRSD = 19.5-19.65	1. St John's wort (500mg = 2 x 250mg ZE117 (drug extract ratio 4-7:1) 2. Fluoxetine (20mg)	1. HRSD-21 mean change scores 2. Non-responders (patients not achieving HRSD≤10 or ≥50% decrease in HRSD) 3. Leaving the study early due to side effects 4. Patients reporting adverse effects		B
Schrader98 Y ? I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	N=162. Age: 18+. Diagnosis: ICD-10 mild or moderate depressive episode and 16=< HRSD≤24. Mean baseline HRSD: SJW - 20.13, placebo - 18.76	1. St John's wort (500mg = 2 x 200mg ZE117: 0.5mg hypericin) 2. Placebo	1. HRSD-21 mean change scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD or HRSD≤10) 3. Patients reporting adverse effects		B
Shelton 2001 Y O I P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT	Outpatients. N=200. Age: 18+. Diagnosis: DSM-IV major depressive disorder and HRSD-17 ≥20. Mean baseline HRSD: SJW - 22, placebo - 23	1. St John's wort (900mg up to 1200mg, mean = 1110mg) 2. Placebo	1. HRSD-17 mean endpoint scores 2. Non-responders (patients not achieving ≥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	3 patients with co-morbid GAD, 4 patients with comorbid social phobia. 12 patients (4 in SJW group, 8 in placebo group) were receiving psychotherapy.	B
van Gurp02 Y O I AL	Allocation: Random (no details) Duration: 12 weeks Analysis: ITT - LOCF	Outpatients. N=87. Age: 18-65. Diagnosis: DSM-IV major depression and HRSD≥16. Mean baseline HRSD: SJW - 18.9 +-3.6, sertraline - 19.7 +-3.5.	1. St John's wort (900mg up to 1800mg = 3-6 x 300mg @ 0.3% hypericum) 2. Sertraline (50mg up to 100mg)	1. HRSD-17 mean change scores 2. Leaving the study early 3. Leaving the study early due to side effects	Only 21% patients received a therapeutic dose of sertraline	B
Volz2000 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=140. Age: 18-65. Diagnosis: DSM-IV mild-moderate depressive episode, HRSD-21≥18. Mean baseline HRSD: SJW - 21, placebo - 20.7	1. St John's wort (500mg = 2 x 250mg D-0496) 2. Placebo	1. HRSD mean endpoint scores 2. Leaving the study early 3. Patients reporting adverse effects		B
Wheatley97 Y O I AL	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=165. Age: 20-65. Diagnosis: DSM-IV major depressive episode and 24=>HRSD≥17. Mean baseline HRSD: SJW - 20.6 +-2.1, amitriptyline - 20.8 +-2.3	1. St John's wort (900mg = 3 x 300mg LI 160 = 720-960µg hypericin) 2. Amitriptyline (75mg)	1. Non-responders (patients not achieving HRSD<10 and ≥50% decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting adverse effects	Dose of amitriptyline was below the therapeutic level	B

Witte1995 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=97. Age: 24-65. Diagnosis: ICD-10 moderate depressive episode.	1.St John's wort (200-240mg) 2. Placebo	1. Non-responders (patients not achieving ≥50% decrease in HRSD) 2. Leaving the study early		B
Woelk2000 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis:	Outpatients. N=324. Age: 18+. Diagnosis: ICD-10 mild or moderate depressive episode and HRSD≥18, baseline = 22.1-22.4	1. St John's wort (500mg = 2 x 250mg ZE117: 0.2% Hypericin) 2. Imipramine (150mg)	1. Non-responders (patients not achieving ≥ 50% decrease in HRSD) 2. Leaving the study early 3. Leaving the study early due to side effects 4. Patients reporting adverse effects		B

Characteristics of excluded studies

Study	Reason for exclusion
Agrawal1994	Unable to obtain full trial report
Halama1991	Includes patients with 'brief depressive reaction'; not clear how many
Harrer1991	Includes patients with 'brief depressive reaction'; not clear how many
Hoffmann1979	Inadequate diagnosis of depression
Hubner1994	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Johnson1991	Patients were not diagnosed with depression
Kniebel1988	Patients were diagnosed with dysthymia according to DSM-IV
Lehrl1993	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Lenoir1999	26% of patients not diagnosed with depression
Mueller1998	Not an RCT
Osterheider1992	Inadequate diagnosis of depression (abstract only no full publication)
Quandt1993	Unable to obtain full trial report
Reh1992	38/50 patients were diagnosed with brief depressive reaction
Rychlik2001	Not an RCT
Schlich1987	Inadequate diagnosis of depression
Schmidt1989	35% of patients not diagnosed with unipolar depression
Schmidt1993	Includes patients with 'brief depressive reaction'; not clear how many
Sommer1994	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Volz2002	Patients were not diagnosed with depression
Vorbach 1994	42% patients diagnosed with dysthymia or adjustment disorder
Vorbach97	'Lithium was allowed if it had been prescribed at least 3 months before the trial and was continued with an unchanged daily dose'; number of patients in each treatment group receiving lithium not specified

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≥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 ≥50% decrease in HRSD) 2. HRSD mean endpoint scores		B

		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 ≥50% decrease in HRSD)	Included in '≤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 '≤25% bipolar' analysis only.	B

Characteristics of excluded studies

Study	Reason for exclusion
Braus2000	Two case studies not an RCT
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

Light therapy - new studies in the guideline update

Comparisons Included in this Clinical Question

Bright light + hypericum vs dim light + hypericum	Bright light + placebo pill vs dim light + fluoxetine	Bright light box vs placebo light box vs HMU light vs HMU placebo	Bright light vs dawn simulation vs placebo dawn simulation
MARTINEZ1994	LAM2006F	LEVITT1996	AVERY2001 TERMAN2006

Bright light vs deactivated negative ion generator	Bright light vs dim light	Bright light vs group CBT vs combo light + CBT vs waitlist control	Bright light vs modified group CBT vs bright light + modified group CBT
DESAN2007	ROSENTHAL1993	ROHAN2007	ROHAN2004

Bright vs medium vs dim light	Bright white light vs dim infrared light vs waitlist control	Bright white light vs dim red light	Gradual dawn vs rapid dawn
JOFFE1993	MEESTERS1999	WILEMAN2001	AVERY1993

Light room vs waitlist control	Morning bright light vs evening bright light vs alternating bright light	Morning vs afternoon bright light	Morning vs afternoon vs evening bright light
RASTAD2008	LAFER1994	AVERY2001A	MEESTERS1995

Morning vs evening bright light	Morning vs evening light vs deactivated negative ion generator	Morning vs evening light vs low-density negative ion generator	Narrow-band blue light vs bright red light
MEESTERS1993A	EASTMAN1998	TERMAN1998	STRONG2008

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
AVERY1993 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 7 Setting: recruited through advertisements; US Notes: RANDOMISATION: stratified according to sex & quarter of menstrual cycle. 1 baseline week prior to treatment	n= 27 Age: Mean 35 Sex: 8 males 19 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode by DSM-III-R Exclusions: psychotropic medication in 2 weeks prior to study Notes: All participants had hypersomnia as part of their winter depression Baseline: HRSD-21 SAD subscale Gradual 17.1 (4.6) 13.1 (3.1) Rapid 18.6 (7.0) 16.1 (6.2)	**Data Used** Leaving treatment early due to lack of efficacy SAD subscale mean endpoint HRSD 21 mean endpoint Side effects reported Leaving treatment early for any reason **Data Not Used** CGI - not relevant Expectations measure - not relevant	**Group 1 N= 14** Dawn simulation - Gradual dawn: over 2 hours between 4-6am, incandescent reflector flood light increased intensity peaking at 250 lux as measured at distance of 122 cm from pillow **Group 2 N= 13** Dawn simulation - Rapid dawn: over 30 mins between 5.30-6am, incandescent reflector flood light increased intensity peaking at 0.2 lux as measured at distance of 122 cm from pillow	SIGN: 1+; funding NIMH
AVERY2001 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 42	n= 95 Age: Mean 41 Sex: 12 males 83 females Diagnosis:	**Data Used** Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 33** Bright light - 10,000 lux light between 6-6.30am, eyes 30 cm from light box used while awake	SIGN: 1+; funding NIMH

& referral; US Notes: RANDOMISATION: stratified according to gender. 1 baseline week prior to treatment	100% major depression or bipolar with seasonal pattern by DSM-IV Exclusions: major medical or other psychiatric conditions, smokers, psychotropic medication in prev month, shift workers, routine wakening after 9am, those who drank > equiv of 4 cups of coffee/day, SIGH-SAD score <20 Notes: All participants had hypersomnia Baseline: not reported, >=20 on SIGH-SAD	Leaving treatment early due to lack of efficacy **Data Not Used** CGI - not relevant Expectations measure - not relevant	**Group 2 N= 31** Dawn simulation - white light with gradually increasing illuminance during sleep from 4.30-6am peaking at 250 lux, positioned 122 cm from pillow **Group 3 N= 31** Placebo dawn simulation - dim red light with gradually increasing illuminance during sleep from 4.30-6.30am peaking at 0.5 lux, positioned 122 cm from pillow	
AVERY2001A Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 14 Setting: recruited through ads; US Notes: RANDOMISATION: no details. 1 baseline week prior to treatment	n= 31 Age: Mean 40 Sex: 3 males 28 females Diagnosis: 100% subsyndromal SAD Exclusions: signif medical problems, eye problems, major psychosocial stress, use of psychiatric medication in month prior to study, routine use of antihistamines, decongestants, asprin, appetite suppressants, sleeping medication Notes: No diagnoses of SAD but GSS score >=6 & SIGH-SAD score >=12 Baseline: SIGH-SAD HDRS21 HDRS17 SAD Morning 23.8 (5.1) 11.8 (2.8) 10.3 (2.6) 12.0 (3.9) Afternoon 22.4 (7.4) 12.1 (5.1) 11.0 (5.0) 9.9 (3.2)	**Data Used** SAD subscale mean endpoint HAMD-17 mean endpoint SIGH-SAD mean endpoint Response: 50% reduction in SIGH-SAD Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** HRSD 21 mean endpoint - HRSD-17 used instead CGI - not relevant Sleep measures - not relevant VAS productivity - not relevant VAS mood - not relevant VAS energy - not relevant VAS alertness - not relevant	**Group 1 N= 16** Bright light (morning) - 2 hours of bright light 2,500 lux at 60 cm from light box, in morning (between 7am-12pm, average 9.26am) **Group 2 N= 15** Bright light (afternoon) - 2 hours of bright light 2,500 lux at 60 cm from light box, in morning (between 12-5pm, average 3.20pm)	SIGN: 1+; Royal Philips Electronics (part-funded)
DESAN2007 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 28 Setting: recruited through media ads & referral; 5 sites across US, Canada, Netherlands Notes: RANDOMISATION: balanced for site & gender. 1 baseline wEEk prior to treatment	n= 26 Age: Mean 46 Sex: 6 males 20 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-IV Exclusions: <18, >65, SIGH-SAD score<20, significant medical illness, retinal disease, pregnancy, use of photosensitising or mood altering medication, treatment for SAD in prior week, antidepressants within 4 weeks, psychotherapy within 3 months, organic mental disorder, panic, eating, OCD, PTSD, psychotic, bipolar, sun use disorder, previous unsuccessful trial with light, no informed consent, poor likelihood of complying with study, suicidal risk, habitual sleep pattern after 1am-9am Baseline: SIGH-SAD Light 28.0 (5.35) Control 25.1 (3.22)	**Data Used** Remission: SIGH-SAD <9 SIGH-SAD mean endpoint Leaving treatment early due to lack of efficacy Leaving treatment early for any reason **Data Not Used** Sleep measures - not relevant Expectations measure - not relevant	**Group 1 N= 15** Bright light - Litebook device - 60 LEDs, approx 1350 lux at 51 cm (spectral emission peak approximately 464 nm & 564 nm, emitted light appears white), used for 30 mins each morning as soon as poss upon arising and before 8am **Group 2 N= 11** Deactivated negative ion generator - Generated faint high-pitched whine at 51 cm, wrist strap worn which is connected to device, used for 30 mins each morning as soon as poss upon arising and before 8am	SIGN: 1+; funding The Litebook Company Ltd
EASTMAN1998				

Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 28 Setting: recruited through advertisements & local media; US Notes: RANDOMISATION: balanced for gender. 1 baseline week prior to treatment	n= 121 Age: Mean 37 Sex: 13 males 83 females Diagnosis: 100% SAD by Rosenthal criteria Exclusions: psychotropic medication, previous treatment with light or negative ions, complicating medical condition Notes: All patients required to have atypical symptoms of increased appetite/weight & increased sleep, & score >=21 on SIGH-SAD. Participants details only given for completers (96) Baseline: BDI-25 Morning 22.0 (9.2) Evening 23.6 (10.8) Placebo 25.7 (10.7)	**Data Used** BDI mean endpoint Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 Leaving treatment early for any reason **Data Not Used** Sleep measures - not relevant Expectations measure - not relevant	**Group 1 N= 41** Bright light (morning) - 6,000 lux light, participants sat 38 cm from light box containing 6 cool-white fluorescent lamps, used for 1.5 hours as soon as possible after waking. 6 days per week **Group 2 N= 40** Bright light (evening) - 6,000 lux light, participants sat 38 cm from light box containing 6 cool-white fluorescent lamps, used for 1.5 hours before bed (max 1 hour between end of treatment & bed). 6 days per week **Group 3 N= 40** Deactivated negative ion generator - generates white noise, has 3 small lights on the front which change rapidly between red & green, 2 generators set up on desk 38 cm from participant, used for 1.5 hours in morning. 6 days per week	SIGN: 1+; funding NIMH
JOFFE1993 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 14 Followup: 1 week Setting: recruited by physician & self referral; 5 sites across Canada & US Notes: RANDOMISATION: stratified for medication status. There was a significant difference between results at different sites	n= 105 Age: Mean 40 Sex: 17 males 88 females Diagnosis: major depression or bipolar with seasonal pattern by DSM-III-R SAD by Rosenthal criteria Exclusions: light therapy in last 2 weeks, changes in dose of psychotropic medication, ophthalmological conditions, major medical illness, additional major psychiatric disorder, shift workers, unable to maintain stable sleep-wake pattern, HRSD-SAD 17 item score <=14 or 17 item score <=10 if total score <22 Baseline: HRDS-SAD Low 32.4 (6.3) Medium 32.2 (6.8) High 29.8 (5.8)	**Data Used** HRSD-SAD mean 1 week follow-up HRSD-SAD mean endpoint Response: 50% reduction in HRSD-SAD Remission: 50% reduction in HRSD-SAD & <=8 **Data Not Used** Expectations measure - not relevant	**Group 1 N= 33** Dim light - mean 67 lux (range 55-118 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily **Group 2 N= 38** Medium intensity light - mean 620 lux (range 520-762 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily **Group 3 N= 34** Bright light - mean 3,524 lux (range 2,800-4,470 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily	SIGN: 1+; funding Bio-Brite
LAFER1994 Study Type: RCT Type of Analysis: Completer Blindness: Double blind Duration (days): Mean 7 Setting: Outpatients; US Notes: RANDOMISATION: randomised, no details Information on Screening Process: Referrals for treatment for SAD; no further details	n= 32 Age: Mean 35 Sex: 11 males 21 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: HAMD-31 < 20; history of psychosis, epilepsy, full manic episode, alcohol/drug misuse in past 3 months, suicidal, used antidepressants in past week	**Data Used** Response: 50% reduction in HAMD-31 Remission: HAMD-31 < 8 HAMD-31 mean endpoint	**Group 1 N= 9** Bright light (morning) - 2,500 lux for 2 hours **Group 2 N= 8** Bright light (evening) - 2,500 lux for 2 hours **Group 3 N= 15** Bright light - Alternating morning and evening; 2,500 lux for 2 hours [data not used]	SIGN: 1+; funding Massachusetts General Hospital and Harvard Medical School Psychiatric Neuroscience Fellowship
LAM2006F				

Study Type: RCT

Type of Analysis: ITT

Blindness: Double blind

Duration (days): Mean 56

Setting: recruited by referral & advertisements in mood disorders clinics; 4 sites across Canada

Notes: RANDOMISATION: codes centrally computer generated & stratified by site. 1 baseline week prior to treatment

Info on Screening Process: 117

n= 96

Age: Mean 43

Sex: 32 males 64 females

Diagnosis:
100% major depression or bipolar with seasonal pattern by DSM-IV

Exclusions: <18 or >65 years, score <20 on HDRS17 or <14 if score on HRSD24 was >23, pregnant or lactating, women of childbearing age not using contraception, serious risk of suicide, organic mental disorder, substance misuse disorder, psychotic disorder, bipolar I, panic or GAD, serious unstable medical illness, retinal disease, severe allergies or multiple drug adverse reactions, current use of psychotropic drugs, beta blockers or antidepressants, previous treatment with fluoxetine or light therapy, psychotherapy in prior 3 months, shift workers, travel during study

Baseline:

	HDRS	Typical	Atypical	BDI-II
Light	30.2 (5.5)	17.3 (3.7)	13.0 (3.6)	24.5 (8.5)
Fuox	29.6 (5.3)	17.9 (3.4)	11.7 (4.3)	22.9 (9.3)

Data Used
BDI II mean endpoint
HRDS 7 (atypical symptoms) mean endpoint
HAMD-17 mean endpoint
HRDS 24 mean endpoint
Response: 50% reduction in HRSD24
Remission: 50% reduction in HRSD & score <=8
Leaving treatment early due to lack of efficacy
Leaving treatment early due to side effects
Leaving treatment early for any reason

Data Not Used
CGI - not relevant
QoL Enjoyment and Satisfaction Questionnaire - not relevant
QoL MOS SF-20 - not relevant

Group 1 N= 48
Bright light - white fluorescent light box 10,000 lux at distance of 36 cm, used for 30 mins as soon as poss after waking between 7-8am daily
Placebo - placebo pill identical to active treatment taken daily between 7-8am

Group 2 N= 48
Dim light - light box identical to active treatment but fitted with neutral density gel filter to reduce light to100 lux at distance of 36 cm, used for 30 mins as soon as poss after waking between 7-8am daily
Fluoxetine. Mean dose 20 mg/day - fixed dose taken daily between 7-8am

SIGN: 1++; funding Canadian Institutes of Health Research (CIHR) and CIHR/Wyeth Postdoctroal Fellowship Award to one of the authors

LEVITT1996

Study Type: RCT

Type of Analysis: completers

Blindness: Single blind

Duration (days): Mean 14

Setting: self-referred or referred by physician to outpatient Seasonal Mood Disorders Clinic; Canada

Notes: RANDOMISATION: controlled by research nurse who did not interview any of the participants

n= 44

Age: Mean 35

Sex: 12 males 31 females

Diagnosis:
100% major depressive episode with seasonal pattern by DSM-III-R

Exclusions: active major medical illness, eye condition that might preclude use of light therapy, travel toward equator in previous 2 weeks or during trial, unable to maintain stable sleep-wake cycle, any other axis I disorder except anxiety but including mania or hypomania, HAM-D-17 typical items score<=12, atypical items score <=10, SIGH-SAD total score <=18.

Baseline:

	SIGH-SAD	Typical	Atypical
Active lightbox	24.6 (7.7)	14.4 (3.4)	10.1 (5.1)
Placebo lightbox	24.8 (6.0)	13.8 (2.5)	10.9 (4.2)
Active HMU	23.2 (4.2)	13.7 (3.6)	9.5 (2.7)
Placebo HMU	25.0 (4.1)	14.4 (1.8)	10.6 (4.2)

Data Used
Expectations measure
HAM-D-17 atypical items mean endpoint
HAM-D-17 typical items mean endpoint
SIGH-SAD mean endpoint
Response: 50% reduction in SIGH-SAD
Side effects reported
Leaving treatment early for any reason

Group 1 N= 10
Bright light - Active light box contained 4 fluorescent lamps, used for 30 mins/day before 9am, mean illuminance = 7,600 lux, range = 7,240-8,320 lux, eyes 30 cm from light source

Group 2 N= 12
No light - Placebo light box, identical to active light box but produced no light but makes similar hum to active light box, used for 30 mins/day before 9am

Group 3 N= 12
HMU light - Active head-mounted unit consists of 2 LEDs mounted on baseball cap, used for 30 mins/day before 9am, mean illuminance = 646 lux, range = 502-764 lux, eyes 8 cm from light source

Group 4 N= 10
HMU no light - Placebo head-mounted unit identical to active HMU but no light produced, used for 30 mins/day before 9am

SIGN: 1+; funding Mood Disorders Program, Clarke Institute of Psychiatry

MARTINEZ1994

Study Type: RCT

Type of Analysis: ITT

Blindness: Single blind

Duration (days): Mean 28

Setting: referral by physicians, self-referral following media ads; Germany

Notes: RANDOMISATION: procedure not reported. 1 week washout prior to treatment

Info on Screening Process: No details

n= 20

Age: Mean 46 Range 29-63

Sex: 7 males 13 females

Diagnosis:
100% major depressive episode with seasonal pattern by DSM-III-R

30% Bipolar disorder (depressed phase) by DSM-III-R

Exclusions: <18, >65 years; HAMD-21 < 16

Baseline:

Data Used
HRSD 21 mean endpoint

Group 1 N= 10
Bright light - 3000 lux light for 2 hours a day, 90 cm from light
Hypericum. Mean dose 900 mg/day - 3 coated tablets of hypericum extract per day each containing 300 mg, hypericum is plant extract thought to be capable of hastening the onset of antidepressant response to light therapy

SIGN: 1+; funding unclear

	HAM-D (SD) Bright light 21.9 (6.5); dim ilght 20.6 (3.9) Dim light 20.6 (3.9)		**Group 2 N= 10** Hypericum. Mean dose 900mg/day - 3 coated tablets of hypericum extract per day each containing 300mg, hypericum is plant extract thought to be capable of hastening the onset of antidepressant response to light therapy Dim light - <300 lux light for 2 hrs a day, 90cm from light	
MEESTERS1993A Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 5 Followup: 15 days follow-up Setting: Netherlands Notes: RANDOMISATION: balanced for gender. 4 baseline days prior to treatment	n= 30 Age: Mean 44 Sex: 7 males 20 females Diagnosis: 100% SAD by Rosenthal criteria Exclusions: medication in month prior to study, score<13 on BDI Notes: Participant info only reported for 27 participants who completed treatment. Baseline: HRSD21 HRSD7 BDI Morning 18.1 (4.8) 11.0 (4.7) 19.5 (5.1) Evening 15.8 (2.9) 13.7 (5.7) 22.6 (3.5)	**Data Used** Response: 50% reduction BDI & < 13 for 10 days Remission: 50% reduction in HRSD & score <=8 HRSD7 10 days post-treatment HRSD21 10 days post-treatment BDI 17 days post-treatment BDI 10 days post-treatment BDI 3 days post-treatment **Data Not Used** Activation-Deactivation Adjective Check List - not relevant Sleep Quality Scale - not relevant Stanford Sleepiness Scale - not relevant VAS-DEP - not relevant Adjective Mood Scale - not relevant Notes: 3 participants dropped out of study, however, the conditions these participants were randomised to is not reported	**Group 1 N= 16** Bright light (morning) - light box consisted of 4 full-spectrum fluorescent light tubes, 2,500 lux at distance of 90 cm, used for 3 hours/day between 9am-12pm on 5 consecutive days **Group 2 N= 11** Bright light (evening) - light box consisted of 4 full-spectrum fluorescent light tubes, 2,500 lux at distance of 90 cm, used for 3hours/day between 6-9pm on 5 consecutive days	SIGN: 1+; funding unclear. No relevant data - study not used
MEESTERS1995 Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 4 Followup: 11 days Setting: outpatients; Netherlands Notes: RANDOMISATION: participants balanced for gender & randomly assigned. 4 baseline days prior to treatment	n= 82 Age: Mean 38 Sex: 16 males 52 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: use of drugs in 3 weeks prior to experiment, score <13 on BDI on day before treatment, Notes: Participant info only reported for 68 participants who completed therapy. Baseline: HRSD HRSDadd BDI BDIadd Morn/eve 19.0 (3.8) 9.1 (4.4) 21.8 (4.5) 5.3 (2.5) Eve/morn 16.2 (4.0) 10.6 (4.7) 18.5 (3.9) 4.9 (2.3) Morning 16.9 (3.8) 9.9 (5.5) 25.0 (8.0) 5.1 (1.6) Evening 17.5 (1.1) 10.6 (2.4) 25.9 (8.6) 6.6 (3.2) Afternoon 15.9 (3.4) 12.0 (4.1) 20.3 (5.9) 5.6 (2.7)	**Data Used** Response: 50% reduction in HRSD & >8 BDIadd (atypical symptoms) 11 days post-treatment BDI mean 11 days post-treatment HRSDadd (atypical symptoms) 11 days post-treatment HRSD-21 mean 11 days post-treatment BDIadd (atypical symptoms) 4 days post-treatment BDI mean 4 days post-treatment HRSDadd (atypical symptoms) 4 days post-treatment HRSD-21 mean 4 days post-treatment **Data Not Used** VAS-DEP - not relevant Adjective Mood Scale - not relevant	**Group 1 N= 13** Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for 1st 2 days Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for last 2 days (interval between morning & evening light treatment is 36 hours) **Group 2 N= 14** Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for 1st 2 days Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for last 2 days (interval between evening & morning light treatment is 36 hours) **Group 3 N= 14** Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for 4 days	SIGN: 1+; funding unclear. No relevant data - study not used

		Notes: 14 participants dropped out of study but the conditions these participants were randomised to is not reported	**Group 4 N= 12** Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for 4 days **Group 5 N= 15** Bright light (afternoon) - 10,000 lux light treatment at clinic for 30 mins a day between 1-1.30pm for 4 days	
MEESTERS1999 Study Type: RCT Study Description: relapse prevention Type of Analysis: completers Blindness: No mention Duration (days): Mean 182 Setting: outpatients; Netherlands Notes: RANDOMISATION: 1st winter equal number of participants were assigned to 3 conditions, 2nd winter 2x as many assigned to light conditions as to control Info on Screening Process: 50	n= 46 Age: Mean 40 Sex: 11 males 27 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: participants who developed depression at the start of the study, those using drugs, Notes: This study looks at relapse prevention. All participants diagnosed with SAD but only participants who had not yet developed winter depression at start of study (in October) were included. Baseline: Not reported, participants not depressed at start of trial	**Data Used** Leaving treatment early due to lack of efficacy Relapse: severe dep SIGH-SAD-SR >=40 Relapse: SIGH-SAD-SR >=20 in 2consec weeks Relapse: severe dep BDI >=22 Relapse: BDI >=13 in 2 consecutive weeks Leaving treatment early for any reason Notes: Significant difference between time of day light visor used between 2 groups.	**Group 1 N= 18** Bright light - 2,500 lux white light visor consisting of 2 krypton incandescent bulbs (12 cm from light source) worn for 30 mins/day between 6-9am, participants asked to choose their own fixed treatment time in their daily routine, mean 7.55am **Group 2 N= 18** Dim light - 0.18 lux infrared light visor consisting of 2 krypton incandescent bulbs (12 cm from light source) with filter worn for 30 mins/day between 6-9am, participants asked to choose their own fixed treatment time in their daily routine, mean 7.10am **Group 3 N= 10** Waitlist control - no light visor	SIGN: 1+; funding Bio Bright supplied equipment
RASTAD2008 Study Type: RCT Type of Analysis: completers Blindness: No mention Duration (days): Mean 21 Setting: recruited from earlier prevalence study; 4 sites across Sweden Notes: RANDOMISATION: restricted randomisation with probability factor of 0.8 was used, with separate lists for men and women Info on Screening Process: 312	n= 51 Age: Mean 46 Sex: 10 males 40 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-IV Exclusions: severe psychiatric or somatic disease, antidepressive medication, antibiotics, St Johns Wort, pregnancy, eye condition that precludes exposure to strong light, shift work, previous treatment with light therapy, unable to schedule 2-4 hours each morning for 10 consecutive weekdays, insufficient knowledge of Swedish Baseline: SIGH-SAD/SR Typical Atypical Light 21.8 (10.1) 14.2 (6.9) 7.6 (4.1) Waitlist 25.4 (8.1) 16.2 (5.8) 9.3 (4.0)	**Data Used** Atypical HAMD (8) mean endpoint HRSD 21 mean endpoint SIGH-SAD/SR mean endpoint Remission: <=8 SIGH-SAD/SR Response: 50% reduction in SIGH-SAD/SR Leaving treatment early for any reason	**Group 1 N= 26** Bright light - Light room at clinic, full-spectrum fluorescent lights on ceiling & walls, for 1.5-2 hours/day Mon-Fri between 6am and 9am in 4 different clinics. Light intensity varied depending on the clinic: 1,100 lux, 1,900 lux, 2,200 lux, 4,300lux. **Group 2 N= 25** Waitlist control - no light treatment	SIGN: 1+; funding Dalama County Council, Center for Clinical Research Dalama and Uppsala University
ROHAN2004 Study Type: RCT Blindness: Single blind Duration (days): Mean 42 Setting: Oupatients; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: Recruited via media	n= 26 Age: Mean 51 Sex: 2 males 24 females Diagnosis: major depressive episode with seasonal pattern by DSM-IV Exclusions: Current psychological or psychiatric treatment; other Axis I disorders; plans for major vacations or absences	**Data Used** Remission: 50% reduction SIGH-SAD + HRSD21 <= 7 Remission: BDI-II <=8	**Group 1 N= 9** Bright light - 10,000 lux, 45 mins x 2/day 6-9 am and 6-9 pm **Group 2 N= 11** Group CBT - CBT tailored for SAD; group format 1.5 hour sessions twice per week over 6 weeks (12 sessions)	SIGN: 1+; funding Uniformed Services University of Health Sciences

advertisement; 265 people screened	during the study period; bipolar-type SAD -	Notes: Alternative remission criterion: HRSD-21 <= 2 + SIGH-SAD <= 10	**Group 3 N= 8** Bright light - As above CBT - As above	
ROHAN2007 Study Type: RCT Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 42 Setting: recruited through print & radio advertisements; US Notes: RANDOMISATION: stratified for gender & race; used randomisation list prepared before recruitment Info on Screening Process: 490	n= 61 Age: Mean 45 Sex: 6 males 55 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-IV Exclusions: current psychiatric treatment, another current axis I disorder, planned absences, bipolar type SAD, <18 years, SIGH-SAD score <20, HRSD score <10, atypical subscale score <5, failure to complete pre-treatment assessment. Baseline: SIGH-SAD HAMD Atypical BDI-II Light 28.4 (6.1) 16.5 (5.2) 11.9 (3.8) 24.8 (8.1) CBT 29.7 (5.3) 19.3 (4.6) 10.4 (4.0) 26.9 (10.7) Combo 28.3 (5.6) 17.4 (5.7) 10.9 (3.1) 24.7 (5.9) Waitlist 27.9 (6.1) 16.3 (3.9) 11.7 (3.7) 25.6 (5.7)	**Data Used** BDI-II summer follow-up mean Atypical HAM-D summer follow-up mean HAM-D summer follow-up mean SIGH-SAD summer follow-up mean BDI II mean endpoint Atypical HAMD (8) mean endpoint HRSD 21 mean endpoint SIGH-SAD mean endpoint Remission: 50% reduction SIGH-SAD & HAMD <=7 Remission: BDI-II <=8 Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 16** Bright light - 10,000 lux white fluorescent light at 46 cm, used for 45 mins twice a day between 6am-9am and 6pm-9pm for 1st week, after this flexible dosing regarding time & duration as directed by consultant, average of 53 mins/day. **Group 2 N= 15** Group CBT - 1.5 hour sessions twice a week over 6 weeks (total 12 sessions) Groups of 4-8 participants, CBT specifically tailored to SAD **Group 3 N= 15** Group CBT - 1.5hr sessions twice a week over 6 wks (total 12 sessions) Groups of 4-8 participants, CBT specifically tailored to SAD Bright light - 10,000 lux white fluorescent light at 46 cm, used for 45 mins twice a day between 6am-9am and 6pm-9pm for 1st week, after this flexible dosing regarding time & duration as directed by consultant, average of 53 mins/day. **Group 4 N= 15** Waitlist control - no treatment	SIGN: 1++; funding NIMH and Uniformed Services University of the Health Sciences
ROSENTHAL1993 Study Type: RCT Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 7 Followup: 1 week follow up Setting: recruited through community referral channels & local news media; 3 sites across US Notes: RANDOMISATION: stratified across centres & balanced according to concomitant medications & prev light therapy. 1 baseline week prior to treatment.	n= 55 Age: Mean 42 Sex: 9 males 46 females Diagnosis: 100% SAD by Rosenthal criteria 100% lifetime history of major depression by DSM-III-R Exclusions: poor physical health, retinal disease or cataracts, untreated hypothyroidism or serious medical conditions, changing dose of medications, shift workers & those unable to maintain consistent sleep schedules, light therapy in 2 weeks prior to trial Baseline: SIGH-SAD HDRS Bright 31.0 (6.6) 16.8 (4.3) Dim 31.2 (7.6) 17.7 (4.7)	**Data Used** Side effects reported Response: 50% reduction in SIGH-SAD Response: 50% reduction in HRSD & >8 HRSD mean 1 week follow-up HRSD 21 mean endpoint SIGH-SAD mean 1 week follow-up SIGH-SAD mean endpoint **Data Not Used** Sleep measures - not relevant Expectations measure - not relevant Notes: No mention of whether any participants left the study early	**Group 1 N= 30** Bright light - Bright light visor (2 krypton incandescent bulbs of approx 6,000 lux (range 4,000-7,800 lux)), approx 6 cm from eyes for 60 mins (N=10) or 30 mins (N=20) 6.30-8.30am. (Time reduced following initial good results in control condition). **Group 2 N= 25** Dim light - Dim light visor (2 krypton incandescent bulbs of approx 400 lux (range 300-415 lux)), approx 6cm from eyes for 60 mins (N=11) or 30mins (N=14) 6.30-8.30am. (Time reduced following initial good results in control condition.)	SIGN: 1+; funding Bio-Brite
STRONG2008 Study Type: RCT Study Description: Open-label phase followed double-blind trial - data extracted from double-	n= 30 Age: Mean 44 Sex: 7 males 23 females	**Data Used** Leaving treatment early for any reason SAD subscale mean change	**Group 1 N= 15** Narrow-band blue light - 470 nm blue light-emitting diode unit; 176 lux; 5.45 E14 photon density/cm-squared/s; 4.5 x 3 inch	SIGN: 1+; trial funded by Apollo Light Systems, but analysis funded elsewhere (unclear where)

blind trial only Type of Analysis: ITT LOCF Blindness: Double blind Duration (days): Mean 21 Setting: Unclear Notes: RANDOMISATION: randomised, no details Info on Screening Process: 35 met admission criteria - number screened unclear	Diagnosis: 100% Recurrent MDD episodes with a seasonal pattern by DSM-IV Exclusions: SIGH-SAD < 20; recently used light therapy; failed previous light therapy treatment; abnormal thyroid-stimulating hormone values; co-occurring psychiatric disorder or medical condition that could affect mental status; ocular or dermatological health problems that might be affected by light therapy Notes: 19 people with pure SAD & 11 major depresison with seasonal intensification (post-hoc diagnosis); control group significantly older than treatment group (51 years vs 40 years) Baseline: SIGH-SAD 34.1 (5.6)	HAMD-17 mean change SIGH-SAD (HAMD-29) mean change **Data Not Used** Leaving treatment early due to side effects - Unclear to which group leaver allocated Notes: Outcomes extracted for whole sample; only mean % change given for subsample with pure SAD	panels; 45 mins a day between 6am and 8am **Group 2 N= 15** Red light - 650 nm red light-emitting diode unit; 201 lux; 3.17 E14 photon density/cm-squared/s; 4.5 x 3 inch panels; 45 mins a day between 6am and 8am	
TERMAN1998 Study Type: RCT Study Description: Cross-over study but pre-cross data available Type of Analysis: Completer Blindness: Single blind Duration (days): Mean 14 Setting: Volunteers; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: volunteers recruited through media announcements (including posters, and physician referrals	n= 158 Age: Mean 39 Range 18-59 Sex: 25 males 99 females Diagnosis: 100% SAD by National Institute for Mental Health criteria 100% mood disorder with seasonal pattern by DSM-III-R 100% major depressive episode by DSM-III-R 23% Bipolar disorder (depressed phase) by DSM-III-R Exclusions: other axis I disorders, suicide attempt within past 3 years, habitual sleep onset later than 1am or awakening later than 9am. Notes: Participant details & data reported for 124 completers who showed relapse during final withdrawal phase	**Data Used** SIGH-SAD mean endpoint **Data Not Used** Remission: <=8 SIGH-SAD/SR - Original N randomised uncler Notes: Continuous data from groups 1 and 2 only	**Group 1 N= 19** Bright light - morning light crossed over to morning light; 10,000 lux, 32 cm from eyes **Group 2 N= 19** Bright light - evening light crossed over to evening light; 10,000 lux, 32 cm from eyes **Group 3 N= 27** Bright light - morning light crossed over to evening light; 10,000 lux, 32 cm from eyes **Group 4 N= 20** Bright light - evening light crossed over to morning light; 10,000 lux, 32 cm from eyes **Group 5 N= 20** High density negative ions - 1.0 x 10 to power of 4 ions per cubic centimeter; continued same treatment post cross-over; data not used **Group 6 N= 19** Low density negative ions - 2.7 x 10 to power of 6 ions per cubic centimeter; continued same treatment post cross-over; data used as control group	SIGN: 1+, funding NIMH
TERMAN2006 Study Type: RCT Blindness: Single blind Duration (days): Mean 21 Setting: outpatients; US Notes: RANDOMISATION: procedure not reported. 1 baseline wk prior to treatment.	n= 126 Age: Mean 40 Sex: 22 males 77 females Diagnosis: 100% major depression or bipolar with seasonal pattern by DSM-III-R 100% SAD by Rosenthal criteria Exclusions: score of < 20 on SIGH-SAD, HAM-D-21 score of <10- or 8-item atypical score <5, poor medical health, consumption of alcohol, psychtropic medication or recreational drugs, comorbid axis I disorder, suicide attempt within 3 years, pregnancy, habitual sleep onset later than 1am or wake-up time later than 9am, past treatment with light or negative ions, Notes: Participant details and data reported only for 99 participants who completed trial and either remained	**Data Used** Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 HRSD 21 mean endpoint SIGH-SAD mean endpoint Leaving treatment early for any reason	**Group 1 N= 23** Bright light - Light box 10,000 lux for 30 mins within 10 mins of rising, 31 cm from head of bed **Group 2 N= 25** Dawn simulation - From 0.0003 lux to 350 lux designed to simulate sunrise on 5 May at 45 degrees north latitude outdoors under tree cover over 3.5 hours **Group 3 N= 26** High density negative ions - Not extracted **Group 4 N= 27** Dawn pulse control - Control for dawn simulation: trapezoidal light pulse of 250 lux (13 mins) before wake-up time **Group 5 N= 25** Low density negative ions - Not extracted	SIGN: 1+; funding unclear (light boxes donated)

	depressed or relapsed during withdrawal phase.			
WILEMAN2001 Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 28 Setting: recruited via GPs; Scotland Notes: RANDOMISATION: using minimisation to ensure balance between groups for age, gender & current antidepressant therapy	n= 59 Age: Mean 41 Sex: 5 males 52 females Diagnosis: major depressive episode with seasonal pattern by DSM-IV Exclusions: SIGH-SAD score < 15, <16, >64 Baseline: SIGH-SAD white 34.91 (9.9) red 34.69 (7.9)	**Data Used** Expectations measure Response: 50% reduction in SIGH-SAD/SR Response: total SIGH-SAD-SR score <18 & atyp <8 Response: 50% reduction in SIGH-SAD-SR & <=8 SIGH-SAD/SR mean endpoint	**Group 1 N= 33** Bright light - Bright white light of 10,000 lux at 51 cm for 30 mins/day for the 1st week, 45 mins/day for the 2nd week and 1 hour/day for last 2 weeks. Participants were advised that most beneficial time is morning but that any time before 7pm is acceptable. **Group 2 N= 26** Dim light - Dim red light of 500 lux at 51 cm for 30 mins/day for the 1st week, 45 mins/day for the 2nd week and 1 hour/day for last 2 weeks. Participants were advised that most beneficial time is morning but that any time before 7pm is acceptable.	SIGN 1+; funding Chief Scientist Office of the Scottish Executive Department of Health

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BENEDETTI2003	Not SAD - patients did not fulfil criteria for seasonal pattern
BIELSKI1992	Does not report whether participants were randomised
BRAINARD1990	Cross-over trial, data not extractable
BROWN2001A	Not SAD - non-seasonal depression
DOGHRAMJI1990	Cross-over design; fewer than 10 participants in each condition (2-hour light therapy vs 4-hour light therapy)
EASTMAN1992	Does not report whether participants were randomised
GLOTH1999	No extractable data; fewer than 10 participants per arm (vitamin D vs phototherapy)
GROTA1989	No extractable data; fewer than 10 participants in each condition (bright light vs dim light)
HOEKSTRA2003	No control condition, all participants received light therapy, compares SAD patients with control group
JACOBSEN1987A	Cross-over study; fewer than 10 participants in each condition (early morning light vs early afternoon light)
JAMES1985	Cross-over study; fewer than 10 participants in each condition (bright light vs dim light)
KOORENGEVEL2001	Intervention not relevant to guideline (extraocular light)
LAM1991	Cross-over study; fewer than 10 participants in each condition (ultra-violet light vs ultra-violet-blocked light vs dim light)
LAM2004	Not an RCT (augmentation or switch: citalopram vs bupropion)
LEPPAMAKI2002A	Light and exercise combination therapy, in exercise review
LINGJAERDE1998	No relevant outcomes reported
LOVING2005	Not SAD - non-seasonal depression
LOVING2005A	Not SAD - non-seasonal depression
MAGNUSSON1991	Cross-over study; fewer than 10 participants in each condition (bright white light vs dim red light)
MARTINY2004B	No control condition, all participants received light therapy

MCGRATH1990	Cross-over trial - data not extractable
MICHALON1997	No relevant outcomes reported
NAGAYAMA1994	Non-randomised design; fewer than 10 participants in each condition (bright light vs dim light)
NORDEN1993	Cross-over trial - data not extractable
OREN1991	Cross-over study; fewer than 10 participants in each condition (green light vs red light)
RAO1990	Not SAD - non-seasonal depression
ROSENTHAL1984	Cross-over study; fewer than 10 participants in each condition (bright light vs dim light)
ROSENTHAL1985	Cross-over study; 20 out of 22 with bipolar disorder
ROSENTHAL1987	Cross-over study - data not extractable
ROSENTHAL1988	Not light therapy - atenolol vs placebo
RUHRMANN1998	17.5% participants (7 out of 40) have a diagnosis of bipolar disorder
SACK1990	Cross-over study; fewer than 10 participants in each condition (morning light vs evening ligth)
SCHWARTZ1997	Data not extractable; fewer than 10 participants in each condition (bright light vs no light)
STEWART1990	Cross-over study; fewer than 10 participants per arm (head-mounted light vs light box)
STEWART1991	Cross-over study; fewer than 10 participants in each condition (green light vs white light)
THORELL1999	Less than 10 participants in each condition
VOLZ1990	Not SAD - non-seasonal depression
WEHR1986	Cross-over study; fewer than 10 participants in each condition (summer-type light vs winter-type light)
WIRZJUSTICE1987	Cross-over study, so data not extractable; also fewer than 10 participants in each condition (bright light (> 2,500 lux): 0.5 hours vs 2 hours)
WIRZJUSTICE1993	Protocol changes part way through trial
WIRZJUSTICE1996	Not randomly assigned to different conditions
ZOU2005A	Not SAD - elderly depression inpatients

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Magnusson, A. & Kristbjarnarson, H. (1991). Treatment of seasonal affective disorder with high-intensity light. A phototherapy study with an Icelandic group of patients. Journal of Affective Disorders, 21, 141-147.

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Rosenthal, N. E., Jacobsen, F. M., Sack, D. A., Arendt, J., James, S. P., Parry, B. L. et al. (1988). Atenolol in seasonal affective disorder: A test of the melatoninn hypothesis. American Journal of Psychiatry, 145, 52-56.

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Wirz-Justice, A., Graw, P., Krauchi, K., Gisin, B., Jochum, A., Arendt, J. et al. (1993). Light therapy in seasonal affective disorder is independent of time of day or circadian phase. Archives of General Psychiatry, 50, 929-937.

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Non-light therapy interventions for depression with a seasonal pattern/SAD

Comparisons Included in this Clinical Question

Fluoxetine v placebo
LAM1995

High ion density v low ion density
TERMAN1995

Moclobemide v fluoxetine
PARTONEN1996

Moclobemide v placebo
LINGJAERDE1993

Relapse Prevention: propanolol v placebo
SCHLAGER1994

Sertraline v placebo
MOSCOVITCH2004

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
LAM1995 Study Type: RCT Type of Analysis: ITT: LOCF Blindness: No mention Duration (days): Mean 35 Setting: Outpatients; Canada Notes: RANDOMISATION: no details	n= 68 Age: Mean 36 Sex: 23 males 45 females Diagnosis: Recurrent MDD episodes with a seasonal pattern by DSM-III-R Exclusions: Satisfying neither: score =/>15 on first 17 items of HAMD-21 or score =/>12 on first 17 items of HAMD-21 and score =/>23 on HAMD-29; pregnancy or lactation; convulsions or non-stabilised serious medical illness; serious active suicide risk; DSM-III-R diagnosis of organic mental disorder, substance use disorder, schizophrenia, paranoid or delusional disorder, other psychotic disorder, panic disorder, GAD not concurrent with MDD, bipolar type I; use of other psychotropic drugs; previous use of fluoxetine; use of heterocyclic antidepressants in past 7 days or MAOI in past 14 days; concurrent use of light therapy or formal psychotherapy. Notes: 1 week placebo washout n= 86 enrolled; n= 68 after washout Baseline: BDI: Flx 21.1 (6.7); Plb 24.4 (7.1) HAMD-21: Flx 18.6 (3.9); Plb 18.9 (3.7) HAMD-29 (m): Flx 33.6 (5.8); Plb 33.3 (5.8)	**Data Used** Side effects reported Leaving treatment early due to side effects Response: 50% reduction in SIGH-SAD Response: 50% reduction in HRSD21 Response: 50% reduction in BDI SIGH-SAD mean endpoint HAMD-21 mean endpoint BDI mean endpoint	**Group 1 N= 36** Fluoxetine. Mean dose 20 mg/d **Group 2 N= 32** Placebo	Funding: Eli Lilly, Canada, Inc
LINGJAERDE1993 Study Type: RCT Type of Analysis: completers Blindness: Double blind Duration (days): Mean 21 Setting: Outpatients; Norway Notes: RANDOMISATION: no details	n= 34 Age: Mean 43 Sex: 9 males 25 females Diagnosis: mood disorder with seasonal pattern by DSM-III-R SAD by Rosenthal criteria subsyndromal SAD by Kasper criteria Exclusions: Not at least moderate depression on CGI; not considered on clinical grounds to be in need of treatment for winter depression; psychotic symptoms or suicidal ideas; serious somatic disorder; active anitdepressant treatment during past 2 weeks; pregnancy or possibility of becoming pregnant during treatment period.	**Data Used** Leaving treatment early due to side effects Leaving treatment early for any reason MADRS (extended) mean endpoint **Data Not Used** CGI - not relevant Atypical - not relevant	**Group 1 N= 16** Moclobemide. Mean dose 400 mg/d **Group 2 N= 18** Placebo	Funding: unclear

	Notes: After acute phsae non-responders swicthed to open moclobemide. Acute phase only extracted here. Baseline: MADRS: Moclobemide 38 (9); Plb 32 (8)			
MOSCOVITCH2004 Study Type: RCT Type of Analysis: 'ITT': minimum 1 post-baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; International Notes: RANDOMISATION: computer generated	n= 187 Age: Mean 40 Sex: 42 males 145 females Diagnosis: 79% Maj dep (single or recurrent)with seasonal pattern by DSM-III-R 13% Depressive disorder NOS with seasonal pattern by DSM-III-R 7% Bipolar disorder depressed with seasonal pattern by DSM-III-R 2% Bipolar Disorder NOS with seasonal pattern by DSM-III-R Exclusions: Score <12 on HAMD-21; score <10 on 8 supplementary items for SAD evaluation; >25% improvement in placebo washout; treatment with psychoactive agent or any drug likely to interact with trial drug; suicide risk; history of alcoholism, drug misuse, poor motivation or other emotional or intellectual problems likely to invalidate informed consent or limit ability to comply with protocol. Notes: Varibale length placebo washout Baseline: HAMD-29: Srtl 36.32 (6.46); Plb 35.01 (6.56) HAMD-21: Srtl 21.11 (5.21); Plb 20.07 (5.4) HAMD-17: Srtl 18.62 (4.73); Plb 17.76 (4.92)	**Data Used** Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason Response: 50% reduction in SIGH-SAD HAMD-17 mean change HAMD-21 mean change SIGH-SAD (HAMD-29) mean change **Data Not Used** HAM-A - not relevant CGI - not relevant HAM-D - not relevant	**Group 1 N= 93** Sertraline. Mean dose 50 mg/d - 200 mg/d **Group 2 N= 94** Placebo	Funding: Supported by grants from Pfizer International Inc.; Dr Lane was formerly an employee of Pfizer Pharmaceuticals.
PARTONEN1996 Study Type: RCT Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Unclear; Finland Notes: RANDOMISATION: no details	n= 32 Age: Mean 44 Sex: 11 males 21 females Diagnosis: 100% Depressive disorder by DSM-III-R 18% mood disorder with seasonal pattern by DSM-III-R Exclusions: Score <16 on HAMD-17; severe suicidality; psychotic symptoms; alcohol or drug misuse; epilepsy or severe somatic disease. Notes: 5 day washout if already on antidepressant At randomisation n=209; data only available for n=183 completers; data extracted here only for n=32 with SAD Baseline: HAMD-17: Moclobemide 22.9 (3.65); Flx 22.7 (3.82) MADRS: Moclobemide 33.8 (3.32); Flx 33.0 (2.97)	**Data Used** MADRS mean endpoint HAMD-17 mean endpoint **Data Not Used** Medical Outcomes Study (MOS) - not relevant CGI - not relevant Response: 50% reduction in HAMD-17 - n at randomisation unclear Remission: HAMD-17 < 7 - n at randomisation unclear Leaving treatment early for any reason - n at randomisation unclear	**Group 1 N= 11** Moclobemide. Mean dose 300 mg/d - 450 mg/d **Group 2 N= 21** Fluoxetine. Mean dose 20 mg/d - 40 mg/d	Funding: unclear
SCHLAGER1994				

Study Type: RCT Study Description: Open treatment phase with responders going on to double blind continuation phase Type of Analysis: Completers: 1 droupout not included in analysis Blindness: Double blind Duration (days): Mean 14 Setting: Unclear; US Notes: RANDOMISATION: no details	n= 23 Age: Sex: Diagnosis: 100% Recurrent MDD episodes with a seasonal pattern by DSM-III-R Exclusions: Non-repsonders to initial open treatment phase; HAMD-21<12; HAMD-21<8 and HAMD-SAD version<18 Baseline: (before open treatment phase; n=33): HAMD-21 14.8 (3.6)	**Data Used** HRSD-SAD mean endpoint Leaving treatment early for any reason **Data Not Used** Response: 50% reduction in HRSD21 - no dat	**Group 1 N= 13** Propanolol. Mean dose 33.2 mg/d **Group 2 N= 11** Placebo	Funding: unclear
TERMAN1995 Study Type: RCT Type of Analysis: Unclear Blindness: Double blind Duration (days): Mean 20 Setting: Unclear; US Notes: RANDOMISATION: no details	n= 25 Age: Mean 38 Sex: 3 males 22 females Diagnosis: SAD by Rosenthal criteria major depressive episode with seasonal pattern by DSM-III-R Bipolar Disorder NOS with seasonal pattern by DSM-III-R Exclusions: <2 weeks baseline depressed mood in fall or winter; symptomatic in spring or summer; other DSM-III-R axis I disorder or potentially complicating illness; experience with light or negative ion treatment; taking psychotropic medication; score <20 on SIGH-SAD; score <10 on HAMD-21; score <5 on Atypical-8 Notes: 7-14 day withdrawal Baseline: Not extractable	**Data Used** Response: 50% reduction in SIGH-SAD **Data Not Used** CGI - not relevant SIGH-SAD mean endpoint - not extractable HRSD 21 mean endpoint - not extractable	**Group 1 N= 12** High density negative ions. Mean dose 30 minute sessions **Group 2 N= 13** Low density negative ions. Mean dose 30 minute sessions	Funding: National Institute of Mental Health Grant

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
DANILENKO2008	n per group <10
OREN1994	No extractable data as n at randomisation and n used in analysis is unclear.
ROSENTHAL1988	n per group <10
TURNER2002	n per group <10; no extractable data
WIRZJUSTICE1990	n per group <10

References of Included Studies

LAM1995 (Published Data Only)

Lam, R.W., Gorman, C.P., Michalon, M., Steiner, M., Levitt, A.J., Corral, M.R., Watson, G.D., Morehouse, R.L., Tam, W., & Joffe, R.T. (1995) Multicentre, placebo-controlled study of fluoxetine in seasonal affective disorder. American Journal of Psychiatry, 152, 1765-1770.

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Lingjaerde, O., Reichborn-Kjennerud, T., Haggag, A., Gartner, I., Narud, K. & Berg, E.M. (1993) Treatment of winter depression in Norway II. A comparison of the selective monoamine oxidase A inhibitor moclobemide and placebo. Acta Psychiatrica Scandinavica, 88, 372-380.

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Moscovitch, A., Blashko, C.A., Eagles, J.M., Darcourt, G., Thompson, C., Kasper, S & Lane, R.M. (2004) A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. Psychopharmacology, 171, 390-397.

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Partonen, T. & Lonnqvist, J. (1996) Moclobemide and fluoxetine in treatment of seasonal affective disorder. Journal of Affective Disorders, 41, 93-99.

SCHLAGER1994 (Published Data Only)

Schlager, D.S. (1994) Early-morning administration of short-acting beta blockers for treatment of winter depression. American Journal of Psychiatry, 151, 1383-1385

TERMAN1995 (Published Data Only)

Terman, M. & Terman, J.S. (1995) Treatment of seasonal affective disorder with a high-output negative ionizer. The Journal of Alternative and Complimentary Medicine, 1, 87-92.

References of Excluded Studies

DANILENKO2008 (Published Data Only)

Danilenko, K.V., Plisov, I.L., Hebert, M., Krauchi, K. & Wirz-Justice, A. (2008) Influence of timed nutrient diet on depression and light sensitivity in seasonal affective disorder. Chronobiology International, 25, 51-64.

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Oren, D.A., Teicher, M.H., Schwartz, P.J., Glod, C., Tuner, E.H., Ito, Y.N., Sedway, J., Rosenthal, N.E. & Wehr, T.A. (1994) A controlled trial of cyanocobalamin (vitamin B12) in the treatment of winter seasonal affective disorder. Journal of Affective Disorders, 32, 197-200.

ROSENTHAL1988 (Published Data Only)

Rosenthal, N. E., Jacobsen, F. M., Sack, D. A., Arendt, J., James, S. P., Parry, B. L. et al. (1988). Atenolol in seasonal affective disorder: A test of the melatoninn hypothesis. American Journal of Psychiatry, 145, 52-56.

TURNER2002 (Published Data Only)

Turner, E.H., Schwartz, P.J., Lowe, C.H., Nawab, S.S., Feldman-Naim, S., Drake, C.L., Myers, F.S., Barnett, R.L. & Rosenthal, N.E. (2002) Double-blind, placebo-controlled study of single-dose metergoline in depressed patients with seasonal affective disorder. Journal of Clinical Psychopharmacology, 22, 216-220.

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Wirz-Justice, A. Graw, Krauchi, K., Gisin, B., Arendt, J., Aldhous, M. & Poldinger, W. (1990) Morning or night-time melatonin is ineffective in seasonal affective disorder. Journal of Psychiatric Research, 24, 129-137.

Non-light therapy interventions for depression with a seasonal pattern/SAD - relapse prevention
New studies in the guideline update

Comparisons Included in this Clinical Question

Bupropion XL v placebo
MODELL2005 study 1
MODELL2005 study2
MODELL2005 study3

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
MODELL2005 study 1 Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Mean 180 Followup: *see notes Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 277 Age: Mean 42 Sex: 72 males 200 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV & SCID modified for SAD Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with Bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 5 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in previous 3 weeks Notes: * trial length is unclear: started Sept/Nov and continued to end March so assumed approx 6 months Baseline: N/R	**Data Used** Recurrence **Data Not Used** Leaving treatment early for any reason - not reported separately by study Leaving treatment early due to side effects - not reported separately by study Notes: 'recurrence': SIGH-SAD score =/>20 for at least 1 week (decision could also be made on 'clinical grounds' based on DSM-IV)	**Group 1 N= 142** Buspirone. Mean dose 150-300 mg/d **Group 2 N= 135** Placebo	Funding: GlaxoSmithKline
MODELL2005 study2 Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 311 Age: Mean 42 Sex: 99 males 207 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV & SCID modified for SAD Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 5 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in previous 3 weeks Baseline: N/R	**Data Used** Recurrence **Data Not Used** Leaving treatment early due to side effects - not reported separately by study Leaving treatment early for any reason - not reported separately by study	**Group 1 N= 158** Bupropion XL. Mean dose 150-300 mg/d **Group 2 N= 153** Placebo	Funding: GlaxoSmithKline

MODELL2005 study3				
Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 473 Age: Mean 41 Sex: 142 males 322 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with Bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 7 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in previous 3 weeks Baseline: N/R	**Data Used** Recurrence **Data Not Used** Leaving treatment early due to side effects - not reported separately by study Leaving treatment early for any reason - not reported separately by study	**Group 1 N= 242** Bupropion XL. Mean dose 150-300 mg/d **Group 2 N= 231** Placebo	Funding: GlaxoSmithKline

References of Included Studies

MODELL2005 study 1 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.

MODELL2005 study2 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.

MODELL2005 study3 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.

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≥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 ≥50% decrease in HRSD + HRSD≤15 + CGI-I 1 or 2 + CGI-S ≤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
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

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Carpenter 2002 Y O	Allocation: random (no details) Double-blind 4 weeks (augmentation trial)	Outpatients. N=26, 16 women. Mean age: mirtazapine - 45.9 (+-9.7) years; placebo - 46.6 (+-66.7) years. Diagnosis: DSM-IV major depressive episode, and had significant persistent symptoms (HRSD-17 > 12) following at least 4 weeks' standard AD monotherapy at maximum recommended or tolerated doses.	1.Mirtazapine (15 mg rising to 30 mg in 3 patients) 2. Placebo (15 mg rising to 30 mg in all patients) Patients continued with previous AD medication (SSRIs, venlafaxine or bupropion) all at therapeutic doses	1. Leaving the study early 2. Non-responders (patients not achieving ≥50% reduction on HRSD) 3. HRSD mean endpoint scores 4. Non-remitters (patients not achieving HRSD ≤7)	Setting: US	B
Fava1994 Y O	Allocation: Random (no details) Duration: 4 weeks Analysis:	N=41. Age: 18-65. Mean =39.6. Diagnosis: DSM-III-R major depressive disorder, HRSD-17 ≥16	Phase 1: Patients treated openly with fluoxetine (20mg) for 8 weeks. Non-responders (≤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	1. HRSD mean endpoint scores 2. Non-remitters (Patients not achieving HRSD≤7) 3. Leaving the study early due to side effects 4. Leaving the study early		B

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 ≥16	Phase 1: Patients treated openly with fluoxetine (20mg) for 8 weeks. Non-responders (≤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	1. HRSD mean endpoint scores 2. Non-remitters (patients not achieving HRSD≤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≥25	Phase 1: 6 weeks' fluoxetine (20mg) patients with HRSD ≥ 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 ≥50% decrease in HRSD) 3. Non-remitters (patients not achieving HRSD≤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 ≥ 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 ≥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 ≥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

	4 weeks	depressive episode and treatment resistance to ≥ 2 antidepressants	moclobemide (200-600mg) 3. Moclobemide (200-600mg)			

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≥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 ≥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

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)) + busprione (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
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

	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 diagn-osed 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 stand-ard 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: 0.7-0.9m Eq/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

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Bordet 1998 Y M I	Allocation: Random (by independent centre using tables of random numbers stratified in blocks of 4). Duration: 21 days. Analysis: ITT	Inpatients and outpatients. N=100, 70 female. Age: 18-65, mean = 42. Diagnosis: DSM-IV unipolar major depressive episode (non psychotic subtype), HRSD-17≥18. 18% had 'past unsuccessful treatment of depression'. Mean baseline HRSD=24	1. Paroxetine (20mg) + pindolol (15mg for 21 days -> 10mg for 4 days -> 5mg for 3 days -> 0mg) 2. Paroxetine (20mg) + placebo	1. HRSD-17 mean endpoint scores at early assessment 2. HRSD-17 mean endpoint scores at late assessment (day 21) 3. Non-remitters at early assessment (patients not achieving HRSD≤10) 4. Non-remitters at late assessment (patients not achieving HRSD≤10) 5. Leaving the study early 6. Leaving the study early due to side effects	Carried out by 20 psychiatrists in France.	A
Maes 1999 Y I 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 ≥16. 22 patients with TRD (Thase and Rush stage 1). Mean baseline scores - pindolol: HRSD-17=21.9+-4.7	1. Fluoxetine (20mg) 2. Fluoxetine (20mg) + Pindolol (7.5mg) 3. Fluoxetine (20mg) + mianserin (30mg). Data Extracted for 1 and 2	1. HRSD-17 mean change scores at late assessment 2. Non-responders at late assessment (patients not achieving ≥50% decrease in HRSD)	Conducted on a treatment resistant depression ward in a Belgian hospital.	B
Perez 1997 Y P I	Allocation: Random (in blocks of 4 by the RANLab programme in a VAX system). Duration 6 weeks (+ 1 week placebo wash-) out). Analysis: LOCF	Outpatients. N=111,79 female, aged: 18+. Diagnosis: DSM-IV unipolar major depression, HRSD-17≥18. Median baseline HRSD=21, range=18-35	1. Fluoxetine (20mg) + pindolol (7.5mg) 2. Fluoxetine (20mg) + placebo	1. HRSD-17 mean change scores at late assessment 2. Leaving the study early 3. Non-responders at last assessment (patients not achieving ≥50% decrease in HRSD) 4. Non-remitters at late assessment (patients not achieving HRSD≤8) 5. Leaving the study early due to side effects	Conducted by 4 psychiatrists in the affective disorders unit of the Sant Pau Hospital, Barcelona.	B
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

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 ≥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 ≥50% decrease in HRSD) 5. Non-responders at late assessment (patients not achieving ≥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	AD + atemoxetine vs AD + placebo	AD + lamotrigine vs AD + lithium	AD + lithium vs AD + T3
BERMAN2007 MARCUS2008	MICHELSON2007		

AD + quetiapine vs AD + placebo	AD + risperidone vs AD + placebo	Bilateral ECT vs unilateral ECT	CBT vs (bupropion or buspirone)
MCINTYRE2007B	KEITNER2009 MAHMOUD2007 SONG2007	ESCHWEILER2007 HEIKMAN2002B MCCALL2002 RANJKESH2005 SACKEIM1993 SACKEIM2000 SACKEIM2008 SIENAERT2009 STOPPE2006 TEW2002	

Duloxetine 60 mg vs duloxetine 120 mg	Escitalopram vs fluoxetine	Fluoxetine + desipramine vs desipramine vs fluoxetine	Fluoxetine + olanzapine vs fluoxetine
WHITMYER2007			CORYA2006 SHELTON2005 THASE2007D

Fluoxetine + olanzapine vs olanzapine	Fluoxetine + olanzapine vs placebo (low-dose drugs)	Fluoxetine + olanzapine vs venlafaxine	Fluoxetine vs nortriptyline
CORYA2006 SHELTON2005 THASE2007D	CORYA2006	CORYA2006	SHELTON2005

Olanzapine + fluoxetine vs nortriptyline	Olanzapine vs fluoxetine	Olanzapine vs nortriptyline	Olanzapine vs venlafaxine
SHELTON2005	CORYA2006 SHELTON2005 THASE2007D	SHELTON2005	CORYA2006

Tranylcypromine vs venlafaxine + mirtazepine	Venlafaxine vs citalopram	Venlafaxine vs sertraline
	LENOXSMITH2008	

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 Additional specifier: Inadequate response to AD	**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

Blindness: Double blind Duration (days): Mean 42 Setting: Outpatients ; US (24 sites) Notes: RANDOMISATION: based on permuted block design wih fixed blocks of 4, stratified by centre, no further details 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	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 derlium, dementia, amnestic/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 Notes: Inadequate response = <50% reduction in symptoms after >= 8 weeks' AD treatment (up to 3 ADs >6 weeks each)	Leaving treatment early for any reason	**Group 2 N= 172** AD + placebo - AD as treatment phase + placebo	
CORYA2006 Study Type: RCT Study Description: H1P1; Open-label treatment for 7 weeks (venlafaxine 75-375 mg), then RCT for non-responders Blindness: Double blind Duration (days): Mean 84 Setting: Unclear; 16 countires (40 sites) Notes: RANDOMISATION: randomised, no details	n= 483 Age: Mean 46 Sex: 133 males 350 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >1 AD + failed prospective trial Exclusions: Age < 18 years; CGI-Severity < 4; psychotic features; no documented history of failure to 6-weeks' SSRI at therapeutic dose Notes: Prospective trial failure: <30% improvement in MADRS during 7-week open-label venlafaxine treatment Baseline: MADRS (SD) 30 (6.8); 51% > 3 lifetime MDD episodes; 22% > 2 lifetime MDD episodes	**Data Used** 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	**Group 1 N= 243** 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 **Group 2 N= 62** Olanzapine **Group 3 N= 60** Fluoxetine **Group 4 N= 59** Venlafaxine **Group 5 N= 59** Placebo (low-dose drugs) - Olz 1 mg/flu 5 mg	SIGN 1+; funding Eli Lilly; 2-7-day screening phase
ESCHWEILER2007 Study Type: RCT Study Description: H3P0 Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 21 Setting: Inpatients; Germany and Austria (4 sites) Notes: RANDOMISATION: code prepared by statistician before study, stored in sealed envelopes Info on Screening Process: 207 screened; 115 excluded; 92 randomised	n= 92 Age: Mean 54 Sex: 39 males 53 females Diagnosis: 100% Major depressive disorder by ICD-10 Additional specifier: Failed >= 2 ADs at adequate dose 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). Notes: 13% bipolar disorder; 'failed' AD = no response over 3-week period 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)	**Data Used** Remission: HAMD-21 <= 8 Response: 50% reduction in HRSD21 **Data Not Used** BDI mean endpoint - no variablility measure HRSD 21 mean endpoint - no variablility measure	**Group 1 N= 46** 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%) **Group 2 N= 46** 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%)	SIGN: 1++; funding Tuebingen University Medical School

HEIKMAN2002B Study Type: RCT Study Description: H0P0 Blindness: Double blind Duration (days): Setting: Inpatients referred for ECT; Finland Notes: RANDOMISATION: randomised in blocks of 6, no further details Info on Screening Process: Screened 81 consecutive patients referred for ECT, 24 met inclusion criteria	n= 24 Age: Mean 57 Sex: 9 males 13 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features 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 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) Baseline: HAMD-17 median (range) Bilateral 27 (16-29); unilateral high-dose 29 (20-40); unilateral low-dose 27 (22-37)	**Data Used** Response: HAMD-17 < 10	**Group 1 N= 7** Bilateral ECT - Just above seizure threshold **Group 2 N= 15** Unilateral ECT - Combined high-dose (400%) and low-dose (150%)	SIGN: 1+; funding Clinical Research Institute of Helsinki University Central Hospital
KEITNER2009 Study Type: RCT 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 Type of Analysis: 'ITT' for those with >1 dose drugs + 1 assessment Blindness: Double blind Duration (days): Mean 28 Setting: Outpatients; US Notes: RANDOMISATION: randomised, no details 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	n= 97 Age: Mean 45 Sex: 42 males 55 females Diagnosis: 100% Major depressive disorder by DSM-IV 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). Notes: 95 in 'ITT' group 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%, mirtazpein 1%, imipramine 1%	**Data Used** Weight change Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 Number of people reporting side effects Leaving treatment early due to side effects Leaving treatment early for any reason Notes: MADRS available but HAMD-17 extracted weight change given in lbs but converted to kgs	**Group 1 N= 64** AD + risperidone. Mean dose 1.6 mg (0.73) - Range of ADs **Group 2 N= 33** AD + placebo - Range of ADs	SIGN 1+; funding Janssen Pharmaceuticals
LENOXSMITH2008 Study Type: RCT Study Description: H1P0 Blindness: Double blind Duration (days): Mean 84 Setting: Inpatients and outpatients; Belguim, France, Germany, Greece, Hungary, Italy, Netherlands, Spain, Sweden, Switzerland, Australia Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 406 Age: Mean 42 Sex: 136 males 170 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Inadequate response to AD 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 baselin; previous unsuccessful treatment with, or hypersensitivity to, study drugs; taken MAOIs within 14 days; received ECT, sumatriptin, or any invetigational or antipsychotic within 30 days; taken any anxiolytic or sedative/hypnotic drugs, or other psychotropic drug or substance within 7 days; taken nonpsychopharmacologic drug with psychotropic effects	**Data Used** Response: 50% reduction in HRSD21 Remission: HAMD-17 <= 8 - no data HRSD 21 mean endpoint - no variablility measure Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 200** Venlafaxine ER. Mean dose 191 mg **Group 2 N= 206** Citalopram. Mean dose 51 mg	SIGN: 1+; funding Wyeth Research, US

	within 7 days unless maintained at stable dose for >= 1 month before baseline; MI within 6 months; uncontrolled hypertension, history or presence of clinically important medical conditions, clinically significant abnormal fundings on lab tests or physical exam; pregnancy or lactation; not using adequate contraception Notes: Inadequate response = HAMD-21 >= 20 after 8 weeks' monotherapy Baseline: HAMD-21 (SD) venlafaxine 28.6 (5.7); citalopram 28.8 (5.4)			
MAHMOUD2007 Study Type: RCT Study Description: H0P1 ;4-week open prospective phase (current AD standard dose), then RCT if inadequate response Type of Analysis: Mixed model repeated measures Blindness: Double blind Duration (days): Mean 42 Setting: Mix of primary care, outpatients, plus some patients recruited via media; US (75 sites) Notes: RANDOMISATION: random code generator accessed via telephone interactive voice response system, stratified by AD class (SSRI/non-SSRI) & site Info on Screening Process: 463 entered open-label phase; 101 prematurely discontinued; 362 completed open-label phase with 274 eligible for randomisation	n= 274 Age: Mean 46 Sex: 71 males 197 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed prospective trial of 1 AD Exclusions: Pregnant; serious suicidal risk or serious medical or neurologic illness; active substance or alcohol use disorders; currently treament with TCA, MAOI, mood stabilizer, anti-epileptic , or centrallly acting gent for ADHD or narcolepsy Notes: Failed trial = still met criteria for MDD Baseline: HAMD-17 (SD) risperidone 24.2 (0.5); placebo 24.4 (0.51); SSRIs 81%; SNRI 31%; Other24%	**Data Used** Number of people reporting side effects Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 HAMD-17 mean endpoint Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 141** AD + risperidone - 1 mg **Group 2 N= 133** AD + placebo	SIGN: 1++; funding Ortho-McNeil Janssen Scientific Affairs
MARCUS2008 Study Type: RCT 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 Type of Analysis: ITT LOCF for those with >=1 dose + 1 assessment Blindness: Double blind Duration (days): Mean 42 Setting: Unclear; US (36 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 1151 patients screened, 830 eligible, 651 completed treatment phase, 266 responded to treatment so not eligible for RCT, 385 eligible	n= 381 Age: Mean 44 Sex: 127 males 254 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR Additional specifier: Failed >=1 AD + failed prospective trial 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 derlium, dementia, amnestic/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 Notes: Failure = < 50% reduction in HAMD scores + HAMD-17 >= 14 or CGI-I >= 3 Baseline: MADRS (SD) placebo: 27 (5.5); aripiprazole 25.2 (6.2)	**Data Used** Remission: MADRS <= 10 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	**Group 1 N= 191** 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) **Group 2 N= 190** AD + placebo - AD as treatment phase	SIGN 1+; funding Bristol Myers-Squibb; 7-28-day screening phase, then 8-weeks prospective treatment before randomisation
MCCALL2002				

Study Type: RCT Study Description: H1P0 (based on 81% received adequate treatment for index episode) Type of Analysis: ITT Blindness: Double blind Duration (days): Setting: Unclear; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 77 Age: Mean 57 Sex: 28 males 49 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: HAMD-21 < 20; history of schizophrenia, schizoaffective disorder, active substance misuse,mental retardation, or neurologic illness; ECT within past 4 months Notes: 81% received adequate treatment before ECT for index episode; no details about psychotic symptoms 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)	**Data Used** Response: 60% decrease in HAMD-21 BDI mean endpoint HRSD 21 mean endpoint Notes: Additional criteria for response: endpoint score < 12	**Group 1 N= 37** Bilateral ECT - 50% seizure threshold; mean 5.8 sessions **Group 2 N= 40** Unilateral ECT - 700% seizure threshold - right unilateral; mean 5.8 sessions	SIGN: 1+; funding NIMH
MCINTYRE2007B Study Type: RCT Study Description: H1P0 Type of Analysis: ITT LOCF for those with >=1 dose Blindness: Double blind Duration (days): Mean 56 Setting: Mixed primary care and outpatients; Canada Notes: RANDOMISATION: randomised, no details Info on Screening Process: 73 patients screened, no further details	n= 58 Age: Mean 44 Sex: 21 males 37 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Inadequate response to AD 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 Notes: Inadequate response - still had HAMD-17 >= 18 after 6 weeks on SSRI or venlafaxine; all had comorbid anxiety Baseline: HAMD-17 (sd) quetiapine 23.4 (3); placebo 23.2 (2.2)	**Data Used** Remission: HAMD-17 <= 7 Response: 50% reduction in HAMD-17 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 **Data Not Used** HAMD-17 mean endpoint - Mean change scores used	**Group 1 N= 29** AD + quetiapine. Mean dose 182 mg - AD is SSRI or venlafaxine **Group 2 N= 29** AD + placebo - AD is SSRI or venlafaxine	SIGN 1+; funding AstraZeneca Pharmaceuticals
MICHELSON2007 Study Type: RCT Study Description: H0P1; 8-weeks' sertraline treatment (100-200 mg); those with inadequate response entered into RCT Type of Analysis: ITT >= baseline + post-baseline assessment Blindness: Double blind Duration (days): Mean 56 Setting: Unclear; US (15 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 276 met entry criteria for open-label phase; 227 completed tretment; 157 were nonresponders or partial respners; 146 continued into RCT	n= 146 Age: Mean 45 Sex: 50 males 46 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Inadequate response to AD Exclusions: Age <18 years; <1 prior episode; HAMD-17 < 18; serious medical illness, BD or ADHD, or treatment-resistant depression (>3 trials of ADs) Notes: Inadequate response = >4 on Maier & Philipp core mood severity subscale of HAMD-17 (MPS) Baseline: HAMD-17 (SD) 23 (4) (entry to study); 15.5 (5.5) entry to RCT	**Data Used** HAMD-17 mean endpoint Remission: MPS<=4 + no single HAMD items > 1 Leaving treatment early due to side effects Leaving treatment early for any reason Notes: MPS = Maier & Philipp core mood severity subscale of HAMD-17	**Group 1 N= 72** Atemoxetine. Mean dose 66 - sertraline [mean dose (SD) 146mg (27)] + atemoxetine (66 mg (30) **Group 2 N= 74** Placebo - sertraline [mean dose (SD) 144 (30)]	SIGN 1+; funding Eli Lilly
RANJKESH2005 Study Type: RCT Study Description: H?P0 Type of Analysis: Completer (>= 8 sessions)	n= 45 Age: Mean 35 Sex: 18 males 27 females	**Data Used** HRDS 24 mean endpoint	**Group 1 N= 15** Unilateral ECT - 'high dose' 400% above seizure threshold	SIGN 1+; funding no details

Blindness: Double blind Duration (days): Setting: Iran; referrals for ECT Notes: RANDOMISATION: randomised, no details Info on Screening Process: All referrals for ECT (n=45) were randomised	Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-24 < 16; history of ECT in prevous 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. Notes: Participants excluded from study if did not receive >= 8 treatments Baseline: HAMD-24 (SD) 33.2 (5.4)	Notes: Outcomes taken just after 8th sessions (used Persian version of HDRS)	**Group 2 N= 15** Bilateral ECT - 'moderate dose' 50% above seizure threshold **Group 3 N= 15** Bilateral ECT - 'low dose' just above seizure threshold (data not used)	
SACKEIM1993 Study Type: RCT Blindness: Double blind Duration (days): Setting: Inpatients; US Notes: RANDOMISATION: in block of 20, no further details Info on Screening Process: No details	n= 100 Age: Mean 57 Sex: 41 males 59 females Diagnosis: 100% Major depressive disorder by Research Diagnostic criteria 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 Notes: 4 patients dropped out, not included in data, allocation not given so added 1 to each group Baseline: HAMD-24 (SD): bilateral low dose 34 (9), high 47 (8); unilateral low dose 36 (9), high 32 (8)	**Data Used** Response: 60% decrease in HAMD-24 Notes: Additional criterion for response: HAMD-24 < 17	**Group 1 N= 24** Bilateral ECT - 0% ST 3x per week; up to 10 treatments **Group 2 N= 28** Bilateral ECT - 250% ST 3x per week; up to 10 treatments **Group 3 N= 24** Unilateral ECT - 0% ST 3x per week; up to 10 treatments **Group 4 N= 24** Unilateral ECT - 250% ST 3x per week; up to 10 treatments	SIGN: 1+; funding NIMH; sourced from Geddes et al. 2003 and added because it is used in dose analysis
SACKEIM2000 Study Type: RCT Type of Analysis: Completer Blindness: Double blind Duration (days): Setting: Inpatients (except 3 outpatients); US Notes: RANDOMISATION: stratified by adequate ADs in index episode, permuted block procedures, used sealed envelopes Info on Screening Process: No details	n= 84 Age: Mean 57 Sex: 33 males 51 females Diagnosis: 100% Major depressive disorder by Research Diagnostic criteria Additional specifier: Psychotic features 31% Bipolar disorder (depressed phase) by Research Diagnostic criteria 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 Notes: 29 with psychotic symptoms; 4 drop-outs not included in data analyses, allocation not given so added 1 to each group 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)	**Data Used** Response: 60% decrease in HAMD-24 Remission: HAMD-24 <= 10 Leaving treatment early for any reason Notes: Additional criteria for outcomes: response - endpoint HAMD-24 < 17; remission - met criteria for response	**Group 1 N= 21** Bilateral ECT - 150% ST; 3x per week; >=5 treatments **Group 2 N= 21** Unilateral ECT - 0% ST; 3x per week; >=5 treatments **Group 3 N= 21** Unilateral ECT - 150% ST; 3x per week; >=5 treatments **Group 4 N= 21** Unilateral ECT - 500% ST; 3x per week; >=5 treatments	SIGN: 1++; funding NIMH; sourced from Geddes et al. 2003 and added because it is used in dose analysis
SACKEIM2008 Study Type: RCT Type of Analysis: ITT	n= 90 Age: Mean 50 Sex: 39 males 51 females	**Data Used** Leaving treatment early for any reason Response: 50% reduction in HAMD-24 Remission: HAMD-24 <= 10	**Group 1 N= 23** Bilateral ECT - Ultrabrief ECT; 150% above ST; mean 8.7 sessions	Emailed author for data by diagnosis as BD population > 15% (21/1/9)

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 referals for ECT screened; 104 offered and consented to protocol participant; 14 left before randomisation - no reasons given	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	Notes: Outcomes taken 1 week after last session	**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	
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	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 28l4 (7.3); olanzapine 28.4 (7.3); nortripytline 28.8 (6.5)	**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	**Group 1 N= 144** Olanzapine. Mean dose 8.3 mg **Group 2 N= 142** Fluoxetine. Mean dose 35.8 mg **Group 3 N= 68** Nortripytline. Mean dose 103.5 mg **Group 4 N= 146** Olanzapine + fluoxetine. Mean dose 8.3 mg/35.6 mg	SIGN 1+; funding Eli Lilly
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	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)	**Data Used** Response: 50% reduction in HAMD-17 Remission: HAMD-17 <= 7 Leaving treatment early for any reason	**Group 1 N= 40** Bilateral ECT - 1.5 times ST; bifrontal **Group 2 N= 41** Unilateral ECT - 6 times ST	SIGN 1+; funding 'study performed without external funding sources'
SONG2007 Study Type: RCT Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 42 Setting: Inpatients and outpatients; China Notes: RANDOMISATION: randomised, no details	n= 100 Age: Mean 44 Sex: 50 males 50 females Diagnosis: 100% depression by Chinese Classification & Diagnostic Criteria Additional specifier: Failed >= 2 ADs at adequate dose Exclusions: Other mental/neurological disorders; severe liver or renal disease; pregnant or breastfeeding	**Data Used** HAMD-17 mean change Remission: >=75% reduction in HAMD Response: 50-74% reduction in HAMD Leaving treatment early due to side effects Leaving treatment early for any reason	**Group 1 N= 50** 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 **Group 2 N= 50** Venlafaxine. Mean dose Not stated - Venlafaxine 50 mg at start increased over 1st week based on response to maximum of 250 mg	Sign 1+; funding not stated; paper in Chinese (Mandarin), data extracted by native speaker

	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 pharmacalogical 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 Study Type: RCT Study Description: RCT for non-responders to 8-week fluoxetine treatment. Paper reports data from 2 studies in the same paper. Type of Analysis: LOCF (MMRM data available) >= 1 dose/assessment Blindness: Double blind Duration (days): Mean 56 Setting: Unclear; US (33 sites) Notes: RANDOMISATION: no details of method, patients randomised and sites randomised to one of 2 concurrent identical	n= 605 Age: Mean 44 Sex: 221 males 383 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >1 AD + failed prospective trial Exclusions: Aged < 18 or > 65 years; HAMD-17 < 22; psychotic features; schizophrenia; schizoaffective disorder; other psychotic disorder; bipolar disroder; PTSD; dissociative disorder; pregnant or breastfeeding; current postpartum depression; MDD with atypical features or seasonal pattern; personality disorder; significant medical	**Data Used** Response: 50% reduction in MADRS Remission: MADRS <= 10 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: Some data given by study and some pooled	**Group 1 N= 200** Olanzapine + fluoxetine. Mean dose 8.6 mg/48.8 mg **Group 2 N= 206** Fluoxetine. Mean dose 49.5 mg **Group 3 N= 199** Olanzapine. Mean dose 8.7 mg	SIGN: 1+; funding Eli Lilly

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, dysthmia 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)
NELSON2004	No mention 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 extracrable 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, nortptyline and lithium)
ZARATE2006	Trial has too few participants (< 10 per arm; total n=18); crossover trial (N-methyl-D-asparate vs placebo)

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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 - older trials not listed elsewhere

Comparisons Included in this Clinical Question

Relapse prevention: nortriptyline + lithium vs nortriptyline	Relapse prevention: paroxetine vs imipramine, paroxetine vs placebo	Relapse prevention: placebo vs nortriptyline + lithium
Sackeim2001	Lauritzen1996	Sackeim2001

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
Lauritzen1996 Study Type: RCT Study Description: 2 separate continuation trials following ECT and antidepressant treatment. Trial A: imipramine vs. paroxetine, and Trial B: paroxetine vs. placebo. Blindness: Double blind Duration (days): Mean 144 Setting: Outpatients at 3 separate hospitals; Denmark. Notes: Randomised: no details. Info on Screening Process: Unknown.	n= 74 Age: Mean 59 Sex: 19 males 55 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Severe cardiovascular disease within the preceding 6 months including intraventricular conduction abnormalities, severe unstabilised somatic diseases, untreated glaucoma, dementia (MMSE score <24), schizophrenia, chronic alcohol/drug misuse, treatment with irreversible monoamine oxidase inhibitors within the preceding 14 days, pregnancy/nursing mothers, epilepsy and prophylactic lithium treatment. Notes: Patients with electrocardiological impairment were entered into trial A, and those without impairment were entered into trial B post-ECT acute phase. Looked at trial A only. Baseline: Group A Paroxetine Imipramine HAM-D post-ECT 9.6 (5.6) 6.6 (4.1)	**Data Used** Relapse	**Group 1 N= 21** Paroxetine. Mean dose 28.5 mg/day - 20-60 mg/day **Group 2 N= 22** Imipramine. Mean dose 138 mg/day - 100-300 mg/day	Funding; pharma (SmithKline Beecham, London and Novo Nordisk, Copenhagen).
Sackeim2001 Study Type: RCT Study Description: RCT for remitters following open-label ECT Blindness: Double blind Duration (days): Mean 168 Setting: US; referrals for ECT (probably inpatients) Notes: RANDOMISATION: randomly permuted block procedure stratified as follows: psychotic, medication-resistant non-psychotic; non-psychotic + non-resistant Info on Screening Process: 349 screened for ECT; 316 entered open-label ECT phase; 159 remitted; 75 dropped out; 84 randomised	n= 84 Age: Mean 57 Sex: 28 males 56 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: Entry to phase I: HAMD-24 < 21; history of bipolar disorder, schizophrenia, schizoaffective disorder, nonmood disorder psychosis, neurological illness, alcohol or drug misuse in past year; ECT in past 6 months; severe medical illness that markedly increased risks of ECT; contraindications to study drugs Notes: 42% had psychotic features; 48% treatment resistant; Entry to RCT based on achieving remission (H-24 < 10 on 2 consecutive visits + H-24 baseline reduced by 60%); 39% had psychotic features; average 2.5 previous episodes Baseline: Entry to phase II: HAMD-24 (SD) pbo 5 (2.7); nort 5.6 (3.1) ; nort + li 6 (3.1)	**Data Used** Relapse Notes: Relapse: 2 consecutive HAMD-24 scores >= 16 + >= 10-point increase in baseline Phase II score; or CGI considerably worsened for 2 consecutive visits; or psychiatric hospitalisation because of suicidality, psychosis or significant reduction in functioning	**Group 1 N= 27** Nortripytline. Mean dose 89.9 (38.2) ng/mL - Dose adjusted to achieve between 75 and 125 ng/mL Placebo **Group 2 N= 28** Nortripytline. Mean dose 89.2 (32.2) ng/mL - Dose adjusted to achieve between 75 and 125 ng/mL Lithium. Mean dose 0.59 (0.2) mEq/L - Dose adjusted to achieve 0.5 to 0.9 mEq/L **Group 3 N= 29** Placebo - Matched both nortripytline and lithium pills	SIGN 1++; funding NIMH

Characteristics of Excluded Studies

References of Included Studies

Lauritzen1996 (Published Data Only)

Lauritzen, L., Odgaard, K., Clemmesen, L., 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. Acta Psychiatrica Scandinavica, 94, 241-251.

Sackeim2001 (Published Data Only)

Sackeim, H. A., Haskett, R. F., Mulsant, B. H., Thase, M. E., Mann, J. J., Pettinati, H. M. et al. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA, 285, 1299-1307.

References of Excluded Studies

Relapse prevention - studies in previous guideline

Characteristics of included studies

Study ID	Inclusion criteria	Participants	Treatment before Rz	Criteria to enter Rz	Interventions	Outcomes	Notes
Alexopoulous 2000	RDC & DSM-IV unipolar major depression without psychotic features, HRSD-24≥19	Age: 65. Outpatients.	Open treatment with Nortriptyline (no dose given, plasma levels 60-150ng/mL) once remission achieved further 16 weeks continuation treatment.	No relapse in continuation phase.	2 years on: 1. Nortriptyline 2. Placebo	Remission (no longer meeting RDC criteria for depression and HRSD≥10 for 3 weeks. Relapse (meeting RDC and DSM-IV for major depression and HRSD≥17). Executive dysfunction and memory	Study designed to investigate the relationship between executive and memory impairment to relapse of

						assessed using the Dementia Rating Scale	depression.
Bauer2000	DSM-III-R major depressive episode and HRSD-21≥15	Age: mean=47.4. Inpatients (25) and outpatients (5). N=30 (patient with unipolar depression: n=27).	Antidepressant treatment for at least 4 weeks, non-responders received adjunctive lithium for 6 weeks	Remission (HRSD≥10, CGI≤3, CGI-I 2 or 3)	4 months on 1. AD + lithium or 2 AD + placebo	Relapse (meeting criteria for DSM-III-R major depressive episode and HRSD-21≥15)	
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), imipramine (150mg), or 2. Placebo	Reoccurrence (HRSD≥18)	Paper gives HRSD baseline and endpoint scores for individual papers so we can use our own criteria for entry and for reoccurrence
Doogan1992	DSM-III major depressive disorder and HRSD-17≥17	Age: 18-70.	8 weeks open treatment with sertraline (50mg up 200mg, mean < 100mg)	CGI-I very much or much improved	44 weeks of: 1. Sertraline (50-200mg, mean=69.3mg) 2. Placebo	Relapse (HRSD≥17)	≤9% patients with bipolar depression
Feiger1999	DSM-III-R non-psychotic major depression and HRSD≥20	N=131. Age: 18+. Outpatients.	16 weeks treatment with nefazodone (100-600mg)	Completers with a response (HRSD≤10 on 2 consecutive visits between weeks 6 and 10 with no 2 consecutive scores of HRSD>10 and with HRSD≤10 at weeks 15 and 16	36 weeks on: 1. Nefazodone (mean=412-438mg) 2. Placebo	Relapse (HRSD≥18 on 2 consecutive visits or early discontinuation due to lack of efficacy)	Paper gives overall results and for two relapse criteria separately.
Frank1990	RDC major depressive episode	N=230. Age: 21-65. (33 [14.3%] with bipolar II disorder)	Imipramine (150-300mg) and interpersonal therapy (IPT) for at least 3 weeks; those in remission for 3 weeks then continued therapy for 17 weeks.	Maintenance of remission (HRSD≤7 and Raskin ≤5 for 20 weeks.	3 years of: 1. IPT 2. IPT + imipramine 3. IPT + placebo 4. Medication clinic + imipramine 5. Medication clinic + placebo	Recurrence (on 2 successive assessments: meeting RDC criteria for MDD and HRSD≥15 and Raskin ≥7)	Geddes used data from 2 and 3
Georgotas	RDC unipolar major	Age: 55+, mean=	Random allocation to:	Free from illness for	1 year of:	Recurrence (meeting RDC	Patients on

1989	depression and HRSD-21≥16	64/65.6. N=52. Outpatients.	1. Phenelzine (mean=53.9mg) 2. Nortriptyline (mean=79mg) or 3.placebo for 7 weeks. Placebo non-responders (HRSD≥10) switched to 1 or 2 for a further 2 weeks. Responders (HRSD≤ 10) continued treatment on 1 or 2 for 4 months.	4 months and sustain HRSD≤10 for 2 months.	1. Phenelzine 2. Nortriptyline 3. Placebo	criteria and HRSD≥16)	phenelzine continued treatment in maintenance phase unless randomimised to placebo; same with nortriptyline. No doses specified for maintenance phase, plasma levels of nortriptyline kept between 190 and 684 nmol/ L, mean=407.5 and platelet MAO inhibition in phenelzine treated patients: > 70%, mean=73.8%
Gilaberte2001	DSM-III-R unipolar major depression, HRSD-17≥18 and CGI severity ≥4	N=140.Age: 18-65. Outpatients.	8 weeks open label fluoxetine (20-40mg), remitters continued with treatment for further 6 months	Remission (no longer meeting DSM-III-R for major depression and HRSD≤8 and CGI≤2)	48 weeks of: 1. Fluoxetine (20mg) 2. Placebo	Recurrence (meeting DSM-III-R criteria for major depression, HRSD≥18 and CGI ≥4)	
Hochstrasser 2001	DSM-IV unipolar recurrent major depressive episode and MADRS≥22	N=269. Age: 18-65. Inpatients and outpatients.	6-9 weeks of open treatment with citalopram (20-60mg). Responders continued treatment for further 16 weeks.	Response (MADRS≤11)	48 weeks on: 1. Citalopram (20-60mg) or 2. Placebo	Recurrence (MADRS≥22, confirmed after 3-7 days.	
Keller1998	DSM-III-R chronic major depression (lasting ≥2years) or major depression + dysthymia and HRSD-24≥18	N=161. Age: 18-65. Outpatients.	Patients randomised to 12 weeks' treatment with 1. Sertraline or 2. Imipramine. Sertraline patients in full remission (HRSD≤7) or with a response (≥50% decrease in HRSD and HRSD≤15)	Sustained response (≥50% decrease in HRSD and HRSD≤15) throughout continuation phase.	76 weeks on: 1. Sertraline (mean=141.6mg) 2. Placebo	Recurrence (at 2 weekly visits: DSM-III-R major depression for ≥3 weeks and CGI severity ≥4 and CGI-I≥3 and ≥4 point increase on HRSD)	Also gives data for re-emergence of depression by consensus assessment.

			entered continuation phase: 4 months further treatment with sertraline (mean=141.6mg).				
Kishimoto 1994	DSM-III major depression	N=26. Age: ≤70.	TCAs (dose not given) or mianserin (mean=29+-9mg)	In remission (HRSD≤9 for at least 3 months)	18 months of: 1. Mianserin (mean=24-26mg) or 2. Placebo	Recurrence (HRSD≥10)	At least 10/26 patients were treated initially with mianserin at a (mean) inadequate dose.
Klysner2002	DSM-IV unipolar major depression and MADRS≥22	N=121. Age: 65+. Outpatients. 85% in first episode.	8 weeks treatment with citalopram (20mg). Patients with MADRS≤11 continued for further 16 weeks on citalopram (20-40mg)	MADRS≤11	48 weeks on: 1. Citalopram (20-40mg) or 2. Placebo	Recurrence (MADRS≥22 confirmed after 3-7 days)	
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 2. Placebo	Recurrence (meeting RCD criteria for major depressive disorder and HRSD≥15)	The 13 patients receiving IPT before randomisation continued to do so afterwards - 6 were in the imipramine group, 7 in placebo.
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≤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 a recurrence.
Montgomery 1992	DSM-III-R major depression and MADRS≥22	N=147.Age: 18-70. Inpatients, outpatients and day patients.	6 weeks treatment with citalopram (20mg or 40mg)	MADRS≤12	24 weeks on: 1.Citalopram (20mg) 2. Citalopram (40mg) or 3. Placebo	Relapse (MADRS≥22)	Collapsed data from 1 and 2
Montgomery 1993	DSM-III-R unipolar major depression and	N=135. Age: 18-65.	8 weeks treatment with paroxetine (20-40mg)	Response (HRSD≤8)	1 year on: 1. Paroxetine (20-	Reappearance (clinical judgement or CGI	Used data for DSM-III-R

	HRSD-21≥18	Outpatients.			30mg) or 2. Placebo	worsening 2 points or CGI≥4 or deterioration for ≥7 days or DSM-III-R major depression)	relapse criteria only.
Prien1984	RDC primary major depressive disorder or manic disorder.	N=150. Age: 21-60. Inpatients or outpatients	Patient treated according to clinician (AD, AD + lithium, lithium, neuropleptic or ECT) until acute symptoms were controlled. Then patients received lithium (0.6-0.9 mEq/L) + imipramine (75-150mg) for ≥2 months.	On stable dose (imipramine ≥75mg, lithium serum level of 0.6 mEq/L) for ≥2 months and GAS≥60 and RSMD total depression score≤7	2 years on: 1. Lithium 2. Imipramine (mean=137mg) 3. Lithium + imipramine 4. Placebo	Recurrence (met RDC criteria for definite major depressive disorder).	Bipolar patients randomised and analysed separately. Data not used in this review.
Reimherr 1998	DSM-III-R major depression and HRSD-17≥16	N=395. Age: 18-65. Outpatients.	12-14 weeks' treatment with fluoxetine (20mg)	Remission (no longer meeting DSM-III-R criteria and HRSD<7 for 3 weeks)	1. Placebo for 50 weeks, 2. Fluoxetine for 50 weeks, 3. Fluoxetine for 14 weeks then placebo for 38 weeks, or 4. Fluoxetine for 38 weeks then placebo for 14 weeks	Relapse (met DSM-III-R criteria for 2 weeks or HRSD>14 for 3 weeks)	Randomised phase includes ≤12.4% bipolar patients. Extracted data for 1 and 2 only.
Robert1995	DSM-III-R major depression and MADRS≥25	N=226. Age: 19-70.	8 weeks treatment with citalopram (20-60mg)	Response (MADRS≤12)	24 weeks on: 1. Citalopram (20-60mg) or 2. Placebo	Relapse (MADRS≥25 and clinical judgement)	
Robinson 1991	RDC major depressive episode and HRSD-17≥18	N=47. Age: 18+. Outpatients.	6-13 weeks treatment with phenelzine (1mg/kg). Responders (HRSD<10) continued treatment for 16 weeks.	HRSD<10 for ≥16 weeks	2 years on: 1.Phenelzine (60mg), 2. Phenelzine (45mg) or 3. Placebo	Relapse (recurrence of depression symptoms within 3 months of randomisation. Recurrence (return of depressive symptoms after 3 months of randomised treatment.)	Collapsed data from groups 1 and 2
Sackheim 2001	RDC unipolar major depressive disorder, HRSD-24≥21	N=84. Age: mean=57.4 Setting unclear.	Open treatment with ECT (3 sessions per week, mean number of sessions = 10)	Remission (60% reduction in HRSD score and HRSD≤10)	24 weeks of: 1. Nortriptyline 2. Placebo 3. Nortriptyline + lithium	Relapse (HRSD≥16 for 1 week and increase in HRSD of more than 10 on 2 consecutive assessments	Used 1 and 2 for main analysis.
Schmidt2000	DSM-IV non-psychotic	N=501.	13 weeks open treatment	Response (no longer	25 weeks of:	Relapse (meeting criteria	Used data from 1

	major depressive disorder, HRSD-17≥18 and CGI≥4	Age: 18-80. Outpatients.	with fluoxetine (20mg)	meeting DSM criteria for major depressive disorder, HRSD≤9 and CGI≤2)	1.Fluoxetine (20mg) 2. Fluoxetine (90mg once weekly) 3. Placebo	for major depressive episode and CGI ≥2)	and 3 only.
Terra1998	DSM-III-R moderate to severe major depressive episode without psychotic symptoms and MADRS>25 and ≥2 episodes in last 5 years	N=204. Age: 18-70.	6 weeks' treatment with fluvoxamine (100-300mg). Responders (MADRS<10 and CGI severity 1 or 2) continued with treatment for 18 weeks	Sustained response (MADRS<12 for 18 weeks)	1 year on: 1. Fluvoxamine (100mg) 2. Placebo	Recurrence (5 symptoms of DSM-III-R criteria for major depression at 2 visits over 8 days [or attempted/completed suicide])	
Thase2001	DSM-IV major depressive disorder and HRSD-17≥18	N=156. Age: 18+. Setting unclear.	8-12 weeks treatment with mirtazapine (15-45mg, mean=30.6mg)	Remission (HRSD≤7 and CGI-I 1 or 2)	40 weeks on: 1. Mirtazapine (15-45mg) or 2. Placebo	Relapse (HRSD≥18 or HRSD≥15 at 2 consecutive visits)	
Versiani1999	DSM-III-R major depressive disorder	N=283.Age: 18-65. Inpatients and outpatients.	6 weeks' treatment with reboxetine (8mg)	Response (≥50% decrease in HRSD-21)	46 weeks on: 1. Reboxetine (8mg) 2. Placebo	Remission (HRSD≤10), relapse (≥50% increase in HRSD and/or HRSD≥18)	
Wilson2003	DSM-III-R major depressive disorder and HRSD-17≥18	N=113. Age: 65+, mean=77.7. Primary care patients. 72% first episode.	8 weeks' open treatment with sertraline (20-200mg), responders(≥50% decrease in HRSD score) received continuation treatment for 16-20 weeks	HRSD≤10 for 4 consecutive weeks	2 years of: 1. Sertraline (50-100mg) 2. Placebo	Recurrence (HRSD≥13 and meeting DSM-III-R criteria for major depressive disorder.	

Characteristics of excluded studies

Study	Reason for exclusion
Bialos1982	Inadequate definition of relapse 'appearance of a depressive episode as decided upon by the patients and the research clinician'
Burke2000	Inadequate diagnosis of depression
Coppen1978	Inadequate diagnosis of depression
Davidson1984	Inadequate definition of relapse 'clinical judgement that the patient was symptomatic enough to warrant a change in treatment or HRSD≥20'
Eric1991	Inadequate definition of relapse: not defined
Glen1984	Inadequate definition of relapse: 'an affective episode of sufficient severity to require a change in treatment'
Harrison1986	43% patients were diagnosed with dysthymia
Jenkins1990	Not a relevant comparison: maintenance treatment with gepirone
Kane1982 Y O S	Unclear description of study, only 6 unipolar patients per treatment group

Klerman1974	Inadequate definition of relapse: not defined
Kocsis1996	At least 30% patients were diagnosed with dysthymia
Lendresse1985	Inadequate definition of relapse: not defined
Mindham1972	Inadequate diagnosis of depression
Old1993	Inadequate definition of relapse: MADRS>10 or clinical judgement
Reynolds1999	43% patients were receiving adjunctive pharmacotherapy
Rouillon1989	43% of patients were diagnosed with dysthymia
Rouillon2000	Not a relevant comparison: maintenance treatment with milnacipran
Stein1980	Inadequate definition of relapse: 'deterioration over 1-2 weeks following an increase in dosage'

Relapse prevention - new studies in the guideline update

Comparisons Included in this Clinical Question

Citalopram + risperidone vs citalopram + placebo
RAPAPORT2006A

Duloxetine vs placebo
PERAHIA2006D

Escitalopram vs placebo
GORWOOD2007
KORNSTEIN2006A
RAPAPORT2004

Fluoxetine + placebo vs fluoxetine + melatonin
GRUNHAUS2001

Fluoxetine vs placebo
MCGRATH2006

Imipramine vs placebo
VAN den BROEK2006

Nortriptyline + lithium vs placebo
KELLNER2006

Nortriptyline vs ECT + nortriptyline
NAVARRO2008

Venlafaxine vs placebo
PREVENT STUDY

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
GORWOOD2007 Study Type: RCT Study Description: RCT followed 12 weeks' open-label escitalopram; responders entered RCT Blindness: Double blind Duration (days): Mean 168 Setting: Outpatients; Czeck Republic, France, Germany, Netherlands, Poland, Slovakia, Spain (46 sites) Notes: RANDOMISATION: computer-generated series contained in sealed opaque envelopes Info on Screening Process: 405 entered open-label phase with 333 completing treatment	n= 305 Age: Mean 73 Range 64-90 Sex: 65 males 240 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR Additional specifier: Responders to acute-phase treatment Exclusions: Mean age 65; Mini-Mental State Examination < 24; current or past history of manic or hypomanic episode, schizophrenia or other psychotic disorder; mental retardation; organic mental disorders; mental disorder resulting from general medical condition; substance misuse disorder; presence or history of clinically significant neurologic disorder; neurodegenerative disorder; personality disorder likely to compromise study; suicide risk; recent/concommitant use of antipsychotics, ECT, lithium, carbemazepine, valoprate, valpromide; use of other psychotropics within week of screening Notes: Response to open-label defined as MADRS <=12 Baseline: MADRS (SD) start of RCT 5.1 (4.8); start of open-label phase 31.1 (4.7)	**Data Used** Relapse Notes: Relapse defined as MADRS >= 22 or unsatisfactory treatment effect as judged by the investigator	**Group 1 N= 152** Escitalopram. Mean dose 10 mg or 20 mg **Group 2 N= 153** Placebo	SIGN: 1++; funding Lundbeck
GRUNHAUS2001 Study Type: RCT Study Description: RCT for remitters to acute-phase ECT Blindness: Single blind Duration (days): Mean 84 Setting: Israel; patients referred for ECT following medication resistance, delusions or hallucinations, and/or very severe depression Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	n= 39 Age: Mean 60 Sex: 13 males 22 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: No specific exclusions beyond basic inclusion criteria (see setting) Notes: N male/female and other demographics based on completers; 17% psychotic features; remission defined as H-17 <= 10 and/or GAS >- 60	**Data Used** Relapse Notes: Relape = return of >= 5 DSM-IV symptoms of MDD + HAMD-17 >= 16	**Group 1 N= 21** Fluoxetine - 20 mg - 40 mg Melatonin - 5 mg or 10 mg **Group 2 N= 18** Fluoxetine - 20 mg - 40 mg Placebo	SIGN: 1+; funding Theodore and Vada Stanley Fuondation; fluoxetine supplied by Eli Lilly; unclear if double-blind

	(5.2); fluox + pbo 26.2 (7); phase 2 7.1 (4.9); 6.8 (4.1)			
KELLNER2006 Study Type: RCT Study Description: RCT for remitters to acute-phase ECT Type of Analysis: N/A Blindness: Open Duration (days): Mean 168 Followup: None Setting: US; patients referred for ECT Notes: RANDOMISATION: random, no details Info on Screening Process: 531 entered phase I; 341 remitted with 70 relapsing and 67 dropping out during the week before the RCT; 204 available for randomisation; 201 randomised	n= 201 Age: Mean 57 Range 18-85 Sex: 65 males 136 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: Entry to phase I: HAM-D-24 < 21; schizophenia or bipolar disorder; significant CNS disease; delirium, dementia; amnestic disorder; illicit substance dependence within 12 months; general medical conditions contraindicating ECT or study medication; prior treatment failure in index episode on heterocyclic AD + lithium; ECT in past 3 months; Entry to phase II based on remission -see notes Notes: Entry to RCT based on achieving remission (H-24 < 10 on 2 consecutive visits + H-24 baseline reduced by 60%); 39% had psychotic features; average 2.2 previous episodes Baseline: HAMD-24 (SD) acute phase: 34.8 (7.2); RCT: 6.4 (2.7)	**Data Used** Relapse Notes: Relapse: 2 consecutive HAMD-24 scores >= 16 + >= 10-point increase in baseline Phase II score; or CGI considerably worsened for 2 consecutive visits; or psychiatric hospitalisation because of suicidality, psychosis or significant reduction in functioning	**Group 1 N= 98** ECT - 10 sessions over 6 months - 1-week intervals x 4, then every other week x 4; the monthly x 2 - final assessments 4 weeks after last treatment **Group 2 N= 103** Nortripytline - Mean blood serum levels at end of study 81.4 (58.5) mEq/L Lithium - Mean blood serum levels at end of study 0.53 (0.38) mEq/L	SIGN: 1+; funding NIMH
KORNSTEIN2006A Study Type: RCT Study Description: RCT for responders to open-label acute-phase SSRI and open-label continuation phase escitalopram Blindness: Double blind Duration (days): Mean 365 Setting: Outpatients; US (28 centres) Notes: RANDOMISTION: randomised, no details Info on Screening Process: 515 entered acute-phase; 234 entered continuation phase	n= 139 Age: Mean 43 Sex: 29 males 110 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Bipolar disorder; schizophrenia or any psychotic disorder; OCD; mental retardation or any pervasive developmental or cognitive disorder; Axis I disorder other than MDD; history of pyschotic disorder; exhibited psychotic features; significant personality disorder; history of substance misuse or dependence in past 6 months; suicide risk; required concomitant psychotropic medication; pregnant or breastfeeding; women not using reliable birth control. Notes: Responders to open-label phases based on MADRS <= 12 Baseline: MADRS (SD) escitalopram 4.7 (4); placebo 4.9 (3.6)	**Data Used** Relapse Notes: Relapse defined as MADRS >= 22	**Group 1 N= 73** Escitalopram. Mean dose 15.2 mg **Group 2 N= 66** Placebo	SIGN: 1+; funding Forest Research Institute
MCGRATH2006 Study Type: RCT Study Description: RCT followed 12-week open-label fluoxetine Blindness: Double blind Duration (days): Mean 365 Setting: Unclear; US Notes: RANDOMISATION: randomised by computer-generated code	n= 262 Age: Mean 38 Sex: 119 males 145 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Significant risk of suicide; pregnant or breastfeeding; women not using effective contraception;	**Data Used** Relapse Notes: Relapse defined as >=2 consecutive weeks or CGI-I of less than 'much improved' compared with ratings at baseline; relapse given as percentage, denominator unclear	**Group 1 N= 131** Fluoxetine. Mean dose 45.8 (15.1) mg **Group 2 N= 141** Placebo	SIGN: 1++; funding NIMH and NY state

for open-label phase with 570 entering treatment; 292 were considered responders of whom 262 agreed to enter RCT	unstable physical disorder; lifetime history of any organic mental disorder, psychotic disoder, or mania; history of seizures; neurological disorder significantly affecting CNS function; active substance misusers or substance dependince in last 6 months; taking medication which may exacerbate depression; hypothyroidism without stabilisation; history of nonresponse to SSRI Notes: 23% had double depression; entry to RCT based one response defined as CGI-I score <= 2 after 2nd week of treatment Baseline: HAMD-17 4.9 (3.1)			
NAVARRO2008 Study Type: RCT Study Description: RCT for remitters to acute-phase ECT Blindness: Double blind Duration (days): Mean 730 Setting: Spain; inpatient and outpatient referrals for ECT Notes: RANDOMISATION: computer-generated Info on Screening Process: 38 in phase I, 33 remitted and randomised	n= 33 Age: Mean 70 Sex: 12 males 21 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features 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) Notes: 100% psychotic symptoms; remission defined as HAMD-17 <8 and no psychotic symptoms Baseline: HAMD-17 (SD) acute phase: nortripyline 35.82 (5.17); nortripyline + ECT 35.31 (2.8); continuation phase: nortripyline 2.88 (1.32); nortripyline + ECT 3.19 (1.33)	**Data Used** Recurrence Relapse Notes: Relapse = reemergence of depressive symptoms within 6 months of remission; recurrence = new episode of depression after at least 6 months without relapse	**Group 1 N= 17** Nortripytline - Maximum dose 100 mg adjusted to acehive 80 to 120 ng/mL + risperidone 2 mg/day for 6 weeks withdrawn by tapering for 4 weeks **Group 2 N= 16** Nortripytline - Maximum dose 100 mg adjusted to achieve 80 to 120 ng/mL ECT - Weekly for first month, every 2 weeks for next month, then monthly (used bilateral ECT)	SIGN 1++; funding unclear
PERAHIA2006D Study Type: RCT Study Description: Acute phase open-label duloxetine 60 mg, then remitters randomised to duloxetine or placebo Type of Analysis: MMRM Blindness: Double blind Duration (days): Mean 182 Setting: Outpatients; Italy, France, Spain, US Notes: RANDOMISATION: randomised, no details Info on Screening Process: 681 people screened; 533 met criteria for acute-phase; 255 dropped out and 280 met criteria for randomisation to relapse prevention phase	n= 278 Age: Mean 45 Sex: 76 males 202 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 18; current Axis I disorder other than MDD; anxiety disorder as a primary diagnosis within 1 year of trial; treatment-resistant depression; serious suicidal risk; serious medical illness Notes: Entry to acute phase >=1 previous episode of MDD; entry to relapse prevention phase HAMD-17 <= 9 with no diagnosis of MDD Baseline: Acute phase: HAMD-17 (SD) 23.7 (3.6); relapse prevention phase: HAMD-17 (SD) 4.9 (2.49)	**Data Used** Relapse Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason Notes: Relapse = increased CGI-Severity score >= 2 points compared with end of acute phase + critria for MDD at 2 consecutive visits >= 2 weeks apart or, if 2nd visit < 2 weeks after 1st, investigator judged additional therapy required	**Group 1 N= 136** Duloxetine. Mean dose 60 mg **Group 2 N= 142** Placebo	SIGN 1+; funding Eli Lilly (code HMBC); allowed 'rescue' to duloxetine 120 mg (duloxetine group) or duloxetine 60 mg (placebo group) for those relapsing during the trial
PREVENT STUDY Study Type: RCT Study Description: Responders to acute-phase RCT randomised to 1-year maintainance after 6-month continuation (study A); responders re-randomised for year (study B) Blindness: Double blind Duration (days): Mean 365 Followup: 1 year (re-randomised)	n= 258 Age: Mean 42 Sex: 82 males 176 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Failed to respond to fluoxetine, venlafaxine or	**Data Used** Relapse Notes: Relapse defined as HAMD-17 > 12, < 50% reduction from acute baseline and meeting criteria for MDD (DSM-IV)	**Group 1 N= 129** Venlafaxine ER. Mean dose 220.8 (71.8) mg - Study B N=43 (mean dose 213.5 (75.2) mg) **Group 2 N= 129** Placebo - Study B N=40	SIGN 1+; funding Wyeth; NOTE: only those on venlafaxine randomised at each stage

Setting: Outpatients; US, 29 sites Notes: RANDOMISATION: randomised, no details Info on Screening Process: 1096 in original RCT; 715 entered continuation phase (6 months); 336 who had been on venlafaxine randomised to study A; 131 who had been on venlafaxine randomised in study B	venlafaxine XR during current episode; treatment resistant (failed >= 3 trials of >=2 classes ADs or ECT or 2 adequate trials of psychotherapy in past 3 years; known hypersensitivity to venlafaxine or fluoxetine; clinically significant heaptic, cardiovascular, renal, or other serious medical disase; seizure disorder; bipolar disorder; OCD; eating disorder;drug/alcohol dependence or misuse within 6 months; psychotic disorder including psychotic depression; current postpartum depression; significant Axis II disorders; mental disorder due to substance or medical condition; anxiety disorder; suicidal; abnormal physical exam; cancer in past 3 years; pregnancy, breastfeeding or inadequate contraception; antipsychotic, MAOI or fluoxetine within 30 days of study. Notes: Response HAMD-17 <= 12 &<50% decrease in baseline scores, or HAMD-17 <= 7; N = efficay sample as large number of protocol violations in placebo group so discounted venlafaxine group recruited in same period (N randomised 336 in 1st study, 83 2nd study) Baseline: HAMD-17 (SD) venlafaxine ER 4.3 (3.3); placebo 4.9 (3.5)			
RAPAPORT2004 Study Type: RCT Study Description: RCT for responders to 8-week open-label escitalopram; participants previously entered RCTs of acute-phase escitalopram Blindness: Double blind Duration (days): Mean 252 Setting: Unclear; US, 53 sites Notes: RANDOMISATION: randomised, no details Info on Screening Process: 502 entered open-label phase	n= 274 Age: Mean 42 Sex: 107 males 167 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Any principal Axis I diagnosis other than MDD; history of schizohrenia or other psychotic disorder; suicide risk; concomitant psychtorpic medication; for women, pregnancy or not using reliable contraception Notes: N randomised not given, so N in efficacy sample used; responders = MADRS <= 12 Baseline: HAMD (SD) escitalopram 7.7 (4.6); placebo 6.6 (4.6)	**Data Used** Relapse Notes: Definition of relapse - MADRS >= 22	**Group 1 N= 181** Escitalopram **Group 2 N= 93** Placebo. Mean dose 10mg-20mg	SIGN 1+; funding Forest Laboratories
RAPAPORT2006A Study Type: RCT Study Description: RCT followed open-label citalopram, followed by open-label risperidone augmentation for non-responders; responders then randomised to present study Blindness: Double blind Duration (days): Mean 168 Setting: Inpatients and outpatients; US, Canada, France (57 sites) Notes: RANDOMISATION: randomised, no details Info on Screening Process: 633 screened for citalopram open-label phase; 502 enrolled; 390 enrolled in open-label augmentation phase; 348 completed of whom 243 had responded	n= 243 Age: Mean 48 Sex: 89 males 154 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >=1 and <=3 ADs Exclusions: Dementia; bipolar disorder; borderline personality disorder; unstable medical conditions Notes: Eligible for RCT if HAMD-17 <= 7 or CGI-Severity = 1 or 2 following risperidone augmentation; 5 patients with psychotic features Baseline: HAMD-17 6 (entry to RCT)	**Data Used** Relapse Notes: Relapse defined as significant increases in HAMD-17 and CGI-C scores (no further definition)	**Group 1 N= 123** Citalopram. Mean dose 53.1 (10.5) mg (modal) Risperidone. Mean dose 1.2 (0.6) mg (modal) **Group 2 N= 120** Citalopram. Mean dose 53.1 (10.5) mg (modal) Placebo	SIGN: 1+; funding Janssen Pharmaceutica
VAN den BROEK2006				

Study Type: RCT Study Description: RCT followed response to ECT in patients with antidepressant failure Blindness: Double blind Duration (days): Mean 168 Setting: Inpatients; Holland (2 sites) Notes: RANDOMISATION: randomised, pharmacist used random number tables Info on Screening Process: 16 patients recruited from other trials; no further details	n= 27 Age: Mean 51 Sex: 7 males 20 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Schizophrenia; bipolar or schizoaffective disorder; organic brain syndrome; chronic alcohol or drug misuse; presence of an absoule contraindication for imipramine; pregnancy or risk of pregnancy; ECT during current episode Notes: Patients entered trial if had responded to ECT with 50% reduction in baseline HAMD scores and maximum HAMD score of 16 within 2 days of ECT and 1-week post-ECT assessment; 9 had psychotic features Baseline: HAMD-17 (SD) at entry to RCT placebo 5.9 (3.8); imipramine 4.9 (2.5)	**Data Used** Relapse Notes: Relapse defined as 'moderately worse' compared with baseline on CGI-I	**Group 1 N= 12** Imipramine. Mean dose 209 mg **Group 2 N= 15** Placebo	SIGN 1++; funding Psychiactric Hospital Parnassia, The Hague, Holland

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
SERRA2006	Very small study (< 10 in one arm) (maintenance ECT + nortriptyline vs nortriptyline following remission with ECT)

References of Included Studies

GORWOOD2007 (Unpublished and Published Data)

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PERAHIA2006D (Published Data Only)

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Keller, M., Trivedi, M., Thase, M., Shelton, R., Kornstein, S., Nemeroff, C. et al. (2007). The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: Outcomes from the 2-year and combined maintenance phases. Journal of Clinical Psychiatry, 68, 1246-1256.

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RAPAPORT2004 (Unpublished and Published Data)

Forest Laboratories Inc. Placebo-Controlled Evaluation of the Safety and Efficacy of Escitalopram in the Prevention of Depression Relapse (SCT-MD-03). Report date: October 2001.

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