Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. The peer reviewers were asked to provide comments on the content, structure, and format of the evidence report and to complete a checklist. Their comments and suggestions formed the basis of our revisions to the evidence report. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

- Susan G. Kornstein, MD., Professor of Psychiatry and Obstetrics and Gynecology, Virginia Commonwealth University, Richmond;
- John Williams, MD, Professor of Medicine and Psychiatry, Duke University, Durham, North Carolina;
- Mark Helfand, MD, MPH, Professor of Medicine and Medical Informatics and Clinical Epidemiology, and Director, Oregon Evidence-based Practice Center, Oregon Health and Science University, Portland;
- Staff of the National Institute for Mental Health, Rockville, Maryland;
- Staff of the Oregon Health and Science University Scientific Resource Center, Portland; and
- Staff of the Agency for Healthcare Research and Quality, Rockville, Maryland

Search Strategy

#16 Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram" [tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] =13604

#22 Search ("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH]) OR "depression, involutional" [tw] OR "Dysthymic Disorder"[MeSH]OR "subsyndronal depressive disorder" [tw] 47030

#23 Search #16 AND #22 = 4043

#24 Search #16 AND #22 Field: All Fields, Limits: All Adult: 19+ years, English, Humans = 2783

#29 Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] = 292497

#30 Search #24 AND #29 = 1056

#35 Search #24 NOT #30 Field: All Fields = 1727

#38 Search "Quality of Life"[MeSH] OR "Hospitalization"[MeSH] = 137196

#39 Search #35 AND #38 = 43

Adverse Events

#42 Search "adverse events" [tw] OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" [mh] OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity [tw] = 124762

Longitudinal Studies

#44 Search longitudinal studies [mh] OR cohort studies [mh] OR case-control studies [mh] OR comparative study [mh] OR "observational studies" [tw] = 1819544

#45 Search #35 AND #42 = 226

#46 Search #35 AND #44 = 371

Drug Interactions

#47 Search drug interactions [mh] = 103115

#48 Search #35 AND #47 = 144

#51 Search "Recurrence"[MeSH] OR remission [tw] OR relapse [tw] = 193920

#52 Search #35 AND #51 = 173

Similar Search Strategy in EMBASE = 133

Total Database = 1922

Excluded Studies

Background

This appendix documents that 525 publications that we identified but did not ultimately include in this report. The citations are numbered consecutively throughout the appendix, but within groupings of the major reasons for exclusion, they are listed alphabetical order by author . The groupings include publication in a language other than English, the wrong outcome, relevant drug(s) not included in the study or publication, population not included, wrong publication type, and wrong study design

Articles by Reason for Exclusion

Not Published in English

1. Berlanga C, Arechavaleta B, Heinze G, Campillo C, Torres M, Caballero A, et al. A double-blind comparison of nefazodone and fluoxetine in the treatment of depressed outpatients. Salud Mental 1997;20(3):1-8.

2. Bremner JD. Double-blind comparison of mirtazapine, amitriptyline and placebo in major depression. <ORIGINAL> DOPPELBLINDVERGLEICH VON MIRTAZAPIN, AMITRIPTYLIN UND PLAZEBO BEI 'MAJOR DEPRESSION". Nervenheilkunde 1996;15(8):533-540.

3. Peters UH, Lenhard P, Metzm M. Therapy of depression in the psychiatrist's office - A double-blind multicenter study. Nervenheilkunde 1990;9(1):28-31.

4. Schone W, Ludwig M. Paratoxetine in the treatment of geriatric depressed patients - A double-blind comparison with fluoxetine. <ORIGINAL> PAROXETIN IN DER DEPRESSIONSBEHANDLUNG GERIATRISCHER PATIENTEN - EINE DOPPELBLINDE VERGLEICHSSTUDIE MIT FLUOXETIN. Fortschr Neurol Psychiatr 1994;62(Suppl 1):16-18.

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Wrong Outcome

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Drug Not Included

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MMA Abbreviations for Evidence Tables

A/S	Aktieselskap (Company type in Denmark)
AD	antidepressant
AE	adverse event
AIDS	acquired immune deficiency syndrome
AMT	awake and moving time
ARV	antiretroviral
ATVI	aortic time velocity interval
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
BQOL	Battelle Quality of Life Measure
BSI	Brief Symptom Inventory of Depression
BUP SR	bupropion sustained release
BUP	bupropion
CBT	cognitive-behavioral therapy
CDC	Centers for Disease Control and Prevention
CESD	Center for Epidemiologic Studies-Depression
CGI	Clinical Global Impressions
CGI–I	Clinical Global Impressions Improvement Scale
CGI–S	Clinical Global Impressions Severity Scale
CI	confidence interval
CIT	citalopram
cm	centimeter
CR	controlled release
D	drug
DBP	diastolic blood pressure
DESS	Discontinuation-Emergent Signs and Symptoms checklist
df	degrees of freedom
diff	difference(s)
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, version III
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, version III revised
DSM–IV	Diagnostic and Statistical Manual of Mental Disorders, version IV
DSP	deliberate self-poisoning
DUL	duloxetine
ECG	electrocardiogram
ECT	Electroconvulsive therapy
EEG	electroencephalogram
ESC	escitalopram
FDA	Food and Drug Administration
FLUO	fluoxetine
FLUV	fluvoxamine
FSQ	Functional Status Questionnaire
GBS	Gottfrey-Brane-Steen
GDS	Geriatric Depression Scale
GP	general physician
GPRD	General Practice Research Database
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
HIV	Human immunodeficiency virus
HSCL-D	Hopkins Depression Scale
HTN	hypertension
ICD10	International Classification of Diseases- 10th revision
IDS	Inventory for Depressive Symptomatology

IDS-C	Inventory for Depressive Symptomatology - Clinician Rated
IDS-SR	Inventory for Depressive Symptomatology - Self Rated
IMI	imipramine
IR	immediate release
ITT	intent to treat
KQ	key question
LOCF	last-observation-carried-forward
LTF	loss to follow-up
MADRS	Montgomery Asberg Depression Rating Scale
MAF	Multidimensional
MAOI	monoamine oxidase inhibitor
m-CPP	meta-chlorophenylpiperazine
MD	medical doctor
MDD	major depressive disorder
MI	myocardial infarction
mil	milnacipran
MINI	Mini International Neuropsychiatric Interview
MIR	mirtazapine
mmHG	millimeters of mercury
MMSE	Mini Mental State Examination
mo	month(s)
N	number
N/A	not applicable
NEF	nefazodone
NIH	National Institute of Health
NIHM	Health Diagnostic Interview Schedule
NIMH	National Institute of Mental Health
NNT	number needed to treat
NoVASC	no other comorbid vascular illness
NR	not reported
NS	not sig
NV	Naamloze Vennootschap (Dutch company type)
OR	odds ratio
P	P-value
PAR	paroxetine
PCP	primary care physician
PGI	Patient Global Impression
PGIS	Patient Global Improvement Scale
Phys-SFR	physicians rating of sexual functioning
PSD	poststroke depression
px	prescription
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLSQ	Q-LES-Q
QOL	quality of life
QRS	time of ventricular contraction
QTcF	Fridericia-corrected time of ventricular contraction
RCT	randomized controlled trial
RD	Risk difference
RNZCGP	Royal New Zealand College of General Practitioners
RR	relative risk
RRR	relative risk ratio
SCID	Structured Clinical Interview for DSM-III Revised
SD	sexual dysfunction
SDS	Self rating Depression Scale

SDS	Sheehan Disability Scale
SER	sertraline
SF-36	Medical Outcomes Study Health Survey - Short Form 36
Sig	significant/significantly
SIP	Sickness Impact Profile
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TMT-A	Trail Making Test – Part A
TMT-B	Trail Making Test – Part B
TRA	Trazodone
UK	United Kingdom
UKU	Utvalg for Kliniske Undersogelse (Side Effect Scale)
US	United States
USA	United States of America
UT	Utah
VAS	visual analog scale
VASC	patients with a history of cardiovascular illness (excluding hypertension)
VEN ER	venlafaxine extended release
VEN XR	venlafaxine extended release
VEN	venlafaxine
VF	verbal fluency test
vs.	versus
WHO	World Health Organization
wk	week(s)
WMS	Wechsler Memory Scale
yr	year(s)

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Aberg-Wistedt et al., 2000 **Country and setting:** Sweden Multicenter **Funding:** Pfizer, Inc	**Research objective:** SER vs. PAR clinical outcomes after 6 mos of continuous therapy **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 353 **Intervention:** **D1:** Sertraline 50-150 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** Overall: 43 **Sex (% female):** Overall: 67.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Response 8 wks- SER: 63% PAR: 63% LOCF at 24 wks: SER: 72% PAR: 69% Response-Observed Cases at 24 wks: SER: 89% PAR: 89% Remission No sig diff at endpoint or at any other study point measures 8 wks: SER: 51.6% PAR: 57.3% 24 wks: SER: 80.2% PAR: 73.7% No sig diff in CGI severity change score or improvement score Relapse during wks 9 to 24: PAR 8.6% SER 1.9% (*P* -value NR) No sig diffs on BQOL	**Constipation:** **D1:** 5.7 **D2:** 16.4 **Diarrhea:** **D1:** 35.2 **D2:** 15.2 **Libido decrease (men):** **D1:** 12.7 **D2:** 3.8 **Libido decrease (women):** **D1:** 1.8 **D2:** 8.8 *P* ≤ 0.05	**Overall attrition rate:** 35.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Allard et al., 2004 **Country and setting:** Sweden and Denmark Multicenter (12 sites) **Funding:** Wyeth	**Research objective:** Compare efficacy and tolerability of VEN ER 75-150 mg/d with of CIT 10-20 mg/d in elderly patients with major depression according to DSM-IV criteria **Duration of study:** 22 wks **Study design:** RCT **Overall study N:** 150 **Intervention:** **D1:** Venlafaxine 37.5-150 mg/d **D2:** Citalopram 10-30 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Uncontrolled hypertension • Sig cardiovascular or cerebrovascular disorders	**Mean age (yrs):** **D1:** 73.6 **D2:** 72.5 **Sex (% female):** **D1:** 73.6 **D2:** 72.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	No statistically sig diffs between treatments in any outcome measures (MADRS, CGI-S, CGI-I) Response rates were 93% in both groups at wk 22 MADRS remission rate was 19% for VEN and 23% for CIT (*P* = NR) Side effects were common during both treatments but differed in tremor being more common during CIT and nausea/vomiting during VEN treatment	**Overall adverse events:** **D1:** 62 **D2:** 43 **Constipation:** **D1:** 6.6 **D2:** 2.7 **Dizziness:** **D1:** 34 **D2:** 30 **Headache:** **D1:** 26 **D2:** 31 **Nausea:** **D1:** 30 **D2:** 16 **Sweating (increase):** **D1:** 2.6 **D2:** 2.7	**Overall attrition rate:** 22.2% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Alves et al., 1999 **Country and setting:** Portugal Multicenter (3 sites) **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUO in MDD **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 87 **Intervention:** **D1:** Venlafaxine 75-150 mg/d **D2:** Fluoxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 45.4 **D2:** 42.3 **Sex (% female):** **D1:** 92.5 **D2:** 91.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs between study groups in any outcome measures at endpoint. HAM-D responders: VEN: 87%, FLUO: 74% (*P* = NR); HAM-D Remitters: VEN: 51%, FLUO: 41% (*P* = NR) VEN showed faster onset with sig diffs in various outcome measures during wks 1 to 4: mean decreases of HAM-D and MADRS scores were sig greater with VEN (*P* < 0.05) during wks 1-4 Suicide ideation scores at wk 6 were sig lower for VEN on MADRS and HAM-D scales Remission (HAM-D < 8) at wk 3 was found in 30% of VEN treated patients and 11% of FLUO treated patients (*P* = 0.03)	**Overall adverse events:** **D1:** 56.4 **D2:** 51.1 **Constipation:** **D1:** 7.7 **D2:** 2.1 **Dizziness:** **D1:** 10.3 **D2:** 2.1 **Insomnia:** **D1:** 5.1 **D2:** 10.6 **Nausea:** **D1:** 33.3 **D2:** 27.7	**Overall attrition rate:** 21.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Baldwin et al., 1996 **Country and setting:** UK, Ireland, Multicenter (20 psychiatric outpatient clinics) **Funding:** Bristol Myers Squibb	**Research objective:** To compare efficacy, safety, and tolerance of NEF and PAR in treatment of depressed outpatients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 206 **Intervention:** **D1:** Nefazodone 200-600 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Rated at least moderately ill on CGI-S **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicidal tendencies • Failed to respond to at least 2 adequate courses of anti-depressant treatment • History of allergy or hypersensitivity to TRA, etoperidone, m-CPP, or PAR	**Mean age (yrs):** **D1:** 38.3 **D2:** 37.9 **Sex (% female):** **D1:** 60 **D2:** 50 **Race (% white):** NR **Baseline (HAM-A):** **D1:** 19 **D2:** 18.3 **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.8	Both groups showed sig improvements from baseline HAM-D, HAM-A and MADRS scores Proportion of CGI responders similar between treatment groups (NEF: 58% vs. PAR: 60%, *P* = NR) No sig diffs between treatment groups	**Overall adverse events:** **D1:** 84 **D2:** 78 **Dizziness:** **D1:** 17 **D2:** 9 **Headache:** **D1:** 35 **D2:** 25 **Nausea:** **D1:** 27 **D2:** 30 **Somnolence (fatigue):** **D1:** 16 **D2:** 24	**Overall attrition rate:** 27.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ballus et al., 2000 **Country and setting:** Spain Multicenter **Funding:** NR	**Research objective:** To compare efficacy and tolerability of VEN and PAR in patients MDD and dsythmia **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 84 **Intervention:** **D1:** Venlafaxine 75-150 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Minimum HAM-D score of 17 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 44 **D2:** 45.1 **Sex (% female):** **D1:** 88 **D2:** 88 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.4 (4.1) **D2:** 24.3 (4.7)	No sig diffs between groups on HAM-D, MADRS, or CGI scales at 24 wks or endpoint At wk 12, percent of patients with HAM-D score < 8 was sig greater in VEN group than PAR group (57% vs. 33%; *P* = 0.011) More patients exhibited a drug response (> 50% decrease in HAM-D) on VEN than PAR at wk 6 (*P* = 0.03) Response rates at wk 24: VEN: 59% vs. PAR: 49%	**Overall adverse events:** **D1:** 68 **D2:** 79 **Constipation:** **D1:** 12.5 **D2:** 16.3 **Diarrhea:** **D1:** 0 **D2:** 9.3 **Headache:** **D1:** 17.5 **D2:** 39.5 **Insomnia:** **D1:** 7.5 **D2:** 9.3 **Nausea:** **D1:** 27.5 **D2:** 9.3 **Sweating (increase):** **D1:** 2.5 **D2:** 7.0	**Overall attrition rate:** 32% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Barrett et al., 2001 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundation	**Research objective:** To compare PAR vs. placebo vs. behavioral treatment for dysthymia and minor depression in primary care patients **Duration of study:** 11 wks **Study design:** RCT **Overall study N:** 241 **Intervention:** **D1:** Paroxetine 10-40 mg/d, individually titrated **D2:** placebo	**Inclusion criteria:** • Adults 18 to 59 • Minimum HAM-D score of 10 • Dysthymia **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies • Current depression treatment	**Mean age (yrs):** **D1:** 45.2 **D2:** 42.6 **Sex (% female):** **D1:** 57.5 **D2:** 66.7 **Race (% white):** **D1:** 90 **D2:** 89 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	ITT analysis: mean decrease in HSCL-D-20; PAR: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no sig diffs between arms Remission by HAM-D-17 score < 6: PAR: 80%, placebo: 44.4%; behavior therapy: 56.8% (*P* = 0.008 for diff among all 3 arms) Minor depression: PAR 60.7%, placebo 65.6%; behavior therapy 65.5% (*P* = 0.906 for diff among all 3 arms)	NR	**Overall attrition rate:** 20.7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Beasley et al., 1991 **Country and setting:** Country NR (appears to be United States) Multicenter **Funding:** Eli Lilly	**Research objective:** To evaluate comparative safety and efficacy of FLUO and TRA in major depression and to evaluate incidence and temporal patterns of activation and sedation **Duration of study:** Up to 6 wks (after a single-blind placebo run-in approximately 1 wk in duration) **Study design:** RCT **Overall study N:** 126 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Trazodone: 100-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • DSM depression but 4 wks in duration **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** **D1:** 40.0 **D2:** 40.0 **Sex (% female):** **D1:** 64.6 **D2:** 68.8 **Race (% white):** NROverall **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.4 (2.7) **D2:** 24.3 (3.6)	Response rates, n (%) (response = ≥ 50% decrease in HAM-D at endpoint) FLUO = 40.5 (62.3%) TRA = 42.0 (68.9%) Remission rates (remission = HAM-D ≤ 7 at endpoint) FLUO = 33.1(50.9%) TRA = 25.7(42.2%) PGIS mean change at endpoint FLUO 2.4 (1.2) vs. TRA 2.3 (1.2) (*P* = NR)	**Diarrhea:** **D1:** 7.7 **D2:** 3.3 **Dizziness:** **D1:** 6.2 **D2:** 21.3 **Headache:** **D1:** 21.5 **D2:** 27.9 **Insomnia:** **D1:** 9.2 **D2:** 3.3 **Nausea:** **D1:** 27.7 **D2:** 24.6 **Somnolence (fatigue):** **D1:** 20.0 **D2:** 45.9 **Sweating (increase):** **D1:** 4.6 **D2:** 0	**Overall attrition rate:** 34.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Behnke et al., 2003 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare onset of antidepressant efficacy of MIR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 346 **Intervention:** **D1:** Mirtazapine: 30-45 mg/d **D2:** Sertraline: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Epilepsy • History of seizure disorder or anti-convulsant treatment • Current eating disorders diagnosis • Previous postpartum depression or anxiety disorder diagnosis	**Mean age (yrs):** **D1:** 42 **D2:** 41 **Sex (% female):** **D1:** 55.7 **D2:** 61.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Onset of action faster in MIR group At all assessments during first 2 wks mean change of HAM-D from baseline sig greater in MIR group than in SER group ($P < 0.05$) After wk 2 diff remained greater with MIR but lacked statistical significance HAM-D response rate showed similar findings HAM-D remission rate higher with MIR than SER at all assessments; diff reached statistical significance at day 14 Reduction in sleep disturbance was sig greater in MIR group at all assessments ($P \leq 0.01$) CGI scores not sig diff	**Overall adverse events:** **D1:** 64 **D2:** 68 **Diarrhea:** **D1:** 4 **D2:** 9.5 **Dizziness:** **D1:** 6.8 **D2:** 10.1 **Headache:** **D1:** 14.2 **D2:** 18.3 **Insomnia:** **D1:** 5.1 **D2:** 8.9 **Nausea:** **D1:** 7.4 **D2:** 22.5 **Somnolence (fatigue):** **D1:** 19.9 **D2:** 7.7 **Sweating (increase):** **D1:** 1.1 **D2:** 5.3 **Libido decrease:** **D1:** 1.1 **D2:** 5.9 $P = 0.02$	**Overall attrition rate:** 20.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Benkert et al., 2000 Szegedi et al., 2003 **Country and setting:** Germany Multicenter (50) **Funding:** Organon, GmBH, Munich, Germany	**Research objective:** Safety and efficacy of MIR and PAR in treatment of major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 275 **Intervention:** **D1:** Mirtazapine: 15-45 mg/d (32.7) **D2:** Paroxetine: 20-40 mg/d (22.9)	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.3 **Sex (% female):** **D1:** 63 **D2:** 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.4 (3.3) **D2:** 22.4 (3.2)	Benkert-MIR and PAR equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) Szegedi-Improvement occurred in majority of analyzed patients within 2 wks, MIR: 72.7% PAR: 64.9% Early improvement was highly sensitive predictor of later stable response or stable remission for both drugs At endpoint, 40.9% of MIR group and 34.1% of PAR group were considered HAM-D remitters (score ≤ 7)	**Overall adverse events:** **D1:** 68.1 **D2:** 63.4 **Changes in weight (increase):** **D1:** 14.8 **D2:** 3.7 **Constipation:** **D1:** 7.4 **D2:** 6.7 **Dizziness:** **D1:** 8.9 **D2:** 8.2 **Headache:** **D1:** 9.6 **D2:** 10.4 **Nausea:** **D1:** 4.4 **D2:** 11.2 **Somnolence (fatigue):** **D1:** 11.1 fatigue-8.9 **D2:** 7.5 fatigue-8.2 **Sweating (increase):** **D1:** 2.2 **D2:** 7.5	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Bennie et al., 1995 **Country and setting:** UK Multicenter (20 centers) **Funding:** Pfizer, Inc	**Research objective:** To compare SER and FLUO in outpatients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 49.9 **D2:** 49.9 **Sex (% female):** **D1:** 57.7 **D2:** 64.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.2 **D2:** 23.4	No sig diffs between treatment groups in any outcome measures at any point in time (changes in HAM-D, HAM-A, CGI, Raskin, Covi scales) Response rate (≥ 50% improvement on HAM-D): SER: 59%, FLUO: 51%	**Overall adverse events:** **D1:** 56 **D2:** 60 **Diarrhea:** **D1:** 4.9 **D2:** 3.5 **Dizziness:** **D1:** 1.4 **D2:** 5.6 **Headache:** **D1:** 14.1 **D2:** 14.6 **Nausea:** **D1:** 21.1 **D2:** 25.0 **Somnolence (fatigue):** **D1:** 4.2 **D2:** 4.2	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Bielski et al., 2004 **Country and setting:** United States Outpatient centers **Funding:** Forrest Laboratories, Inc	**Research objective:** To compare ESC and VEN XR in depressed outpatients at highest recommended doses in United States **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 198 **Intervention:** **D1:** Escitalopram: 20mg **D2:** Venlafaxine: XR 225mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D24>20 • Normal physical exam, labs, and ECG (or any abnormality insignficant) • Using contraceptive **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with VEN or ESC • Failure to respond to adequate trials of 2+ antidepressants	**Mean age (yrs):** **D1:** 37.3 **D2:** 37.5 **Sex (% female):** **D1:** 69.4 **D2:** 47.0 **Race (% white):** **D1:** 77.6 **D2:** 73.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 28.6 (4.1) **D2:** 27.4 (4.5)	Response (≥ 50% dec in MADRS): ESC: 58.8% VEN :48% Response (≥ 50% decrease in HAM-D): ESC: 61% VEN: 48% Response (CGI-I ≤ 2): ESC: 65% VEN: 57% Remission (MADRS < 12): ESC: 50.5 VEN: 41.8 Remission (MADRS ≤ 10): ESC: 41.2 VEN: 36.7 Remission (HAM-D17 ≤ 7): ESC: 36.1 VEN: 31.6 LOCF results, mean change from baseline (SD): ESC: CES-D -15.1 (11.9) Q-LES-Q 12.8 (11.4) VEN: CES-D -12.8 (12.7) Q-LES-Q 9.9 (11.1)	**Overall adverse events:** **D1:** 68 **D2:** 85 **Headache:** **D1:** 15.3 **D2:** 14.0 **Nausea:** **D1:** 6.1 **D2:** 24.0 **Sexual dysfunction :** **D1:** 6.7 **D2:** 22.6 **Somnolence (fatigue):** **D1:** 9.2 **D2:** 17.0 **Sweating (increase):** **D1:** 5.1 **D2:** 11.0	**Overall attrition rate:** 30% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Boyer et al., 1998 **Country and setting:** France Multicenter, primary care settings (57 general practitioners) **Funding:** NR	**Research objective:** To compare efficacy, tolerability, QOL outcomes, and costs of SER and FLUO in treatment of depression **Duration of study:** 180 days **Study design:** RCT **Overall study N:** 242 **Intervention:** **D1:** Fluoxetine: 50-150 mg/d **D2:** Sertraline: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • History of serious allergy or AE reaction related to medicines	**Mean age (yrs):** **D1:** 43.7 **D2:** 43.0 **Sex (% female):** **D1:** 79.1 **D2:** 77.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in changes in MADRS, FSQ, CGI-I, and CGI-S scores between treatment groups No sig diffs in response rates (improvement of MADRS ≥ 50%) between treatment groups Day 120: FLUO: 54.3% SER: 49% Day 180: FLUO: 42.6% SER: 47.4% Sig improvements observed in both treatment groups in all dimensions of FSQ	**Overall adverse events:** **D1:** 51.3 **D2:** 57.8	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Burke et al., 2002 **Country and setting:** United States Multicenter (35 centers) **Funding:** Forest Laboratories	**Research objective:** To evaluate efficacy and tolerability of ESC in treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 491 **Intervention:** **D1:** placebo **D2:** Escitalopram 10 mg/d **D3:** Escitalopram 20 mg/d **D4:** Citalopram 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of at least 2 on item 1 (depressed mood) • Depressive episode ≥ 4 wks • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies • Any DSM-IV Axis I disorder other than MDD • Score at least 5 on item 10 of MADRS	**Mean age (yrs):** **D1:** 40.1 **D2:** 40.7 **D3:** 39.6 **D4:** 40.0 **Sex (% female):** **D1:** 60 **D2:** 70 **D3:** 68 **D4:** 62 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.8 (5.9) **D2:** 24.3 (6.2) **D3:** 25.8 (5.7) **D4:** 25.9 (5.9)	Responders (50 % improvement in MADRS from baseline): 50% vs. 51.2% vs. 45.6% for ESC 10 mg/d, ESC 20 mg/d and CIT 40 mg/d, placebo treatment (27.7%, $P < 0.01$) For QOL, diff in mean change from baseline for ESC vs. placebo treatment was 2.4 for 10 mg/d group ($P = 0.04$) and 4.8 for 20 mg/d group ($P < 0.01$) ESC 10 mg/d was equally effective as CIT 40 mg/d on majority of outcome measures (MADRS, HAM-D, CGI-I, CGI-S) All treatment groups were sig more efficacious than placebo group	**Overall adverse events:** **D1:** 70.5 **D2:** 79 **D3:** 85.6 **D4:** 86.4 **Diarrhea:** **D1:** 7 **D2:** 10 **D3:** 14 **D4:** 11 **Insomnia:** **D1:** 3 **D2:** 10 **D3:** 14 **D4:** 11 **Nausea:** **D1:** 6 **D2:** 21 **D3:** 14 **D4:** 22 **Sexual dysfunction :** **D1:** 0 **D2:** 9 **D3:** 12 **D4:** 4	**Overall attrition rate:** 24% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cassano et al., 2002 **Country and setting:** Italy Multicenter (38 centers) **Funding:** SmithKline, Beecham	**Research objective:** To assess efffects of PAR and FLUO on mood and cognitive function in depressed non-demented geriatric patients **Duration of study:** 1 yr **Study design:** RCT **Overall study N:** 242 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Minimum HAM-D score of 18 • ICD-10, mini mental state, Raskin, Covi Anxiety **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 75.6 **D2:** 74.9 **Sex (% female):** **D1:** 61 **D2:** 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Both treatment groups showed sig improvements in cognitive performance on all test scales No sig diffs between treatment groups and cognitive performance except for Buschke test at wk 3 and 6 where PAR showed a sig greater improvement on a number of tests Both treatment groups sig improved HAM-D total scores but overall no diffs in HAM-D improvement between treatment groups A Kaplan Meier analysis evaluating percentage of responders (HAM-D < 10) over time showed a sig diff in favor of PAR ($P < 0.03$) No sig diffs on CGI scores	**Overall adverse events:** **D1:** 27.6 **D2:** 32.8 **Cardiovascular adverse events:** **D1:** 6.5 **D2:** 7.5	**Overall attrition rate:** 39.3% **ITT Analysis** No another type of analysis was used (define): Observed case **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Chouinard et al., 1999 **Country and setting:** Canada Multicenter (8) **Funding:** SmithKline, Beecham	**Research objective:** Antidepressant and anxiolytic efficacy of PAR and FLUO were compared **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 **Intervention:** **D1:** Paroxetine: 20-50 mg/d **D2:** Fluoxetine: 20-80 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 2 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 40.6 **D2:** 41.2 **Sex (% female):** **D1:** 63.7 **D2:** 59.4 **Race (% white):** **D1:** 96.5 **D2:** 96.5 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.91 (0.46) **D2:** 25.45 (0.46)	No statistically sig diffs in response rates: (Observed cases at 12 wks) PAR: 85.7% FLUO: 88.4% (LOCF endpoint) PAR: 67.0% FLUO: 68.4% No statistically sig diffs in remission rates: (Observed cases at 12 wks) PAR: 77.8% FLUO: 81.2% (LOCF endpoint) PAR: 58.0% FLUO: 59.2%	**Changes in weight (decrease):** **D1:** 11.88 **D2:** 2.94 **Constipation:** **D1:** 17.65 **D2:** 3.96 **Diarrhea:** **D1:** 11.76 **D2:** 18.81 **Headache:** **D1:** 36.27 **D2:** 36.63 **Insomnia:** **D1:** 26.47 **D2:** 22.77 **Nausea:** **D1:** 37.25 **D2:** 31.68 **Somnolence (fatigue):** **D1:** 18.63 **D2:** 16.83 **Sweating (increase):** **D1:** 13.73 **D2:** 5.94	**Overall attrition rate:** 36% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Coleman et al., 2001 **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUO and placebo on safety, efficacy, and sexual functioning in patients with recurrent major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 456 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d (26) placebo **D2:** Bupropion: 150-400 mg/d (319) **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Have sexual activity at least once every 2 wks • Currently experiencing episode lasting 2 to 24 mos • Currently in stable relationship **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 37.1 **D2:** 36.6 **D3:** 36.7 **Sex (% female):** **D1:** 66 **D2:** 63 **D3:** 61 **Race (% white):** **D1:** 82 **D2:** 83 **D3:** 82 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.5 **D3:** 24.4	No diff in responders (> 50 decrease in HAM-D) FLUO: 57% vs BUP: 56% (*P* = NR), remitters (HAM-D < 8) FLUO: 40% vs. BUP: 47% (*P* = NR) More BUP SR remitters (47%) compared to placebo (32%) Orgasm dysfunction occurred sig more in FLUO patients compared with placebo or BUP SR patients (*P* < 0.001) At endpoint, more FLUO treated patients had sexual desire disorder than BUP SR treated patients (*P* < 0.05) More FLUO-treated patients dissatisfied with sexual function beginning at wk 1 (*P* < 0.05)	**Diarrhea:** **D1:** 12 **D2:** 9 **D3:** 9 **Headache:** **D1:** 31 **D2:** 28 **D3:** 20 **Insomnia:** **D1:** 15 **D2:** 21 **D3:** 10 **Nausea:** **D1:** 12 **D2:** 21 **D3:** 16 **Somnolence (fatigue):** **D1:** 11 **D2:** 3 **D3:** 4	**Overall attrition rate:** 34% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Coleman et al., 1999 **Country and setting:** United States Multicenter (9 centers) **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare sexual functioning as well as safety and efficacy of BUP SR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 364 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Bupropion: 150-400 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Stable relationship • Have normal sexual functioning • Sexual activity at least once every 2 wks **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 38.3 **D2:** 38.1 **D3:** 38.5 **Sex (% female):** **D1:** 54 **D2:** 56 **D3:** 59 **Race (% white):** **D1:** 92 **D2:** 87 **D3:** 88 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 34.5 **D2:** 34.8 **D3:** 34.0	No sig diff between BUP SR and SER groups. HAM-D responders: SER: 61% vs. BUP: 66% (*P* = NR) CGI-I and CGI-S for BUP SR sig better than placebo but not better than SER SER not statistically better than placebo No diffs in HAM-A; sig fewer BUP SR patients had sexual desire disorder than SER patients (*P* < 0.05) Orgasm dysfunction occurred sig more in SER patients compared with placebo or BUP SR patients (*P* < 0.05) Diagnosed with at least one sexual dysfunction: SER: 39%, BUP SR: 13%, placebo: 17%	**Diarrhea:** **D1:** 12 **D2:** 18 **Headache:** **D1:** 34 **D2:** 27 **Insomnia:** **D1:** 20 **D2:** 17 **Nausea:** **D1:** 19 **D2:** 23 **Sexual dysfunction :** **D1:** 39 **D2:** 13	**Overall attrition rate:** 30% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Colonna, et al., 2005 **Country and setting:** Mulitnational Primary care centers **Funding:** H Lundbeck A/S, Denmark	**Research objective:** Compare efficacy and safety of ESC to CIT in patients with moderate to severe MDD **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 357 **Intervention:** **D1:** Escitalopram: 10 mg/d **D2:** Citalopram: 20 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 and <40 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications or ECT • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • History of severe drug allergy • Had lack of response to more than 1 antidepressant treatment	**Mean age (yrs):** **D1:** 46 **D2:** 46 **Sex (% female):** **D1:** 127 (73) **D2:** 138 (76) **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MADRS responders: Wk 8: ESC: 63% vs. CIT 55% Wk 24: ESC 80%; CIT 78% MADRS remitters: Wk 8: ESC 55% vs. CIT 45% Wk 24: ESC 76%; CIT 71% CGI-S mean change: ESC -2.49 CIT -2.24	**Overall adverse events:** **D1:** 62.9 **D2:** 72 **Changes in weight (increase):** **D1:** 1.1 **D2:** 6.6 **Headache:** **D1:** 6.9 **D2:** 8.8 **Nausea:** **D1:** 16 **D2:** 9.9	**Overall attrition rate:** 17.7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Costa e Silvia, 1998 **Country and setting:** South America Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN versus FLUO in patients with depression in Latin America and Brazil **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 382 **Intervention:** **D1:** Venlafaxine: 75-225 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 60 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • Suicidal tendencies	**Mean age (yrs):** **D1:** 40.5 **D2:** 39.8 **Sex (% female):** **D1:** 80.1 **D2:** 77.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	HAM-D and MADRS scores decreased sig in both treatment groups ($P < 0.05$) No sig diffs between treatment groups in primary efficacy measures (HAM-D, MADRS, CGI) Global response (≥ 50% decrease in HAM-D or MADRS and CGI score of 1 or 2) was achieved by 86.8% in VEN group and 82% in FLUO group ($P = 0.074$) Remission was observed in 60.2% of patients in each group Patients who increased dose to VEN 150 mg and FLUO 40 mg after 3 wks sig more achieved CGI score of 1 in VEN group ($P < 0.05$)	**Overall adverse events:** **D1:** 69.4 (whole study) **D2:** 65 (whole study) **Dizziness:** **D1:** 8.3 **D2:** 3.2 **Headache:** **D1:** 11.3 **D2:** 7 **Insomnia:** **D1:** 6.2 **D2:** 8.1 **Nausea:** **D1:** 28.9 **D2:** 18.9 **Somnolence (fatigue):** **D1:** 8.3 **D2:** 1.6	**Overall attrition rate:** 12.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Croft et al., 1999 **Country and setting:** United States Multicenter (8 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and effects on sexual functioning of depressed patients using BUP, SER, or placebo **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 360 **Intervention:** **D1:** Sertraline: 50-200 mg/d (mean = 121) **D2:** Bupropion: 150-400 mg/d (mean = 293) **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • In stable relationship • Have normal sexual functioning and sexual activity at least once every 2 wks • Current depressive episode of 8 wks to 24 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 36.0 **D2:** 35.9 **D3:** 37.4 **Sex (% female):** **D1:** 50 **D2:** 51 **D3:** 50 **Race (% white):** **D1:** 87 **D2:** 86 **D3:** 88 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Mean HAM-D scores in both BUP and SER group were statistically better than placebo ($P < 0.05$) No sig diff in HAM-D scores between BUP and SER groups HAM-D responders: BUP: 66% vs. SER 68% CGI-S and CGI-I improvement compared to placebo but no diffs between drugs at any wk Orgasmic dysfunction occurred sig more in SER patients compared with placebo or BUP patients ($P < 0.001$) At day 56 no diff in overall satisfaction with sexual function between treatment groups	**Diarrhea:** **D1:** 26 **D2:** 7 **D3:** 11 **Headache:** **D1:** 40 **D2:** 34 **D3:** 30 **Insomnia:** **D1:** 18 **D2:** 13 **D3:** 4 **Nausea:** **D1:** 31 **D2:** 18 **D3:** 10 **Somnolence (fatigue):** **D1:** 17 **D2:** 3 **D3:** 6	**Overall attrition rate:** 32% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cunningham et al., 1994 **Country and setting:** 5 United States sites and 1 in Montreal, Canada Multicenter **Funding:** Wyeth-Ayerst Research	**Research objective:** To compare efficacy and safety of VEN, TRA, and placebo in outpatients with major depression **Duration of study:** Short-term study: 6 wks Long-term study: 1 yr **Study design:** RCT **Overall study N:** 225 **Intervention:** **D1:** Venlafaxine: 156-160 mg/d **D2:** Trazodone: 294-300 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Must have major depression • Symptoms for at least 1 mo prior to initial visit **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 2 yrs • ECT within last 14 days • Suicidal tendencies • No formal psychotherapy allowed during study period	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.02 **D2:** 24.66 **D3:** 24.41	Results for HAM-D, MADRS, CGI available (results below) At wk 6, CGI response rates based on score of 1 or 2 were 72% for VEN group and 60% for TRA group ($P \leq 0.05$)	**Overall adverse events:** **D1:** 18 **D2:** 23 **D3:** 4 **Constipation:** **D1:** 22 **D2:** 9 **D3:** 4 **Dizziness:** **D1:** 17 **D2:** 36 **D3:** 5 **Nausea:** **D1:** 44 **D2:** 19 **D3:** 5 **Somnolence (fatigue):** **D1:** 43 **D2:** 61 **D3:** 12 **Sweating (increase):** **D1:** 12 **D2:** 3 **D3:** 1	**Overall attrition rate:** 33.78% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Dalery and Honig 2003 **Country and setting:** Europe Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 184 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Fluvoxamine: 100 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of ≥ 17 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 42.0 **D2:** 42.1 **Sex (% female):** **D1:** 63.3 **D2:** 62.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.3 **D2:** 22.2	Both treatment groups resulted in sig improvements of symptoms No sig diffs between study groups in changes of HAM-D scores from baseline at any point in time. At end of study, 60% of both groups were considered responders After 2 wks of treatment, percentage of patients who responded was sig higher in FLUV group (29% vs. 16%; $P \geq 0.05$), as was improvement of CGI-I scores ($P \geq 0.05$). Sig diff not evident after wk 2 Improvement in sleep disturbance sub scores (HAM-D) was sig greater in FLUV group at wk 4 and at endpoint ($P \geq 0.05$)	**Headache:** **D1:** 14 **D2:** 13 **Nausea:** **D1:** 20 **D2:** 24	**Overall attrition rate:** 20.9% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: De Nayer et al., 2002 **Country and setting:** Belgium Psychiatric practices (14) **Funding:** NR	**Research objective:** To compare efficacy and safety of VEN and FLUO in patients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 146 **Intervention:** **D1:** Venlafaxine: 75-150 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 70 • HAM-D score of 18-25 • Covi Anxiety scale >8 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 41.6 **D2:** 43.9 **Sex (% female):** **D1:** 71.2 **D2:** 65.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23 **D2:** 23.1	VEN group showed sig higher response rates in MADRS scores (75.0 vs. 49.3%, *P* = 0.001) and HAM-D scores (71.9% vs. 49.3%; *P* = 0.008) compared to FLUO group VEN treated patients also showed sig greater improvements in Covi Anxiety scores (*P* = 0.0004) and CGI scores (*P* = 0.016) At final visit 59.4% of VEN patients were in remission vs. 40.3 % of FLUO patients (*P* = 0.028) Fewer VEN patients required dose increase (37.1% vs. 52.9%)	**Overall adverse events:** **D1:** 55.7 **D2:** 67.1 **Headache:** **D1:** 8.6 **D2:** 11.4 **Nausea:** **D1:** 28.6 **D2:** 21.4	**Overall attrition rate:** 36.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: De Wilde et al., 1993 **Country and setting:** Belgium Multicenter **Funding:** SmithKline, Beecham	**Research objective:** To compare efficacy and tolerability of PAR and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score > 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidal tendencies • MAOIs or oral neuroleptics in last 14 days • Depot neurolecptics in last 4 wks • Lithium use	**Mean age (yrs):** **D1:** 44.6 **D2:** 44.1 **Sex (% female):** **D1:** 57 **D2:** 66 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 27 (4.8) **D2:** 28.2 (5.3)	Responders at wk 6 (i.e., reduction > 50% from baseline HAM-D21): PAR: ~ 67% FLUO: ~ 62% no sig diff HAM-A score reduction statistically sig diff for PAR vs. FLUO at wk 3; no sig diff at wks 4 or 6 At wk 4, 53% of PAR patients and 23% of FLUO patients showed CGI response of at least 2; diff is sig ($P < 0.01$) No sig diffs in CGI response noted at wks 1,3, or 6	**Overall adverse events:** **D1:** 43 **D2:** 58 **Changes in weight (increase):** **D1:** 6 **D2:** 4 **Nausea:** **D1:** 20 **D2:** 20 **Sweating (increase):** **D1:** 2 **D2:** 14	**Overall attrition rate:** 21.2% **ITT analysis:** NR **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2004 **Country and setting:** United States Multicenter, university clinics **Funding:** Eli Lilly	**Research objective:** To determine comparative efficacy and safety of DUL and PAR for treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 367 **Intervention:** **D1:** Duloxetine 80 mg/d **D2:** Duloxetine 120 mg/d **D3:** Paroxetine: 20 mg/d **D4:** placebo	**Inclusion criteria:** • Adults 18 or older • Met DSM-IV and MINI criteria for MDD • CGI-S rating > 4 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 43.1 **D2:** 44.7 **D3:** 42.0 **D4:** 42.0 **Sex (% female):** **D1:** 70 **D2:** 70 **D3:** 58 **D4:** 58 **Race (% white):** **D1:** 95 **D2:** 92 **D3:** 86 **D4:** 86 **Baseline (HAM-A):** **D1:** 17.8 **D2:** 18.0 **D3:** 18.5 **D4:** 17.9 **Mean HAM-D score at baseline:** **D1:** 19.9 (3.6) **D2:** 20.2 (3.4) **D3:** 20.3 (4.1) **D4:** 19.9	Response and remission rates did not differ sig among DUL 120 mg (71%; 52%), DUL 80 mg (65%; 46%) and PAR (74%; 44%) (*P* = NR) PGI scores were sig superior in patients receiving PAR than patients receiving 80 mg/d DUL (*P* < 0.05)	**Headache:** **D1:** 5.3 **D2:** 5.4 **D3:** 4.7 **Nausea:** **D1:** 12.6 **D2:** 5.4 **D3:** 11.6 **Somnolence (fatigue):** **D1:** 2.1 **D2:** 7.5 **D3:** 5.8 **Sweating (increase):** **D1:** 4.2 **D2:** 8.6 **D3:** 5.8	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Devanand et al., 2005 **Country and setting:** United States Outpatient clinic **Funding:** NIMH	**Research objective:** FLUO vs. placebo for treatment of dysthymia in patients over 60 **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg (individually titrated by protocol according to response) **D2:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 8, max score 25 • Dysthymia • Adults at least 60 yrs old • CGI-s score ≥ 3 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Active suicidal ideation or plan • MDD during current dysthymia episode • Lack of response of current episode to prior trial of any SSRI • Major neurologic disorder • MMSE <24	**Mean age (yrs):** **D1:** 69.0 **D2:** 70.8 **Sex (% female):** **D1:** 32.6 **D2:** 40.9 **Race (% white):** **D1:** 86.4 **D2:** 89.1 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 15.3 (5.1) **D2:** 14.4 (3)	No sig diffs in response rates between treatment groups Responders: FLUO: 27.3% placebo: 19.6% (*P* = 0.4) No sig diffs in QOL measures on Q-LES-Q	NR	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Dierick et al., 1996 **Country and setting:** France NR **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of efficacy and safety of VEN and FLUO in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 314 **Intervention:** **D1:** Venlafaxine: 75-150 mg/d (mean daily dose for Venlafaxine: 109-122 mg/d from day 15 forward) **D2:** Fluoxetine: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 14 days • ECT within last 14 days • Suicidal tendencies	**Mean age (yrs):** **D1:** 43.7 **D2:** 43.2 **Sex (% female):** **D1:** 65 **D2:** 64 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 27.0 (4.2) **D2:** 26.6 (4.1)	Response rate on HAM-D scale was sig higher in VEN group at wk 6: VEN: 72% FLUO: 60% (P = 0.023) In low dose comparison, no sig diffs between groups	**Overall adverse events:** **D1:** 63 **D2:** 56 **Headache:** **D1:** 10 **D2:** 12 **Insomnia:** **D1:** 6 **D2:** 4 **Nausea:** **D1:** 28 **D2:** 14 **Somnolence (fatigue):** **D1:** 5 - Asthenia **D2:** 2- Asthenia **Sweating (increase):** **D1:** 6 **D2:** 4	**Overall attrition rate:** 25% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ekselius et al., 1997 **Country and setting:** Sweden Multicenter (general physicians) **Funding:** Swedish Medical Research Council, Pfizer	**Research objective:** To compare efficacy and safety of SER with CIT in patients with major depression **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 400 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Citalopram: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 21 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with SER or CIT w/o sig effect	**Mean age (yrs):** **D1:** 47.0 **D2:** 47.2 **Sex (% female):** **D1:** 71 **D2:** 72.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Both treatment groups showed sig decreases in MADRS and CGI scores from baseline at all wks starting at wk 2 No sig diffs between treatment groups in any primary outcome variables at any time Response rates Wk 12: SER: 69.5%; CIT: 68.0% Wk 24: SER: 75.5%; CIT: 81.0% Compliance: SER 90.3%, CIT 94.5%	**Overall adverse events:** **D1:** 90 **D2:** 85.5 **Cardiovascular adverse events:** **D1:** 3 **D2:** 4 **Changes in weight (decrease):** **D1:** 4.5 **D2:** 9.5 **Changes in weight (increase):** **D1:** 15 **D2:** 13 **Constipation:** **D1:** 3 **D2:** 2 **Diarrhea:** **D1:** 8.5 **D2:** 5.5 **Headache:** **D1:** 9 **D2:** 6.5 **Insomnia:** **D1:** 3.5 **D2:** 6 **Nausea:** **D1:** 6 **D2:** 2.5 **Sexual dysfunction :** **D1:** 4 **D2:** 6.5	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ekselius et al., 1997 (continued)					**Somnolence (fatigue):** **D1:** 5 **D2:** 4.5 **Sweating (increase):** **D1:** 13 **D2:** 17	

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2002 **Country and setting:** United States Multicenter (15 academic centers) **Funding:** Eli Lilly Research	**Research objective:** To assess effects of SSRI treatment interruption after successful initial treatment (acute phase) of major depression. Acute treatment phase of study reported here **Duration of study:** 10 to 16 wks **Study design:** RCT **Overall study N:** 284 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • MDD for at least 1 mo **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Presence of seizure disorder with seizure occurring in last yr • History of allergy to study drugs • Use of MAOIs within 2 wks of active therapy	**Mean age (yrs):** **D1:** 42.1 **D2:** 44.0 **D3:** 42.5 **Sex (% female):** **D1:** 63.0 **D2:** 57.3 **D3:** 58.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.1/18.4 **D2:** 23.5/19.2 **D3:** 22.6/18.9	No statistically sig diffs between FLUO, SER and PAR on all outcome measures of HAM-D No statistically sig diffs between FLUO, SER and PAR in response rates (50% or greater reduction in total HAM-D score from baseine) or remission rates (HAM-D total score of 7 or less at endpoint); response rates: 64.8%, 72.9%, and 68.8% respectively; remission rates: 54.4%, 59.4%, and 57.0% respectively	**Diarrhea:** **D2:** 26.0 **Headache:** **D1:** 25 **D2:** 28.1 **D3:** 21.9 **Insomnia:** **D2:** 26 **D3:** 20.8 **Nausea:** **D2:** 20.8 **D3:** 25.0 **Sexual dysfunction :** **D1:** 11.8 **D2:** 4.9 **D3:** 20.0	**Overall attrition rate:** 27.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2000 **Country and setting:** United States Multicenter (15 sites) **Funding:** Eli Lilly Research	**Research objective:** To compare tolerability and efficacy of FLUO, PAR and SER in treatment of anxious depression **Duration of study:** 10 to 16 wks (4 wks with additional wks determined by response on CGI) **Study design:** RCT **Overall study N:** 108 (drawn from larger sample of 284 MDD outpatients) **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • HAM-D-Anxiety/ Somatization Factor score of at least 7 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Presence of seizure disorder with seizure in last yr • History of allergy to study drugs • Use of MAOIs within 2 wks of active therapy	**Mean age (yrs):** **D1:** 40.3 **D2:** 44.1 **D3:** 41.4 **Sex (% female):** **D1:** 65.7 **D2:** 62.8 **D3:** 66.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.6 (3.9) **D2:** 23.9 (3.4) **D3:** 25.0 (3.8)	No statistically sig diffs between FLUO, SER and PAR in baseline-to-endpoint improvement in HAM-D total (overall $P = 0.323$) No sig diffs in efficacy and tolerability of FLUO, SER, and PAR in treating anxious depression For all treatments, incidence of substantial emergence or any worsening was low with improvement at highest frequency for all HAM-D items	**Diarrhea:** **D2:** 25.6 **D3:** 20.0 **Headache:** **D1:** 22.9 **D2:** 25.6 **D3:** 23.3 **Insomnia:** **D1:** 17.1 **D2:** 23.3 **D3:** 23.3 **Nausea:** **D3:** 26.7 **Somnolence (fatigue):** **D1:** 11.4 **D2:** 16.3 **D3:** 10.0	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 1998 **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUO **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** **D1:** Paroxetine: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) **D2:** Fluoxetine: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) **D3:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 18 • Raskin Depression score of > 8 (and larger in value than Covi anxiety scale) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 41.3 **D2:** 41.3 **D3:** 41.3 **Sex (% female):** **D1:** 50 **D2:** 50 **D3:** 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.1 (3.4) **D2:** 23.9 (3.8) **D3:** 23.7 (12.2)	No sig diffs among 3 treatment groups in degree of depression and anxiety improvement	**Cardiovascular adverse events:** **D1:** 5 **D2:** 11 **D3:** 11 **Insomnia:** **D1:** 29 **D2:** 20 **D3:** 11 **Sexual dysfunction :** **D1:** 25 **D2:** 7 **D3:** 0	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: FDA Center for Drug Evaluation & Research (Unpublished study SCT-MD-02), 2000 **Country and setting:** US Multicenter (22) **Funding:** Forest Laboratories, Inc.	**Research objective:** To assess efficacy and safety of ESC vs. CIT and placebo **Duration of study:** 8 weeks **Study design:** RCT **Overall study N:** 375 **Intervention:** **D1:** Escitalopram: 10-20 mg/d **D2:** Citalopram: 20-40 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 to 80 • MDD diagnosis according to DSM III or IV • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (years):** **D1:** 41.4 **D2:** 42.0 **D3:** 42.3 **Sex (% female):** **D1:** 52 **D2**: 48 **D3:** 58 **Race (% white):** **D1:** 82 **D2:** 86 **D3:** 82 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.8 **D2:** 25.0 **D3:** 25.0 **Mean MADRS score at baseline:** **D1:** 28.7 **D2:** 28.3 **D3:** 28.8	Mean change from baseline (*P*-values vs. placebo) **HAM-D** **D1:** 10.4 (*P* = 0.506) **D2:** 11.4 (*P* = 0.068) **D3:** 9.6 **MADRS** **D1:** 12.9 (*P* = 0.251) **D2:** 13.0 (*P* = 0.151) **D3:** 11.2 MADRS response rate (≥ 50% decrease from baseline): **D1:** 46 **D2:** 51 **D3:** 41 (*P* = NR)	**Diarrhea:** **D1:** 9.6 **D2:** 14.6 **D3:** 8.7 **Fatigue:** **D1:** 12.0 **D2:** 4.1 **D3:** 2.4 **Headache:** **D1:** 21.6 **D2:** 22.8 **D3:** 18.1 **Insomnia:** **D1:** 13.6 **D2:** 11.4 **D3:** 6.3 **Nausea:** **D1:** 16.0 **D2:** 14.6 **D3:** 12.6 **Somnolence:** **D1:** 10.4 **D2:** 7.3 **D3:** 4.7	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Feiger et al., 1996 **Country and setting:** Europe Multicenter (4) **Funding:** Bristol Myers Squibb	**Research objective:** To compare safety and efficacy of NEF with SER in outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 160 **Intervention:** **D1:** Nefazodone: 100-600 mg/d **D2:** Sertraline: 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Illicit drug and alcohol abuse • Investigational drug use • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 44.5 **Sex (% female):** **D1:** 48 **D2:** 55 **Race (% white):** **D1:** 90 **D2:** 79 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.5 **D2:** 23.5	No statistically sig diffs between treatment groups Response rates: NEF: 59% SER: 57% Difficulty with ejaculation: SER: had sig AEs on sexual function NEF: no sig AE on sexual function $P < 0.01$	**Overall adverse events:** **D1:** 96 **D2:** 95 **Diarrhea:** **D1:** 9 **D2:** 20 **Dizziness:** **D1:** 32 **D2:** 7 **Headache:** **D1:** 55 **D2:** 55 **Insomnia:** **D1:** 21 **D2:** 23 **Nausea:** **D1:** 32 **D2:** 27 **Somnolence (fatigue):** **D1:** asthenia- 18 somnolence- 23 **D2:** asthenia- 24 somnolence- 21 **Sweating (increase):** **D1:** 6 **D2:** 17	**Overall attrition rate:** 24.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Feighner et al., 1991 **Country and setting:** United States Multicenter (2) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficay and safety of BUP and FLUO in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Bupropion: 225-450 mg/d (382) **D2:** Fluoxetine: 20-80 mg/d (38)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 40.9 **D2:** 42.9 **Sex (% female):** **D1:** 62 **D2:** 61 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.3 **D2:** 26.1	No sig diffs in changes of HAM-D score between treatment groups No sig diffs in percentage of clinical responders (more than 50% HAM-D scale reduction) between treatment groups: BUP: 62.7% FLUO: 58.3% No sig diffs in changes of CGI-S, CGI-I, and HAM-A scores	NR	**Overall attrition rate:** 7.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gagiano, 1993 **Country and setting:** South Africa University hospital **Funding:** NR	**Research objective:** Safety and efficacy comparison of PAR and FLUO in patients with MDD **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 39.6 **D2:** 37.8 **Sex (% female):** **D1:** 80 **D2:** 80 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in mean total scores for HAM-D, CGI-I or CGI-S, HAM-A, and MADRS at endpoint or any other study point measures No sig diff in patients responding (at least 50% improvement of HAM-D) between treatment groups (PAR: 70%, FLUO: 63%; no *P* value reported) No sig diffs in groups on HAM-D (item 3) measure for suicidal ideation, both groups showed reduction over six-wk period	**Diarrhea:** **D1:** 13.0 **D2:** 13.0 **Headache:** **D1:** 47.0 **D2:** 53.0 **Insomnia:** **D1:** 20.0 **D2:** 11.0 **Nausea:** **D1:** 33.0 **D2:** 36.0	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Goldstein et al., 2002 **Country and setting:** United States Multicenter (8 sites) **Funding:** Eli Lilly and company	**Research objective:** Evaluation of DUL for efficacy and safety versus placebo and FLUO in patients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 173 **Intervention:** **D1:** Placebo **D2:** Duloxetine: 40-120 mg/d **D3:** Fluoxetine: 20 mg/d	**Inclusion criteria:** • Adults 19 to 65 yrs • Minimum HAM-D score of 15 • Mini confirmation of MDD • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Illicit drug and alcohol abuse • Failed 2 or more courses of antidepressant therapy during current episode • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** **D1:** 41.4 **D2:** 42.3 **D3:** 39.7 **Sex (% female):** **D1:** 68.6 **D2:** 62.9 **D3:** 57.6 **Race (% white):** **D1:** 81.4 **D2:** 88.6 **D3:** 72.7 **Baseline (HAM-A):** **D1:** 15.4 (4.8) **D2:** 14.2 (4.2) **D3:** 15.5 (5.8) **Mean HAM-D score at baseline:** **D1:** 19.2 (5.0) **D2:** 18.4 (4.0) **D3:** 17.9 (4.3)	No statistically sig diffs between DUL and FLUO in response (49% vs. 45%) and remission (43% vs. 30%) Change from baseline on HAM-D subscale of anxiety was DUL (-2.92) which showed a statistically better result in comparison to placebo (-1.95) *P* = 0.027 and FLUO (-1.82) (*P* = 0.041) Change from baseline on HAM-A subscale of anxiety was DUL (-6.87) in comparison to placebo (-5.05) *P* = 0.077 and FLUO (-6.97) (*P* = NR)	**Constipation:** **D1:** 5.7 **D2:** 11.4 **D3:** 15.2 **Diarrhea:** **D1:** 10.0 **D2:** 14.3 **D3:** 30.3 **Dizziness:** **D1:** 7.1 **D2:** 15.7 **D3:** 6.1 **Headache:** **D1:** 31.4 **D2:** 20.0 **D3:** 33.3 **Insomnia:** **D1:** 7.1 **D2:** 20.0 **D3:** 9.1 **Nausea:** **D1:** 12.9 **D2:** 12.9 **D3:** 18.2 **Somnolence (fatigue):** **D1:** 10.0 **D2:** 18.6 **D3:** 21.2 **Sweating (increase):** **D1:** 8.6 **D2:** 18.6 **D3:** 9.1	**Overall Attrition Rate:** 35% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Guelfi et al., 2001 **Country and setting:** France, Denmark, Belgium, The Netherlands Multicenter (33) **Funding:** N.V. Organon, Oss, The Netherlands	**Research objective:** To compare antidepressant efficacy and tolerability of MIR and VEN in treatment of hospitalized patients with DSM-IV diagnosis of severe depressive episode with melancholic features **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 157 **Intervention:** **D1:** Mirtazapine: 49.5 mg **D2:** Venlafaxine: 255.0 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 • DSM-IV melancholic features **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use • ECT within last 3 mos • Suicidal tendencies • Current episode > 12 mos • > 2 previous episodes of major depression that did not respond to AD therapy	**Mean age (yrs):** **D1:** 45.9 **D2:** 44.5 **Sex (% female):** **D1:** 62.8 **D2:** 68.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 29.5 (3.0) **D2:** 29.2 (2.9)	Although not statistically sig, at all assessment times higher percentages of patients treated with MIR were classified as responders (≥ 50% reduction) on HAM-D (at endpoint, 62% vs. 52%) and MADRS (at endpoint: 64% vs. 58%). Likewise were percentages of remitters (HAM-D score ≤ 7; MADRS score ≤ 12) also higher in MIR group Q-LES-Q- estimate of treatment diff (MIR minus VEN) = -3.0, 95% CI: -11.0, 4.9 (*P* = 0.46) QLDS- estimate of treatment diff (MIR minus VEN) = 2.6, 95% CI: -2.1, 7.3 (*P* = 0.289)	**Overall adverse events:** **D1:** 74.4 **D2:** 65.8 **Changes in weight (increase):** **D1:** 10.3 **D2:** 5.1 **Constipation:** **D1:** 3.8 **D2:** 15.2 **Headache:** **D1:** 7.7 **D2:** 11.4 **Nausea:** **D1:** 6.4 **D2:** 10.1 **Somnolence (fatigue):** **D1:** 7.7 **D2:** 5.1 **Sweating (increase):** **D1:** 0 **D2:** 19.0	**Overall attrition rate:** 29.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Haffmans et al., 1996 **Country and setting:** The Netherlands Multicenter **Funding:** Lundbeck	**Research objective:** To evaluate and compare efficacy and tolerability of CIT and FLUV; to determine diff in incidence of gastrointestinal side-effects based on UKU side effects scale **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 217 **Intervention:** **D1:** Citalopram: 20-40 mg/d **D2:** Fluvoxamine: 100-200 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Reasonable knowledge of Dutch language **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Treated with MAOIs or FLUO within last 3 wks	**Mean age (yrs):** **D1:** 44.2 **D2:** 40.2 **Sex (% female):** **D1:** 58 **D2:** 60 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.7 **D2:** 24.5	No diff in mean HAM-D-17 scores after 6 wks Complete Response (HAM-D17) < 7: CIT: 14% FLUV: 8% no sig diff Mean % reduction in score at wk 6: CIT: 33% FLUV: 26% Responders (reduction in score from baseline > 50%): CIT: 30.5%, FLUV: 28.4%	**Diarrhea:** higher incidence for FLUV: +13% (P = 0.026) **Nausea:** higher incidence for FLUV: +16% (P = 0.017)	**Overall attrition rate:** 23% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **Country and setting:** United States University **Funding:** Organon, Inc	**Research objective:** To assess clinical efficacy and safety of "Org 3770" (MIR) and TRA in treatment of elderly outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Age 55+ • Able to complete Zung Self Rating Depression Scale (SDS) • Chloral hydrate (500 mg) at bedtime was permitted **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos of baseline • Suicidal tendencies • Rapid placebo responders (reduction of 20%+ in total HAM-D score)	**Mean age (yrs):** **D1:** 63 **D2:** 61 **D3:** 62 **Sex (% female):** **D1:** 42.9 **D2:** 60.4 **D3:** 59.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.6 **D3:** 23.5	On 21-item HAM-D, diffs between MIR and placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig)	**Cardiovascular adverse events:** **D1:** 2% Tachycardia; 4% Palpitations **D2:** 12% Tachycardia; 12% Palpitations **D3:** 2% Tachycardia; 2% Palpitations **Constipation:** **D1:** 18 **D2:** 24 **D3:** 16 **Dizziness:** **D1:** 22 **D2:** 27 **D3:** 8 **Headache:** **D1:** 14 **D2:** 20 **D3:** 20 **Nausea:** **D1:** 10 **D2:** 14 **D3:** 14 **Somnolence (fatigue):** **D1:** 54 **D2:** 55 **D3:** 22	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hicks et al., 2002 **Country and setting:** UK Outpatient clinic **Funding:** Bristol Myers Squibb	**Research objective:** Compare NEF and PAR for treatment of depression and sleep in patients with mod-severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** **D1:** Nefazodone: 400-600 mg/d **D2:** Paroxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Shift workers • Current sleep disorders	**Mean age (yrs):** **D1:** 42.75 **D2:** 42.95 **Sex (% female):** **D1:** 60 **D2:** 55 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22 **D2:** 22.5	NEF sig increased objective sleep efficiency and total sleep time. Total sleep time for PAR: 388; NEF: 396 (P = 0.05) PAR decreased sleep efficiency in early treatment and some disruption remained at wk 8 % Remission for NEF = 23 PAR = 6% (P = 0.1)	**Constipation:** **D1:** 5 **D2:** 15 **Dizziness:** **D1:** 25 **D2:** 15 **Headache:** **D1:** 50 **D2:** 50 **Sexual dysfunction :** **D1:** 0 **D2:** 20 **Somnolence (fatigue):** **D1:** 40 **D2:** 55 **Suicidality:** **D1:** 0 **D2:** 5 **Sweating (increase):** **D1:** 0 **D2:** 35	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hong et al., 2003 **Country and setting:** Taiwan Multicenter **Funding:** NV Organon, Oss, The Netherlands	**Research objective:** To compare efficacy and tolerability of MIR and FLUO treatment in sample population of Chinese patients with moderate-to-severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 133 **Intervention:** **D1:** Mirtazapine: 15 mg-45 mg/d **D2:** Fluoxetine: 20 mg-40 mg/d	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 • Current episode between 1 wk and 1 yr **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • History of seizures • Epilepsy	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.2 **Sex (% female):** **D1:** 62 **D2:** 64 **Race (% white):** **D1:** 0 **D2:** 0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 23.1	No sig diffs in HAM-D responders (MIR: 58% vs. FLUO: 51%) At day 42, diff in HAM-D remitters (MIR: 35% vs. FLUO: 27%, *P* = NR) MIR had more remitters and responders at all time points; however, no statistical significance in diffs was reached Based on LOCF approach, approximately 50% of subjects in both treatment groups were CGI responders by endpoint Weight increase ≥ 7% in 8 MIR patients Weight decrease ≥ 7% in 2 MIR patients and 2 FLUO patients Mean body weight increase MIR + 1.84 kg FLUO -0.54 kg *P* = 0.0001	**Overall adverse events:** **D1:** 71.2 **D2:** 57.6 **Changes in weight (decrease):** **D2:** 3 **Changes in weight (increase):** **D1:** 13.6 **Constipation:** **D1:** 15.2 **D2:** 9.1 **Dizziness:** **D1:** 19.7 **D2:** 13.6 **Nausea:** **D2:** 12.1 **Somnolence (fatigue):** **D1:** 12.1	**Overall attrition rate:** 39.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Judd et al., 2004 **Country and setting:** United States Multicenter **Funding:** Eli Lilly and Co NIMH grants; Roher fund of University of California, San Diego	**Research objective:** To examine efficacy of FLUO in treatment of outpatients with minor depressive disorder **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 162 **Intervention:** **D1:** Fluoxetine: 10-20 mg/d **D2:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with minor depression according to NIHM Health Diagnostic Interview Schedule • Healthy with normal physical exam and labs **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Clinically sig medical disease • Investigational drug use with no response or adverse reaction • ECT • Suicidal tendencies • MDD • Dysthmymia • Seizure disorder • Severe allergies • Loss of loved one within past yr	**Mean age (yrs):** Overall: 43.5 **Sex (% female):** Overall: 59.3 **Race (% white):** Overall: 90.1 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 11.7 (3.9) **D2:** 11.0 (3.9)	Sig greater improvement on 30-item IDS for FLUO than for placebo (-1.19 vs. -0.61; $P < 0.02$) Statistically greater rate of improvement in FLUO groups than placebo in 30-item IDS scores (z = 2.40, $P < 0.02$), 17-item HAM-D (z = 2.06, $P = 0.04$), and 21-item HAM-D (z = 2.19, $P < 0.03$). GAF score sig greater in FLUO group (z = 2.10, $P < 0.04$). At endpoint, 40.5% (FLUO) vs. 24.1%(placebo) patients were rated as "normal/not at all depressed" on CGI-S (chi sq = 6.63, df = 1, $P = 0.01$)	**Insomnia:** **D1:** 24.7	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper S., 2005 **Country and setting:** Mulitnational Multicenter **Funding:** ACRAF SpA	**Research objective:** To evaluate efficacy and safety of TRA prolonged release vs. PAR in patients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 108 **Intervention:** **D1:** Trazodone: (prolonged release) 150-450 mg/d **D2:** Paroxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D score of 18-24 • MADRS <30 • Depression symptoms at least 1 mo **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT • MDD refractory to treatment • Psychosis or melancholia • High risk of suicide	**Mean age (yrs):** **D1:** 43.5 **D2:** 44.3 **Sex (% female):** **D1:** 58 **D2:** 68 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 21.0 (SE 0.21) **D2:** 20.9 (SE 0.21)	No statistically sig diff in responder rates (95% CI): 87.3% (78.5 - 96.1) in TRA group; 90.6% (82.7 - 98.4) in PAR group. (No *P* value reported) No statistically sig diff in remission rates (95% CI): 69.1% (56.9 - 81.3) in trazodone group; 67.9% (55.4 - 80.5) in PAR group. (No *P* value reported)	**Overall adverse events:** **D1:** 34.5 **D2:** 26.4 **Diarrhea:** **D1:** 0 **D2:** 1.9 **Dizziness:** **D1:** 3.6 **D2:** 1.9 **Headache:** **D1:** 7.3 **D2:** 0 **Insomnia:** **D1:** 5.5 **D2:** 5.7 **Nausea:** **D1:** 1.8 **D2:** 11.3 **Somnolence (fatigue):** **D1:** 1.8 **D2:** 1.9 **Sweating (increase):** **D1:** 0 **D2:** 1.9	**Overall attrition rate:** 4.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper et al., 2005 **Country and setting:** Multinational (11 countries) Multicenter (76 general practice and specialist settings) **Funding:** Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmith-Kline, Organon, Servier	**Research objective:** To compare efficacy and tolerability of ESC in a fixed dose of 10 mg with placebo in elderly patients with MDD, using FLUO at fixed dose of 20 mg as a reference drug **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 518 **Intervention:** **D1:** placebo **D2:** Escitalopram: 10 mg **D3:** Fluoxetine: 20 mg placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Age 65 or more • MADRS of 22-40 • MMSE 22+ **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Current ECT • MADRS score $\geq$ 5 on Item 10 (suicidal thoughts) • Current behavior therapy or psychotherapy • History of severe drug allergy or hypersensitivity • Lack of response to more than one antidepressant treatment (including CIT) during present depressive episode	**Mean age (yrs):** **D1:** 75 **D2:** 75 **D3:** 75 **Sex (% female):** **D1:** 76 **D2:** 75 **D3:** 77 **Race (% white):** **D1:** 100 **D2:** 99 **D3:** 100 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	With LOCF, "responders" (≥ 50% decrease from baseline in MADRS total score) = 46% ESC group, 47% placebo group, 37% FLUO group (all NS). At last assessment (LOCF), "remitters" (MADRS total score ≤ 12): 40% ESC group, 42% placebo group, 30% FLUO group. Diff between placebo and ESC groups NS, but fewer remitters in FLUO vs. placebo groups ($P < 0.05$)	**Overall adverse events:** **D1:** 2.8 **D2:** 9.8 **D3:** 12.2 **Changes in weight (decrease):** **D1:** 1.1 **D2:** 1.2 **D3:** 2.4 **Constipation:** **D1:** 4.4 **D2:** 1.2 **D3:** 4.3 **Diarrhea:** **D1:** 5.0 **D2:** 1.7 **D3:** 4.9 **Dizziness:** **D1:** 0.6 **D2:** 2.9 **D3:** 3.7 **Headache:** **D1:** 8.3 **D2:** 5.2 **D3:** 4.3 **Insomnia:** **D1:** 2.2 **D2:** 2.3 **D3:** 1.8 **Nausea:** **D1:** 1.7 **D2:** 6.9 **D3:** 7.3 **Somnolence (fatigue):** **D1:** 0.6 **D2:** 2.3 **D3:** 0	**Overall attrition rate:** 17.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kavoussi et al., 1997 Goes with Rush et al., 2001 **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome, Inc	**Research objective:** To compare efficacy and safety of BUP SR and SER, and to determine whether baseline anxiety predicts antidepressant response **Duration of study:** 16 wks **Study design:** RCT **Overall study N:** 248 **Intervention:** **D1:** Bupropion: 100-300 mg/d (mean 238 mg/d) **D2:** Sertraline: 50-200 mg/d (mean 114 mg/d)	**Inclusion criteria:** • Adults 18 to 76 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Stable relationship with normal sexual functioning **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Suicidal tendencies • History/current diagnosis of eating disorders • Known predisposition to seizures	**Mean age (yrs):** **D1:** 39 **D2:** 40 **Sex (% female):** **D1:** 48 **D2:** 48 **Race (% white):** **D1:** 93 **D2:** 94 **Baseline (HAM-A):** **D1:** 16.6 (5.2) **D2:** 16.6 (5.2) **Mean HAM-D score at baseline:** **D1:** 24.8 (4.6) **D2:** 24.8 (4.6)	HAM-D-21: similar changes in scores over study (both groups showed 50% improvement in scores), no diffs at any point in study CGI-S and CGI-I scores improved steadily throughout treatment phase	**Diarrhea:** **D1:** 3 **D2:** 22 **Dizziness:** **D1:** 8 **D2:** 5 **Headache:** **D1:** 34 **D2:** 32 **Insomnia:** **D1:** 18 **D2:** 19 **Nausea:** **D1:** 10 **D2:** 30 **Sexual dysfunction :** **D1:** 10 **D2:** 61 **Somnolence (fatigue):** **D1:** 2 **D2:** 13 **Sweating (increase):** **D1:** 2 **D2:** 10	**Overall attrition rate:** 31.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kiev and Feiger, 1997 **Country and setting:** United States Multicenter (2 centers) **Funding:** Solvay Pharmaceuticals, Upjohn	**Research objective:** To compare FLUV and PAR in treatment of outpatients with major depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 60 **Intervention:** **D1:** Fluvoxamine: 50-150 mg/d **D2:** Paroxetine: 20-50 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 20; minimum score of 2 on "depressed mood" item **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Used a drug within 30 days with anticipated major organ toxicity • Participation in previous FLUV studies • Transportation difficulties	**Mean age (yrs):** **D1:** 42.7 **D2:** 39.9 **Sex (% female):** **D1:** 53 **D2:** 53 **Race (% white):** **D1:** 87 **D2:** 93 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.35 **D2:** 24.36	No statistically sig diff between treatment groups for HAM-D depressed mood item or CGI severity of illness item at each wk or at endpoint No statistically sig treatment diffs in HAM-D retardation and cognitive disturbance factors, HAM-A totoal score or SCL-56 CGI-I mean score at endpoint: FLUV: 1.93 PAR: 2.21	**Cardiovascular adverse events:** **D1:** 13 **D2:** 3 **Constipation:** **D1:** 7 **D2:** 13 **Diarrhea:** **D1:** 13 **D2:** 30 **Dizziness:** **D1:** 20 **D2:** 27 **Headache:** **D1:** 40 **D2:** 57 **Insomnia:** **D1:** 30 **D2:** 20 **Nausea:** **D1:** 37 **D2:** 47 **Sexual dysfunction:** **D1:** 7 **D2:** 21 **Somnolence (fatigue):** **D1:** 40 **D2:** 30 **Sweating (increase):** **D1:** 10 **D2:** 33	**Overall attrition rate:** 31% **Overall adverse events:** **D1:** 97 **D2:** 100 **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** United States Primary care (76 physicians) **Funding:** Eli Lilly	**Research objective:** To compare efficacy of PAR, FLUO. and SER in depressed primary care patients **Duration of study:** 9 mos **Study design:** Open-label, randomized trial **Overall study N:** 601 **Intervention:** **D1:** Paroxetine: 20 mg/d **D2:** Fluoxetine: 20 mg/d **D3:** Sertraline: 50 mg/d	**Inclusion criteria:** • Adults 18 or older • Depressive disorder as determined by PCP • Had home telephone **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.1 **D3:** 44.1 **Sex (% female):** **D1:** 76 **D2:** 86 **D3:** 75 **Race (% white):** **D1:** 85 **D2:** 88 **D3:** 79 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	All 3 treatment groups showed sig improvements in depression and other health related QOL domains (social function, work function, physical function) No sig diffs between treatment groups in any of 3 and 9 mos outcome measures Subgroup analysis showed no diffs in treatment effects for patients with MDD and for patients older than 60 yrs Switch rate to other medication: PAR: 22% FLUO: 14% SER: 17%	NR	**Overall attrition rate:** 24.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Leinonen et al., 1999 **Country and setting:** Multinational **Funding:** Clinical research grant from NV Organon, Oss, The Netherlands	**Research objective:** To compare andtidepressant, anxiolytic, and QOL effects of MIR and CIT **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 270 **Intervention:** **D1:** Mirtazapine: 15-60 mg/d **D2:** Citalopram: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 1 to 4 wks • ECT within last 3 mo • Suicidal tendencies • Present depressive episode >12 mos • Non-responders to antidepressant treatment • Fast placebo-responders	**Mean age (yrs):** **D1:** 42.1 **D2:** 41.1 **Sex (% female):** **D1:** 66.9 **D2:** 57.1 **Race (% white):** NR **Baseline (HAM-A):** **D1:** 21.1 **D2:** 20.9 **Mean HAM-D score at baseline:** NR	Responders by CGI criterion = 85.3% (MIR) vs. 88.7% (CIT) (*P* = 0.59) CGI-QOL scale: 77.1% (MIR) vs. 62.4% (CIT) of patients showed any degree of improvement (*P* = 0.039) Q-LES-Q: both groups improved; no statistically sig diff between groups; estimate of treatment diff = -0.01 (95% CI -2.65 to -2.63, *P* = 0.99)	**Changes in weight (increase):** **D1:** 15.3 **D2:** 4.5 **Diarrhea:** **D1:** 2.9 **D2:** 6.0 **Dizziness:** **D1:** 8.8 **D2:** 4.5 **Headache:** **D1:** 9.5 **D2:** 14.3 **Nausea:** **D1:** 10.2 **D2:** 20.2 **Somnolence (fatigue):** **D1:** 8 **D2:** 6 **Sweating (increase):** **D1:** 2.2 **D2:** 15.0	**Overall attrition rate:** 19.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lepola et al., 2003 **Country and setting:** Europe and Canada Primary care **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy and tolerability of ESC compared to CIT and placebo in depression in primary care setting **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 471 **Intervention:** **D1:** Citalopram: 20-40 mg/d (mean 28.4) **D2:** Escitalopram: 10-20 mg/d (mean 14.0) **D3:** placebo	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 43 **D3:** 43 **Sex (% female):** **D1:** 69.4 **D2:** 74.8 **D3:** 72.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Sig more ESC patients responded to treatment at study endpoint on MADRS scale than CIT patients (63.7% vs. 52.6%; *P* = 0.021) Sig more ESC than CIT-treated patients were in remission at endpoint (52.1% vs. 42.8%; *P* < 0.036) ESC was numerically better than CIT at all time points on all 3 efficacy scales Analysis of time to response showed that ESC–treated patients were responders 8.1 days faster than CIT-treated patients	**Overall adverse events:** **D1:** 59.7 **D2:** 69.7 **D3:** 65 **Diarrhea:** **D1:** 3.2 **D2:** 6.5 **D3:** 7.5 **Insomnia:** **D1:** 1.9 **D2:** 6.5 **D3:** 4.4 **Nausea:** **D1:** 9.1 **D2:** 17.4 **D3:** 14.4 **Sexual dysfunction :** **D1:** 0 **D2:** 5.1 (male impotence) **D3:** 0 **Somnolence (fatigue):** **D1:** 1.3 **D2:** 5.2 **D3:** 3.1 **Suicidality:** **D1:** 1.9 **D2:** 7.7 **D3:** 5.6	**Overall attrition rate:** 7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: McPartlin et al., 1998 **Country and setting:** UK Multicenter (43 general practice sites) **Funding:** Wyeth-Ayerst International	**Research objective:** To evaluate efficacy and safety of VEN XR and PAR for treatment of depression in general practice **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 361 **Intervention:** **D1:** Venlafaxine: XR 75 mg/d **D2:** Paroxetine: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Symptoms of depression at least 14 days • Minimum baseline MADRS score of 19 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 30 days • Suicidal tendencies • Hypersensitive to or previous treatment with VEN or PAR	**Mean age (yrs):** **D1:** 45 **D2:** 44 **Sex (% female):** **D1:** 68.3 **D2:** 68.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23 (4) **D2:** 23 (4)	No sig diffs in outcome measures between treatment groups Global response (HAM-D, CGI, MADRS rates were at 76% for both treatment groups Remission rates (6 or less on MADRS) were 48% for VEN XR and 46% for PAR Both treatment groups produced sig improvements on QOL scale without showing diffs between groups	**Overall adverse events:** **D1:** 70 **D2:** 70 **Constipation:** **D1:** 9.9 **D2:** 6.8 **Diarrhea:** **D1:** 4.4 **D2:** 5.1 **Dizziness:** **D1:** 16.6 **D2:** 9.6 **Headache:** **D1:** 8.8 **D2:** 11.9 **Insomnia:** **D1:** 5.5 **D2:** 4.5 **Nausea:** **D1:** 25.4 **D2:** 24.9 **Somnolence (fatigue):** **D1:** 5.5 **D2:** 5.6 **Sweating (increase):** **D1:** 2.2 **D2:** 6.2	**Overall attrition rate:** 27.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Mehtonen et al., 2000 **Country and setting:** Scandinavia Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and safety of SER and VEN in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 147 **Intervention:** **D1:** Venlafaxine: 75-150 mg/d **D2:** Sertraline: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease	**Mean age (yrs):** **D1:** 44.1 **D2:** 41.0 **Sex (% female):** **D1:** 65 **D2:** 67 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.5 (3.5) **D2:** 25.8 (4.5)	Both treatment groups showed sig reductions of MADRS, CGI, and HAM-D scores from baseline to wk 8 Response rates (decrease of 50% on HAM-D) were higher for VEN at wk 6 (74% vs. 59%; $P = 0.04$) and at endpoint (83% vs. 68%; $P = 0.05$) Remission rates (HAM-D < 10) at endpoint were higher for VEN treated group (68% vs. 45%; $P = 0.008$) No sig diffs were noted in response rates on MADRS and CGI scales Remission rates for patients who increased dose was higher for VEN group (67% vs. 36%; $P < 0.05$)	**Diarrhea:** **D1:** 8.0 **D2:** 13.9 **Headache:** **D1:** 28.0 **D2:** 29.2 **Nausea:** **D1:** 36.0 **D2:** 29.2 **Sexual dysfunction :** **D1:** 8.0 **D2:** 5.6 **Somnolence (fatigue):** **D1:** 6.7 **D2:** 11.1 **Sweating (increase):** **D1:** 18.7 **D2:** 11.1	**Overall attrition rate:** 19% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery et al., 2004 **Country and setting:** Mulitnational Primary care **Funding:** H. Lundbeck A/S	**Research objective:** To compare efficacy and tolerability of ESC to VEN XR in primary care patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 293 **Intervention:** **D1:** Escitalopram: 10-20 mg/d (12.1) **D2:** Venlafaxine: 75-150 mg/d (95.2)	**Inclusion criteria:** • Adults 18 to 85 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 49 **D2:** 47 **Sex (% female):** **D1:** 73 **D2:** 71 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 19.9 **D2:** 20.4	Rates of respone and remission-equal numbers in both groups of responders and remitters Endpoint: ESC 77.4% and VEN 79.6% responders ESC 69.9% and VEN. 69.7% remitters	**Overall adverse events:** **D1:** 67 **D2:** 71 **Constipation:** **D1:** 2 **D2:** 6 **Nausea:** **D1:** 17 **D2:** 26 **Sweating (increase):** **D1:** 6 **D2:** 12.5	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Moore et al., 2005 **Country and setting:** France Psychiatric and general practice **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy of ESC vs. CIT in outpatients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 294 (ITT = 280) **Intervention:** **D1:** Escitalopram: 20 mg/d **D2:** Citalopram: 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS of at least 30 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** **D1:** 44.1 **D2:** 46.2 **Sex (% female):** **D1:** 81.7 **D2:** 72 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Responders: (50% decrease in MADRS) ESC 76.1% CIT 61.3 (P = 0.008) Remitters: ESC 56.1% CIT 43.6% (P = 0.04); NNT for remission: 9 MADRS-S ESC -9.9 CIT -8.6 (P < 0.05) CGI-S ESC -2.3 CIT -2.12 (P = 0.65) Overall discontinuation was sig higher in CIT (10.6%) than ESC (4.3%) group (P = 0.005)	**Overall adverse events:** **D1:** 14.8 **D2:** 16.4 **Changes in weight (increase):** **D1:** 1.4 **D2:** 1.3 **Dizziness:** **D1:** 0.7 **D2:** 1.3 **Headache:** **D1:** 4.2 **D2:** 5.3 **Insomnia:** **D1:** 1.4 **D2:** 0.7 **Nausea:** **D1:** 3.5 **D2:** 3.9 **Sexual dysfunction :** **D1:** 0 **D2:** 0.7 **Somnolence (fatigue):** **D1:** 0 **D2:** 2.0	**Overall attrition rate:** 7.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nemeroff et al., 2005 **Country and setting:** United States Multicenter (13 university-affiliated and private research clinics) **Funding:** NR	**Research objective:** To assess relative efficacy and safety of VEN and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 308 **Intervention:** **D1:** Venlafaxine: 75-225 mg/d **D2:** Fluoxetine: 20-60 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Symptoms present for at least 1 mo **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 3 mos • Suicidal tendencies • History of nonresponse to VEN or FLUO • Received VEN within 6 mos	**Mean age (yrs):** **D1:** 40.1 **D2:** 37.9 **D3:** 40.4 **Sex (% female):** **D1:** 65 **D2:** 69 **D3:** 56 **Race (% white):** **D1:** 91 **D2:** 93 **D3:** 92 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.5 (3.2) **D2:** 23.7 (3.2) **D3:** 23.7 (3.3)	Overall diffs among treatment groups on HAM-D did not quite reach statistical significance, although diff between VEN and placebo was statistically sig HAM-D response: VEN: 53% vs. FLUO: 45% (P = 0.034); HAM-D remission rates: VEN: 32% vs. FLUO: 28% (P = 0.25) Fluoxetine was sig more effective than placebo according to CGI and PGI definitions in response only; neither active therapy separated sig from placebo on remission definitions A statistically sig diff observed on only 1 of 5 QOL measures; greater improvement in VEN compared with both FLUO and placebo groups on variable	**Constipation:** **D1:** 10 **D2:** 2 **D3:** 5 **Diarrhea:** **D1:** 9 **D2:** 13 **D3:** 9 **Dizziness:** **D1:** 13 **D2:** 8 **D3:** 3 **Headache:** **D1:** 36 **D2:** 24 **D3:** 33 **Insomnia:** **D1:** 22 **D2:** 15 **D3:** 14 **Nausea:** **D1:** 40 **D2:** 22 **D3:** 8 **Somnolence (fatigue):** **D1:** 10 **D2:** 10 **D3:** 5 **Sweating (increase):** **D1:** 14 **D2:** 4 **D3:** 2	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nemeroff et al., 1995 **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and SER in treatment of depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 95 **Intervention:** **D1:** Sertraline: 50-200 mg/d (137.1) **D2:** Fluvoxamine: 50-150 mg/d (123.8)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • HAM-D depressed mood item of at least 2 • Covi anxiety score less than Raskin score • Minimum score of 8 on Raskin Depression Scale **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Patients itolerant of SSRI side effects	**Mean age (yrs):** **D1:** 41.2 **D2:** 38.5 **Sex (% female):** **D1:** 60.9 **D2:** 61.2 **Race (% white):** **D1:** 84.8 **D2:** 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.15 (2.77) **D2:** 24.57 (3.66)	Both treatment groups resulted in sig improvements of depression scores compared to baseline No sig diff in efficacy between treatment groups	**Overall adverse events:** **D1:** 93.5 **D2:** 85.7 **Diarrhea:** **D1:** 23.9 **D2:** 14.3 **Dizziness:** **D1:** 15.2 **D2:** 12.2 **Headache:** **D1:** 32.6 **D2:** 26.5 **Insomnia:** **D1:** 34.8 **D2:** 26.5 **Nausea:** **D1:** 21.7 **D2:** 30.6 **Sexual dysfunction :** **D1:** 28 **D2:** 10 **Somnolence (fatigue):** **D1:** 17.4 asthenia-13 **D2:** 24.5 asthenia-6.1 **Sweating (increase):** **D1:** 10.9 **D2:** 6.1	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Newhouse et al., 2000 Finkel et al., 1999 **Country and setting:** United States Outpatient **Funding:** NR	**Research objective:** To assess efficacy of SER vs. FLUO on depressive symptoms in patients aged 60 or older and 70 or older **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 75 (n = 236 in full trial, subgroup analysis of 75 patients who were 70 or older) **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 18 • Age ≥ 60 overall; ≥ 70 for subgroup analysis **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Failure to respond to either ECT or adequate antidepressant trials	**Overall/Subgroup** **Mean age (yrs):** **D1:** 68/74 **D2:** 67/75 **Sex (% female):** **D1:** 63/57 **D2:** 51/49 **Race (% white):** **D1:** 96/95 **D2:** 100/100 **Baseline (HAM-A):** **D1:** NR **D2:** NR **Mean HAM-D score at baseline:** **D1:** 25.1/24.2 **D2:** 25.0/25.4	**Overall:** No sig diffs in SER and FLUO on primary efficacy measures Responders: SER: 73% FLUO: 71% Remitters: SER: 45% FLUO: 46% **Sugroup analysis:** Sig more responders in SER group (P = 0.027): 58.5% (SER) vs. 42.4% (FLUO) Psychological Health subscale: SER group improved from 46.0 (9.2) to 51.4 (8.8) and FLUO group improved from 43.0 (7.0) to 45.3 (9.3). No data given on total Q-LES-Q scores	**Overall adverse events:** **D1:** 88/93 **D2:** 89/94 **Nausea:** **D1:** 14.7/16.7 **D2:** 18.6/15.2	**Overall attrition rate:** 32.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Patris et al., 1996 **Country and setting:** France Multicenter (general practices) **Funding:** NR	**Research objective:** To compare CIT with FLUO treatment in patients with unipolar major depression treated in general practice **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 357 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Fluoxetine: 20 mg/d	**Inclusion criteria:** • Adults 18 to 73 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Dysthymia or cyclothmia • MAOI treatment within last 2 wks	**Mean age (yrs):** **D1:** 44 **D2:** 43 **Sex (% female):** **D1:** 79 **D2:** 76 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No diff in mean MADRS at endpoint or in mean change from baseline; mean change: CIT: -20.7 FLUO: -19.4 Responders (reduction in score from baseline > 50%) at endpoint: CIT: 78% FLUO: 76% Remitters (MADRS ≤ 12) at endpoint: CIT: 75% FLUO: 86% (*P* = 0.26)	**Overall adverse events:** **D1:** 50 **D2:** 52 **Changes in weight (decrease):** **D1:** 3.5 **D2:** 8.2 **Constipation:** **D1:** 1.2 **D2:** 3.3 **Diarrhea:** **D1:** 3.5 **D2:** 0 **Headache:** **D1:** 3.5 **D2:** 3.8 **Insomnia:** **D1:** 4.6 **D2:** 5.4 **Nausea:** **D1:** 9.8 **D2:** 7.6	**Overall attrition rate:** 12.6% **ITT analysis:** No **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Perry et al., 1989 **Country and setting:** United States **Funding:** NR	**Research objective:** To compare clinical efficacy of FLUO and TRA in patients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Trazodone: 50-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Duration of illness ≥ 1 mo • Outpatient • Unipolar **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Investigational drug use within last 4 wks • Suicidal tendencies • Hypertensive patient using guanethidine, reserpine, clonidine, or methyldopa	**Mean age (yrs):** **D1:** 42 **D2:** 39 **Sex (% female):** **D1:** Male:female ratio = 9:12 **D2:** Male:female ratio = 10:9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.2 (2.8) **D2:** 23.6 (3.0)	At endpoint no sig diffs in health outcomes between FLUO and TRA	**Overall adverse events:** **D1:** 43% reported 2+ events **D2:** 37% reported 2+ events **Cardiovascular adverse events:** **D1:** 0 **D2:** 11 **Diarrhea:** **D1:** 14 **D2:** 0 **Dizziness:** **D1:** 14 **D2:** 21 **Headache:** **D1:** 29 **D2:** 26 **Nausea:** **D1:** 24 **D2:** 26 **Somnolence (fatigue):** **D1:** 19 **D2:** 37	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rapaport et al., 1996 **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals, Inc.; The Upjohn Company	**Research objective:** To compare efficacy, safety, and tolerance of FLUV and FLUO in a depressed outpatient population **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Fluvoxamine: 100-150 mg; endpoint mean = 101.85 (25.22) **D2:** Fluoxetine: 20-80 mg; endpoint mean = 34.17 (18.84)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Minimum score of 2 on depressed mood item at screening and baseline visits (HAM-D) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies: acute (score of ≥ 21 on Modified Scale for Suicidal Ideation) • Previous treatment with FLUO or FLUV • History of seizure disorder	**Mean age (yrs):** **D1:** 40.0 **D2:** 38.6 **Sex (% female):** **D1:** 62 **D2:** 63.2 **Race (% white):** **D1:** 92.2 **D2:** 98 **Baseline (HAM-A):** **D1:** 16.0 **D2:** 16.2 **Mean HAM-D score at baseline:** **D1:** 25.2 **D2:** 25.6	No statistically sig diffs observed between 2 groups on any efficacy parameter. Medications well tolerated, with only 2 patients in each group terminated because of side effects. FLUV was associated with less nausea than FLUO	**Headache:** **D1:** 50 **D2:** 53 **Insomnia:** **D1:** 36 **D2:** 28 **Nausea:** **D2:** 42.5 **Suicidality:** **D1:** 2 **D2:** 2	**Overall attrition rate:** 16% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ravindran et al., 2000 **Country and setting:** Canada and Europe Multicenter **Funding:** Pfizer, Inc	**Research objective:** To determine safety, tolerability, and efficacy of SER vs. placebo in treatment of dysthymia **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** placebo	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 12 • Dysthymia • Duration ≥ 5 yrs **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** **D1:** 46.0 **D2:** 44.2 **Sex (% female):** **D1:** 65.8 **D2:** 67.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 19.2 (6.98) **D2:** 18.6 (6.62)	Number of responders sig higher in SER group HAM-A: SER: 51.9%, placebo: 33.8% (P = 0.001) MADRS: SER: 53.2%, placebo: 37.5% (P = 0.006) CGI-I: SER: 60.1%, placebo: 39.5%, (P < 0.001) Number of remitters was also sig higher in SER group 33.8% vs. 21.6% (P = 0.02) BQOL showed sig greater improvements in 8 of 9 domains in SER group	**Overall adverse events:** **D1:** 75.3 **D2:** 64.5 **Constipation:** **D1:** 6.3 **D2:** 3.3 **Diarrhea:** **D1:** 12.7 **D2:** 7.2 **Dizziness:** **D1:** 12.7 **D2:** 3.9 **Headache:** **D1:** 30.4 **D2:** 33.6 **Insomnia:** **D1:** 22.2 **D2:** 16.4 **Nausea:** **D1:** 20.9 **D2:** 17.8 **Sexual dysfunction :** **D1:** 9.3 **D2:** 0 **Somnolence (fatigue):** **D1:** 11.4 fatigue-7.0 **D2:** 7.2 fatigue-2.6 **Sweating (increase):** **D1:** 13.9 **D2:** 2	**Overall attrition rate:** 24.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rocca et al., 2005 **Country and setting:** Italy University clinic **Funding:** University of Turin, Italy	**Research objective:** To compare effect of SER and CIT on depression symptoms and cognitive functions in nondemented elderly patients with minor depressive disorder or sybsyndromal depressive symptomatology **Duration of study:** 12 mos **Study design:** Nonrandomized controlled trial **Overall study N:** 138 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Sertraline: 50 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 10 • Nondemented elderly (65 or older) • Minor depressive disorder or subsyndromal depressive disorder according to SCID **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Any other current Axis I or II psychiatric disorder • Impairment and decline of global cognitive functions on MMSE • Score of at least 12 on Alzheimer's Disease Assessment Scale-Cognitive Subscale	**Mean age (yrs):** **D1:** 72.4 **D2:** 71.9 **Sex (% female):** **D1:** 24.2 **D2:** 31.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 12.9 **D2:** 12.9	Both treatments induced a sig, sustained, comparable improvement in depressive symptoms and social functioning Change from baseline to endpoint on HAM-D CIT and SER groups decrease 55% vs. 52.7%; *(P* = NR) or GDS Remission observed at any timepoint between treatment groups 12 mos: 53% vs. 42%; *P* = 0.25 Sig within-group improvements seen in all cognitive measures for both SER and CIT WMS, TMT-A, TMT-B, VF, and MMSE	**Dizziness:** **D1:** 15.2 **D2:** 9.7 **Headache:** **D1:** 10.1 **D2:** 9.7 **Nausea:** **D1:** 24.2 **D2:** 18.1	**Overall attrition rate:** 27.5 **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rossini et al., 2005 **Country and setting:** Italy One inpatient center **Funding:** NR	**Research objective:** To compare efficacy and tolerability of FLUV and SER in elderly patients **Duration of study:** 7 wks (after a 7-day single-blind placebo washout) **Study design:** RCT **Overall study N:** 93 **Intervention:** **D1:** Fluvoxamine: 200 mg/d (100mg twice daily) **D2:** Sertraline: 150 mg/d (75mg twice daily)	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • 59 yrs of age and older • MDD diagnosed by MD using unstructured interviews and medical records according to DSM-IV, and after a best estimate procedure **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • MMSE score <23 • Nonreversible MAOI or slow release neuroleptics within 1 mo of study • Bipolar patients had to be on mood stabilizers • Depression or bipolar disorder due to a medical condition or induced by a substance	**Mean age (yrs):** **D1:** 67.80 **D2:** 68.24 **Sex (% female):** **D1:** 61.5 **D2:** 82.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 31.23 (5.12) **D2:** 29.23 (3.45)	HAM-D: No sig diff in final response rates found between 2 treatment groups, 55.6% (25/45) and 71.8% (28/39) for SER and FLUV (P = 0.12). Repeated-measures analysis of variance on HAM-D scores revealed a sig different decrease of depressive symptoms between 2 treatment groups, favoring FLUV (P = 0.007)	NR	**Overall attrition rate:** 4.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rudolph and Feiger, 1999 **Country and setting:** United States Multicenter (12 outpatient psychiatric practices) **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of efficacy and tolerability of VEN XR to FLUO **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 301 **Intervention:** **D1:** Venlafaxine: XR 75-225 mg/d **D2:** Fluoxetine: 20-60 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Bipolar disorder	**Mean age (yrs):** **D1:** 40 **D2:** 40 **D3:** 40 **Sex (% female):** **D1:** 73 **D2:** 69 **D3:** 64 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25 **D2:** 26 **D3:** 25	No sig diff between VEN and FLUO treatment on 21-HAM-D or MADRS at endpoint in LOCF analysis At wk 8 of LOCF, 57% of VEN group and 50% of FLUO group (P = 0.07) were HAM-D responders At end of treatment 37% of VEN group and 22% of FLUO ($P \leq 0.05$) group were in remission (HAM-D score ≤ 7) At endpoint in LOCF analysis, VEN patients showed a sig diff from placebo in MADRS, CGI, and HAM-D depressed mood item FLUO patients only showed a sig diff in HAM-D depressed mood item	**Changes in weight (decrease):** **D1:** 9 **D2:** 10 **Diarrhea:** **D1:** 14 **D2:** 19 **Dizziness:** **D1:** 26 **D2:** 6 **Nausea:** **D1:** 36 **D2:** 20 **Somnolence (fatigue):** **D1:** 8 **D2:** 12 **Sweating (increase):** **D1:** 10 **D2:** 8	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 1998 **Country and setting:** United States and Canada Multicenter **Funding:** please list name: Seay Center for Research (UT Southwestern), NIMH	**Research objective:** Effect of NEF and FLUO on sleep in patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 125 **Intervention:** **D1:** Nefazodone: 200-500 mg/d (mean = 424) **D2:** Fluoxetine: 20-40 mg/d (mean = 32)	**Inclusion criteria:** • Adults 19 to 55 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 • Concomitant condition: sleep disturbances **Exclusion criteria:** • Pregnant • Lactating • Clinically sig medical disease	**Mean age (yrs):** **D1:** 36 **D2:** 37 **Sex (% female):** **D1:** 59 **D2:** 70 **Race (% white):** **D1:** 78 **D2:** 85 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.9 (2.9) **D2:** 23.3 (2.7)	No diff in efficacy between groups as measured by change in HAM-D17 Response (< 10 on HAM-D17): NEF: 47% FLUO: 45% On EEG: increased sleep efficiency, decreased awakenings and decreased % AMT for NEF as compared to FLUO Also sig diffs on sleep disturbance factors of HAM-D and IDS-C and IDS-SR favoring NEF over FLUO	**Constipation:** **D1:** 17 **D2:** 11 **Diarrhea:** **D1:** 16 **D2:** 26 **Dizziness:** **D1:** 22 **D2:** 8 **Headache:** **D1:** 56 **D2:** 48 **Insomnia:** **D1:** 6 **D2:** 11 **Nausea:** **D1:** 36 **D2:** 25 **Somnolence (fatigue):** **D1:** 22 **D2:** 21	**Overall attrition rate:** 17% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schatzberg et al., 2002 **Country and setting:** United States Mutli-center (recruited from advertising, private practice, routine intake at clinics and other healthcare facilities) **Funding:** Organon Pharmacueticals	**Research objective:** To compare efficacy and tolerability of MIR with PAR in elderly patients with MDD **Duration of study:** 8 wk acute phase, optional 16 wk continuation phase **Study design:** RCT **Overall study N:** 255 **Intervention:** **D1:** Mirtazapine: 15 mg/d up to 45 mg/d **D2:** Paroxetine: 20 mg/d up to 40 mg/d	**Inclusion criteria:** • Adults 65 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 • MMSE above 25% for age and educational level **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicide attempts • MAOIs within 14 days, other psychotropic drugs or herbals within 7 days • PAR or MIR for current depressive episode • Patients requiring drugs for memory deficit • Patients who did not respond to or tolerate MIR or PAR during a previous depressive episode	**Mean age (yrs):** **D1:** 71.7 **D2:** 72.0 **Sex (% female):** **D1:** 50% **D2:** 53% **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.2 (3.5) **D2:** 22.4 (3.5)	CGI-I responders (CGI-I of much or very much improved) At endpoint MIR (80) 64.0% PAR (68) 56.7% chi square 1.23 (*P* = 0.267)	**Overall adverse events:** **D1:** 79.7 **D2:** 82.5 **Changes in weight (increase):** **D1:** 10.9 **D2:** 0 **Constipation:** **D1:** 11.7 **D2:** 11.1 **Diarrhea:** **D1:** 14.8 **D2:** 17.5 **Dizziness:** **D1:** 15.6 **D2:** 14.3 **Headache:** **D1:** 15.6 **D2:** 24.6 **Insomnia:** **D1:** 11.7 **D2:** 11.1 **Nausea:** **D1:** 6.3 **D2:** 19.0 **Somnolence (fatigue):** **D1:** 30.5 **D2:** 29.4 **Sweating (increase):** **D1:** 6.3 **D2:** 13.5	**Overall attrition rate:** 26.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schone and Ludwig, 1993 **Country and setting:** Austria and Germany 6 centers **Funding:** SmithKline, Beecham	**Research objective:** Comparison of efficacy and safety with PAR and FLUO in geriatric outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 108 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 65 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos	**Mean age (yrs):** **D1:** 74.3 **D2:** 73.7 **Sex (% female):** **D1:** 83 **D2:** 90 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diff in mean changes on HAM-D or MADRS HAM-D responders at wk 6 (i.e., reduction > 50% from baseline HAM-D21) sig greater in PAR group than FLUO group MADRS responders at wk 6 (i.e., reduction > 50% from baseline MADRS) sig greater in PAR than FLUO	**Constipation:** **D1:** 5.6 **D2:** 3.8 **Diarrhea:** **D1:** 1.9 **D2:** 11.5 **Dizziness:** **D1:** 7.4 **D2:** 3.8 **Headache:** **D1:** 7.4 **D2:** 5.8 **Insomnia:** **D1:** 9.3 **D2:** 13.5 **Nausea:** **D1:** 9.3 **D2:** 11.5 **Somnolence (fatigue):** **D1:** asthenia 1.9 **D2:** asthenia 7.7 **Sweating (increase):** **D1:** 7.4 **D2:** 7.7	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Sechter et al., 1999 **Country and setting:** France Multicenter (45) **Funding:** Pfizer, Inc	**Research objective:** Comparison of efficacy and safety in patients being treated with SER and FLUO with MDD **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 234 **Intervention:** **D1:** Sertraline: 50-150 (mean = 76.5) **D2:** Fluoxetine: 20-60 (mean = 33.6)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Epilepsy • FLUO or lactose allergy	**Mean age (yrs):** **D1:** 43.4 **D2:** 42.5 **Sex (% female):** **D1:** 66.7 **D2:** 68.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Response was observed in 74% in SER patients vs. 64% in FLUO patients on HAM-D No diff in QOL (SIP)	**Constipation:** **D1:** 1 **D2:** 2 **Diarrhea:** **D1:** 3 **D2:** 2 **Headache:** **D1:** 5 **D2:** 7 **Nausea:** **D1:** 23 **D2:** 17 **Somnolence (fatigue):** **D1:** 5 **D2:** 6	**Overall attrition rate:** 29.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Silverstone and Ravindran, 1999 **Country and setting:** Canada Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of VEN XR and FLUO in outpatients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 368 **Intervention:** **D1:** placebo **D2:** Venlafaxine: 75-225 mg/d (could be increased to 150 mg/d on day 14 and 225 mg/d on day 28) **D3:** Fluoxetine: 20-60 mg/d (could be increased to 40 mg/d on day 14 and 60 mg/d on day 28)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Depression for 1 mo before study **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug • ECT within last 30 days • Suicidal tendencies	**Mean age (yrs):** **D1:** 41.6 **D2:** 41.1 **D3:** 43.2 **Sex (% female):** **D1:** 64 **D2:** 60 **D3:** 57.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 27.6 (5.1) **D2:** 27.0 (4.6) **D3:** 27.1 (4.5)	No statistical comparisons between FLUO and VEN (just placebo) At wk 12 response rates were 67% for VEN and 62% for FLUO ($P < 0.05$) HAM-D scores in VEN and FLUO groups dropped sig when compared with placebo VEN had sig more HAM-A responders at wk 12 than FLUO HAM-D remission rate in VEN group was sig compared to placebo at wks 3, 4, 6, 8, 12 and final HAM-D remission rate in FLUO group was sig compared to placebo at wks 8, 12, and final Patients in VEN group showed a sig decrease in HAM-D and HAM-A scores compared to placebo ($P < 0.05$)	**Changes in weight (decrease):** **D2:** 10 **D3:** 7 **Dizziness:** **D2:** 38 **D3:** 18 **Insomnia:** **D2:** 32 **D3:** 25 **Somnolence (fatigue):** **D2:** 13 **D3:** 14 **Sweating (increase):** **D2:** 10 **D3:** 10	**Overall attrition rate:** 32% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Sir et al., 2005 **Country and setting:** Australia and Turkey Clinics (Turkey 7 and Australia 6) **Funding:** Pfizer, Inc	**Research objective:** Test for diffs between SER and VEN XR on measures of QOL.Test for efficacy diffs on measures of depressive symptoms and tolerability, including discontinuation symptoms **Duration of study:** 8 wks then up to 2 wks discontinuation **Study design:** RCT **Overall study N:** 163 **Intervention:** **D1:** Sertraline: 50-150 mg/d **D2:** Venlafaxine: 75-225 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Non-response to an adequate trial of 2 ADs in current episode	**Mean age (yrs):** **D1:** 37.3 **D2:** 36.8 **Sex (% female):** **D1:** 72.2 **D2:** 66.7 **Race (% white):** **D1:** 96.2 **D2:** 100 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.4 (4.4) **D2:** 23.5 (4.4)	Efficacy: No sig diff exists in terms of efficacy between VEN and SER. HAM-D responders: SER: 70.9% VEN: 70.9% (*P* = 0.95) HAM-D remitters: SER: 59.5% VEN: 54.4% (*P* = 0.47) Discontinuation of SER is associated with fewer discontinuation-emergent symptoms than for discontinuation of VEN Change in Q-LES-Q: SER 16.8 + 1.77 VEN 17.5 + 14.5 (*P* = 0.74)	**Dizziness:** **D1:** 32.9 **D2:** 26.2 **Headache:** **D1:** 44.3 **D2:** 32.1 **Insomnia:** **D1:** 35.4 **D2:** 27.4 **Nausea:** **D1:** 51.9 **D2:** 47.6 **Somnolence (fatigue):** **D1:** 21.5 **D2:** 26.2 **Sweating (increase):** **D1:** 31.6 **D2:** 21.4	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thase et al., 1996 Kocsis et al., 1997 **Country and setting:** United States Multicenter (17 United States centers) **Funding:** NR	**Research objective:** To evaluate safety and efficacy of SER and IMI in treating dysthymia **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 416 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Imipramine: 50-300 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 25 to 65 • Minimum HAM-D score of 12 • Dysthymia • Early onset dysthmia • Duration ≥ 5 yrs • Depression symptom-free mos ≤ 2 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies • Previous nonresponse to at least 2 adequate antidepressant trials • Concurrent MDD	**Mean age (yrs):** **D1:** 42 **D2:** 42 **D3:** 42 **Sex (% female):** **D1:** 65 **D2:** 65 **D3:** 65 **Race (% white):** **D1:** 95 **D2:** 95 **D3:** 95 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 12.7 (4) **D2:** 13.4 (3.8) **D3:** 12.7 (3.9)	SER group showed sig more responders than placebo (59.0% vs. 44.3%; $P < 0.02$) A sig greater proportion of patients in SER group increased in psychosocial functioning compared to placebo (61% vs. 45%; $P = 0.01$) as measured by Global Assessment of Functioning Score of 71 or more Sig improvements in family relationships, marital relationships, and parental role functioning Sig more SER patients than placebo patients were classified as harm avoidance responders ($P = 0.001$)	**Cardiovascular adverse events:** **D1:** 4 **D2:** 9 **D3:** 2 **Constipation:** **D1:** 16 **D2:** 40 **D3:** 9 **Diarrhea:** **D1:** 21 **D2:** 7 **D3:** 10 **Dizziness:** **D1:** 14 **D2:** 28 **D3:** 16 **Headache:** **D1:** 41 **D2:** 39 **D3:** 46 **Insomnia:** **D1:** 24 **D2:** 12 **D3:** 17 **Nausea:** **D1:** 27 **D2:** 26 **D3:** 20 **Somnolence (fatigue):** **D1:** 23 **D2:** 32 **D3:** 12 **Sweating (increase):** **D1:** 12 **D2:** 28 **D3:** 6	**Overall attrition rate:** 24.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tignol, 1993 **Country and setting:** France Multicenter **Funding:** SmithKline Beecham Pharmaceuticals	**Research objective:** To compare PAR and FLUO in treatment of inpatients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 178 **Intervention:** **D1:** Paroxetine: 20 mg **D2:** Fluoxetine: 20 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS total score of 24 or more • Hospital inpatient at screening and for first 2 wks of trial **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 6 mos • ECT within last 3 mos • Suicidal tendencies • Receiving oral anticoagulant • Severe drug allergy/reaction in past	**Mean age (yrs):** **D1:** 43.0 **D2:** 44.7 **Sex (% female):** **D1:** 64 **D2:** 75 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	A reduction of 50% or more in MADRS scores among 75% of PAR and 78% of FLUO patients. MADRS scores fell to ≤ 11 among 67% of PAR and 64% of FLUO patients After 6 wks of treatment, CGI-S scores were 1 or 2 among 78% of PAR and 73% of FLUO patients	**Nausea:** **D1:** 4 **D2:** 10	**Overall attrition rate:** 1.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tylee et al., 1997 **Country and setting:** UK **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN and FLUO in depression treated in general practice **Duration of study:** 12 wks + 7 day post follow-up **Study design:** RCT **Overall study N:** 341 **Intervention:** **D1:** Venlafaxine: 75 mg/d **D2:** Fluoxetine: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Depressive symptoms for more than 2 wks **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • ECT within last 1 mo • Suicidal tendencies	**Mean age (yrs):** **D1:** 43.5 **D2:** 45.5 **Sex (% female):** **D1:** 67.8 **D2:** 74.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MADRS, HAM-D, and CGI scores decreased sig for both treatment groups but there were no sig diffs between treatment groups MADRS, HAM-D, or CGI responders: FLUO: 62.8% VEN: 55.1% (*P* = NR) MADRS remitters (MADRS ≤ 6): FLUO: 34.1% VEN: 35.4% (*P* = NR) No sig diffs in effects on sleep	**Overall adverse events:** **D1:** 80.7 **D2:** 71.8 **Diarrhea:** **D1:** 4.1 **D2:** 6.5 **Dizziness:** **D1:** 11.1 **D2:** 6.5 **Headache:** **D1:** 11.1 **D2:** 17.1 **Nausea:** **D1:** 34.5 **D2:** 18.2 **Somnolence (fatigue):** **D1:** 7.0 **D2:** 4.7 **Sweating (increase):** **D1:** 5.8 **D2:** 1.2	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tzanakaki et al., 2000 **Country and setting:** Greece and Italy Hospitalized and day care **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUO in patients with major depression and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 109 **Intervention:** **D1:** Venlafaxine: 225 mg/d **D2:** Fluoxetine: 60 mg/d	**Inclusion criteria:** • Adults 18 to 64 • Diagnosed with MDD according to DSM-III or -IV • Concomitant condition: melancholia • MADRS ≥ 25 **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 30 days • Suicidal tendencies	**Mean age (yrs):** **D1:** 47 **D2:** 49 **Sex (% female):** **D1:** 75 **D2:** 83 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 27.8 (5.6) **D2:** 27.1 (5.6)	At 6 wks, 70% of patients with VEN and 66% with FLUO had ≥ 50% reduction in MADRS score, and 70% with VEN and 62% with FLUO had a CGI-I score of 1 or 2. A CGI-I score of 1 was observed in 51% of patients with VEN and 32% with FLUO (P = 0.018). Final HAM-D score < 7 was attained in 41% of VEN and 36% of FLUO patients	**Overall adverse events:** **D1:** 49.1 **D2:** 46.3 **Constipation:** **D1:** 7.3 **D2:** 1.9 **Dizziness:** **D1:** 5.5 **D2:** 0 **Headache:** **D1:** 5.5 **D2:** 1.9 **Insomnia:** **D1:** 12.7 **D2:** 1.9 **Nausea:** **D1:** 5.5 **D2:** 14.8 **Sweating (increase):** **D1:** 5.5 **D2:** 3.7	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Van Moffaert et al., 1995 **Country and setting:** Belgium, Multicenter trial (15 psychiatric centers, in- and out-patient) **Funding:** Pfizer	**Research objective:** To evaluate comparative efficacy and tolerability of SER and FLUO in acute and continuation treatment of MDD **Duration of study:** 8 wks acute phase, responders and partial responders could continue in 24 wk continuation phase **Study design:** RCT **Overall study N:** 165 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 80 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal ideation • MADRS score greater than 40 • Concomitant serotonergic drugs (including lithium and carbamazepine)	**Mean age (yrs):** **D1:** 46.1 **D2:** 48.4 **Sex (% female):** **D1:** 66.3 **D2:** 65.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.5 **D2:** 23.2	**ACUTE PHASE** % responders/partial responders at end of acute phase (defined as ≥ 50% reduction in HAM-D or MADRS, or a score ≤ 10 on HAM-D, and much/very much improved on CGI-GI and a CGI-S within nonmental illness range) : SER = 71% FLUO = 77% **CONTINUATION PHASE** Relapse rates SER = 10% FLUO = 13% Response rate (see defintion above) SER = 81% FLUO = 80%	**Overall adverse events:** **D1:** 48 **D2:** 54 **Cardiovascular adverse events:** **D1:** 4 **D2:** 4	**Overall attrition rate:** 17% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: van Moffaert et al., 1995 **Country and setting:** Belgium Psychiatric centers (6 sites) **Funding:** NV Organon	**Research objective:** Safety and efficacy of MIR and TRA in depressed hospital patients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 200 **Intervention:** **D1:** Mirtazapine: 24-72 mg/d **D2:** Trazodone: 150-450 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT • Suicidal tendencies 3 mos • > 6 episodes of depression requiring hospitalization	**Mean age (yrs):** **D1:** 46.1 **D2:** 46.3 **Sex (% female):** **D1:** 69 **D2:** 71 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MIR had sig higher response rates on HAM-D at study endpoint than TRA (61% vs. 51%; *P* < NR) MIR was also more efficacious on other outcome scales (MADRS, Beck, Brief Psychiatric Rating Scale total score, General Psychiatric Impression Global Assessment Scale) but not all diffs reached statistical significance	NR	**Overall attrition rate:** 24.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Vanelle et al., 1997 **Country and setting:** France, Psychiatric centers **Funding:** NR	**Research objective:** To investigate whether FLUO is effective in treatment of dysthymia **Duration of study:** 6 mos (Phase 1 = 3 mos, Phase 2 = 3 mos) **Study design:** RCT **Overall study N:** 140 (randomized) **Intervention:** **D1:** Fluoxetine: 20 mg/d (Phase I), 20-40 mg/d (Phase II) **D2:** placebo	**Inclusion criteria:** • Adults 18 or older • Minimum HAM-D score of 16 • Dysthymia • Dysthymia not secondary to any other axis I disorder **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • MDD, other types of depression • Uncontrolled serious somatic disease • FLUO for depressive disorder which had not been effective • Received a psychotropic drug during previous wk (except for authorized benzodiazepines) • Requiring one of following during study: neuroleptic, lithium, or other mood regulator	**Mean age (yrs):** NR **Sex (% female):** **D1:** 76.9 **D2:** 73.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 20.5 (3.1) **D2:** 20.9 (3.0)	# of responders at mo 3 (>50% decrease in HAM-D associated with a score of 1 (very much improved) or 2 (much improved) on CGI-I), FLUO = 42 placebo = 14 (P = 0.03) Remission n at mo 3 (HAM-D $\leq$ 7), FLUO = 32, placebo = 10 (P = 0.07) # of responders at mo 6: FLUO = 33 placebo = 9 (P = 0.48) Remission n at mo 6: FLUO: 29 placebo: 4 (P = 0.01) Increase in GAF scores by mo 3 sig greater in FLUO (P = 0.02); mean score indicated return to functioning level compatible with normal social and relational life (mean GAF score = 70) No sig change in GAF scores from mo 3 to 6 for either treatment group	**Overall adverse events:** **D1:** 38.5% **D2:** 44.9%	**Overall attrition rate:** 22.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani et al., 2005 **Country and setting:** Multinational, Multicenter (30 sites) **Funding:** Organon, NV	**Research objective:** To compare effectiveness and tolerability of MIR and FLUO in severe MDD and compare effects on anxiety, sleep and QOL **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 **Intervention:** **D1:** Mirtazapine: 30-60 mg **D2:** Fluoxetine: 20-40 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 47 **Sex (% female):** **D1:** 74 **D2:** 69 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 29 (3) **D2:** 28(3)	No sig diff in percent of responders at day 56, (MIR: 40.1% vs. FLUO: 41.4 %) Both treatment groups showed 18 point improvement on QLSQ	**Overall adverse events:** **D1:** 50 **D2:** 45 **Changes in weight (increase):** **D1:** 6.9 **D2:** 1.3 **Dizziness:** **D1:** 9 **D2:** 12.8 **Headache:** **D1:** 19.3 **D2:** 18.8 **Insomnia:** **D1:** 4.8 **D2:** 8.7 **Nausea:** **D1:** 15.9 **D2:** 24.1 **Somnolence (fatigue):** **D1:** 13.8 **D2:** 9.4	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2000 **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and safety of BUP and PAR with PAR in treatment of MDD in elderly **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 10-40 mg/d (22)	**Inclusion criteria:** • Adults 60+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 69.2 **D2:** 71.0 **Sex (% female):** **D1:** 54 **D2:** 60 **Race (% white):** **D1:** 98 **D2:** 90 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in any outcome measures between treatment groups (LOCF and observed) Response rates ≥ 50% reduction in HAM-D) were similar in both groups: BUP SR: 71%, PAR: 77% No sig diffs in Quality of Life scales (QLDS, SF-36) between treatment groups at endpoint; overall sig improvement in QLDS and QOL at day 42 ($P < 0.0001$)	**Constipation:** **D1:** 4 **D2:** 15 **Diarrhea:** **D1:** 6 **D2:** 21 **Dizziness:** **D1:** >10 **D2:** >10 **Headache:** **D1:** 35 **D2:** 19 **Insomnia:** **D1:** >10 **D2:** >10 **Nausea:** **D1:** >10 **D2:** >10 **Somnolence (fatigue):** **D1:** 6 **D2:** 27	**Overall attrition rate:** 16% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weisler et al., 1994 **Country and setting:** Country NR, appears to be United States 2 private psycho-pharmacology clinics **Funding:** Burroughs Wellcome Co	**Research objective:** To compare safety and efficacy of BUP and TRA **Duration of study:** 6 wks (after a 1 wk single-blind placebo lead-in to eliminate placebo responders and placebo nontolerators) **Study design:** RCT **Overall study N:** 124 **Intervention:** **D1:** Bupropion: 225-450 mg/d **D2:** Trazodone: 150-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Episode of at least 4 wks but < 2 yrs • Clinically appropriate for therapy **Exclusion criteria:** • Pregnant/Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Male with history of priapism or being treated with meds associated with priapism • Prior treatment with BUP or TRA, currently taking digoxin or phenytoin	**Mean age (yrs):** **D1:** 40.2 **D2:** 40.8 **Sex (% female):** **D1:** 52.4 **D2:** 65.6 **Race (% white):** **D1:** 90.5 **D2:** 90.2 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.8 **D2:** 25.0	**HAM-D (LOCF)** **Center 1** BUP: at day 42, BUP stat sig better than TRA ($P < 0.01$) When centers combined, no statistically sig diffs between TRA and BUP were observed Responder analysis (responder = > 50% reduction in HAM-D score between baseline and discontinuation) BUP = 33 (55.9%) TRA = 21 (40.4%) Remitters (>50% reduction and a HAM-D score<10) BUP = 27 (46%) TRA = 16 (31%) CGI-I responders BUP = 34 (57.6%) TRA = 24 (46.2%)	**Constipation:** **D1:** 9.68 **D2:** 11.67 **Diarrhea:** **D1:** 4.84 **D2:** 11.67 **Dizziness:** **D1:** 20.97 **D2:** 30.00 **Headache:** **D1:** 33.87 **D2:** 23.33 **Insomnia:** **D1:** 14.52 **D2:** 5.00 **Nausea:** **D1:** 11.29 **D2:** 6.67 **Somnolence (fatigue):** **D1:** 8.06 **D2:** 45.00 **Sweating (increase):** **D1:** 9.68 **D2:** 5.00	**Overall attrition rate:** 40.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Wheatley et al., 1998 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in depressed inpatients and outpatients **Duration of study:** 6 wks (after a 3-7 day single-blind, placebo washout period) **Study design:** RCT **Overall study N:** 133 **Intervention:** **D1:** Mirtazapine: 15-60 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • HAM-D item 1 (depressed mood) score ≥ 2 • Depressive episode duration 2 wks to 12 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Nonresponders to antidepressant treatment	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.5 **Sex (% female):** **D1:** 55 **D2:** 58.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 26.0 (4.4) **D2:** 26.1 (4.3)	HAM-D responders at endpoint (≥ 50% improvment) MIR ~65% (n = 39) FLOU ~45% (n = 28) (*P* = NS) Remission from depression (HAM-D < 7 at endpoint): MIR 23.3% FLUO 25.4% (*P* = 0.39) CGI responders (much or very much approved): MIR 63.3% FLUO 54.0% (*P* = 0.677) Q-LES-Q estimated treatment diff (MIR minus FLUO): 2.14 95% CI (-2.30, 6.58) (*P* = 0.348)	**Dizziness:** **D1:** 7.6% **D2:** 9.0% **Headache:** **D1:** 9.1% **D2:** 17.9% **Nausea:** **D1:** 3.0% **D2:** 10.4% **Somnolence (fatigue):** **D1:** 18.2% **D2:** 13.4%	**Overall attrition rate:** 28.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Williams, 2000 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundations	**Research objective:** To compare effectiveness of PAR vs. placebo vs. behavioral treatment for dysthymia or minor depression in primary care patients older than 60 yrs **Duration of study:** 11 wk **Study design:** RCT **Overall study N:** 415 **Intervention:** **D1:** Paroxetine: 10-40, individually titrated **D2:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 10 • Dysthymia • Age 60+ **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Severe Suicidal tendencies • MMSE <24 • Current depression treatment	**Mean age (yrs):** **D1:** 71 **D2:** 71 **Sex (% female):** **D1:** 39 **D2:** 45 **Race (% white):** **D1:** 82.5 **D2:** 75.7 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Mean decrease in HSCL-D-20: PAR: 0.61 (*P* = 0.05) placebo: 0.40 (*P* = 0.05) Behavior Therapy 0.52 (*P* = 0.05) *P* = 0.004 for PAR vs. placebo PAR only statistically and clinically sig better than placebo for subjects with dysthymia and high baseline mental health function HAM-D results NR for ITT population	**Overall adverse events:** NR	**Overall attrition rate:** 25.1% **TT Analysis:** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Baldomero et al., 2005 **Country and setting:** Spain Psychiatric outpatient centers **Funding:** Wyeth Pharma, S.A	**Research objective:** To compare efficacy of VEN to conventional treatments in patients that failed to tolerate or respond to initial treatment **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 3502 **Intervention:** **D1:** Venlafaxine: 75-225 mg/d **D2:** Conventional txt: Citalopram: 20-40 mg/d Fluoxetine: 20-40 mg/d Mirtazapine: 30-45 mg/d Paroxetine: 20-40 mg/d Sertraline: 50-150 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Adults 18 and over • Minimum HAM-D score > 16 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • ECT within 30 days • MAOI or St. Johns Wort in last 14 days	**Mean age (yrs):** **D1:** 46.6 **D2:** 46.0 **Sex (% female):** **D1:** 72.8 **D2:** 68.9 **Race (% white):** NR **Baseline HAM-A:** **D1:** 22.8 **D2:** 22.2 **Baseline HAM-D:** **D1:** 23.9 (4.9) **D2:** NR	Conventional therapy (pooled): Response 1034(71%) Remission 754(52%) CIT 20-40: Response 209 (71%) Remission 153 (52%) FLUO 20-40: Response 174 (70%) Remission 128 (52%) MIR 30-45: Response 75 (65%) Remission 52 (45%) PAR 20-40: Response 226 (73%) Remission 161 (52%) SER 50-150: Response 197 (71%) Remission 147 (53%) VEN 75-225: Response 1262 (78%) Remission 963 (59%) VEN sig better than conventional therapy on response and remission ($P < 0.001$)	**Overall adverse events:** **D1:** 26.4 **D2:** 28.2 **Cardiovascular adverse events:** **D1:** 3.3 **D2:** 1.1 **Sexual dysfunctional:** **D1:** 8.7 **D2:** 13.6	**Overall attrition rate:** 21.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Claghorn and Feighner, 1993 **Country and setting:** United States, outpatient **Funding:** SmithKline Beecham	**Research objective:** To compare effectiveness of PAR vs. IMI and placebo maintaining antidepressant response up to 1 yr after acute treatment response, and to compare tolerability and safety **Duration of study:** 1 yr **Study design:** 1-yr extension of a 6-wk placebo-controlled trial **Overall study N:** 219 of 717 patients randomized to acute phase continued in double-blind extension **Intervention:** **D1:** Paroxetine: 10-50 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Successful completion of 6-wk trial • Raskin Depression rating of 7+; Raskin score > Covi Anxiety score **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	**Mean age (yrs):** **D1:** 42.2 **D2:** 40.6 **Sex (% female):** **D1:** 60.6 **D2:** 28.3 **Race (% white):** **D1:** 87.2 **D2:** 89.1 **Baseline HAM-A:** NR **Baseline HAM-D (SD):** **D1:** 9.9 **D2:** 8.7	Response rates = 63.8%(PAR) vs. 69.6% (placebo). HAM-D: declined from 26.2 to 9.9 during short-term trial, then stabalized over 1 yr in PAR group; declined from 26.4 to 10.1 during short-term, then to 6.3 at 1 yr in placebo group. CGI-S: 4.2 baseline to 2.0 at 1 yr (PAR) vs. 4.3 baseline to 1.6 at 1 yr (placebo) Relapse rates in responders: PAR 15%, placebo 25%	**Constipation:** **D1:** 19 **Diarrhea:** **D1:** 17 **Dizziness:** **D1:** 15 **Headache:** **D1:** 21 **Insomnia:** **D1:** 20 **Nausea:** **D1:** 16 **Sexual dysfunctional (male ejaculation):** **D1:** 16 **Somnolence (fatigue):** **D1:** 20 **Sweating (increase):** **D1:** 14	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cunningham et al., 1994 **Country and setting:** 5 United States sites and 1 in Montreal, Canada Multicenter **Funding:** Wyeth-Ayerst Research	**Research objective:** To compare efficacy and safety of VEN, TRA, and placebo in outpatients with major depression **Duration of study:** Short-term study: 6 wks Long-term study: 1 yr **Study design:** RCT **Overall study N:** Enrolled: 227 Analyzed: 225 **Intervention:** Average daily doses after titration: **D1:** Venlafaxine: 156-160 mg/d **D2:** Trazodone: 294-300 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Must have major depression symptoms for at least 1 mo prior to initial visit **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 2 yrs • ECT within last 14 days • Suicidial tendencies • No formal psychotherapy allowed during study period	**Mean age (yrs):** Overall: 40.7 **Sex (% female):** Overall: F:M ratio 2:1 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 25.02 **D2:** 24.66 **D3:** 24.41	CGI response rates (score or 1 or 2): VEN 72% TRA 60% placebo 55% (*P* = NR) 30 TRA- and 37 VEN-treated clinical responders (CGI-I score of 1 or 2) were allowed to continue on in long-term phase Relapse rates: TRA 13% VEN, 8% placebo 14% (*P* = NR)	**Overall adverse events:** **D1:** 18 **D2:** 23 **D3:** 4 **Constipation:** **D1:** 22 **D2:** 9 **D3:** 4 **Dizziness:** **D1:** 17 **D2:** 36 **D3:** 5 **Nausea:** **D1:** 44 **D2:** 19 **D3:** 5 **Somnolence (fatigue):** **D1:** 43 **D2:** 61 **D3:** 12 **Sweating (increase):** **D1:** 12 **D2:** 3 **D3:** 1	**Overall attrition rate:** 33.78% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Doogan and Caillard, 1992 **Country and setting:** Multinational (France, Germany, Austria, Switzerland, Great Britain, Ireland), multicenter **Funding:** Pfizer Central Research	**Research objective:** To investigate whether SER could alter course of affective symptoms and episodes in patients who had satisfactory response to acute therapy **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 480 entered single-blind placebo period; 295 entered double-blind therapy **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • History of peptic ulceration • Hypersensitivity or resistance to antidepressant drugs	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 9.4 (6.7) **D2:** 10.2 (6.8)	Statistically sig lower proportion of SER patients relapsed compared to placebo patients (13.0% vs. 45.7%; *P* < 0.001). Protective effect of SER was maintained throughout 44 wks of double-blind portion of study. SER prevents relapse of index episode of depression as well as recurrence of further episodes and has few side effects	**Overall adverse events:** **D1:** 36.8 **D2:** 29.1 **Cardiovascular adverse events:** **D1:** < 1 **D2:** < 1 **Constipation:** **D1:** < 1 **D2:** 1.8 **Diarrhea:** **D1:** 1.1 **D2:** 2.7 **Dizziness:** **D1:** 4.9 **D2:** 5.5 **Headache:** **D1:** 5.9 **D2:** 7.3 **Insomnia:** **D1:** 3.8 **D2:** 4.5 **Nausea:** **D1:** 3.8 **D2:** < 1 **Somnolence (fatigue):** **D1:** 3.2 **D2:** 1.85 **Suicidality:** **D1:** 1 **D2:** 0 **Sweating (increase):** **D1:** 0 **D2:** 0	**Overall attrition rate:** 51.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Feiger et al., 1999 **Country and setting:** United States; outpatient **Funding:** Bristol Meyers Squibb	**Research objective:** To evaluate efficacy of NEF in prevention of relapse during continuation phase treatment of patients with MDD **Duration of study:** 36 wks **Study design:** RCT **Overall study N:** 131 **Intervention:** **D1:** Nefazodone: 400-600 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Must have responded to 16 wks of single-blind NEF treatment (≤ 10 HAMD-D for 2 consecutive visits) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • ECT • MAOI use in past 4 wks	**Mean age (yrs):** **D1:** 40 **D2:** 42.6 **Sex (% female):** **D1:** 72 **D2:** 71 **Race (% white):** **D1:** 94 **D2:** 98 **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 24.4 (0.3) **D2:** 24.2 (0.3)	Kaplan-Meier survival curves show relapse rate sig lower (P = 0.0009) in nefazodone (1.8%) group vs. placebo (18.3%) group Discontinuation due to lack of efficacy 17.3% for NEF and 32.8% for placebo Relative risk of relapse (HAM-D)was sig lower for NEF than placebo overall (0.094; P = 0.003) and stratified by recurrent depression, melancholia, and sex (P < 0.005 for all) Relative risk of relapse based on discontinuation due to lack of efficacy also was sig lower for NEF than placebo (0.445; P = 0.04)	**Changes in weight (increase):** **D1:** +0.6kg **D2:** +0.9kg **Headache:** **D1:** 20 **D2:** 14 **Nausea:** **D1:** 12 **D2:** 8	**Overall attrition rate:** 45% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Gelenberg et al., 2003 **Country and setting:** United States Multiclinic **Funding:** Bristol-Myers-Squibb	**Research objective:** Comparison of nefazodone and placebo in prevention of depression recurrence **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 165 for maintenance phase **Intervention:** **D1:** Nefazodone: 300-600 mg/d (495.2) **D2:** Placebo **D3:** Overall	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidial tendencies	**Mean age (yrs):** **D1:** 44.4 **D2:** 44.1 **D3:** 44.0 **Sex (% female):** **D1:** 69.7 **D2:** 65.5 **D3:** 67.5 **Race (% white):** Overall: 96.5 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	At end of 1 yr, conditional probability of recurrence was 30.3% for NEF-treated patients, compared with 47.5% for placebo-treated patients	**Changes in weight (decrease):** **D1:** 14.1 **D2:** 9.5 **Changes in weight (increase):** **D1:** 4.7 **D2:** 14.3 **Headache:** **D1:** 41.0 **D2:** 32.2 **Insomnia:** **D1:** 17.9 **D2:** 19.5 **Nausea:** **D1:** 10.3 **D2:** 6.9 **Sexual dysfunctional (male ejaculation):** **D1:** 2.6 **D2:** 3.4 **Somnolence (fatigue):** **D1:** 15.4 **D2:** 4.6	**Overall attrition rate:** 50.6% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gilaberte et al., 2001 **Country and setting:** Spain; multicenter (10) **Funding:** Eli Lilly and Co	**Research objective:** To evaluate efficacy and safety of FLUO compared to placebo in maintenance treatment of recurrent unipolar depression **Duration of study:** 1 yr for maintenance (2 yrs total) **Study design:** RCT **Overall study N:** 140 (double-blind maintenance phase) **Intervention:** **D1:** Fluoxetine: 20-40 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • At least one prior depressive episode in last 5 yrs • CGI-S score at least 4 in index episode **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidial tendencies • Previous resistance to pharmacologic treatment	**Mean age (yrs):** **D1:** 44.4 **D2:** 43.8 **Sex (% female):** **D1:** 78.6 **D2:** 78.6 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 2.8 (2.0) **D2:** 3.1 (2.7)	20% recurrence rate with FLUO vs. 40% with placebo (P = 0.010); symptom-free period sig longer for FLUO vs. placebo (295 days vs. 192 days, P = 0.002); mean end-point HAMD sig lower in FLUO vs. placebo (6.5 ± 8.6 vs. 9.9 ± 9.4; P = 0.027)	**Overall adverse events:** **D1:** 62.9 **D2:** 68.6 **Changes in weight (decrease):** **D1:** 11.4 **D2:** 7.1 **Dizziness:** **D1:** 10.0 **D2:** 17.1 **Headache:** **D1:** 20 **D2:** 27.1 **Insomnia:** **D1:** 21.4 **D2:** 14.3 **Nausea:** **D1:** 12.9 **D2:** 12.9	**Overall attrition rate:** 44.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hochstrasser et al., 2001 **Country and setting:** Multinational, multicenter **Funding:** H. Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT vs. placebo in unipolar, recurrent depression following response to treatment with CIT in previous study periods **Duration of study:** 48-77 wks **Study design:** RCT **Overall study N:** (For period III): 269 **Intervention:** **D1:** Citalopram: 20, 40, or 60 mg (3 groups + placebo) **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 • Two or more previous depressive episodes (one within last 5 yrs) **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 days to 8 wks • Suicidial tendencies • MADRS item 10 ≥ 5 • Current depressive episode longer than 6 mos • Family history of bipolar disorder	**Mean age (yrs):** **D1:** 43.8 (9.7) **D2:** 42.4 (11.5) **Sex (% female):** **D1:** 67.4 **D2:** 75 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Time to recurrence was longer in patients taking CIT than in patients taking placebo CIT 24/132 (18.2%); placebo 59/132 (44.7%) ($P < 0.001$). Prophylactic treatment well tolerated. Risk ratio related to recurrence of depression (CIT / placebo) estimated at 0.321 (95% CI: 0.199-0.516). Diff in time to recurrence between CIT and placebo groups statistically sig at all dose levels (log rank test: 20 mg, $P = 0.0043$; 40 mg, $P = 0.0008$; 60 mg, $P = 0.0157$). In Period III of study, AE profile of CIT was comparable to placebo group	**Cardiovascular adverse events:** **D1:** 5.3 **D2:** 2.9 **Diarrhea:** **D1:** 3.8 **D2:** 2.2 **Dizziness:** **D1:** 8.3 **D2:** 16.1 **Headache:** **D1:** 16.7 **D2:** 15.3 **Insomnia:** **D1:** 15.9 **D2:** 14.6 **Nausea:** **D1:** 6.1 **D2:** 10.2 **Somnolence (fatigue):** **D1:** 8.3 **D2:** 7.3 **Sweating (increase):** **D1:** 6.1 **D2:** 8.8	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Keller et al., 1998 Kocsis et al., 2002 **Country and setting:** United States (10) outpatient psychiatric clinics and (2) academic centers **Funding:** Pfizer	**Research objective:** To determine if maintenance therapy with SER can effectively prevent recurrence of depression in patients with chronic major depression or double depression **Duration of study:** 76 wks **Study design:** RCT **Overall study N:** 161 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • MDD with or without dysthymic disorder • Chronic depression defined as depression of at least 2 yrs duration • This was a 3 phase study **Exclusion criteria:** NR	**Mean age (yrs):** **D1:** 40.8 **D2:** 42.4 **Sex (% female):** **D1:** 62 **D2:** 69 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 5.5 (4.2) **D2:** 6.3 (3.7)	Recurrence %: By strict protocol criteria: SER = 6%, placebo = 23% (P = 0.002) By consensus agreement: SER = 26%, placebo = 50% (P = 0.001) Showed first symptoms of recurrence by consensus agreement: SER = 34%, placebo = 60% (P = 0.001) Patients receiving placebo were 2.18 (1.27, 3.74) times as likely to experience reemergence of depression and 4.07 (1.51, 10.95) times as likely to experience depression recurrence as patients taking ser during maintenance therapy, adjusted for pooled study site, type of depression, and randomization strata (P < 0.02 for both outcomes)	**Overall adverse events:** **D1:** 80.5 **Changes in weight (increase):** **D1:** 15.6 **Diarrhea:** **D1:** 15.6 **Dizziness:** **D1:** 11.7 **Headache:** **D1:** 28.6 **Insomnia:** **D1:** 19.5 **Nausea:** **D1:** 13 **Sexual dysfunctional (male ejaculation):** **D1:** 0 **Somnolence (fatigue):** **D1:** 11.7 **Sweating (increase):** **D1:** 15.6	**Overall attrition rate:** 63.4% **ITT Analysis** No, time to event of the full population **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Klysner et al., 2002 **Country and setting:** Denmark Single center study - out patient **Funding:** H.Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT and placebo in elderly patients: to evaluate long-term tolerability of CIT **Duration of study:** 48 wks **Study design:** RCT **Overall study N:** 230 in acute; 172 entered continuation phase; 121 entered maintenance phase **Intervention:** **D1:** Citalopram: 20-40 mg/d **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Adults 65 or older • MADRS score of 22 or greater **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • FLUO within 5 wks • Other antidepressants within 3 days • ECT within last 8 wks • Suicidial tendencies MADRS item 10 ≥ 10 • Severe somatic disorders	**Mean age (yrs):** **D1:** 74 **D2:** 75 **Sex (% female):** **D1:** 82 **D2:** 72 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Nineteen of 60 patients (32%) using CIT and 41 of 61 patients (67%) using placebo had recurrence. Time to recurrence was sig different between CIT- and placebo-patients, in favour of CIT (log-rank test, $P < 0.0001$)	**Overall adverse events:** **D1:** 5.4 **D2:** 12.2 **Diarrhea:** **D1:** 5 **D2:** 4.9 **Dizziness:** **D1:** 1.7 **D2:** 6.6 **Headache:** **D1:** 1.7 **D2:** 6.6 **Insomnia:** **D1:** 0 **D2:** 4.9 **Nausea:** **D1:** 0 **D2:** 3.3 **Sexual dysfunctional:** **D1:** 0 **D2:** 0 **Somnolence (fatigue):** **D1:** 16.7 **D2:** 9.8 **Sweating (increase):** **D1:** 6.7 **D2:** 4.9	**Overall attrition rate:** 76% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lepine et al., 2004 **Country and setting:** France Psychiatric centers (83 sites) **Funding:** Pfizer	**Research objective:** To determine whether SER prevents recurrence of major depressive disorder among patients with recurrent depression who had been treated to remission with medications other than SER **Duration of study:** 20 mos 18 mos double-blind phase **Study design:** RCT **Overall study N:** 299 **Intervention:** **D1:** Sertraline 50 **D2:** Sertraline 100 **D3:** Placebo	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • At least 3 documented episodes in previous 4 yrs • Treated for at least 4 mos, currently in full remission **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** **D1:** 47.3 **D2:** 48.0 **D3:** 45.5 **Sex (% female):** **D1:** 60.0 **D2:** 77.7 **D3:** 73.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Recurrences were sig lower in SER groups compared with placebo (SER, 50 mg: 16 [16.8%] of 95; SER, 100 mg: 16 [17.0%] of 94; placebo: 33 [33.3%] of 99). Patients treated with SER also had sig longer time until recurrence compared with placebo-treated patients	**Overall adverse events:** **D1:** 76 **D2:** 80 **D3:** 71 **Headache:** **D1:** 11.2 **D2:** 7.1 **D3:** 7.8 **Insomnia:** **D1:** 12.2 **D2:** 11.2 **D3:** 12.6 **Nausea:** **D1:** 6.1 **D2:** 10.2 **D3:** 4.9 **Somnolence (fatigue):** **D1:** 6.1 asthenia- 9.2 **D2:** 5.1 asthenia- 10.2 **D2:** 6.8 asthenia-5.8	**Overall attrition rate:** 41.1% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery et al., 2004 **Country and setting:** United States and Europe Psychiatric centers (31 sites) **Funding:** Wyeth Research	**Research objective:** Long-term efficacy and safety of prophylactic VEN treatment in patients with recurrent major depression **Duration of study:** 12 mos double-blind phase **Study design:** RCT **Overall study N:** 235 (ITT = 225) **Intervention:** **D1:** Venlafaxine: 100-200 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Hypersensitivity to VEN • HAM-D score >12 after acute and continuation treatment	**Mean age (yrs):** **D1:** 43.8 **D2:** 43.5 **Sex (% female):** **D1:** 71 **D2:** 67 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Survival analysis determined a 22% cumulative probability of recurrence in VEN-treated patients after 12 mos compared with 55% for placebo group ($P < 0.001$) More than twice as many placebo-treated patients (48%) as VEN-treated patients (21%) discontinued treatment because of lack of efficacy ($P < 0.001$)	**Overall adverse events:** **D1:** TAES- 80 **D2:** TAES- 79 **Diarrhea:** **D1:** 12 **D2:** 7 **Dizziness:** **D1:** 17 **D2:** 25 **Headache:** **D1:** 27 **D2:** 21 **Nausea:** **D1:** 19 **D2:** 14 **Somnolence (fatigue):** **D1:** asthenia-11 **D2:** asthenia-7	**Overall attrition rate:** 63% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Montgomery and Dunbar 1993 **Country and setting:** NR (UK) 5 psychiatric outpatient centers **Funding:** Second author is with SmithKline Beecham NR	**Research objective:** Efficacy of PAR in relapse prevention and prophylaxis of depression **Duration of study:** 1 year **Study design:** RCT **Overall study N:** 135 **Intervention:** **D1**: Paroxetine: 20-30 mg/d **D2**: Placebo	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM III or IV • Minimum HAM-D score of 18 • Recurrence of at least 3 episodes **Exclusion criteria:** • Pregnant • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Neuroleptics	**Mean age (years):** **D1**: 45.9 **D2**: 48.3 **Sex (% female):** **D1**: 79 **D2**: 78 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1**: 5.5 (1.9) **D2**: 5.7 (1.8)	PAR 16% vs. placebo 43% in reappearance of depression ($P < 0.01$) and in time to reappearance ($P < 0.001$) over 1-year study. Sig advantage was seen for PAR 3% vs. placebo 19% in first 4mos in relapse prevention ($P < 0.01$) and in time to relapse ($P < 0.005$), and later period of treatment in preventing recurrence PAR 14% vs. placebo 30% ($P < 0.05$)	**Dizziness** **D1**: 4 Vertigo **Insomnia:** **D1**: 13 **Nausea:** **D1**: 8 **Suicidality:** **D1**: 1 Suicide **Sweating (increase):** **D1**: 5	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery et al., 1993 **Country and setting:** NR Multicenter (18) **Funding:** H Lundbeck A/S employs second author	**Research objective:** A total of 147 patients who had responded in a placebo-controlled study to 6 wks treatment of an episode of DSM-III-R major depression with either 20 mg or 40 mg CIT were randomized double-blind to continue on same dose of CIT or to receive placebo during a 24-wk study of efficacy of CIT in prevention of relapse **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 147 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Citalopram: 40 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS of at least 22 in initial study • Had response to CIT (20 or 40 mg) resulting in MADRS score of 12 or less **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotherapeutic or psychotropic medications • Duration of depression more than 12 mos	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	CIT 20 and 40 mg groups showed a sig advantage in relapse(overall 10.5% ciotalopram 20 8% and CIT 40 12%) compared with placebo (31%) ($P < 0.05$) and in survival analysis of time to relapse ($P = 0.01$ and $P = 0.02$, respectively)	NR	**Overall attrition rate:** 26.5% for reasons other than relapse **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Poirier and Boyer, 1999 **Country and setting:** France inpatients and outpatients **Funding:** Wyeth-Lederle	**Research objective:** To compare efficacy and safety of PAR and VEN in patients with treatment resistant depression **Duration of study:** 4 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Paroxetine: 30-40 mg/d **D2:** Venlafaxine: 200-300 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Depression duration less than 8 mos • For current episode, history of resistance to 2 previous antidepressant treatments, 2nd of which had to have been prescribed by investigator prior to study • Adults 19 to 60 • HAM-D ≥ 18 **Exclusion criteria:** • Pregnant/Lactating • Suicidal tendencies • Illicit drug or alcohol abuse • Concomitant psychotheraputic or psychotropic medications • ECT • Additional mental illnesses or organic mental disorder not related to depression • VEN or PAR during current episode	**Mean age (yrs):** **D1:** 42.5 **D2:** 44.1 **Sex (% female):** **D1:** 73.8 **D2:** 69.4 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 24.6 (3.9) **D2:** 24.5 (4.1)	HAM-D Response: VEN 45% PAR 36% (*P* = 0.07) HAM-D Remission: VEN 37% PAR 18% (*P* = 0.02) Mean change in HAM-D: VEN -11.1 (8.5) PAR -10.2 (6.8) (*P* = 0.55) CGI-I improvement (1 or 2): VEN 73% PAR 84% (*P* = 0.39)	**Overall adverse events:** **D1:** 69 **D2:** 63 **Diarrhea:** **D1:** 2.9 **D2:** 4.2 **Headache:** **D1:** 6.7 **D2:** 4.2 **Insomnia:** **D1:** 4.8 **D2:** 1.0 **Nausea:** **D1:** 14.3 **D2:** 15.6 **Somnolence (fatigue):** **D1:** 2.9 **D2:** 9.4	**Overall attrition rate:** 11.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rapaport et al., 2004 **Country and setting:** United States Multicenters (53 sites) **Funding:** Forest Labs	**Research objective:** Evaluation of efficacy and safety of continuation ESC treatment **Duration of study:** 36 wks **Study design:** RCT **Overall study N:** 274 **Intervention:** **D1:** Escitalopram: 10-20 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 81 • Diagnosed with MDD according to DSM-III or -IV • MADRS of 22 or more **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Suicidial tendencies	**Mean age (yrs):** **D1:** 42.9 **D2:** 41.8 **Sex (% female):** **D1:** 60.2 **D2:** 62.4 **Race (% white):** **D1:** 86.7 **D2:** 84.9 **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 7.7 (4.6) **D2:** 6.6 (4.6) (P < = 0.05)	Time to depression relapse was sig longer (P = 0.013) and cumulative rate of relapse was sig lower in patients who received ESC (26% ESC vs. 40% placebo; hazard ratio = 0.56; P = 0.01). ESC-treated subjects had sig lower depression ratings than placebo-treated patients	**Headache:** **D1:** 8.8 **D2:** 8.6 **Insomnia:** **D1:** 5.5 **D2:** 7.5 **Nausea:** **D1:** 5.5 **D2:** 4.3	**Overall attrition rate:** 55% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Reimherr et al., 1998 **Country and setting:** United States 5 outpatient psychiatric clinics **Funding:** Lilly Research Laboratories	**Research objective:** To determine prospectively optimal length of therapy in long-term, placebo-controlled continuation study of patients who responded to acute FLUO treatment for major depression **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 395 (randomized) **Intervention:** **D1:** Fluoxetine 20 mg/d 14 wks **D2:** Fluoxetine 20 mg/d 38 wks **D3:** Fluoxetine 20 mg/d 50 wks **D4:** Placebo	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Type II bipolar disorder **Exclusion criteria:** • Type I bipolar disorder	**Mean age (yrs):** **D1:** 40.1 **D2:** 40.3 **D3:** 40.3 **D4:** 40.5 **Sex (% female):** **D1:** 64.9 **D2:** 70 **D3:** 62.7 **D4:** 80.2 **Race (% white):** **D1:** 97.9 **D2:** 96 **D3:** 93.1 **D4:** 87.5 **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 20.5 (3.4) **D2:** 20.5 (3.6) **D3:** 20.5 (3.6) **D4:** 21.5 (3.7)	Relapse rates lower among patients who continued to take FLUO compared with those transferred to placebo in both first interval, after 24 total wks of treatment (FLUO, 26.4%; placebo, 48.6%, $P < 0.001$), and second interval, after 38 total wks of treatment (FLUO, 9.0%; placebo, 23.2% $P < 0.04$) In third interval, after 62 total wks of treatment, rates were not sig different between groups (FLUO, 10.7%; placebo, 16.2% $P = 0.54$)	NR	**Overall attrition rate:** N/A **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating

Author: Robert et al., 1995
 	
Country and setting: France, multicenter outpatient trial
 	
Funding: NR
	Research objective: To evaluate whether there was therapeutic benefit in continuation treatment for patients with depression who had responded favorably to CIT
	
	Duration of study: 6 mos (24 wks)
	
	Study design: RCT
	
	Overall study N: 226
	
	Intervention:
	D1: Citalopram: 20-60 mg/d
	D2: Placebo
		Inclusion criteria:
		• Diagnosed with MDD according to DSM-III or -IV
		• MADRS < 12 after 8 wks on CITor placebo
		
		Exclusion criteria:
		• Concomitant psychotheraputic or psychotropic medications
		• Depression lasted for >3 mos
			Mean age (yrs):
			D1: 49.5
			D2: 46.5
			
			Sex (% female):
			D1: 69%
			D2: 73%
			
			Race (% white):
			NR
			
			Baseline HAM-A:
			NR
			
			Baseline HAM-D:
			D1: 4.7 (3.6)
			D2: 5 (3.4)
				# relapses (defined as a MADRS>25 and clinical judgment of investigator):
				CIT = 21 (13.8%)
				placebo = 18 (24.3%)
				P = 0.04
					Constipation:
					D1: 15
					D2: 5
						Overall attrition rate:
						N/A
						
						ITT Analysis
						Yes
						
						Quality rating:
						Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 2006 **Country and setting:** United States Primary and psychiatric public and private practices **Funding:** NIMH	**Research objective:** To compare remission rates among three antidepressants in patients with major depressive disorder that did not respond or tolerate an SSRI (CIT) **Duration of study:** 14 wks **Study design:** RCT **Overall study N:** 727 **Intervention:** **D1:** Bupropion: SR 150-400 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Venlafaxine: XR 37.5-375 mg/d	**Inclusion criteria:** • Adults 18 and over • QIDS-C-16 > 5 **Exclusion criteria:** • NR	**Mean age (yrs):** **D1:** 41.9 **D2:** 42.6 **D3:** 41.1 **Sex (% female):** **D1:** 56.9 **D2:** 55.0 **D3:** 64.0 **Race (% white):** **D1:** 74.9 **D2:** 78.2 **D3:** 74.4 **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 18.5 (7.7) **D2:** 19.3 (6.9) **D3:** 18.9 (7.3)	HAM-D Remission at end of study: • BUP 21.3% • SER 17.6% • VEN XR 24.8% (*P* = 0.16) QIDS-SR-16 Remission: • BUP 25.5% • SER 26.6% • VEN XR 25.0% (*P* = NR; ns) QIDS-SR-16 Response: • BUP 26.1% • SER 26.7% • VEN XR 25.0% (*P* = NR; ns)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Good Effectiveness trial

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schmidt et al., 2000 Dinan et al and Schmidt et al. 2002 and 2001 **Country and setting:** United States Multicenter **Funding:** Eli Lilly	**Research objective:** To assess efficacy of FLUO 20 mg daily vs. FLUO 90 mg wkly vs. placebo in continuation treatment of MDD **Duration of study:** 25 wks **Study design:** RCT **Overall study N:** 501 **Intervention:** **D1:** Fluoxetine 90 mg/wk **D2:** Fluoxetine 20 mg/wk **D3:** Placebo	**Inclusion criteria:** • Minimum HAM-D score of 18 • Diagnosed with MDD according to DSM-III or -IV • Adults 18 or older • CGI-S > 4 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	**Mean age (yrs):** **D1:** 40.9 **D2:** 41.7 **D3:** 42 **Sex (% female):** **D1:** 68.4 **D2:** 70.9 **D3:** 63.9 **Race (% white):** **D1:** 91.6 **D2:** 86.8 **D3:** 91.0 **Baseline HAM-A:** NR **Mean HAM-D score at baseline:** NR	Relapse rates 25 wks: • FLUO 90 37% • FLUO 20 26% • placebo 50%	**Diarrhea:** **D1:** 8.4 **D2:** 1.6 **D3:** 4.9 **Dizziness:** **D1:** 5.3 **D2:** 5.8 **D3:** 4.9 **Headache:** **D1:** 10.5 **D2:** 12.2 **D3:** 9.0 **Insomnia:** **D1:** 7.4 **D2:** 5.3 **D3:** 4.1 **Nausea:** **D1:** 6.3 **D2:** 4.2 **D3:** 7.4 **Somnolence (fatigue):** **D1:** 8.4 **D2:** 10.6 **D3:** 8.2	**Overall attrition rate:** NA **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Simon et. al., 2004 **Country and setting:** United States Multicenter study **Funding:** Wyeth	**Research objective:** To evaluate efficacy of VEN XR in prevention of relapse of depression by continuation treatment **Duration of study:** 8 wk acute phase; 6 mo continuation phase **Study design:** RCT **Overall study N:** 318 entered relapse prevention study (490 in acute phase) **Intervention:** **D1:** Venlafaxine XR 75-225 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of >20 • No greater than 20% decrease in HAM D between evaluations **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Investigational drug use • Suicidial tendencies • Seizure • Antipsychotic medication • FLUO within 30 days	**Mean age (yrs):** **D1:** 43 **D2:** 41 **Sex (% female):** **D1:** 102 (66%) **D2:** 86 (62%) **Race (% white):** NR **Baseline HAM-A:** NA **Baseline HAM-D:** **D1:** 6.5 **D2:** 6.4	HAM-D-6.4 (at day 56) placebo 6.5 (at day 56) VEN XR MADRS-7.2 (56 day) placebo 7.4 (day 56) VEN XR 6-mo relapse rates were sig higher for placebo (52%) than for VEN XR (28%) ($P < 0.001$)	**Overall adverse events:** **D1:** 97% **D2:** 93% **Cardiovascular adverse events:** **D1:** 6% **D2:** 2% **Constipation:** **D1:** 7% **D2:** 3% **Sexual dysfunctional:** **D1:** 5% **D2:** 2% **Sweating (increase):** **D1:** 11% **D2:** 5%	**Overall attrition rate:** 62% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Terra and Montgomery, 1998 **Country and setting:** France Multicenter, outpatient **Funding:** NR	**Research objective:** To evaluate efficacy of FLUV in reducing risk of new episodes of depression **Duration of study:** 1 yr **Study design:** RCT **Overall study N:** 204 (number enrolled in double-blind prophylactic treatment phase) **Intervention:** **D1:** Fluvoxamine: 100 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Acute phase:, MADRS>25 • History of at least 2 episodes of major depression in previous 5 yrs **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications, but benzos and hypnotics were also allowed during acute/continuation phases if started more than 3 mos before start • Clinically sig medical disease • ECT within last 2 wks • Epilepsy or history of convulsions, • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** **D1:** 44.5 **D2:** 45.0 **Sex (% female):** **D1:** 70 **D2:** 77.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Incidence of recurrence was lower in FLUV (12.7%) than placebo (35.1%) ($P < 0.001$) Highly sig diff between FLUV and placebo in distribution of time to recurrence ($P < 0.001$). time to recurrence sig longer for FLUV and placebo (181 vs. 96 days, $P < 0.005$)	**Changes in weight (decrease):** **D1:** 1 **Headache:** **D1:** 5 **Sexual dysfunctional:** **D1:** 0 **Somnolence (fatigue):** **D1:** 4	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thase et al., 2001 **Country and setting:** United States Multicenter (12) Outpatient **Funding:** Organon Inc	**Research objective:** Evaluate efficacy and safety of mirazapine in continuation phase therapy **Duration of study:** Acute Phase- 8-12 wks Continuation Phase- up to 40 wks **Study design:** RCT **Overall study N:** 410 for open-label; 156 randomized to continuation treatment **Intervention:** **D1:** Mirtazapine: 15-45 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 and up • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use	**Mean age (yrs):** **D1:** 40.1 **D2:** 40.7 **Sex (% female):** **D1:** 52.6 **D2:** 48.8 **Race (% white):** **D1:** 93.4 **D2:** 86.3 **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 5.0 (4.0) **D2:** 7.7 (6.7)	Relapse rates during 40-wk double blind continuation phase were 19.7% for MIR and 43.8% for placebo ($P < 0.001$) Between group diff in distribution of relapse risk over time was statistically sig ($P < 0.001$) Mean HAM-D for MIR was 6.1(7.2) and for placebo 10.7(8.8)	**Overall adverse events:** **D1:** 36 **D2:** 30 **Cardiovascular adverse events:** **D1:** 21 **D2:** 23 **Changes in weight (increase):** **D1:** 7.9 **D2:** 7.3 **Dizziness:** **D1:** 3 **D2:** 4 **Headache:** **D1:** 12 **D2:** 16 **Somnolence (fatigue):** **D1:** 4 **D2:** 1	**Overall attrition rate:** 46% in acute phase 11.8% in continuation phase **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Van Moffaert et al., 1995 **Country and setting:** Belgium, multicenter trial (15 psychiatric centers, in- and out-patient) **Funding:** Pfizer	**Research objective:** To evaluate comparative efficacy and tolerability of SER and FLUO in acute and continuation treatment of MDD **Duration of study:** 8 wks acute phase, responders and partial responders could continue in 24 wk continuation phase **Study design:** RCT **Overall study N:** Acute 165 Continuation 105 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 80 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidial ideation • MADRS score greater than 40 • History of mania, hypomania or psychosis • Concomitant serotonergic drugs (including lithium and carbamazepine	**Mean age (yrs):** **D1:** 46.1 **D2:** 48.4 **Sex (% female):** **D1:** 66.3 **D2:** 65.9 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 24.5 **D2:** 23.2	Relapse during 32 wk continuation SER 10/49 (20%) FLUO 13/53 (23%) Partial relapse during 32 wk continuation SER 6/49 (12%) FLUO 2/53 (4%)	**Overall adverse events:** **D1:** 48 **D2:** 54 **Cardiovascular adverse events:** **D1:** 4 **D2:** 4	**Overall attrition rate:** 17% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2002 **Country and setting:** United States outpatient, mulitcenter **Funding:** GlaxoSmithKline	**Research objective:** To evaluate safety and efficacy of BUP SR for decreasing risk for relpase of depression in patients who responded to BUP SR **Duration of study:** Up to one yr (52 wks) **Study design:** RCT **Overall study N:** 828 in open label phase; 423 entered double-blind phase **Intervention:** **D1:** Bupropion: 300 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 18 and older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use • Suicidial tendencies • Propensity for seizures	**Mean age (yrs):** **D1:** 39.4 **D2:** 39.9 **Sex (% female):** **D1:** 66 **D2:** 64 **Race (% white):** **D1:** 88 **D2:** 86 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	423 patients were randomized to continuation treatment A statistically sig diff in favor of BUP SR (37% relapse) over placebo (52% relapse) was seen in time to treatment intervention for depression when survival curves were compared (log-rank test, $P = 0.004$) Statistically sig separation between BUP SR and palcebo began at double-blind wk 12 ($P < 0.05$) AEs in BUP SR-treated patients accounted for 9% and 4% of discontinuations from open-label and double-blind phases, respectively	**Overall adverse events:** **D1:** 54 **D2:** 46 **Cardiovascular adverse events:** **D1:** mean sbp -1.1 **D2:** Mean sbp +2.1 **Changes in weight (decrease):** **D1:** -2.5 lbs **D2:** 0 **Constipation:** **D1:** 1 **D2:** 1 **Diarrhea:** **D1:** 1 **D2:** 5 **Dizziness:** **D1:** 1 **D2:** 3 **Headache:** **D1:** 16 **D2:** 13 **Insomnia:** **D1:** 3 **D2:** 3 **Nausea:** **D1:** 4 **D2:** 2	**Overall attrition rate:** 75.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Wilson et al., 2003 **Country and setting:** UK, outpatient clinic(s) **Funding:** NR	**Research objective:** To examine efficacy of SER in preventing recurrence of depression in older people living in community **Duration of study:** 8 wk treatment phase and a 16-20 wk continuation phase (open-label ser) 100 wk randomized, double-blind phase (ser and placebo) (article focuses on results of this maintenance phase) **Study design:** RCT **Overall study N:** 113 (randomised to double-blind phase) **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 65 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Geriatric Mental State AGECAT depression ≥ 3 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Sig suicidal or delusional experiences • MMSE ≤ 11 • Concomitant drugs excluded include psychotropic drugs, warfarin, and anticonvulsants	**Mean age (yrs):** **D1:** 76.6 **D2:** 76.8 **Sex (% female):** **D1:** 66.1 **D2:** 75.4 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 20.7 (3.7) **D2:** 20.3 (3.3)	ANALYSIS OF RECURRENCE Kaplan Meier analysis, SER vs placebo, log rank test = 1.55, df = 1, (*P* = 0.21) Cumulative survival function SER = 39%, median survival 92 wks placebo 31%, median survival 48 wks Reduction in risk of recurrence: 8.4% over 100 wks (SER vs. placebo) % experiencing recurrence in first 26 wks: SER = 57% placebo = 60% % experiencing recurrence between wks 27 and 52 SER = 16% placebo = 32% Cox regression model predicting recurrence: hazard ratio (95% CI) included variables: SER vs. placebo = 1.21 (0.704, 2.082)	NR	**Overall attrition rate:** 72.6% **ITT Analysis** N/A because recurrence trial **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Baldwin et al., 1996 **Country and setting:** Europe, multicenter (20 psychiatric clinics) **Funding:** Bristol-Myers Squibb	**Research objective:** To compare efficacy of NEF and PAR for treatment of moderate-severe major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 206 randomized; 196 included in analysis **Intervention:** **D1:** Nefazodone 200-600 mg/d (mean 472) **D2:** Paroxetine 20-40 mg/d (mean 32.7)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-17 score of 18 • Rated at least moderately ill on CGI-S **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • ECT within 6 mos • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Pregnant or lactating • Suicidal (serious risk) • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 38.3 **D2:** 37.9 **Sex (% female):** **D1:** 60 **D2:** 50 **Race (% white):** **D1:** NR **D2:** NR **Baseline HAM-D-17:** **D1:** 24.6 **D2:** 24.8 **Baseline HAM-A:** **D1:** 19 **D2:** 18.3	**Anxiety outcomes:** Improvement in HAM-A score was 6.5 for NEF vs. 8.0 for PAR (95% CI for diff between groups: -0.7 to 3.8)	**Overall adverse events:** **D1:** 84 **D2:** 78 **Dizziness:** **D1:** 17 **D2:** 9 **Headache:** **D1:** 35 **D2:** 25 **Nausea:** **D1:** 27 **D2:** 30 **Somnolence:** **D1:** 16 **D2:** 24	**Overall attrition rate:** 23.1% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Beasley et al., 1991 **Country and setting:** United States, multicenter (3 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare FLUO and TRA for treatment of major depression and to evaluate activation and sedation effects **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 126 randomized; 120 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d (median 20 mg/d) **D2:** Trazodone 50-400 mg/d (median 250 mg/d)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III • Minimum HAM-D-21 score of 20 • Duration at least 4 wks **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • Substance abuse (within one yr) • Placebo response during lead-in	**Mean age (yrs):** **D1:** 40.0 **D2:** 40.0 **Sex (% female):** **D1:** 64.6 **D2:** 68.8 **Race (% white):** **D1:** 98.5 **D2:** 98.4 **Baseline HAM-D-21:** **D1:** 23.4 (2.7) **D2:** 24.3 (3.6) **Baseline HAM-D Sleep Factor:** **D1:** 3.8 (1.7) **D2:** 3.8 (1.8) **Baseline HAM-A:** NR	**Sleep outcomes** Improvement in HAM-D Sleep Disturbance Factor was 1.6 points in FLUO-treated group vs. 2.7 points in TRA group (P = 0.001)	**Diarrhea:** **D1:** 7.7 **D2:** 3.3 **Dizziness:** **D1:** 6.2 **D2:** 21.3 **Headache:** **D1:** 21.5 **D2:** 27.9 **Insomnia:** **D1:** 9.2 **D2:** 3.3 **Nausea:** **D1:** 27.7 **D2:** 24.6 **Somnolence:** **D1:** 20.0 **D2:** 45.9 **Sweating (increase):** **D1:** 4.6 **D2:** 0	**Overall attrition rate:** 34.1% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Brannan et al., 2005 **Country and setting:** United States, multicenter (25 psychiatry clinics) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL for treatment of pain and depression in patients with major depression and painful physical symptoms **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 282 randomized; 268 included in analysis **Intervention:** **D1:** Duloxetine 60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S of 4 or more • BPI average pain score of 2 or more **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance abuse or dependence • Clinically sig medical disease • Suicidal (serious risk) • Primary pain disorder with diagnosis such as arthritis, migraine, or fibromyalgia • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 40.8 **D2:** 40.3 **Sex (% female):** **D1:** 68.1 **D2:** 62.4 **Race (% white):** **D1:** 81.6 **D2:** 79.4 **Baseline HAM-D-17:** **D1:** 23.4 (3.5) **D2:** 22.4 (3.4) **BPI average pain:** **D1:** 4.85 (1.69) **D2:** 4.62 (1.54) **Baseline 100mm VAS (overall pain):** **D1:** 49.8 (22.2) **D2:** 46.8 (19.7) **Baseline HAM-A:** NR	**Depression outcomes in patients with pain:** Mean HAM-D-17 improvement was similar for both groups (-10.9 for DUL vs. -10.3 for placebo, $P = 0.544$). Response rates were similar for DUL and placebo (42% vs. 40%, $P = 0.901$). Remission rates were also similar (23% vs. 24%, $P = 0.887$) **Pain outcomes:** Mean reduction in BPI average pain was 2.32 (0.21) for DUL-treated patients compared to 1.80 (0.20) for those receiving placebo ($P = 0.066$). Mean changes in BPI worst pain, least pain, and current pain did not differ between groups ($P > 0.10$ for all). Mean changes in VAS overall pain did not differ between groups (values NR and P = NR)	**Cardiovascular adverse events (high systolic BP):** **D1:** 4.1 **D2:** 4.1 **(high diastolic BP):** **D1:** 1.6 **D2:** 5.5 **Changes in weight (decrease):** **D1:** 7.1 **D2:** 0.7 **Constipation:** **D1:** 9.2 **D2:** 6.4 **Diarrhea:** **D1:** 17.7 **D2:** 10.6 **Dizziness:** **D1:** 9.9 **D2:** 5.7 **Headache:** **D1:** 14.2 **D2:** 13.5 **Insomnia:** **D1:** 10.6 **D2:** 6.4 **Nausea:** **D1:** 39.7 **D2:** 9.9 **Fatigue:** **D1:** 16.3 **D2:** 1.4	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Chouinard et al., 1999 **Country and setting:** Canada, multicenter (8 sites) **Funding:** SmithKline Beecham	**Research objective:** To evaluate antidepressant and anxiolytic efficacy of FLUO and PAR in patients with major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 randomized; 198 included in analysis **Intervention:** **D1:** Fluoxetine 20-80 mg/d (mean 27.5) **D2:** Paroxetine 20-50 mg/d (mean 25.5)	**Inclusion criteria:** • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 20 and score of 2 on HAM-D item 1 • Depression symptoms for at least 1 mo **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • ECT within 2 mos • Concurrent formal psychotherapy • Illicit drug or alcohol abuse (past or present) • Suicidal (sig risk) • Pregnant or lactating • Clinically sig medical disease	**Mean age (yrs):** **D1:** 41.2 **D2:** 40.6 **Sex (% female):** **D1:** 59.4 **D2:** 63.7 **Race (% white):** **D1:** 98.0 **D2:** 95.1 **Baseline HAM-D-21:** **D1:** 25.45 (0.46) **D2:** 25.91 (0.46) **Baseline HAM-A:** NR	**Anxiety outcomes** Improvements in Covi Anxiety Scale, State-Trait Anxiety Inventory, and HAM-D Anxiety/Somatization Factor were similar in 2 treatment groups (scores NR; *P* = NR) Mean improvement from baseline in HAM-D Psychic Anxiety item was 1.21 for FLUO and 1.17 for PAR (*P* = 0.823). Improvement from baseline in HAM-D Agitation item was 0.39 for FLUO and 0.40 for PAR (*P* = 0.978)	**Changes in weight (decrease):** **D1:** 11.9 **D2:** 2.9 **(increase):** **D1:** 13.9 **D2:** 10.8 **Constipation:** **D1:** 4.0 **D2:** 17.7 **Diarrhea:** **D1:** 18.8 **D2:** 11.8 **Headache:** **D1:** 36.6 **D2:** 36.3 **Insomnia:** **D1:** 22.8 **D2:** 26.5 **Nausea:** **D1:** 31.7 **D2:** 37.3 **Sexual dysfunction:** **D1:** 7.3 of males **D2:** 10.8 of males **Somnolence:** **D1:** 16.8 **D2:** 18.6 **Suicidality:** **D1:** 2.0 **D2:** 2.0 **Sweating (increase):** **D1:** 5.9 **D2:** 13.7	**Overall attrition rate:** 36% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Clerc et al., 1994 **Country and setting:** France and Belgium, multicenter (hospitals) **Funding:** Wyeth-Ayerst	**Research objective:** To compare efficacy and short-term safety of VEN and FLUO in hospitalized patients with MDD and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 68 **Intervention:** **D1:** Fluoxetine 40 mg/d **D2:** Venlafaxine 200 mg/d	**Inclusion criteria:** • Adults 18 or older • Hospitalized patients • MDD with melancholia according to DSM-III-R • Depression duration at least 1 mo • MADRS at least 25 **Exclusion criteria:** • Clinically sig medical disease • Concurrent ECT • Concurrent psychotherapy	**Mean age (yrs):** **D1:** 53.6 **D2:** 49.0 **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 29.7 (4.2) **D2:** 29.1 (5.2) **Baseline HAM-A:** NR	**Depression outcomes in patients with melancholia:** Mean decrease in HAM-D score was sig better for VEN (-18) compared to FLUO (-12.4) (*P* = 0.027) HAM-D response rates were 73% in VEN-treated group compared to 50% in FLUO-treated group. Diff not statistically sig (*P* = NR)	**Headache:** **D1:** 9 **D2:** 3 **Insomnia:** **D1:** 9 **D2:** 9 **Nausea:** **D1:** 12 **D2:** 9	**Overall attrition rate:** 23% **ITT Analysis** Yes **Quality rating:** Poor High differential attrition

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cunningham et al., 1994 **Country and setting:** United States and Canada, multicenter (6 sites) **Funding:** Wyeth-Ayerst	**Research objective:** To compare efficacy and safety of TRA, VEN, and placebo in outpatients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 227 randomized; 225 included in analysis **Intervention:** **D1:** Trazodone 150-400 mg/d **D2:** Venlafaxine 75-200 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 20 • Depression duration at least 1 mo **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • Drug or alcohol dependence (within 2 yrs) • ECT within 14 days • Investigational drug use within 2 yrs • Suicidal (serious risk) • Pregnant, lactating, or child-bearing potential without contraception • Unstable medical disease • History of seizure disorder • Placebo response during washout (20% improvement on HAM-D)	**Mean age (yrs):** Overall: 40.7 **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 24.66 **D2:** 25.02 **D3:** 24.41 **Baseline HAM-D Sleep Factor:** **D1:** 3.60 **D2:** 3.52 **D3:** 3.20 **Baseline HAM-A:** NR	**Sleep outcomes** HAM-D Sleep Factor scores at endpoint were sig better for TRA (1.42) than for VEN (2.22; $P < 0.05$) and placebo (1.95; $P < 0.05$)	**Constipation:** **D1:** 9 **D2:** 22 **D3:** 4 **Dizziness:** **D1:** 36 **D2:** 17 **D3:** 5 **Nausea:** **D1:** 19 **D2:** 44 **D3:** 5 **Somnolence:** **D1:** 61 **D2:** 43 **D3:** 12 **Sweating (increase):** **D1:** 3 **D2:** 12 **D3:** 1	**Overall attrition rate:** 33.78% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke, 2004 **Country and setting:** United States Multicenter, university clinics **Funding:** Eli Lilly	**Research objective:** To determine comparative efficacy and safety of DUL and PAR for treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 367 **Intervention:** **D1:** Duloxetine 80 mg/d **D2:** Duloxetine 120 mg/d **D3:** Paroxetine: 20 mg/d **D4:** placebo	**Inclusion criteria:** • Adults 18 or older • Met DSM-IV and MINI criteria for MDD • CGI-S rating > 4 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 43.1 **D2:** 44.7 **D3:** 42.0 **D4:** 42.0 **Sex (% female):** **D1:** 70 **D2:** 70 **D3:** 58 **D4:** 58 **Race (% white):** **D1:** 95 **D2:** 92 **D3:** 86 **D4:** 86 **Baseline (HAM-A):** **D1:** 17.8 **D2:** 18.0 **D3:** 18.5 **D4:** 17.9 **Mean HAM-D score at baseline:** **D1:** 19.9 (3.6) **D2:** 20.2 (3.4) **D3:** 20.3 (4.1) **D4:** 19.9	Response and remission rates did not differ sig among DUL 120 mg (71%; 52%), DUL 80 mg (65%; 46%) and PAR (74%; 44%) (*P* = NR) PGI scores were sig superior in patients receiving PAR than patients receiving 80 mg/d DUL (*P* < 0.05) Improvments in pain scores similar between active medications: DUL 80 mg and placebo (*P* = 0.063), DUL 120 mg and placebo (*P* = 0.086). Improvement in pain was superior to placebo (*P* = 0.035)	**Headache:** **D1:** 5.3 **D2:** 5.4 **D3:** 4.7 **Nausea:** **D1:** 12.6 **D2:** 5.4 **D3:** 11.6 **Somnolence (fatigue):** **D1:** 2.1 **D2:** 7.5 **D3:** 5.8 **Sweating (increase):** **D1:** 4.2 **D2:** 8.6 **D3:** 5.8	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2002 **Country and setting:** United States, multicenter (18 sites) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL vs. placebo for treatment of MDD and associated painful symptoms **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 245 **Intervention:** **D1:** Duloxetine 60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • Other: CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illness or organic mental disorder • Psychotherapy within 6 wks • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 42.44 **D2:** 42.34 **Sex (% female):** **D1:** 65.0 **D2:** 68.0 **Race (% white):** **D1:** 87.0 **D2:** 84.4 **Baseline HAM-D-17:** **D1:** 21.42 (4.11) **D2:** 21.14 (3.72) **Baseline 100mm VAS (overall pain):** **D1:** 29.02 (25.10) **D2:** 28.16 (23.21) **Baseline HAM-A:** NR	**Pain outcomes:** Mean reduction in 100mm VAS for overall pain was statistically sig greater for duloxetine (~8.5 mm) compared to placebo (~2.5 mm) (Mean change estimated from figure; *P* = 0.019)	**Cardiovascular adverse events (new hypertension):** **D1:** 0.8 **D2:** 0 **Constipation:** **D1:** 13 **D2:** 1.6 **Diarrhea:** **D1:** 18.7 **D2:** 6.6 **Dizziness:** **D1:** 20.3 **D2:** 8.2 **Insomnia:** **D1:** 15.4 **D2:** 5.7 **Nausea:** **D1:** 46.3 **D2:** 9.0 **Sexual dysfunction:** NR but 2.4% of DUL-treated patients dropped out due to abnormal ejaculation **Somnolence:** **D1:** 21.1 **D2:** 4.9	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2002 **Country and setting:** United States, multicenter (21 psychiatric clinical sites) **Funding:** Not reported but authors worked for Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL compared to placebo for treatment of emotional and painful physical symptoms of MDD **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 267 **Intervention:** **D1:** Duloxetine 60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illness or organic mental disorder • Psychotherapy within 6 wks • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 41 **D2:** 41 **Sex (% female):** **D1:** 66 **D2:** 71 **Race (% white):** **D1:** 78.1 **D2:** 78.4 **Baseline HAM-D:** **D1:** 20.33 (3.39) **D2:** 20.46 (3.39) **Baseline 100mm VAS (overall pain):** **D1:** 25.40 (23.98) **D2:** 26.20 (23.10) **Baseline HAM-A:** NR	**Pain outcomes:** Mean reduction in VAS for overall pain was ~10 mm for DUL compared to ~6 mm for placebo at endpoint (change score estimated from figure; *P* = 0.037)	**Cardiovascular adverse events (new hypertension):** **D1:** 0.8 **D2:** 0 **Constipation:** **D1:** 14.1 **D2:** 5.0 **Diarrhea:** **D1:** 10.2 **D2:** 7.9 **Dizziness:** **D1:** 14.8 **D2:** 2.9 **Headache:** **D1:** 25.8 **D2:** 22.3 **Insomnia:** **D1:** 16.4 **D2:** 13.7 **Nausea:** **D1:** 29.7 **D2:** 11.5	**Overall attrition rate:** 36.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2002 **Country and setting:** United States, multicenter (15 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy and tolerability of FLUO vs. PAR and SER for treatment of depression associated with sleep disturbance **Duration of study:** 10 to 16 wks (depending on response to initial dose; all received 6 wks of therapy at effective dose) **Study design:** RCT **Overall study N:** 284 overall; 125 in sleep disturbance subgroup **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 20-60 mg/d **D3:** Sertraline: 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 16 • Note: Sleep disturbance defined as HAM-D Sleep Disturbance Factor score of at least 4 **Exclusion criteria:** • Additional mental illness or organic mental disorder • Concomitant psychotropic medications • Substance use or dependence (within 6 mos) • Pregnant, lactating, or child-bearing potential without contraception • Clinically sig medical disease • Suicide risk (serious) • Seizure within 1 yr • Response to placebo in lead-in phase	**Mean age (yrs) in sleep disturbance subgroup:** **D1:** 42.2 **D2:** 41.9 **D3:** 43.0 **Sex (% female) in sleep disturbance subgroup:** **D1:** 60.5 **D2:** 65.2 **D3:** 63.4 **Race (% white):** NR **Baseline HAM-D-17 in sleep disturbance subgroup:** **D1:** 23.4 (3.9) **D2:** 22.6 (4.2) **D3:** 23.5 (3.9) **Baseline HAM-D Sleep Disturbance factor in sleep disturbance subgroup:** **D1:** 5.1 (0.9) **D2:** 4.8 (0.8) **D3:** 5.1 (0.8) **Baseline HAM-A:** NR	**Depression outcomes in patients with sleep disturbance:** No statistically sig diffs between FLUO, PAR and SER in HAM-D-17 total score improvement (overall *P* = 0.853) **Sleep outcomes:** Improvement in HAM-D Sleep Disturbance factor was similar for all 3 groups: FLUO (-3.1), PAR (-2.9), SER (-3.1) (overall *P* = 0.852)	**Changes in weight (increase 7%):** **D1:** 1.6 **D2:** 9.0 **D3:** 2.9 **Diarrhea:** **D3:** 26.0 **Headache:** **D1:** 25.0 **D2:** 21.9 **D3:** 28.1 **Insomnia:** **D2:** 20.8 **D3:** 26.0 **Nausea:** **D2:** 25.0 **D3:** 20.8 **Sexual dysfunction (abnormal ejaculation):** **D2:** 20.0 (of males)	**Overall attrition rate:** 49% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2000 **Country and setting:** United States, multicenter (15 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy and tolerability of FLUO vs. PAR and SER for treatment of anxious depression **Duration of study:** 10 to 16 wks (depending on response to initial dose; all received 6 wks of therapy at effective dose) **Study design:** RCT **Overall study N:** 108 (subset of patients with high anxiety from larger trial involving 284 patients with MDD) **Intervention:** **D1:** Fluoxetine: 20-60 mg/d (mean 44) **D2:** Paroxetine: 20-60 mg/d (mean 36) **D3:** Sertraline: 50-200 mg/d (mean 104)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 16 Note: High anxiety defined as HAM-D Anxiety/Somatization Factor score of at least 7 **Exclusion criteria:** • Additional mental illness or organic mental disorder • Concomitant psychotropic medications • Substance use or dependence (within 6 mos) • Pregnant, lactating, or child-bearing potential without contraception • Clinically sig medical disease • Suicide risk • Seizure within 1 yr • Response to placebo in lead-in phase	**Mean age (yrs):** **D1:** 40.3 **D2:** 41.4 **D3:** 44..1 **Sex (% female):** **D1:** 65.7 **D2:** 66.7 **D3:** 62.8 **Race (% white):** NR **Baseline HAM-D-17:** **D1:** 23.6 (3.9) **D2:** 25.0 (3.8) **D3:** 23.9 (3.4) **Baseline HAM-D Anxiety/Somatization factor:** **D1:** 7.8 (0.9) **D2:** 8.2 (1.3) **D3:** 8.1 (1.3) **Baseline HAM-A:** NR	**Depression outcomes in patients with anxiety:** No statistically sig diffs between FLUO, SER and PAR in improvement on HAM-D-17 total scores (overall *P* = 0.323) Response rates were similar for FLUO, PAR, and SER (73%, 77%, and 86%, overall *P* = 0.405). Remission rates were also similar (53%, 50%, and 62%, overall *P* = 0.588) **Anxiety outcomes:** No statistically sig diffs between FLUO, SER and PAR in improvement on HAM-D Anxiety/ Somatization Factor scores (overall *P* = 0.199)	**Diarrhea:** **D2:** 20.0 **D3:** 25.6 **Headache:** **D1:** 22.9 **D2:** 23.3 **D3:** 25.6 **Insomnia:** **D1:** 17.1 **D2:** 23.3 **D3:** 23.3 **Nausea:** **D2:** 26.7 **Somnolence:** **D1:** 11.4 **D2:** 10.0 **D3:** 16.3	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 1998 **Country and setting:** United States, multicenter (5 sites) **Funding:** SmithKline Beecham	**Research objective:** To evaluate efficacy of FLUO vs. PAR vs. placebo for treatment of depression **Duration of study:** 12 wks **Study design:** Pooled analysis of data from 5 sites of 2 multicenter trials **Overall study N:** 128 **Intervention:** **D1:** Fluoxetine 20-80 mg/d **D2:** Paroxetine 20-50 mg/d **D3:** Placebo	**Inclusion criteria:** • Outpatients • Minimum HAM-D-17 score of 18 • Raskin Depression score of 8 or more • Raskin score higher than Covi Anxiety Scale score **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • Alcohol or drug abuse (within 6 mos) • ECT within 3 mos • Investigational drug within 1 mo • Suicidal (high risk) • Clinically sig medical disease • Pregnant, lactating, or child-bearing potential without contraception • Placebo response during washout (25% improvement on HAM-D)	**Mean age (yrs):** Overall: 41.3 **Sex (% female):** Overall: 50 **Race (% white):** NR **Baseline HAM-D-17:** **D1:** 23.9 (3.8) **D2:** 23.1 (3.4) **D3:** 23.7 (2.7) **Baseline Covi Anxiety score:** **D1:** 6.3 (1.7) **D2:** 6.2 (1.7) **D3:** 5.8 (1.2) **Baseline HAM-A:** NR	**Anxiety outcomes:** Improvement in Covi Anxiety was similar for FLUO (1.2), PAR (1.2) and placebo (1.1; *P* = NR)	**Cardiovascular adverse events:** **D1:** 11 **D2:** 5 **D3:** 11 **Insomnia:** **D1:** 20 **D2:** 29 **D3:** 11 **Sexual dysfunction:** **D1:** 7 **D2:** 25 **D3:** 0 **Somnolence:** **D1:** 26 **D2:** 35 **D3:** 11	**Overall attrition rate:** 28% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Flament et al., 1999 **Country and setting:** UK, multicenter (20 psychiatric clinics) **Funding:** Not reported, but 2nd author employed by Pfizer Inc	**Research objective:** To compare response rates of FLUO vs. SER for treatment of depression in subgroups of patients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 randomized; 248 included in analysis; 174 in melancholia subgroup (defined by DSM-III-R criteria); 131 in anxiety subgroup (7 or more on Covi Anxiety Scale); 47 in psychomotor retardation group (HAM-D item 8 ≥2 and item 9 ≤ 1); 78 in psychomotor agitation subgroup (HAM-D item 8 ≤ 1 and item 9 ≥2) **Intervention:** **D1:** Fluoxetine 20-40 mg/d (mean 25) **D2:** Sertraline 50-100 mg/d (mean 62.5)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD or bipolar, depressed by DSM-III-R criteria • Minimum HAM-D-17 score of 18 • Raskin Depression score higher than Covi Anxiety score **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic drugs • Concomitant ECT or psychotherapy • Substance use or dependence (within 6 mos) • Pregnant, lactating, or child-bearing potential without contraception • Clinically sig medical disease • Suicide risk • Placebo response during washout • Previous use of study drugs	**Mean age (yrs):** **D1:** 49.9 **D2:** 49.9 **Sex (% female):** **D1:** 65 **D2:** 57 **Race (% white):** NR **Baseline HAM-D-17:** **D1:** 23.4 **D2:** 23.2 **Baseline HAM-A:** NR	**Depression results in patients with melancholia:** Mean HAM-D change did not differ between groups (-9.8 FLUO vs. -11.0 SER). Response rates were higher for SER (59%) vs. FLUO (44%) ($P < 0.05$) **Depression results in anxiety:** FLUO and SER groups had similar HAM-D mean change (-10.6 vs. -9.7) and response rates (48% vs. 47%; P = NR) **Depression results in psychomotor change:** In retardation, HAM-D change and response were similar (Change/ response: -10.7/46% for FLUO vs. -9.1/ 48% for SER; P = NR). In agitation, HAM-D improvement was 8.7 for FLUO vs. 12.4 for SER ($P = 0.02$); response rate was 39% for FLUO vs. 62% for SER ($P = 0.04$)	**Overall adverse events:** **D1:** 60 **D2:** 57	**Overall attrition rate:** 13.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gagiano, 1993 **Country and setting:** South Africa University hospital **Funding:** NR	**Research objective:** To evaluate efficacy of FLUO and PAR in patients with MDD **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine 20-60 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 18 **Exclusion criteria:** • Additional mental illness or organic mental disorder • Recent psychotherapeutic medications • ECT within 3 mos • Alcohol or drug abuse • Pregnant or lactating • Clinically sig medical disease • Suicidal (severe risk)	**Mean age (yrs):** **D1:** 39.6 **D2:** 37.8 **Sex (% female):** **D1:** 80 **D2:** 80 **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 24.5 (5.0) **D2:** 25.0 (4.7) **Baseline HAM-A:** **D1:** 22.6 (5.1) **D2:** 23.4 (5.5)	**Anxiety outcomes:** Improvement in HAM-A scores was similar for FLUO and PAR groups (*P* = NR)	**Diarrhea:** **D1:** 13 **D2:** 13 **Headache:** **D1:** 47 **D2:** 53 **Insomnia:** **D1:** 20 **D2:** 11 **Nausea:** **D1:** 33 **D2:** 36	**Overall attrition rate:** 21% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Goldstein et al., 2004 **Country and setting:** United States, multicenter (19 psychiatric research centers) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate DUL vs. PAR and placebo for treatment of emotional and painful physical symptoms in patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 353 **Intervention:** **D1:** Duloxetine 40 mg/d **D2:** Duloxetine 80 mg/d **D3:** Paroxetine 20 mg/d **D4:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illnesses or organic mental disorder (except anxiety disorders) • Substance abuse or dependence (within 1 yr) • Positive urine drug screen • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 41 **D2:** 41 **D3:** 40 **D4:** 40 **Sex (% female):** **D1:** 56 **D2:** 62 **D3:** 64 **D4:** 64 **Race (% white):** **D1:** 84 **D2:** 85 **D3:** 74 **D4:** 83 **Baseline HAM-D-17:** **D1:** 18.74 (5.97) **D2:** 17.86 (4.66) **D3:** 17.83 (5.19) **D4:** 17.20 (5.08) **Baseline HAM-A:** **D1:** 15.24 (5.87) **D2:** 14.70 (4.83) **D3:** 14.70 (6.00) **D4:** 14.47 (5.3) **Median baseline 100mm VAS (overall pain):** **D1:** 17.5 **D2:** 18.0 **D3:** 15.0 **D4:** 15.0	**Pain outcomes:** Median change in VAS overall pain was 0 for placebo, -4 mm for DUL 40 mg (*P* vs. placebo = 0.172), -7.5 mm for DUL 80 mg (*P* vs. placebo = 0.005), and -3 for placebo (*P* vs. placebo = 0.088)	**Constipation:** **D1:** 8.1 **D2:** 8.8 **D3:** 13.8 **D4:** 3.4 **Dizziness:** **D1:** 4.7 **D2:** 16.5 **D3:** 10.3 **D4:** 5.6 **Insomnia:** **D1:** 17.4 **D2:** 19.8 **D3:** 8.0 **D4:** 5.6 **Nausea:** **D1:** 22.1 **D2:** 25.3 **D3:** 16.1 **D4:** 2.2 **Somnolence:** **D1:** 17.4 **D2:** 11.0 **D3:** 8.0 **D4:** 2.2 **Sweating (increase):** **D1:** 9.3 **D2:** 12.1 **D3:** 6.9 **D4:** 0.0	**Overall attrition rate:** 41% **ITT Analysis:** Yes **Quality rating:** Poor: High overall attrition

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Joliat et al., 2004 Pooled data from 1. Reimherr et al., 1998 2. Schmidt et al., 2000 **Country and setting:** United States, multicenter **Funding:** Eli Lilly and Company	**Research objective:** To assess efficacy of FLUO 20 mg daily vs. FLUO 90 mg wkly vs. placebo in continuation treatment of depression in patients with MDD and associated anxiety who initially responded to therapy **Duration of study:** 25 wks **Study design:** Pooled analysis of data from 2 RCTs **Overall study N:** 374 with anxiety (data for 425 patients without anxiety not considered for KQ 3) **Intervention:** **D1:** Fluoxetine 20 mg/d **D2:** Fluoxetine 90 mg/wk **D3:** Placebo	**Inclusion criteria:** • Adults 18 to 65 (Study 1) and 18 to 80 (Study 2) • Outpatients • MDD according to DSM-III-R or IV • Minimum HAM-D-17 score of 16 for Study 1 and 18 for Study 2. Study 2 also required CGI-S score of 4 or more • Duration of 1 mo or more Note: High anxiety defined as score of 7 or more on HAM-D Anxiety-Somatization subscale **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance abuse (within 1 yr) • Pregnant or lactating • Unstable medical conditions • Lack of response of current episode to FLUO or to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 40.6 **D2:** 40.8 **D3:** 41.5 **Sex (% female):** **D1:** 72.1 **D2:** 70.1 **D3:** 76.2 **Race (% white):** **D1:** 84.3 **D2:** 91.8 **D3:** 86.7 **Baseline HAM-D:** **D1:** 3.79(2.56) **D2:** 4.17(2.77) **D3:** 3.45(2.34) **Baseline HAM-A:** NR	**Depression outcomes in patients with anxiety:** Relapse rates for patients with anxiety were 28.5% in FLUO wkly group, 27.8% in FLUO daily group, and 53.3% in placebo-treated group (*P* = NR) **Anxiety outcomes:** HAM-D Anxiety-Somatization scores increased (worsened) 1.92 and 1.93 in FLUO daily and wkly groups, respectively, and 3.12 points in placebo group (*P* = NR)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Khan et al., 1998 **Country and setting:** United States, multicenter (12 sites) **Funding:** Not reported but 3 authors employed by Wyeth-Ayerst	**Research objective:** To evaluate efficacy of 3 different doses of VEN vs. placebo for treatment of MDD or MDD with associated anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 403 randomized; 353 in modified ITT analysis; 346 with associated anxiety **Intervention:** **D1:** Venlafaxine 75 mg/d **D2:** Venlafaxine 150 mg/d **D3:** Venlafaxine 200 mg/d **D4:** Placebo	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III -R • Minimum HAM-D-21 score of 20 • Depression symptoms for at least 1 mo Note: Anxiety defined as score of 2 or more on HAM-D Anxiety-Psychic Item **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs or ECT • Drug or alcohol dependence (within 2 yrs) • Suicidal • Women with child-bearing potential • Clinically sig medical disease • Decrease of >20% in HAM-D during palcebo washout	**Mean age (yrs):** **D1:** 43.3 **D2:** 40.0 **D3:** 43.6 **D4:** 40.2 **Sex (% female):** **D1:** 68 **D2:** 64 **D3:** 60 **D4:** 61 **Race (% white):** NR **Baseline HAM-D:** **D1:** 24.3 **D2:** 24.5 **D3:** 24.8 **D4:** 25.1 **Baseline HAM-A:** NR	**Anxiety outcomes in patients with anxiety:** All 3 VEN-treated groups had statistically sig improvement in HAM-D Anxiety-Psychic Item and Anxiety-Somatization Factor scores compared to placebo group ($P < 0.05$)	**Dropouts due to dizziness:** **D1:** 5 **D2:** 2 **D3:** 6 **D4:** 1 **Dropouts due to insomnia:** **D1:** 5 **D2:** 3 **D3:** 5 **D4:** 0 **Dropouts due to nausea:** **D1:** 8 **D2:** 7 **D3:** 17 **D4:** 1 **Dropouts due to somnolence:** **D1:** 7 **D2:** 4 **D3:** 4 **D4:** 0	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** United States, multicenter (37 primary care clinics) **Funding:** Eli Lilly and Company	**Research objective:** To compare effectiveness of PAR, FLUO and SER for treatment of depression in primary care **Duration of study:** 9 mos **Study design:** RCT **Overall study N:** 601 randomized; 546 included in analysis **Intervention:** **D1:** Fluoxetine: 20 mg/d (mean 23.4) **D2:** Paroxetine: 20 mg/d (mean 23.5) **D3:** Sertraline: 50 mg/d (mean 72.8)	**Inclusion criteria:** • Adults 18 or older • Depressive disorder diagnosed by primary care physician • Access to telephone at home **Exclusion criteria:** • Concomitant psychotherapeutic medications (SSRI within 2 mos or current non-SSRI antidepressant) • Suicidal tendencies (active) • Bipolar disorder, severe cognitive impairment, terminal illness • Active cocaine or opiate abuse • Pregnant, lactating or pregnancy planned within 9 mos • Unable to read, write, or speak English	**Mean age (yrs):** **D1:** 47.1 **D2:** 47.2 **D3:** 44.1 **Sex (% female):** **D1:** 86 **D2:** 76 **D3:** 75 **Race (% white):** **D1:** 88 **D2:** 85 **D3:** 79 **Baseline HAM-D:** NR **Baseline HAM-A:** NR	**Somatization severity outcomes:** Scores on Patient Health Questionnaire Somatization Severity scale (possible range 0-28) improved similarly in all 3 treatment groups. Scores decreased 3.1, 3.2, and 4.1 points for FLUO, PAR, and SER-treated groups (nonsig diff; *P* value NR)	**Dropouts due to changes in weight (increase):** **D1:** 0 **D2:** 1 **D3:** 1 **Dropouts due to gastrointestinal symptoms:** **D1:** 4 **D2:** 8 **D3:** 4 **Dropouts due to headache:** **D1:** 2 **D2:** 3 **D3:** 1 **Dropouts due to sexual dysfunction:** **D1:** 1 **D2:** 2 **D3:** 0	**Overall attrition rate:** 24.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lader et al., 2005 Pooled data from 1. Burke et al., 2002 2. Rapaportet al., 2004 3. Lepola et al., 2003 **Country and setting:** United States and Europe **Funding:** H. Lundbeck A/S, Forest Laboratories	**Research objective:** To evaluate effect of ESC vs. CIT and placebo on sleep in patients with depression **Duration of study:** 8 wks **Study design:** Pooled analysis of 3 RCTs **Overall study N:** 1321 included in analysis; 638 with sleep problems **Intervention:** **D1:** Citalopram: 20-40 mg/d (mean 28.9) **D2:** Escitalopram: 10-20 mg/d (mean 13.3) **D3:** Placebo	**Inclusion criteria:** • Adults 18 to 65 (Study 1, 3), 18 to 80 (Study 2) • Outpatients • MDD according to DSM-IV • Minimum MADRS score of 22 Note: Sleep problems defined as MADRS item 4 score of 4 or more (possible range 0-6) **Exclusion criteria:** • Concomitant psychotherapeutic medications • Full criteria not reported	**Mean age (yrs):** **D1:** 42 **D2:** 41 **D3:** 42 **Sex (% female):** **D1:** 61 **D2:** 67 **D3:** 64 **Race (% white):** NR **Baseline HAM-D:** NR **Baseline MADRS:** **D1:** 28.9 (4.6) **D2:** 28.7 (4.5) **D3:** 29.0 (4.6) **Baseline HAM-A:** NR	**Depression outcomes in patients with sleep problems** Mean improvement in MADRS total score was 16.47 points for ESC group ($P < 0.05$ vs. CIT; $P < 0.05$ vs. placebo) compared to 14.02 for CIT (P vs. placebo not sig) and 12.2 for placebo **Sleep outcomes:** Mean improvement in MADRS item 4 was 1.65 points for ESC ($P < 0.01$ vs. CIT; $P < 0.01$ vs. placebo), 1.31 for CIT (P vs. placebo not sig), and 1.26 for placebo. Rate of improvement (end MADRS sleep score of 0 or 1) was 43.6% for ESC vs. 28.4% for CIT and 24.4% for placebo ($P < 0.001$)	**Insomnia:** **D1:** 8.6 **D2:** 9.2 **D3:** 3.9 **Somnolence:** **D1:** 4.7 **D2:** 6.9 **D3:** 2.2	**Overall attrition rate:** 16.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Leinonen et al., 1999 **Country and setting:** European, multicenter (21 psychiatric sites) **Funding:** Organon	**Research objective:** To evaluate efficacy of MIR vs. CIT for treatment of major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 270 randomized; 269 included in analysis **Intervention:** **D1:** Citalopram 20-60mg/d (mean 36.6) **D2:** Mirtazapine 15-60mg/d (mean 35.9)	**Inclusion criteria:** • Adults 18 to 65 • Outpatient and inpatient • MDD according to DSM-IV • Minimum MADRS score of 22 • Duration of current depression episode less than 12 mos **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic medications • ECT within 3 mos • Substance abuse (within 12 mos) • Pregnant or lactating • Clinically sig medical disease • Suicidal (high risk) • Lack of response of current MDD episode to 2 prior courses of therapy • Placebo response during washout (25% improvement on MADRS)	**Mean age (yrs):** **D1:** 41.1 **D2:** 42.1 **Sex (% female):** **D1:** 57.1 **D2:** 66.9 **Race (% white):** NR **Baseline HAM-D:** NR **Baseline MADRS:** **D1:** 29.1 (4.5) **D2:** 29.6 (4.9) **Baseline HAM-A:** **D1:** 20.9 (6.1) **D2:** 21.1 (6.2)	**Anxiety outcomes:** Mean reduction in HAM-A scores was similar (approximately -13 points) in both treatment groups (change estimated from figure; *P* = 0.75)	**Overall adverse events:** **D1:** 70.7 **D2:** 66.4 **Changes in weight (increase):** **D1:** 4.5 **D2:** 15.3 **Diarrhea:** **D1:** 6.0 **D2:** 2.9 **Dizziness:** **D1:** 4.5 **D2:** 8.8 **Headache:** **D1:** 14.3 **D2:** 9.5 **Nausea:** **D1:** 20.2 **D2:** 10.2 **Somnolence:** **D1:** 6 **D2:** 8 **Fatigue:** **D1:** 13.5 **D2:** 12.4 **Sweating (increase):** **D1:** 15.0 **D2:** 2.2	**Overall attrition rate:** 19.1% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Mallinckrodt et al., 2005 **Country and setting:** United States, multicenter **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy of DUL for treatment of depression in patients with melancholia to those without melancholia **Duration of study:** 9 wks **Study design:** Pooled analysis of 8 RCTs (all RCTs included in DUL's New Drug Application to FDA) **Overall study N:** 1572 with melancholia **Intervention:** **D1:** Duloxetine 40-120 mg **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S score of 4 or more Note: Melancholic features defined by DSM-IV criteria **Exclusion criteria:** • Additional mental illness or organic mental disorder • Concomitant psychotherapeutic or chronic prescription analgesic drugs • Substance abuse or dependence (within one yr); positive urine drug screen • Clinically sig medical disease • Suicidal (serious risk) • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** All melancholic: 42.1 **Sex (% female):** All melancholic: 69.5 **Race (% white):** NR **Baseline HAM-D:** All melancholic: 22.3 (3.9) **Baseline HAM-A:** NR	**Depression outcomes in patients with melancholia:** Mean reduction in HAM-D-17 score was 8.97 for DUL-treated group and 6.57 for those receiving placebo ($P < 0.001$)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 1998 **Country and setting:** United States, multicenter (10 sites) **Funding:** Bristol-Myers Squibb	**Research objective:** To evaluate effects of FLUO vs. NEF on sleep in patients with depression and insomnia **Duration of study:** 8 wks **Study design:** Pooled analysis of 3 RCTs **Overall study N:** 125 randomized; 122 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d (mean 32) **D2:** Nefazodone 200-500 mg/d (mean 424)	**Inclusion criteria:** • Adults 19 to 55 • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-17 score of 18 • One of following sleep problems was required: difficulty falling asleep, waking up during night, or inability to fall asleep again after getting up **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance use disorder (within 1 yr) • Clinically sig medical disease • Pregnant, lactating, or child-bearing potential without contraception • Shift-workers; sleep/wake disorder on polysomnograph	**Mean age (yrs):** **D1:** 37 **D2:** 36 **Sex (% female):** **D1:** 70 **D2:** 59 **Race (% white):** **D1:** 85 **D2:** 78 **Baseline HAM-D:** **D1:** 23.3 (2.7) **D2:** 22.9 (2.9) **Baseline HAM-D Sleep Disturbance Factor:** **D1:** 4.2 (1.3) **D2:** 4.2 (1.3) **Baseline Depression Symptomatology-Self Report (IDS-SR) Sleep Factor:** **D1:** 5.8 (2.1) **D2:** 5.3 (2.2) **Baseline HAM-A:** NR	**Depression outcomes in patients with insomnia:** Mean improvement in HAM-D-17 was 12.2 for FLUO-treated group and 11.4 for NEF-treated group (95% CI for diff: -1.7, 2.8) Response rates were similar for FLUO (45%) and NEF (47%; *P* = NR) **Sleep outcomes:** Mean improvement in HAM-D Sleep Disturbance Factor was 1.6 points for FLUO-treated group and 2.3 for NEF-treated group (*P* < 0.05) Improvement in IDS-SR Sleep Factor was 1.7 points for FLUO-treated group and 2.4 for NEF-treated group (*P* < 0.01)	**Constipation:** **D1:** 11 **D2:** 17 **Diarrhea:** **D1:** 26 **D2:** 16 **Dizziness:** **D1:** 8 **D2:** 22 **Headache:** **D1:** 48 **D2:** 56 **Insomnia:** **D1:** 11 **D2:** 6 **Nausea:** **D1:** 25 **D2:** 36 **Sexual dysfunction:** **D1:** 11 of males **D2:** 0 of males **Somnolence:** **D1:** 21 **D2:** 22	**Overall attrition rate (%):** 17% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 2001 (original report: Kavoussi, 1997) **Country and setting:** United States, multicenter **Funding:** Glaxo-Wellcome	**Research objective:** To determine whether baseline anxiety levels are associated with response to BUP SR and SER **Duration of study:** 16 wks **Study design:** RCT **Overall study N:** 248 **Intervention:** **D1:** Bupropion SR 100-300 mg/d **D2:** Sertraline 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-21 score of 18 • Depression duration 1 to 24 mos **Exclusion criteria:** • Concomitant or recent psycho-therapeutic drugs • Suicidal (active) • Pregnant or lactating • History of eating disorder or predisposition to seizures • Previous treatment with BUP or SER	**Mean age (yrs):** **D1:** 39 **D2:** 40 **Sex (% female):** **D1:** 48 **D2:** 48 **Race (% white):** **D1:** 93 **D2:** 94 **Baseline HAM-D:** **D1:** 24.8 (4.6) **D2:** 24.8 (4.6) **Baseline HAM-A:** **D1:** 16.6 (5.2) **D2:** 16.6 (5.4)	**Depression outcomes in patients with high anxiety:** In patients with high anxiety (top quartile of HAM-A scores), response and remission rates were similar for BUP SR and SER (estimated from figure: approximately 60% remission and 70% response in both groups, *P* = NR) **Anxiety outcomes in all patients:** Mean reduction in HAM-A was 9.7 for BUP-treated group and 10.0 for SER treated group (*P* = NR)	**Diarrhea:** **D1:** 3 **D2:** 22 **Dizziness:** **D1:** 8 **D2:** 5 **Headache:** **D1:** 34 **D2:** 32 **Insomnia:** **D1:** 18 **D2:** 19 **Nausea:** **D1:** 10 **D2:** 30 **Sexual dysfunction (orgasm in men):** **D1:** 10 **D2:** 61 **Sexual dysfunction (orgasm in women):** **D1:** 7 **D2:** 41 **Somnolence:** **D1:** 2 **D2:** 13 **Sweating (increase):** **D1:** 2 **D2:** 10	**Overall attrition rate (%):** 31% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Sir et al., 2005 **Country and setting:** Australia and Turkey (13 sites) **Funding:** Pfizer, Inc	**Research objective:** To evaluate diffs in efficacy between SER and VEN XR on measures of QOL, depression, anxiety and pain in patients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 163 overall; 120 in anxiety subgroup **Intervention:** **D1:** Sertraline 50-150 mg/d **D2:** Venlafaxine XR 75-225 mg/d	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 18 Note: Anxious depression subgroup defined by HAM-D Anxiety-Somatization score of 7 or more **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Substance abuse or dependence (within 6 mos) • Pregnant or child-bearing potential without contraception • Lack of response of current MDD episode to 2 prior courses of therapy • History of nonresponse to SER or VEN	**Mean age (yrs):** **D1:** 37.3 **D2:** 36.8 **Sex (% female):** **D1:** 72.2 **D2:** 66.7 **Race (% white):** **D1:** 96.2 **D2:** 100 **Baseline HAM-D:** **D1:** 23.4 (4.4) **D2:** 23.5 (4.4) **Baseline HAM-A:** NR	**Depression outcomes in anxiety subgroup:** Mean reduction in HAM-D was 17.3 for SER and 14.8 for VEN XR (P = 0.70) Response rates SER 79.6% VEN 68.9% (P = 0.26) Remission rates were SER 63.0% VEN 54.1 (P = 0.44) **Anxiety outcomes:** In overall study population, mean reduction in HAM-A was similar for treatment groups: 14.1 for SER vs. 12.9 for VEN XR (P = 0.32) In high-anxiety subgroup, response on HAM-D Anxiety-Somatization subscale was similar for treatment arms: 83.3% for SER, 70.5% for VEN (P = 0.12)	**Dizziness:** **D1:** 32.9 **D2:** 26.2 **Headache:** **D1:** 44.3 **D2:** 32.1 **Insomnia:** **D1:** 35.4 **D2:** 27.4 **Nausea:** **D1:** 51.9 **D2:** 47.6 **Somnolence:** **D1:** 21.5 **D2:** 26.2 **Sweating (increase):** **D1:** 31.6 **D2:** 21.4	**Overall attrition rate (%):** 23% **ITT Analysis:** **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Trivedi et al., 2001 and Rush et al., 2001 **Country and setting:** United States, multicenter **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare effects of bupropion SR and SER on anxiety in patients with MDD **Duration of study:** 8 wks **Study design:** Analysis of pooled data from 2 RCTs **Overall study N:** 724 randomized; 692 included in analysis **Intervention:** **D1:** Bupropion SR 150-400 mg/d **D2:** Sertraline 50-200 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Recurrent major depression episode of 2 to 24 mo duration • Minimum HAM-D-21 score of 18 Note: Anxiety subgroup defined as top quartile on HAM-A (score > 24) **Exclusion criteria:** • Additional mental illness or organic mental disorder (except GAD) • Concomitant psychotherapeutic medications (within one wk) • Substance abuse or dependence (within one yr) • Pregnant or lactating • Prior treatment with BUP or SER	**Mean age (yrs):** **D1:** 37 **D2:** 37 **D3:** 38 **Sex (% female):** **D1:** 53 **D2:** 51 **D3:** 55 **Race (% white):** **D1:** 87 **D2:** 91 **D3:** 88 **Baseline HAM-D:** **D1:** 25.2 (5.2) **D2:** 25.2 (5.2) **D3:** 24.9 (5.2) **Baseline HAM-A:** **D1:** 18.8 (7.3) **D2:** 18.6 (7.4) **D3:** 18.6 (7.1)	**Depression outcomes in patients with anxiety:** Response rates were similar for BUP SR, SER, and placebo (approximately 70%, 64% and 58%; rates estimated from figure; *P* = NR). Remission rates were also similar for all 3 treatment groups (*P* = NR) **Anxiety outcomes in all patients:** Mean reduction in HAM-A was similar for BUP SR and SER-treated groups (9.9 and 9.4 points) and slightly less for those receiving placebo (8.4 points). No statistically sig diff between active drug groups (*P* > 0.41). Diff between active drug and placebo was statistically sig for BUP group (*P* = 0.04) but not for SER (*P* = NR)	**Dizziness:** **D1:** 7 **D2:** 8 **D3:** 5 **Insomnia:** **D1:** 16 **D2:** 18 **D3:** 5 **Somnolence:** **D1:** 3 **D2:** 13 **D3:** 5	**Overall attrition rate:** 28% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tzanakaki et al., 2000 **Country and setting:** Greece and Italy, multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** To evaluate efficacy of FLUO vs. VEN in patients with major depression and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 109 **Intervention:** **D1:** Fluoxetine 60 mg/d **D2:** Venlafaxine 225 mg/d	**Inclusion criteria:** • Adults 18 to 64 • Outpatient or hospitalized • MDD with melancholia according to DSM-IV • MADRS of 25 or more • Depression symptoms for one mo or more **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • ECT within 30 days • Drug or alcohol dependence (within 2 yrs) • Pregnant or without contraception • Clinically sig medical disease • Investigational drug use within 30 days • Suicidal (acute)	**Mean age (yrs):** **D1:** 49 **D2:** 47 **Sex (% female):** **D1:** 83 **D2:** 75 **Race (% white):** NR **Baseline HAM-D:** **D1:** 27.1 (5.6) **D2:** 27.8 (5.6) **Baseline HAM-A:** NR	**Depression outcomes in melancholia:** Response rates were similar for FLUO-treated group (58%) and VEN group (65%; *P* = NR). Remission rates were similar for FLUO (36%) and VEN (41%; *P* = NR)	**Overall adverse events:** **D1:** 46.3 **D2:** 49.1 **Constipation:** **D1:** 1.9 **D2:** 7.3 **Dizziness:** **D1:** 0 **D2:** 5.5 **Headache:** **D1:** 1.9 **D2:** 5.5 **Insomnia:** **D1:** 1.9 **D2:** 12.7 **Nausea:** **D1:** 14.8 **D2:** 5.5 **Sweating (increase):** **D1:** 3.7 **D2:** 5.5	**Overall attrition rate:** 22% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani, 2005 **Country and setting:** Europe and South America, multicenter (30 sites) **Funding:** Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 randomized; 292 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d **D2:** Mirtazapine 30-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD according to DSM-IV • Minimum HAM-D-17 score of 25 **Exclusion criteria:** • Current depression episode duration >12 mos • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • Investigational drug use within 30 days • ECT within 3 mos • Alcohol or substance abuse (within 6 mos) • Pregnant or lactating • Clinically sig medical disease • Suicidal risk • Response during placebo washout (25% improvement in HAM-D-17)	**Mean age (yrs):** **D1:** 47 **D2:** 43 **Sex (% female):** **D1:** 69 **D2:** 74 **Race (% white):** NR **Baseline HAM-D:** **D1:** 28 (3) **D2:** 29 (3) **Baseline HAM-A:** NR	**Sleep outcomes:** Scores on Leeds Sleep Evaluation Questionnaire improved similarly for both groups	**Overall adverse events:** **D1:** 45 **D2:** 50 **Changes in weight (increase):** **D1:** 1.3 **D2:** 6.9 **Dizziness:** **D1:** 12.8 **D2:** 9 **Headache:** **D1:** 18.8 **D2:** 19.3 **Insomnia:** **D1:** 8.7 **D2:** 4.8 **Nausea:** **D1:** 24.1 **D2:** 15.9 **Somnolence:** **D1:** 9.4 **D2:** 13.8	**Overall attrition rate:** 14% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Aberg-Wistedt et al., 2000 **Country and setting:** Sweden Multicenter **Funding:** Pfizer, Inc	**Research objective:** SER vs. PAR clinical outcomes after 6 mos of continuous therapy **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 353 **Intervention:** **D1:** Sertraline 50-150 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** Overall: 43 **Sex (% female):** Overall: 67.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Response 8 wks- SER: 63% PAR: 63% LOCF at 24 wks: SER: 72% PAR: 69% Response-Observed Cases at 24 wks: SER: 89% PAR: 89% Remission No sig diff at endpoint or at any other study point measures 8 wks: SER: 51.6% PAR: 57.3% 24 wks: SER: 80.2% PAR: 73.7% No sig diff in CGI severity change score or improvement score Relapse during wks 9 to 24: PAR 8.6% SER 1.9% (*P* -value NR) No sig diffs on BQOL	**Constipation:** **D1:** 5.7 **D2:** 16.4 **Diarrhea:** **D1:** 35.2 **D2:** 15.2 **Libido decrease (men):** **D1:** 12.7 **D2:** 3.8 **Libido decrease (women):** **D1:** 1.8 **D2:** 8.8 *P* ≤ 0.05	**Overall attrition rate:** 35.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Behnke et al., 2003 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare onset of antidepressant efficacy of MIR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 346 **Intervention:** **D1:** Mirtazapine: 30-45 mg/d **D2:** Sertraline: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Epilepsy • History of seizure disorder or anti-convulsant treatment • Current eating disorders diagnosis • Previous postpartum depression or anxiety disorder diagnosis	**Mean age (yrs):** **D1:** 42 **D2:** 41 **Sex (% female):** **D1:** 55.7 **D2:** 61.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Onset of action faster in MIR group At all assessments during first 2 wks mean change of HAM-D from baseline sig greater in MIR group than in SER group ($P < 0.05$) After wk 2 diff remained greater with MIR but lacked statistical significance HAM-D response rate showed similar findings HAM-D remission rate higher with MIR than SER at all assessments; diff reached statistical significance at day 14 Reduction in sleep disturbance was sig greater in MIR group at all assessments ($P \leq 0.01$) CGI scores not sig diff	**Overall adverse events:** **D1:** 64 **D2:** 68 **Diarrhea:** **D1:** 4 **D2:** 9.5 **Dizziness:** **D1:** 6.8 **D2:** 10.1 **Headache:** **D1:** 14.2 **D2:** 18.3 **Insomnia:** **D1:** 5.1 **D2:** 8.9 **Nausea:** **D1:** 7.4 **D2:** 22.5 **Somnolence (fatigue):** **D1:** 19.9 **D2:** 7.7 **Sweating (increase):** **D1:** 1.1 **D2:** 5.3 **Libido decrease:** **D1:** 1.1 **D2:** 5.9 $P = 0.02$	**Overall attrition rate:** 20.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Benkert et al., 2000 Szegedi et al., 2003 **Country and setting:** Germany Multicenter (50) **Funding:** Organon, GmBH, Munich, Germany	**Research objective:** Safety and efficacy of MIR and PAR in treatment of major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 275 **Intervention:** **D1:** Mirtazapine: 15-45 mg/d (32.7) **D2:** Paroxetine: 20-40 mg/d (22.9)	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.3 **Sex (% female):** **D1:** 63 **D2:** 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.4 (3.3) **D2:** 22.4 (3.2)	Benkert-MIR and PAR equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) Szegedi-Improvement occurred in majority of analyzed patients within 2 wks, MIR: 72.7% PAR: 64.9% Early improvement was highly sensitive predictor of later stable response or stable remission for both drugs At endpoint, 40.9% of MIR group and 34.1% of PAR group were considered HAM-D remitters (score ≤ 7)	**Overall adverse events:** **D1:** 68.1 **D2:** 63.4 **Changes in weight (increase):** **D1:** 14.8 **D2:** 3.7 **Constipation:** **D1:** 7.4 **D2:** 6.7 **Dizziness:** **D1:** 8.9 **D2:** 8.2 **Headache:** **D1:** 9.6 **D2:** 10.4 **Nausea:** **D1:** 4.4 **D2:** 11.2 **Somnolence (fatigue):** **D1:** 11.1 fatigue-8.9 **D2:** 7.5 fatigue-8.2 **Sweating (increase):** **D1:** 2.2 **D2:** 7.5	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Buckley et al., 2005 **Country and setting:** United Kingdom Database **Funding:** NR	**Research objective:** To establish relative frequency with which venlafaxine and other new antidepressants result in fatal poisoning **Duration of study:** 1993-1999 data **Study design:** NR **Overall study N:** 121,927 **Intervention:** TCAs and related drugs Serotoninergic drugs	**Inclusion criteria:** • Deaths due to acute poisoning of a single drug **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Among second generation antidepressants, VEN had highest fatal toxicity index (deaths/million prescriptions): VEN: 13.2 (9.2-18.5) FLUV: 3.0 (0.3-10.9) CIT: 1.9 (0.6-4.5) SER: 1.2 (0.5-2.4) FLUO: 0.9 (0.5-1.4) PAR: 0.7 (0.4-1.3) NEF: 0 (0-6.4) Highest rate of fatal toxicity for VEN	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** N/A

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events	Analysis Quality Rating
Author: Clayton et al., 2002 **Country and setting:** US Multicenter 1101 primary care clinics) **Funding:** Glaxo Wellcome Inc.	**Research objective:** To estimate prevalence of sexual dysfunction among patients taking newer antidepressants **Duration of study:** N/A **Study design:** Cross-sectional survey **Overall study N:** 6297 **Intervention:** Bupropion: IR: 255.0; SR: 273.7 Citalopram: 24.9 Fluoxetine: 25.5 Mirtazapine: 28.6 Nefazodone: 293.2 Paroxetine: 23.3 Sertraline: 81.4 Venlafaxine: Regular: 124.9; XR: 114.9	**Inclusion criteria:** • Adults 18+ • Taking monotherapy for depression (no trazodone in addition, e.g. with one of newer antidepressants earlier specified, sexually active within last 12 mos, willing to discuss his/her sexual functioning with physician **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Taking monotherapy antidepressants for reason other than treatment of depression	**Mean age (years):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:**	Overall population: BUP IR (22%) and SR (25%) and NEF (28%) were associated with lowest risk for sexual dysfunction Highest rates in PAR (43%) and MIR (41%) groups CSFQ scores averaged 24% for all antidepressants combined and ranged from 7% (BUP SR) to 30% (CIT and VEN XR) Patients aged 50-59 had sigly higher odds of having sexual dysfunction compared with reference age group of 20 to 29 yr. old patients. OR 1.42 (95 CI 1.14-179)	N/A	**Overall attrition rate:** NR **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coleman et al., 2001 **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUO and placebo on safety, efficacy and sexual functioning in patients with recurrent major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 456 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d (26) **D2:** Bupropion: 150-400 mg/d (319) **D3:** Placebo	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Have sexual activity at least once every 2 wks • Currently experiencing episode lasting 2 to 24 mos • Currently in a stable relationship **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 37.1 **D2:** 36.6 **D3:** 36.7 **Sex (% female):** **D1:** 66 **D2:** 63 **D3:** 61 **Race (% white):** **D1:** 82 **D2:** 83 **D3:** 82 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.6 **D2:** 24.5 **D3:** 24.4	More BUP SR remitters (47%) compared to placebo (32%) Orgasm dysfunction occurred sig more in FLUO patients compared with placebo or BUP SR patients ($P < 0.001$) At endpoint, more FLUO treated patients had sexual desire disorder than BUP SR treated patients ($P < 0.05$) Sig more buproion SR-treated patients were satisfied with sexual function (analysis only for patients satisfied at baseline; no data reported) $P<0.05$ Compliance: 96.8% to 98.8% in all groups	**Diarrhea:** **D1:** 12 **D2:** 9 **D3:** 9 **Headache:** **D1:** 31 **D2:** 28 **D3:** 20 **Insomnia:** **D1:** 15 **D2:** 21 **D3:** 10 **Nausea:** **D1:** 12 **D2:** 21 **D3:** 16 **Somnolence (fatigue):** **D1:** 11 **D2:** 3 **D3:** 4	**Overall attrition rate:** 34% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coleman et al., 1999 **Country and setting:** United States Multicenter (9 centers) **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare sexual functioning as well as safety and efficacy of BUP SR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 364 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Bupropion: 150-400 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 wks • Currently experiencing recurrent major episode of depression **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 38.3 **D2:** 38.1 **D3:** 38.5 **Sex (% female):** **D1:** 54 **D2:** 56 **D3:** 59 **Race (% white):** **D1:** 92 **D2:** 87 **D3:** 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 34.5 **D2:** 34.8 **D3:** 34.0	Mean HAM-D scores in BUP SR but not SER group were statistically better than placebo (by day 28 $P < 0.05$) Sig fewer BUP SR patients had sexual desire disorder than SER patients ($P < 0.05$) Orgasm dysfunction occurred sig more in SER patients compared with placebo or BUP SR patients ($P < 0.05$) Diagnosed with at least one sexual dysfunction: SER: 39%, BUP SR: 13%, placebo: 17% Sig more BUP patients were satisfied with their sexual functioning (endpoint BUP 85% vs. SER 62%; $P< 0.05$) Mean Compliance: Tablet: placebo: 96.1%, BUP 96.4%, SER 97.1% Capsule: placebo: 98.4%, 97.9%, SER 98.3%	**Diarrhea:** **D1:** 12 **D2:** 18 **Headache:** **D1:** 34 **D2:** 27 **Insomnia:** **D1:** 20 **D2:** 17 **Nausea:** **D1:** 19 **D2:** 23 **Sexual dysfunction :** **D1:** 39 **D2:** 13	**Overall attrition rate:** 30% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coogan et al., 2005 **Country and setting:** United States, inpatient, multicenter (3 hospitals) **Funding:** Not reported	**Research objective:** To evaluate SSRI use and breast cancer risk **Duration of study:** Enrollment was from 1998 to 2002. Duration of treatment was not specified and use ranged from <2 yrs to ge 4 yrs **Study design:** Case control study **Overall study N:** 4,996 **Intervention:** **D1:** Fluoxetine **D2:** Paroxetine **D3:** Sertraline	**Inclusion criteria:** • Adults 18 to 79 • Concomitant condition: breast cancer for cases • Able to complete interview • Lived in eligible zip code **Exclusion criteria:** • Patients did not have certain excluded diagnoses (e.g., psychiatric diagnoses)	**Mean age (yrs):** NR **Sex (% female):** 100 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Adjusted OR (95% CI) for breast cancer and breast cancer association = 1.1 (0.8, 1.7) OR for use of SSRI for 4 or more yrs = 0.7 (0.4, 1.5) OR for recent use of SSRIs = 1.2 (0.8, 1.8) OR for SSRI use stopped at least a yr prior to interview = 1.1 (0.5, 2.6) OR for sporadic SSRI use = 1.1 (0.6, 2.1)	NR	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Croft et al., 1999 **Country and setting:** United States Multicenter (8 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and effects on sexual functioning of depressed patients using BUP, SER, or placebo **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 360 **Intervention:** **D1:** Sertraline: 50-200 mg/d (mean = 121) **D2:** Bupropion: 150-400 mg/d (mean = 293) **D3:** Placebo	**Inclusion criteria:** • Adults 18 and over • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • In stable relationship • Have normal sexual functioning and sexual activity at least once every 2 wks • Current depressive episode of 8 wks to 24 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** **D1:** 36.0 **D2:** 35.9 **D3:** 37.4 **Sex (% female):** **D1:** 50 **D2:** 51 **D3:** 50 **Race (% white):** **D1:** 87 **D2:** 86 **D3:** 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Mean HAM-D scores in both BUP and SER group were statistically better than placebo ($P < 0.05$) At day 56, both BUP and SER had higher sexual arousal disorder ($P < 0.05$) than placebo Orgasmic dysfunction occurred sig more in SER patients compared with placebo or BUP patients ($P < 0.001$) Beginning at day 7 through day 42 sig more BUP patients were satisfied with their overall sexual functioning. At day 56 no sig diff between treatment groups (BUP 75% vs SER 65%; $P < 0.05$) Compliance: BUP 98% SER 97.2% Placebo 97.9% Endpoint: RRR: 0.29 RD: 0.10 NNT: 10	**Diarrhea:** **D1:** 26 **D2:** 7 **D3:** 11 **Headache:** **D1:** 40 **D2:** 34 **D3:** 30 **Insomnia:** **D1:** 18 **D2:** 13 **D3:** 4 **Nausea:** **D1:** 31 **D2:** 18 **D3:** 10 **Somnolence (fatigue):** **D1:** 17 **D2:** 3 **D3:** 6	**Overall attrition rate:** 32% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: CSM Expert Working Group, 2004 **Country and setting:** UK **Funding:** Not reported **Research objective:** Evaluating safety of SSRI antidepressants (CIT, ESC, FLUO, FLUV, MIR, PAR, SER, VEN)	**Study design:** Systematic review **Number of Patients:** NR **Studies Included:** All published and unpublished trials including output from GPRD- 477 studies **Intervention:** **D1:** Venlafaxine **D2:** Other SSRIs	**Characteristics of Included Studies:** • Studies that included safety information on suicide, withdrawal, and dose response **Characteristics of Included Populations** • Individuals taking SSRIs **Characteristics of Interventions:** SSRIs	**Study Results:** Suicide No diffs in risk among second-generation antidepressants Withdrawal Based on observational studies, spontaneous reporting data, and clinical trials data, experts concluded that discontinuation syndromes occur most commonly with PAR and VEN and least commonly with FLUO	N/A	**Publication Bias:** No- however review was designed to eliminate publication bias **Heterogeneity**: Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Clinical trial data from pharmaceutical companies, spontaneous reporting data, GPRD, expert evidence, regular searches of published literature **Quality Rating:** Good

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Delgado et al., 2005 **Country and setting:** Country not reported, pooled analysis of 4 studies - setting not described in article **Funding:** Eli Lilly	**Research objective:** To assess sexual functioning in patients receiving DUL or PAR **Duration of study:** 8 wk acute phase followed by a 26 wk extension phase (for 2 of 4 studies) **Study design:** Pooled analysis of 4 RCTs **Overall study N:** 1,466 **Intervention:** **D1:** Duloxetine: 40, 80, or 120 mg/d **D2:** Paroxetine: 20 mg/d **D3:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Acute Phase Treatment-Emergent Dysfunction (ASEX) in 475 patients who did not have sexual dysfunction at baseline, incidence of treat-emergent sexual dysfunction was sig higher for DUL vs. placebo DUL = 46.4% placebo = 28.8% t = 2.69, df = 1337, *P* = 0.007 PAR vs. Placebo PAR = 61.4% placebo = 28.8% *P* < 0.001 DUL vs. PAR, *P* = 0.015 (incidence for DUL sig lower than incidence for PAR)	**Overall adverse events:** NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Didham et al., 2005 **Country and setting:** New Zealand RNZCGP Research Unit Database **Funding:** New Zealand Government	**Research objective:** Identify incidence and risk of suicide and self-harm among patients prescribed ADs **Duration of study:** 120 days **Study design:** Observational **Overall study N:** 57,361 **Intervention:** Citalopram Fluoxetine Paroxetine	**Inclusion criteria:** • Patients that received a prescription for an anti-depressant from 1996 to 2001 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Less than 10 yrs old	**Mean age (yrs):** Median- 46 **Sex (% female):** Overall: 68.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No sig increase in suicides for SSRIs as a class: OR 1.28; 95% CI 0.38-4.35 No sig diff in suicides between drugs FLUO: 0.80 (0.22-2.89) PAR: 2.25 (0.47-10.72) Self-harm SSRIs vs. TCAs incidence rate 2.57 95% CI 2.03-3.28 Increased risk of self-harm for SSRIs as a class OR 1.66 95% CI 1.23-2.23 No sig diffs in self-harm between drugs FLUO; 1.30 (0.96-1.75) PAR 1.21 (0.84-1.72)	Not Reported	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Dunner et al., 1998 **Country and setting:** United States Multicenter (105 sites) **Funding:** Glaxo Wellcome Inc	**Research objective:** Safety of BUP sustained-release in acute and continuation treatment, especially in regards to seizures **Duration of study:** Acute phase of 8 wks with continuation up to one yr **Study design:** Uncontrolled, open-label trial **Overall study N:** 3100 **Intervention:** **D1:** Bupropion: 100-300 mg/d	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Bipolar I or II depression; depression not otherwise specified bipolar depression not otherwise specified **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Suicidal tendencies • Known predisposition for seizures or previous treatment with BUP • History or current diagnosis of bulimia and/or anorexia	**Mean age (yrs):** **D1:** 42 **Sex (% female):** **D1:** 62.4 **Race (% white):** **D1:** 89.5 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Observed seizure rate during 8-wk acute phase was 2 seizures in 3094 evaluable patients, or 0.06% and for acute and continuation phases combined was 3 seizures in 3094 patients, or 0.10% Survival analysis yielded cumulative seizure rate of 0.08% for acute phase and 0.15% for both phases combined Rate of seizures for BUP within range of other antidepressants	**Overall adverse events:** **D1:** 50 patients experienced 54 serious AEs	**Overall attrition rate:** 34% **ITT Analysis** No, Survival analysis **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ekselius et al., 1997 **Country and setting:** Sweden Multicenter (general physicians) **Funding:** Swedish Medical Research Council, Pfizer	**Research objective:** To compare efficacy and safety of SER with CIT in patients with major depression **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 400 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Citalopram: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 21 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with SER or CIT w/o sig effect	**Mean age (yrs):** **D1:** 47.0 **D2:** 47.2 **Sex (% female):** **D1:** 71 **D2:** 72.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Both treatment groups showed sig decreases in MADRS and CGI scores from baseline at all wks starting at wk 2 No sig diffs between treatment groups in any primary outcome variables at any time Response rates Wk 12: SER: 69.5% CIT: 68.0% Wk 24: SER: 75.5% CIT: 81.0% Compliance: SER 90.3% CIT 94.5%	**Overall adverse events:** **D1:** 90 **D2:** 85.5 **Cardiovascular adverse events:** **D1:** 3 **D2:** 4 **Changes in weight (decrease):** **D1:** 4.5 **D2:** 9.5 **Changes in weight (increase):** **D1:** 15 **D2:** 13 **Constipation:** **D1:** 3 **D2:** 2 **Diarrhea:** **D1:** 8.5 **D2:** 5.5 **Headache:** **D1:** 9 **D2:** 6.5 **Insomnia:** **D1:** 3.5 **D2:** 6 **Nausea:** **D1:** 6 **D2:** 2.5 **Sexual dysfunction :** **D1:** 4 **D2:** 6.5 **Somnolence (fatigue):** **D1:** 5 **D2:** 4.5 **Sweating (increase):** **D1:** 13 **D2:** 17	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Ekselius et al., 2001 **Country and setting:** Sweden General practice **Funding:** Pfizer AB Swedish Medical Research Council	**Research objective:** Examination of occurance and severity of sexual dysfunction symptoms in depressed patients before and after 6 mos of treatment **Duration of study:** 24 wks **Study design:** RCT, completers only analysis **Overall study N:** 308 **Intervention:** **D1:** Citalopram: 20-60 mg/d (33.9) **D2:** Sertraline: 50-150 mg/d (82.4)	**Inclusion criteria:** • Adults 18 and over • Diagnosed with MDD according to DSM-III or -IV • MADRS of 21 or more **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No statistically sig diffs between SER and CIT in magnitude or frequency of adverse sexual side effects Female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported orgasmic dysfunction Male patients reporting no sexual dysfunction at baseline, 16.7% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction	**Overall adverse events:** NR	**Overall attrition rate:** N/A **ITT Analysis** No, completers analysis **Quality rating:** Fair for adverse event reporting

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2000 **Country and setting:** United States Multicenter (15 sites) **Funding:** Eli Lilly Research	**Research objective:** To compare tolerability and efficacy of FLUO, PAR and SER in treatment of anxious depression **Duration of study:** 10 to 16 wks (4 wks with additional wks determined by response on CGI) **Study design:** RCT **Overall study N:** 108 (drawn from larger sample of 284 MDD outpatients) **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • HAM-D-Anxiety/ Somatization Factor score of at least 7 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Presence of seizure disorder with seizure in last yr • History of allergy to study drugs • Use of MAOIs within 2 wks of active therapy	**Mean age (yrs):** **D1:** 40.3 **D2:** 44.1 **D3:** 41.4 **Sex (% female):** **D1:** 65.7 **D2:** 62.8 **D3:** 66.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.6 (3.9) **D2:** 23.9 (3.4) **D3:** 25.0 (3.8)	No statistically sig diffs between FLUO, SER and PAR in baseline-to-endpoint improvement in HAM-D total (overall $P = 0.323$) No sig diffs in efficacy and tolerability of FLUO, SER, and PAR in treating anxious depression For all treatments, incidence of substantial emergence or any worsening was low with improvement at highest frequency for all HAM-D items	**Diarrhea:** **D2:** 25.6 **D3:** 20.0 **Headache:** **D1:** 22.9 **D2:** 25.6 **D3:** 23.3 **Insomnia:** **D1:** 17.1 **D2:** 23.3 **D3:** 23.3 **Nausea:** **D3:** 26.7 **Somnolence (fatigue):** **D1:** 11.4 **D2:** 16.3 **D3:** 10.0	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 1998 **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUO **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** **D1:** Paroxetine: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) **D2:** Fluoxetine: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) **D3:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 18 • Raskin Depression score of > 8 (and larger in value than Covi anxiety scale) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 41.3 **D2:** 41.3 **D3:** 41.3 **Sex (% female):** **D1:** 50 **D2:** 50 **D3:** 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.1 (3.4) **D2:** 23.9 (3.8) **D3:** 23.7 (12.2)	No sig diffs among 3 treatment groups in degree of depression and anxiety improvement	**Cardiovascular adverse events:** **D1:** 5 **D2:** 11 **D3:** 11 **Insomnia:** **D1:** 29 **D2:** 20 **D3:** 11 **Sexual dysfunction :** **D1:** 25 **D2:** 7 **D3:** 0	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Feighner et al., 1991 **Country and setting:** United States Multicenter (2 sites) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficacy and safety of BUP and FLUO in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Bupropion: 225-450 mg/d (382) **D2:** Fluoxetine: 20-80 mg/d (38)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 40.9 **D2:** 42.9 **Sex (% female):** **D1:** 62 **D2:** 61 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.3 **D2:** 26.1	No sig diffs in changes of HAM-D score between treatment groups No sig diffs in percentage of clinical responders (more than 50% HAM-D scale reduction) between treatment groups, BUP: 62.7%, FLUO: 58.3% No sig diffs in changes of CGI-S, CGI-I, and HAM-A scores Higher rate of impotence (4.7% vs 0%), anorgasmia (1.7% vs 0%), and libido decrease (1.7% vs 0%) for FLUO (*P* = NR)	NR	**Overall Attrition rate:** 7.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Ferguson et al., 2001 **Country and setting:** United States Multicenter (9 sites) **Funding:** Bristol Myers Squibb	**Research objective:** To compare effects of NEF and SER on reemergence rates of sexual dysfunction in depressed patients who'd had sexual dysfunction with previous SER treatment **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 75 **Intervention:** **D1:** Nefazodone: 200-400 mg/d **D2:** Sertraline: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Receiving SER and experiencing attributable sexual dysfunction **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days	**Mean age (yrs):** **D1:** 43.2 **D2:** 44.8 **Sex (% female):** **D1:** 46 **D2:** 48 **Race (% white):** **D1:** 95 **D2:** 97 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 11.5 **D2:** 10.5	More SER treated patients had reemergence of sexual dysfunction than nefazadone-treated (76% vs. 26%; $P < 0.001$); similar response rate for both treatments (numerical data NR)	**Overall adverse events:** **D1:** 100 **D2:** 97 **Sexual dysfunctional (male ejaculation):** **D1:** 76 **D2:** 26	**Overall attrition rate:** 32% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Goldstein et al., 1997 **Country and setting:** United States multicenter, outpatient trial **Funding:** Lilly	**Research objective:** To assess effect of FLUO 20 mg/d on weight loss in older patients **Duration of study:** 6 wks (after a 1-wk placebo lead-in) **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Adults 60+ **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Clinically sig medical disease • Suicidal tendencies • Score less than 25 on MMSE • History of allergic reaction to FLUO • History of nonresponse to at least 2 antidepressants at usual doses	**Mean age (yrs):** **D1:** 68 **D2:** 68 **Sex (% female):** **D1:** 55 **D2:** 55 **Race (% white):** **D1:** 94 **D2:** 94 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Mean change (SD) in body weight: Low/normal BMI: FLUO -0.88 (2.11) Placebo 0.11 (1.96) (P < 0.001) High BMI: FLUO -1.14 (1.99) Placebo 0.04 (1.72) (P < 0.001) Pooled: FLUO -1.01 (2.05) Placebo 0.08 (1.85) (P < 0.001) % with weight loss of at least 5% low/normal BMI: FLUO 2.4 Placebo 1.1 (P = 0.225) High BMI: FLUO 3.7 Placebo 0 (P = 0.021) Pooled: FLUO 3.1 Placebo 0.6 (P = 0.017)	**Cardiovascular adverse events:** **D1:** 2.7 **D2:** 3.3 **Changes in weight (decrease):** **D1:** 3.3 **D2:** 1.2	**Overall attrition rate:** NR **ITT Analysis** No another type of analysis was used (define): included patients with complete data only **Quality rating:** Fair for AE reporting

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **Country and setting:** United States University **Funding:** Organon, Inc	**Research objective:** To assess clinical efficacy and safety of "Org 3770" (MIR) and TRA in treatment of elderly outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Age 55+ • Able to complete Zung Self Rating Depression Scale • Chloral hydrate (500 mg) at bedtime was permitted **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos of baseline • Suicidal tendencies • Rapid placebo responders (reduction of 20%+ in total HAM-D score)	**Mean age (yrs):** **D1:** 63 **D2:** 61 **D3:** 62 **Sex (% female):** **D1:** 42.9 **D2:** 60.4 **D3:** 59.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.6 **D3:** 23.5	On 21-item HAM-D, diffs between MIR and placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig) Mean weight gain in MIR group = 1.3 kg	**Cardiovascular adverse events:** **D1:** 2% Tachycardia; 4% Palpitations **D2:** 12% Tachycardia; 12% Palpitations **D3:** 2% Tachycardia; 2% Palpitations **Constipation:** **D1:** 18 **D2:** 24 **D3:** 16 **Dizziness:** **D1:** 22 **D2:** 27 **D3:** 8 **Headache:** **D1:** 14 **D2:** 20 **D3:** 20 **Nausea:** **D1:** 10 **D2:** 14 **D3:** 14 **Somnolence (fatigue):** **D1:** 54 **D2:** 55 **D3:** 22	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Harto et al., 1988 **Country and setting:** United States NR **Funding:** Not Reported	**Research objective:** To determine if FLUO produces weight loss and to examine predictive factors **Duration of study:** 6 wks **Study design:** Cannot determine **Overall study N:** 35 **Intervention:** **D1:** Placebo **D2:** Fluoxetine 5mg **D3:** Fluoxetine 20 **D4:** Fluoxetine 40	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Investigational drug is within last 28 days • Additional mental illnesses or organic mental disorder • Concomitant psychotheraputic or psychtropic medications • History of seizure	**Mean age (yrs):** **D1:** 39 **D2:** 38.4 **D3:** 43.8 **D4:** 36.4 **Sex (% female):** **D1:** 75 **D2:** 50 **D3:** 70 **D4:** 56 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	FLUO reduces sig reduction of body mass in depressed patients BMI change score- at wk 6 a statistically sig diff was evident between placebo and FLUO (F 3.23) = 6.81 ($P < 0.002$)	NR	**Overall attrition rate:** NR **ITT analysis:** No **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Jick et al., 2004 **Country and setting:** UK General practices using GPRD **Funding:** Boston Collaborative Drug Surveillance Program	**Research objective:** To estimate risk ratios of nonfatal suicidal behavior in patients starting treatment with 1 of 3 antidepressant drugs vs. patients starting treatment with dothiepin **Duration of study:** 1993-1999 **Study design:** Matched case-control **Overall study N:** 159,810 **Intervention:** **D1:** Case **D2:** Controls	**Inclusion criteria:** • Using anti-depressants **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** **D1:** 65.4 **D2:** 66.8 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	**Suicidal behavior risk:** **D1:** RR 1.16 (95% CI 0.90-1.50) **D2** vs **D3:** RR 1.29 (95% CI 0.97-1.70) Suicide risk increased in first mo after starting antidepressants, especially during first 9 days (RR 4.07; 95% CI 2.89-5.74)	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** N/A

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Jick et al., 1995 **Country and setting:** UK General practices in UK using VAMP database **Funding:** Various pharmaceutical companies (Berlex, Boots, Burroughs Wellcome, Ciba-Geigy, Hoeschst, Hoffman-LaRoche, RW Johnson, Pfizer, Proctor and Gamble, Sanofi Winthrop)	**Research objective:** To estimate rate and means of suicide among people taking 10 commonly prescribed antidepressants **Duration of study:** Patient records from Jan 1988 to Feb 1993 **Study design:** Cohort study with nested case-control analysis **Overall study N:** 172,598 **Intervention:** Fluoxetine Trazodone Dothiepin Amitriptyline Clomipramine Imipramine Flupenthixol Lofepramine Mianserin Doxepin	**Inclusion criteria:** • Received a prescription for 1 or more antidepressant in VAMP database (General Practice Research Database) • All patients who committed suicide identified in cohort evaluation were included as cases **Exclusion criteria:** • Not reported	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	143 sucides within 6 mos of using antidepressants Rates of suicide higher in men than women (RR 2.8, 95% CI: 1.9 - 4.0), people with history of feeling suicidal (RR 19.2, 95% CI: 9.5 - 38.7), and people who had taken several different antidepressants (RR 2.8, 95% CI: 1.8 - 4.3) From cohort analysis: overall rate of suicide for all antidepressant users: 8.5/10,000 person yrs (95% CI 7.2 - 10.0); FLUO: 19.0/10,000, adjusted RR: 2.1 (95% CI 1.1-4.1); TRA: 14.8/10,000, adjusted RR: 1.7 (95% CI 0.6 - 4.6), both relative to dothiepin Compared with dothiepin, only FLUO and mianserin yielded RRs that were sig raised	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Jick et al., 1992 **Country and setting:** United Kingdom General practice **Funding:** Burroughs Wellcome	**Research objective:** Evaluate whether FLUO causes important increased risk of suicidal behavior by reiviewing previously gathered data from practitioners **Duration of study:** Jan 1988 to April 1990 **Study design:** Database review **Overall study N:** 8730 **Intervention:** Mianserin and Lofepramine **D1:** Fluoxetine **D2:** Trazodone	**Inclusion criteria:** • Age 15 to 74 • Patients who received a px for FLUO, lofepramine, mianserin, or TRA. From this list, all who had diagnosis of aggressive, abusive, suicidal behavior **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUO does not directly cause suicidal behavior at a substantially higher frequency than do lofepramine, mianserin, and TRA	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Johnston et al., 1991 **Country and setting:** United States Multicenter (102 sites) **Funding:** Burroughs Wellcome	**Research objective:** To determine incidence of seizures associated with use of BUP **Duration of study:** 8 wk treatment stage with unlimited humanitarian continuation phase **Study design:** Uncontrolled, open-label trail **Overall study N:** 3341 **Intervention:** **D1:** Bupropion: 300-450 mg/d	**Inclusion criteria:** • Adults 18 and over • Diagnosis of depression for which antidepressant treatment was clinically appropiate **Exclusion criteria:** • Pregnant • Lactating • Investigational drug use within last 30 days • Previous diagnosis of bulimia or anorexia nervosa • Known predisposition of seizures	**Mean age (yrs):** Overall: 43.5 **Sex (% female):** Overall: 59.4 **Race (% white):** Overall: 96 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Observed seizure rate was 0.24% for treatment phase and 0.40% for entire study. 8-wk survival analysis performed on patients with a dosing regimen of 300 to 450 mg/d yielded a cumulative rate of 0.36% Rate of seizure for BUP within range of other antidepressants	NR	**Overall attrition rate:** 39% **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Judge et al., 2002 **Country and setting:** Multinational; outpatient **Funding:** Eli Lillly	**Research objective:** To compare mean number of interruption-emergent events during 3 to 5 day placebo interruption period in remitted, depressed patients on maintenance therapy with FLUO or PAR **Duration of study:** Placebo interruption period = 3-5 days, but unclear total duration of observation **Study design:** Open-label, parallel-group study with double-blind, crossover, placebo interruption phase **Overall study N:** 150 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 20-50 mg/d	**Inclusion criteria:** • Adults 18 and older • Unipolar depression on effective maintenance with FLUO or PAR • Current maintenance lasting between 4 and 24 mos • MADRS ≤ 12 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Seizure within last yr	**Mean age (yrs):** **D1:** 41.5 **D2:** 44.7 **Sex (% female):** **D1:** 80 **D2:** 73.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUO group experienced fewer interruption-emergent symptoms (DESS mean diff in change = -2.4 with 95% CI = -3.9 to -1.0; *P* = 0.001) than PAR group Symptoms occuring sig more in PAR patients were: panic, depersonalization, shaking, muscle aches, dyspnoe, stomach cramps, agitation, sleeping problems, dizziness, chills, vomiting, nausea or diarrhea, parasthesia	**Diarrhea:** **D2:** 10+ **Dizziness:** **D2:** 33+ **Headache:** **D1:** 14 **D2:** 10+ **Insomnia:** **D2:** 20+ **Nausea:** **D2:** 20+ **Somnolence (fatigue):** **D1:** 17 **D2:** 20+ **Suicidality:** **Sweating (increase):** **D2:** 20+	**Overall attrition rate:** 6% **ITT Analysis** N/A: Cannot tell if ITT was used; however, attrition was so low that ITT would have made little diff in results **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Keene et al., 2005 **Country and setting:** United States IHCIS National Managed Care Benchmark Database **Funding:** GlaxoSmithKline	**Research objective:** To evaluate differential compliance rates between IR SSRIs and CR SSRIs in patients initiating SSRI therapy **Duration of study:** 6 mos of follow-up **Study design:** Observational **Overall study N:** 116,090 **Intervention:** Citalopram Escitalopram Fluoxetine Paroxetine(IR and CR formulations) Sertraline **D1:** SSRI IR **D2:** Paroxetine CR	**Inclusion criteria:** • Adults 18 and older • Anxiety or depression according to ICD9CM • Patients with an SSRI script but no diagnosis also included **Exclusion criteria:** • Antidepressant in 6 mos prior to index date, continuously eligible for 6 mos prior to index date and during follow-up period • Patients with a psychosis-related diagnosis of schizophrenia or bipolar disorders • Antipsychotic within 6 mos previous to or within 1 yr of index date	**Mean age (yrs):** **D1:** 42.9 **D2:** 41.8 **Sex (% female):** **D1:** 69.3 **D2:** 62.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	After controlling for baseline covariates (age, gender, insurance type, titration rates, mental health specialty care, diagnoses, and comorbidity) patients initiating IR SSRIs were 13.6% less likely to be compliant than patients initiating par CR (P = 0.0001) Patients on PAR IR least likely to be compliant when compared to PAR CR (21.2% less likely, P = 0.0001), followed by ESC (15.0% less likely, P = 0.0179), SER (12.3% less likely, P = 0.0005), CIT (9.1% less likely, P = 0.0114), and FLUO (8.4% less likely, P = 0.0250)	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Kennedy et al., 2000 **Country and setting:** Canada Depression clinic **Funding:** Centre for Addiction and Mental Health Foundation	**Research objective:** To evaluate disturbances in sexual drive/desire and arousal/orgasm in depressed patients who completed 8 wks of study **Duration of study:** 14 wks (primary endpoint is 8 wks) **Study design:** Prospective cohort study **Overall study N:** 174 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Paroxetine: 10-80 mg/d **D3:** Venlafaxine: 37.5-375 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Sexual activity within past mo • Major depression with or without other secondary non-psychotic axis I disorders • No antidepressants within 2 wks (or 5 wks for FLUO) **Exclusion criteria:** • Clinically sig medical disease	**Mean age (yrs):** NR **Sex (% female):** **D1:** 84.6 **D2:** 33.3 **D3:** 61.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Men reported sig greater drug-induced impairment of drive/desire [mean (SD) = 2.26 (2.02) vs. 1.43(2.12), t = 6.23, df = 107, (P < 0.05) No signficant diffs between anti-depressants among men reporting antidepressant-induced sexual dysfunction Women showed lower rates of dysfunction on VEN compared to PAR and SER, however, only one item ("difficulty achieving orgasm") reached statistical significance (chi-sq = 8.51, df = 1, P < 0.004). for VEN vs. PAR, VEN introduced sig less difficulty with having an orgasm than PAR (chi-sq = 2.98, df = 1, P < 0.08)	NR	**Overall attrition rate:** 38.5% **ITT Analysis** N/A completer analysis only **Quality rating:** Fair for AE reporting

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Landen et al., 2005 **Country and setting:** Sweden and Norway Multicenter (13 sites) **Funding:** NR	**Research objective:** To determine: 1) concordance of sexual dysfunction AE rates between open-ended questioning and directed questioning 2) incidence of sexual side effects of CIT and PAR 3) correlation between sexual side effects and illness severity, treatment duration and drug/dose combination **Duration of study:** 4 wks **Study design:** Non-randomized trial of AE elicitation methods embedded in RCT **Overall study N:** 119	**Inclusion criteria:** • No response to CP or px for a minimum of 4 wks prior to start of study **Exclusion criteria:** • Epilepsy	**Mean age (yrs):** 46 **Sex (% female):** 69 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	By objective 1. Side effect elicitation method: sig more patients (49 versus 6) reported sexual side effects in response to direct questioning than open questioning ($P < 0.001$) 2. Incidence of side effects by drug: no statistically sig diffs between paroxetine and paroxetine groups in sexual side effects reported or sexual dysfunction score; open-ended questioning: CIT 5%, PAR 7% ($P = 0.98$); direct questioning: CIT 44%, PAR 36% ($P = 0.37$) 3. Correlations with illness severity and treatment parameters: only weak correlation with duration of current depression episode ($P = 0.043$)	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Lopez-Ibor, 1993 **Country and setting:** Spain Database analysis **Funding:** Not reported	**Research objective:** Effect of PAR on suicidality in depressed patients **Duration of study:** Up to 6 wks **Study design:** **Database analysis** **Overall study N:** 4668 **Intervention:** **D1:** Paroxetine **D2:** Placebo	**Inclusion criteria:** • Depressed patients in a clinical trial **Exclusion criteria:** • NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	PAR and active control were sig better than palcebo in reducing suicidal thoughts and behavior from wk 1 onwards	N/A	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Mackay et al., 1997, 1999 **Country and setting:** UK General practice **Funding:** Reported as "many pharmacetical companies"	**Research objective:** To compare safety and side-effect profiles of four selective serotonin reuptake inhibitor antidepressants (SSRIs), FLUV, FLUO, SER and PAR in a cohort study **Duration of study:** NA **Study design:** Cross sectional – prescription event monitoring **Overall study N:** 50,150 **Intervention:** **D1:** Fluvoxamine **D2:** Fluoxetine **D3:** Sertraline **D4:** Paroxetine	**Inclusion criteria:** • Patients prescribed SSRIs **Exclusion criteria:** None	**Survey Response rate:** 60% **Mean age (yrs):** **D1:** 51 **D2:** 50 **D3:** 49 **D4:** 49 **Sex (% female):** **D1:** 70.1 **D2:** 69.8 **D3:** 68.6 **D4:** 67.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUV had a considerably higher incidence of side-effects associated with its use than other 3 SSRIs and 36% of GPs expressing an opinion reported FLUV as effective, compared with approximately 60% for FLUO, SER, and PAR The most common reason for stopping treatment was nausea/vomitting for all 4 SSRIs	**Dizziness:** **D1:** 9.6 **D2:** 2.7 **D3:** 2.8 **D4:** 4.0 **Headache:** **D1:** 10.1 **D2:** 5.7 **D3:** 5.4 **D4:** 4.8 **Nausea:** **D1:** 42.8 **D2:** 9.0 **D3:** 8.6 **D4:** 13.0	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Martinez et al., 2005 **Country and setting:** UK General practice research database (clinical primary care records in UK) **Funding:** Medicines and Healthcare Products Regulatory Agency	**Research objective:** To compare risk of non-fatal self harm and suicide in patients taking SSRIs with that of patients taking tricyclic antidepressants, as well as between different SSRIs and different tricyclic **Duration of study:** 1995 to 2001 **Study design:** Nested case-control study **Overall study N:** 146,095 **Intervention:** **D1:** Citalopram **D2:** Fluoxetine **D3:** Fluvoxamine **D4:** Paroxetine **D5:** Sertraline	**Inclusion criteria:** • Age < 90 • First prescription for antidepressants between 1/1/1995 and 12/31/2001 **Exclusion criteria:** • None	**Mean age (yrs):** 31 of patients in age cohort 31 to 45 yrs old **Sex (% female):** Overall: 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No diff in risk of non-fatal self harm among different SSRIs (P = 0.35) No diff in risk of self-harm between SSRIs and tricyclic antidepressants (OR: 0.99 CI: 0.86 to 1.14) No diff in risk of suicide between SSRIs and tricyclic antidepressants (OR: 0.57 CI: 0.26 to 1.25)	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Good

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Meijer et al., 2002 **Country and setting:** The Netherlands Multicenter (109 psychiatrists in general hospitals, regional institutes of mental health, or private practices) **Funding:** Pfizer, Inc	**Research objective:** To evaluate safety profile of SER versus other SSRIs directly following introduction of SER to Dutch market **Duration of study:** 12 mo observation period **Study design:** Cohort study **Overall study N:** 1,251 **Intervention:** **D1:** Sertraline **D2:** Other SSRIs (Fluoxetine Fluvoxamine Paroxetine)	**Inclusion criteria:** • All patients with a new SER prescription; consecutive patients taking FLUO, FLUV, or PAR used as controls **Exclusion criteria:** • No additional exclusion criteria were applied	**Mean age (yrs):** 41 (median) **Sex (% female):** 64.1% **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	2.2 AEs per SER patient vs. 2.1 AEs per other SSRIs patient 73.4% of SER patients and 75.0% of other SSRI patients reported an AE Diarrhea was reported more frequently by SER patients than patients taking other SSRIs ($P < 0.05$) Abdominal pain was reported more frequently by other SSRI users ($P < 0.05$) No sig diffs in serious adverse event (SAE) reporting found between SER patients (5.0%) and patients using other SSRIs (4.6%) Suicide attempt: SER: 0.9% vs. other SSRIs: 1.2%	**Overall adverse events:** **D1:** 73.4 **D2:** 75 **Cardiovascular adverse events:** **D1:** 3.2 **D2:** 2.2 **Diarrhea:** **D1:** 14 **D2:** 6.8 **Dizziness:** **D1:** 11.4 **D2:** 11.8 **Headache:** **D1:** 19.3 **D2:** 17.1 **Insomnia:** **D1:** 8 **D2:** 5.9 **Nausea:** **D1:** 24.3 **D2:** 27 **Sexual dysfunctional (male ejaculation):** **D1:** 2.1 **D2:** 3.7 **Sweating (increase):** **D1:** 13.4 **D2:** 11.7	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Michelson et al., 1999 (goes with Reimherr et al., 1998) **Country and setting:** United States Academic centers (5 sites) **Funding:** Eli Lilly	**Research objective:** To assess changes in weight during long-term treatment with FLUO or placebo **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 839 acute phase 395 remission phase **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 **Exclusion criteria:** • None reported	**Mean age (yrs):** **D1:** 40.8 **D2:** 42.2 **Sex (% female):** **D1:** 68.3 **D2:** 73.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No diff in weight change between FLUO and placebo groups after 50 wks (1.6 kg vs. 1.6 kg)	**Changes in weight (increase):** **D1:** 1.6kg **D2:** 1.6kg	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Montejo et al., 2001 **Country and setting:** Spain Multicenter **Funding:** Bristol-Myers Squibb	**Research objective:** Incidence of sexual dysfunction associated with anti-depressant agents **Duration of study:** Carried out between April 1995 and February 2000 **Study design:** Prospective cohort study **Overall study N:** 1,022 **Intervention:** Citalopram Fluoxetine Fluvoxamine Mirtazapine Nefazodone Paroxetine Sertraline Venlafaxine	**Inclusion criteria:** • Normal sexual functioning prior to taking antidepressants • Treatment with antidepressant alone or combine with benzodiazepine • Previous regular and satisfactory sexual practices • Occurrence of sexual dysfunction within 2 mos after introduction of antidepressant **Exclusion criteria:** • Prior sexual dysfunction • Combination of antidepressant and neuroleptic treatment • Treatment with hormones or any other drug capable of interfering with sexual intercourse • Sig intercurrent diseases affecting sexual function • Substance abuse	**Mean age (yrs):** Overall: 39.8 **Sex (% female):** Overall: 60 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Overall incidence of sexual dysfunction was 59.1% Incidence of overall sexual dysfunction: FLUO, 57.7% SER, 62.9% FLUV, 62.3% PAR, 70.7% CIT, 72.7% VEN, 67.3% MIR, 24.4% NEF, 8% Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nemeroff et al., 1995 **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and SER in treatment of depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 95 **Intervention:** **D1:** Sertraline: 50-200 mg/d (137.1) **D2:** Fluvoxamine: 50-150 mg/d (123.8)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • HAM-D depressed mood item of at least 2 • Covi anxiety score less than Raskin score • Minimum score of 8 on Raskin Depression Scale **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Patients itolerant of SSRI side effects	**Mean age (yrs):** **D1:** 41.2 **D2:** 38.5 **Sex (% female):** **D1:** 60.9 **D2:** 61.2 **Race (% white):** **D1:** 84.8 **D2:** 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.15 (2.77) **D2:** 24.57 (3.66)	Both treatment groups resulted in sig improvements of depression scores compared to baseline No sig diff in efficacy between treatment groups	**Overall adverse events:** **D1:** 93.5 **D2:** 85.7 **Diarrhea:** **D1:** 23.9 **D2:** 14.3 **Dizziness:** **D1:** 15.2 **D2:** 12.2 **Headache:** **D1:** 32.6 **D2:** 26.5 **Insomnia:** **D1:** 34.8 **D2:** 26.5 **Nausea:** **D1:** 21.7 **D2:** 30.6 **Sexual dysfunction :** **D1:** 28 **D2:** 10 **Somnolence (fatigue):** **D1:** 17.4 asthenia-13 **D2:** 24.5 asthenia-6.1 **Sweating (increase):** **D1:** 10.9 **D2:** 6.1	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events	Analysis Quality Rating
Author: Philip et al., 2000 **Country and setting:** Autralia, Germany; outpatient private practice **Funding:** Not reported	**Research objective:** To compare emergent sexual effects of moclobemide and SSRIs during acute and maintenance therapy in routine practice **Duration of study:** 6 mo **Study design:** Prospective cohort study **Overall study N:** 268 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Fluvoxamine: 50-300 mg/d **D3:** Paroxetine: 10-50 mg/d **D4:** Sertraline: 50-150 mg/d **D5:** Other: moclobemide 300-1200 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Depressive disorder of at least mild severity • On either moclobemide or SSRI (FLUO, FLUV, PAR, SER) • Interested in sexual activity **Exclusion criteria:** • No combination therapy	**Mean age (yrs):** Overall: 42 **Sex (% female):** Overall: 49.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Incidence of sexual function impairment was 61.5% (Phys-SFR) with SSRIs. Male erection and ejacualation impaired in 44.3% and 39.3% of SSRI group, respectively. No statistical diff between each SSRI Higher rates in SSRI's vs. moclobemide	NR	**Overall attrition rate:** 27.2% **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Rapaport et al., 1996 **Country and setting:** United States, multicenter **Funding:** Solvay Pharmaceuticals, Inc.; The Upjohn Company	**Research objective:** To compare efficacy, safety, and tolerance of FLUV and FLUO in a depressed outpatient population **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Fluvoxamine: 100-150 mg; endpoint mean = 101.85 (25.22) **D2:** Fluoxetine: 20-80 mg; endpoint mean = 34.17 (18.84)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Minimum score of 2 on depressed mood item at screening and baseline visits (HAM-D) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with FLUO or FLUV • History of seizure disorder	**Mean age (yrs):** **D1:** 40.0 **D2:** 38.6 **Sex (% female):** **D1:** 62 **D2:** 63.2 **Race (% white):** **D1:** 92.2 **D2:** 98 **Baseline (HAM-A):** **D1:** 16.0 **D2:** 16.2 **Baseline HAM-D:** **D1:** 25.2 **D2:** 25.6	No statistically sig diffs observed between 2 groups on any efficacy parameter Medications were well tolerated, with only 2 patients in each group terminated because of side effects. FLUV was associated with less nausea than FLUO	**Headache:** **D1:** 50 **D2:** 53 **Insomnia:** **D1:** 36 **D2:** 28 **Nausea:** **D2:** 42.5 *P* = 0.030 **Suicidality:** **D1:** 2 **D2:** 2 **Vomiting** **D1:** 4 **D2:** 13	**Overall attrition rate:** 16% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schatzberg et al., 2002 **Country and setting:** United States Mutli-center (recruited from advertising, private practice, routine intake at clinics and other healthcare facilities) **Funding:** Organon Pharmacueticals	**Research objective:** To compare efficacy and tolerability of MIR with PAR in elderly patients with MDD **Duration of study:** 8 wk acute phase, optional 16 wk continuation phase **Study design:** RCT **Overall study N:** 255 **Intervention:** **D1:** Mirtazapine: 15 mg/d up to 45 mg/d **D2:** Paroxetine: 20 mg/d up to 40 mg/d	**Inclusion criteria:** • Adults 65 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 • MMSE above 25% for age and educational level **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicide attempts • MAOIs within 14 days, other psychotropic drugs or herbals within 7 days • PAR or MIR for current depressive episode • Patients requiring drugs for memory deficit • Patients who did not respond to or tolerate MIR or PAR during a previous depressive episode	**Mean age (yrs):** **D1:** 71.7 **D2:** 72.0 **Sex (% female):** **D1:** 50% **D2:** 53% **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.2 (3.5) **D2:** 22.4 (3.5)	CGI-I responders (CGI-I of much or very much improved) At endpoint MIR (80) 64.0% PAR (68) 56.7% chi square 1.23 (P = 0.267)	**Overall adverse events:** **D1:** 79.7 **D2:** 82.5 **Changes in weight (increase):** **D1:** 10.9 **D2:** 0 **Constipation:** **D1:** 11.7 **D2:** 11.1 **Diarrhea:** **D1:** 14.8 **D2:** 17.5 **Dizziness:** **D1:** 15.6 **D2:** 14.3 **Headache:** **D1:** 15.6 **D2:** 24.6 **Insomnia:** **D1:** 11.7 **D2:** 11.1 **Nausea:** **D1:** 6.3 **D2:** 19.0 **Somnolence (fatigue):** **D1:** 30.5 **D2:** 29.4 **Sweating (increase):** **D1:** 6.3 **D2:** 13.5	**Overall attrition rate:** 26.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thapa et al., 1998 **Country and setting:** United States 53 rest homes **Funding:** CDC and FDA	**Research objective:** To compare rate of falls between nursing home residents using SSRIs and TCAs **Duration of study:** N/A **Study design:** Observational **Overall study N:** Cohort- 2,428 **Intervention:** **D1:** Non-users (847) **D2:** TCAs (665) **D3:** SSRIs (612) **D4:** Trazodone (304)	**Inclusion criteria:** • Adults 65 or older • Nursing home residents who were new users of antidepressants, in facility more than 30 days **Exclusion criteria:** NR	**Mean age (yrs):** **D1:** 83 **D2:** 82.1 **D3:** 82.1 **D4:** 82.2 **Sex (% female):** **D1:** 75.9 **D2:** 75.2 **D3:** 74 **D4:** 73 **Race (% black):** **D1:** 13.2 **D2:** 5.1 **D3:** 5.9 **D4:** 6.6 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Rate of falls per 100 person-yr PAR- 301 RR 95% CI 2.3 (2.1-2.6) Adjusted RR 1.7 (1.5-1.9) FLUO- 314 RR 95% CI 2.4 (2.1-2.8) Adjusted RR 1.8 (1.6-2.1) SER- 342 RR 95% CI 2.6 (2.3-3.0) Adjusted RR 1.8 (1.5-2.1) TRA- 244 RR 95% CI 1.9 (1.7-2.1) Adjusted RR 1.2 (1.0-1.4)	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A Retrospective Cohort **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani et al., 2005 **Country and setting:** Multinational, Multicenter (30 sites) **Funding:** Organon, NV	**Research objective:** To compare effectiveness and tolerability of MIR and FLUO in severe MDD and compare effects on anxiety, sleep and QOL **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 **Intervention:** **D1:** Mirtazapine: 30-60 mg **D2:** Fluoxetine: 20-40 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 47 **Sex (% female):** **D1:** 74 **D2:** 69 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 29 (3) **D2:** 28(3)	No sig diff in percent of responders at day 56, (MIR: 40.1% vs. FLUO: 41.4 %) Both treatment groups showed 18 point improvement on QLSQ	**Overall adverse events:** **D1:** 50 **D2:** 45 **Changes in weight (increase):** **D1:** 6.9 **D2:** 1.3 **Dizziness:** **D1:** 9 **D2:** 12.8 **Headache:** **D1:** 19.3 **D2:** 18.8 **Insomnia:** **D1:** 4.8 **D2:** 8.7 **Nausea:** **D1:** 15.9 **D2:** 24.1 **Somnolence (fatigue):** **D1:** 13.8 **D2:** 9.4	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2000 **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and safety of BUP and PAR with PAR in treatment of MDD in elderly **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 10-40 mg/d (22)	**Inclusion criteria:** • Adults 60+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 69.2 **D2:** 71.0 **Sex (% female):** **D1:** 54 **D2:** 60 **Race (% white):** **D1:** 98 **D2:** 90 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in any outcome measures between treatment groups (LOCF and observed) Response rates ≥ 50% reduction in HAM-D) were similar in both groups: BUP sr: 71% PAR: 77% No sig diffs in QOL scales (QLDS, SF-36) between treatment groups at endpoint; overall sig improvement in QLDS and QOL at day 42 ($P < 0.0001$) Compliance: BUP 95% PAR 98%	**Constipation:** **D1:** 4 **D2:** 15 **Diarrhea:** **D1:** 6 **D2:** 21 **Dizziness:** **D1:** >10 **D2:** >10 **Headache:** **D1:** 35 **D2:** 19 **Insomnia:** **D1:** >10 **D2:** >10 **Nausea:** **D1:** >10 **D2:** >10 **Somnolence (fatigue):** **D1:** 6 **D2:** 27	**Overall Attrition Rate:** 16% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weisler et al., 1994 **Country and setting:** Country NR, appears to be United States 2 private psychopharma-cology clinics **Funding:** Burroughs Wellcome Co	**Research objective:** To compare safety and efficacy of BUP and TRA **Duration of study:** 6 wks (after a 1 wk single-blind placebo lead-in to eliminate placebo responders and placebo nontolerators) **Study design:** RCT **Overall study N:** 124 **Intervention:** **D1:** Bupropion: 225-450 mg/d **D2:**Trazodone: 150-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Episode of 4 wks to 2 yrs • Clinically approrpiate for therapy **Exclusion criteria:** • Pregnant/Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Male with a history of priapism or being treated with medications associated with priapism • Prior treatment with BUP or TRA, currently taking digoxin or phenytoin	**Mean age (yrs):** **D1:** 40.2 **D2:** 40.8 **Sex (% female):** **D1:** 52.4 **D2:** 65.6 **Race (% white):** **D1:** 90.5 **D2:** 90.2 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 25.8 (NR) **D2:** 25.0 (NR)	HAM-D (LOCF) Center 1 BUP: at day 42, BUP stat sig better than TRA ($P < 0.01$) When centers were combined, no statistically sig diffs between TRA and BUP were observed Responder analysis (responder ≥ 50% reduction in HAM-D score between baseline and discontinuation) BUP = 33 (55.9%) TRA = 21 (40.4%) Remitters (>50% reduction and a HAM-D score<10) BUP = 27 (46%) TRA = 16 (31%) CGI-I responders BUP = 34 (57.6%) TRA = 24 (46.2%) Compliance BUP 94.7% TRA 90.1%	**Constipation:** **D1:** 9.68 **D2:** 11.67 **Diarrhea:** **D1:** 4.84 **D2:** 11.67 **Dizziness:** **D1:** 20.97 **D2:** 30.00 **Headache:** **D1:** 33.87 **D2:** 23.33 **Insomnia:** **D1:** 14.52 **D2:** 5.00 **Nausea:** **D1:** 11.29 **D2:** 6.67 **Somnolence (fatigue):** **D1:** 8.06 **D2:** 45.00 **Sweating (increase):** **D1:** 9.68 **D2:** 5.00	**Overall attrition rate:** 40.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Wheatley et al., 1998 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in depressed inpatients and outpatients **Duration of study:** 6 wks (after a 3-7 day single-blind, placebo washout period) **Study design:** RCT **Overall study N:** 133 **Intervention:** **D1:** Mirtazapine: 15-60 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • HAM-D item 1 (depressed mood) score ≥ 2 • Depressive episode duration 2 wks to 12 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Nonresponders to antidepressant treatment	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.5 **Sex (% female):** **D1:** 55 **D2:** 58.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 26.0 (4.4) **D2:** 26.1 (4.3)	HAM-D responders at endpoint (≥ 50% improvment) MIR ~65% (n = 39) FLOU ~45% (n = 28) (*P* = NS) Remission from depression (HAM-D < 7 at endpoint): MIR 23.3% FLUO 25.4% (*P* = 0.39) CGI responders (much or very much approved): MIR 63.3% FLUO 54.0% (*P* = 0.677) Q-LES-Q estimated treatment diff (MIR minus FLUO): 2.14 95% CI (-2.30, 6.58) (*P* = 0.348)	**Dizziness:** **D1:** 7.6% **D2:** 9.0% **Headache:** **D1:** 9.1% **D2:** 17.9% **Nausea:** **D1:** 3.0% **D2:** 10.4% **Somnolence (fatigue):** **D1:** 18.2% **D2:** 13.4%	**Overall attrition rate:** 28.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Whyte et al., 2003 **Country and setting:** Australia Hospital (Hunter Area Toxicology Service Database) **Funding:** NR	**Research objective:** To assess toxicity in overdose of venlafaxine and SSRIs compared to TCAs **Duration of study:** Taken from database records between November 1994 and April 2000 **Study design:** Cohort study of prospectively collected data **Overall study N:** 538 (284 venlafaxine and other SSRI records) **Intervention:** **D1:** Venlafaxine **D2:** Other SSRIs	**Inclusion criteria:** • First time admissions for overdose with an SSRI or TCA **Exclusion criteria:** • Patients who took a MAOI • Patients ingesting more than one drug of interest • Second and subsequent admissions for deliberate DSPs	**Mean age (yrs):** **D1:** 36 **D2:** 29 **Sex (% female):** **D1:** 68.6 **D2:** 67 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Overdosing and seizure experience on venlafaxine: **D1:** 13.7% **D2:** 1.3% ($P < 0.001$) Overdosing required ICU admission: **D1:** 29.4% **D2:** 7.3% ($P < 0.01$) No other sig diffs between venlafaxine and SSRI overdoses	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Good

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Aursnes et al., 2005 **Country and setting:** NR **Funding:** None	**Study design:** Pooled analysis **Number of Patients:** 1,466 **Studies Included:** 16 studies with unpublished data	**Included Studies:** Clinical data on paroxetine as presented to world's drug regulatory agencies in 1989 **Included Populations** NR **Interventions:** Paroxetine versus placebo, no other info provided	**Study Results:** 7 suicide attempts in patients on drug and 1 in a patient on placebo. Probability of increased intensity of suicide attempts per yr in adults taking paroxetine was 0.90 with a "pessimistic" prior, and somewhat less with 2 more neutral priors	NR	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** NR **Quality Rating:** Fair

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Brambilla et al., 2005 **Country and setting**: NR **Funding:** Multinational **Research objective:** To assess frequency of side-effects in FLUO compared to other SSRIs, TCAs and other anti-depressants	**Study design:** Meta-analysis **Number of Patients:** 15,920 **Studies Included:** 131 studies	**Included Studies:** • All studies with random assigned patients that received FLUO or any other anti-depressant • Cross-over studies and those with patients with concomitant medical illness were excluded **Included Populations** Patients with MDD **Interventions:** • Fluoxetine vs. tricyclic antidepressant (65 studies) • Fluoxetine vs. SSRI (22 studies) • Fluoxetine vs. another AD (44 studies)	**Study Results:** • 59.4% of patients treated with FLUO and 59.3% of patients treated with other SSRIs experienced AEs.RR 1.00 95% CI 0.95, 1.04 • FLUO less withdrawals due to side effects than TCAs and other related Ads RR 0.61 95% CI 0.52, 0.71 but not in comparison to other SSRIs RR 1.04 95% CI 0.84, 1.29 • FLUO had less side effects (50.9%) than TCAs (60.3%) RR = 0.84 95% CI 0.76 to 0.94(P = 0.03) • FLUO patients had more activating and GI adverse effects and less cholinergic side effects than other ADs	NR	**Publication Bias:** Yes **Heterogeneity**: Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Fergusson et al., 2005 **Country and setting:** Canada **Funding:** Canadian Institutes of Health Research **Research objective:** To establish if an association exists between SSRI use and suicide attempts	**Study design**: Systematic review **Number of Patients:** 36,445 **Studies Included**: 345 RCTs	**Included Studies:** RCTs comparing an SSRI with either placebo or an active non-SSRI **Included Populations** • All patients included in trials comparing SSRIs to either placebo or non-SSRI control • No age, gender, or diagnosis restrictions **Interventions:** Patients randomized to either an SSRI, placebo, or non-SSRI control for any clinical condition	**Study Results:** A sig increase in odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving placebo (OR: 2.28; CI: 1.144 - 4.55, *P* = 0.02) No diffs in actual suicides between SSRIs and placebo were found (OR: 0.95; CI: 0.24-3.78) No sig diff found in odds of suicide attempts between patients receiving SSRIs and patients receiving tricyclic antidepressants (OR: 0.88; CI: 0.54 - 1.42)	NR	**Publication Bias:** NR **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes--independent review of all citations by 3 authors **Comprehensive Search Strategy:** Yes Systematic literature search to identify all RCTs of SSRIs indexed on Medline between 1967 and 2003; search of Cochrane Collaboration's register of controlled trials for trials produced by Cochrane depression, anxiety, and neurosis group; reviewed biliographies of 3 systematic reviews to identify relevant trials and reports **Quality Rating:** Good

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Greist et al., 2004 **Country and setting:** US (6 studies); Europse (2 studies) **Funding:** Eli Lilly **Research objective:** To assess incidence, severity and onset of nausea among MDD patients treated with DUL	**Study design:** Pooled analysis **Number of Patients:** 2,345 **Studies Included:** • Detke et al., 2002 • Detke et al., 2002 • Goldstein et al., 2002 • Goldstein et al., 2004 • 4 unpublished studies submitted for FDA approval of DUL	**Included Studies:** Double-blind, randomized, placebo or active-controlled trials of DUL **Included Populations** Adult outpatients with MDD **Interventions:** • Duloxetine vs. Placebo (8 studies) • Duloxetine vs. Paroxetine (4 studies) • Duloxetine vs. Fluoxetine (2 studies)	**Study Results:** No sig diffs in nausea between DUL (40-120 mg/d), PAR (20 mg/d) (14.4% vs. 12%, *P* -NR), and FLUO (20mg) (17.1% vs. 15.7%, *P* -NR) No sig diffs between DUL (120 mg/d) and FLUO (20 mg/d) (17.1% vs. 15.7%, *P* -NR) Sig more DUL- than placebo-treated patients reported nausea (19% vs. 6.9%, $P < 0.001$) Incidence of treatment-emergent nausea dudring 6-mo continuation of DUL (80 mg/d or 120 mg/d) was similar to placebo (2.1% vs. 1.3% vs. 1.6%) Following abrupt discontinuation after 8 mos of treatment, nausea was reported by 1.6% of DUL (120 mg/d) patients vs. 0% for those receiving DUL (80 mg/d) and 0% for placebo	NR	**Publication Bias**: No **Heterogeneity**: No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No; analysis of all published and unpublished trials **Quality Rating:** N/A

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Gunnell et al., 2005 **Country and setting:** Multinational **Funding:** NR **Research objective**: To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults	**Study design:** Meta-analysis **Number of Patients:** 40,826 **Studies Included:** • Published and unpublished data submitted by pharmaceutical companies to Medicine and Healthcare Products Regulatory Agency (MHRA) (2004) • 342 placebo controlled trials included in report – citations not given in bibliography	**Included Studies:** Randomized, placebo controlled trials of SSRIs (CIT, ESC, FLUO, FLUV, PAR, and SER) submitted by pharmaceutical companies **Included Populations** Adult patients with various indications included in trials comparing SSRIs to placebo **Interventions:** Patients randomized to either SSRI or placebo	**Study Results:** No sig diff was found between SSRI treatment and placebo treatment in odds ratios for suicide (OR: 0.85 CI: 0.2 to 3.4), or suicidal thought (OR: 0.77 CI: 0.37 to 1.55) Non-fatal self harm (OR: 1.57 CI: 0.99 to 2.55) was more common in SSRI-treated than in placebo treated patients but did not reach statistical significance. For non-fatal self-harm NNH is 759	NR	**Publication Bias:** Yes **Heterogeneity:** Yes, vaguely	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies) **Quality Rating:** Good

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Khan et al., 2003 **Country and setting:** US **Funding:** NR **Research objective:** Compare suicide rates among depressed patients	**Study design:** Meta-analysis **Number of Patients:** 48,277 **Studies Included:** • Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs • 2000 publication reports on 1987 to 1997 (same data)	**Included Studies:** FDA clinical trial data **Included Populations** • Major depression according to DSM-III-R criteria • Minimum score of 18 or 20 on HAM-D-17 or HAM-D-21 **Interventions:** Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine, Nefazodone, Mirtazapine, Bupropion, Venlafaxine, Imipramine, Amitrptyline, Maprotiline, Trazodone, Mianserin, Dothiepin	**Study Results:** No statistically sig diff in suicide rates between SSRIs, other antidepressants, and placebo ($P > 0.05$) Absolute Suicide Rate • SSRI: 0.15% (0.10-0.20% 95% CI) • "Other": 0.20% (0.09-0.27% 95% CI) • Placebo: 0.10% (0.01-0.19% 95% CI) • $P > 0.05$ for diff Suicide Rate by Patient Exposure Yrs (PEY) • SSRI: 0.59%/PEY (0.31-0.87 95% CI) • "Other": 0.76%/PEY (0.49-1.03 95% CI) • Placebo: 0.45%/PEY (0.01-0.89 95% CI) • $P > 0.05$ for diff	NR	**Publication Bias:** NR **Heterogeneity**: No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Nieuwstraten and Dolovich, 2001 **Country and setting:** Canada **Funding:** NR	**Study design:** Meta-analysis **Number of Patients:** 1,332 **Studies Included:** • Kavoussi RJ et al. 1997 • Segraves RT, et al. 2000 • Weihs KL, et al. 2000 • Croft H, et al. 1999 • ColemanCC, et al. 1999 • Feighner JP, et al. 1991	**Included Studies:** • RCTs • Study durations: 6 to 16 wks • Median 7 wks **Included Populations** • Age: 36 to 70 yrs • Proportion of females: 48.0% to 61.8% **Interventions:** Bupropion vs. sertraline (3 trials) Bupropion vs. paroxetine (1 trial) Bupropion vs. fluoxetine (1 trial)	**Study Results:** Results of HAM-D scores and CGI-I scores could not be pooled due to unavailability of data; weighted mean diffs of CGI-S and HAM-A scores not sig different between bupropion and SSRIs	**Adverse Events:** Nausea, diarrhea, and somnolence occurred sig less frequently in BUP group compared to SSRI group RR: nausea: 0.6 (95%CI: 0.41-0.89), diarrhea: 0.31 (95%CI: 0.16-0.57), somnolence: 0.27 (95% CI: 0.15-0.48). Satisfaction with sexual function was sig less in SSRI group RR: 1.28 (95% CI: 1.16-1.41)	**Publication Bias:** No **Heterogeneity:** Yes- indirectly	**Standard Method of Study Appraisals:** Yes **Quality Rating:** Good **Comprehensive Search Strategy:** Yes

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Pedersen, 2005 **Country and setting:** Denmark **Funding:** Drug Development, H. Lundbeck A/S	**Study design:** Retrospective cohort study **Number of Patients:** 4091 **Studies Included:** 12 placebo-controlled studies and 2 relapse prevention studies	**Included Studies:** Studies are from adult clinical database at H. Lund **Included Populations** Adult outpatients with MDD (2,277) or anxiety (371) **Interventions:** Escitalopram and placebo	**Study Results:** MADRS item 10 (suicidal thoughts): ESC patients had fewer suicidal thoughts than placebo from wks 1 ($P < 0.05$) to 8 ($P < 0.001$) Suicides in placebo-controlled studies: ESC n = 0 Rate = 0 Incidence = 0 Placebo n = 1 Rate = 0.003 Incidence = 0.1 Non-fatal self harm in placebo controlled studies: ESC n = 5 Rate = 0.011 Incidence = 0.2 Placebo n = 1 Rate = 0.003 Incidence = 0.1	NR	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Yes **Quality Rating:** Fair **Comprehensive Search Strategy:** No

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Perahia et al., 2005 **Country and setting:** NR **Funding:** Eli Lilly and Company **Research objective:** To characterize DEAEs of DUL hydrochloride	**Study design:** Pooled analysis (9 trials: 6 short-term treatment trials, 2 extension trials and 1 open trial) **Number of Patients:** 3,624 **Studies Included:** 9 multicenter clinical trials assessing efficacy and safety of DUL in treatment of major depressive disorder	**Characteristics of Included Studies:** • Conducted in US, Europe, and Latin America • 8 studies randomized, double blind, placebo controlled trials, examining 8-9 wks of acute treatment (2 had 26-wk placebo-controlled extension phase and grouped as long-term treatment) • 1 study was a 52-wk open-label trial **Characteristics of Included Populations** • Depression defined by DSM-IV • Baseline total HAMD-17≥15 • Baseline CGI-S >+4 **Characteristics of Interventions:** • DUL (40-120 mg/d) • DUL discontinued, followed by lead-out phase of 1 or 2 wks • Placebo-controlled trials, placebo given during lead-out phase	**Study Results:** In 6-study pooled analysis, significanlty more DUL patients (44.3%) had > 1 DEAE than placebo (22.9%) (*P* = NR). Dizziness most common symptom in all groups analyzed. Mild, moderate, and severe DEAEs were 39.8%, 50.6%, and 9.6% for DUL vs. 46%, 48.9%, and 5.0% for placebo. Withdrawal due to DEAEs occured in 3.1% of DUL patients and 0% of placebo. A higher, but nonlinear, incidence of DEAEs was seen with 120 mg/d compared to lower doses In 2 long-term studies, significanlty more DUL patients (9.1%) had > = 1 DEAE than placebo-treated (2.0%) (*P* = NR). Mild, moderate, and severe DEAEs were 70.6%, 26.5%, and 2.9% for DUL group. No difference in DEAEs between 80 and 120 mg/d groups. 47.5% of DEAEs resolved prior to final contact with study patients. In open label study 50.8% reported ≥1 DEAE	**Adverse Events:** Events registered as DEAEs if they occured for first time or worsened following discontinuation of treatment. Observation period for DEAEs was 2 wks	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Not described **Comprehensive Search Strategy:** Not described **Quality Rating:** Fair

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Thase et al., 2005 **Country and setting:** Multinational **Funding:** Eli Lilly and Mental Health Intervention Center	**Study design:** Pooled analysis **Number of Patients:** 2,345 **Studies Included:** 8 placebo-controlled studies	**Included Studies:** • Placebo-controlled studies **Included Populations** • 18 yrs of age or older • Current primary MDD diagnosis as defined in DSM-IV • HAM-D score >15 • CGI-S score >4 **Interventions:** Duloxetine Fluoxetine Paroxetine	**Study Results:** Greater change in heart rate for DUL vs. FLUO and PAR: mean change of 2.8 bpm for DUL vs. -1.0 bpm for FLUO ($P < 0.01$); mean change of 1.0 bpm for DUL vs. -1.4 bpm for PAR ($P < 0.001$) DUL had slightly lower mean change in systolic BP than FLUO (2.3 mm Hg vs. 3.2 mm Hg) No statistically sig diffs in systolic and diastolic BP for DUL vs. FLUO or PAR Mean changes in QTcF and QRS intervals not sig different for DUL vs. PAR	N/A	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Thase et al., 1998 **Country and setting:** United States **Funding:** NR **Research objective:** To assess effects of VEN on BP	**Study design:** Meta-analysis **Number of Patients**: 3,744 **Studies Included:** Original data for statistical analysis were provided by Wyeth-Ayerst Laboratories	**Included Studies:** Acute and continuation phase data from randomized controlled trials comparing VEN with placebo and IMI (21 outpatient and 6 inpatient trials at 180 different sites) **Included Populations** • Meet DSM-III-R criteria for a current principal diagnosis of major depression • Score at least 20 on 21-item HAM-D • Have no poorly controlled or serious medical illness **Interventions:** **D1:** Venlafaxine **D2:** Imipramine **D3:** Placebo	**Study Results:** Acute phase at 6 wks: • Mean increase in supine DBP: VEN 1.02 mmHG • Sustained elevation in supine DBP: VEN: 4.8%, placebo 2.1% (P = 0.015 for crude group comparison and P = 0.086 after adjustment for age/sex) • Incidence of supine DBP > 90 mmHg: VEN: 11.5%, placebo 5.7% (P < 0.001 VEN vs placebo) Continuation Phase Results: • Mean supine DBP: no drug effect P = 0.58 • 4.5% (21 of 467) with normal supine DBPs developed elevated readings during this phase and it was sig higher in VEN group P = 0.058 • A sig dose response effect on BP was seen in VEN group (P < 0.001)	NR	**Publication Bias:** Yes **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy**: No **Quality Rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Allard et al., 2004 **Country and setting:** Sweden and Denmark Multicenter (12) **Funding:** Wyeth	**Research objective:** Compare efficacy and tolerability of VEN ER 75-150 mg/d with CIT 10-20 mg/d in elderly patients with major depression according to DSM-IV criteria **Duration of study:** 6 mos **Study design:** RCT **Overall study N:** 151 **Intervention:** **D1:** Venlafaxine: 37.5-150 mg/d **D2:** Citalopram: 10-30 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Uncontrolled hypertension, sig cardiovascular or cerebrovascular disorders	**Mean age (yrs):** **D1:** 73.6 **D2:** 72.5 **Sex (% female):** **D1:** 73.6 **D2:** 72.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No statistically sig diffs between treatments in any outcome measures (MADRS, CGI-S, CGI-I) Response rates were 93% in both groups at wk 22 MADRS remission rate was 19% for VEN and 23% for CIT (*P* = NR) Side effects were common during both treatments but differed in tremor being more common during CIT and nausea/vomiting during VEN treatment.	**Overall adverse events:** **D1:** 62 **D2:** 43 **Constipation:** **D1:** 6.6 **D2:** 2.7 **Dizziness:** **D1:** 34 **D2:** 30 **Headache:** **D1:** 26 **D2:** 31 **Nausea:** **D1:** 30 **D2:** 16 **Sweating (increase):** **D1:** 2.6 **D2:** 2.7	**Overall attrition rate:** 22.2 **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Andersen et al., 1994 **Country and setting:** Denmark 2 hospitals and an outpatient clinic **Funding:** Lundbeck Foundation	**Research objective:** To investigate efficacy and safety of CIT in treatment of post-stroke depression in post-stroke patients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 66 **Intervention:** **D1:** Citalopram: 10-40 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 25 to 80 • Minimum HAM-D score of 13 • Concomitant condition: post-stroke • Diagnosed with PSD according to DSM-III **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Subarachnoid or Binswanger's disease or other degenerative diseases • Patients with decreased consciousness, dementia, or aphasia to such a degree that they could not explain themselves or gave conflicting verbal and nonverbal signals	**Mean age (yrs):** **D1:** 68.2 **D2:** 65.8 **Sex (% female):** **D1:** 64 **D2:** 58 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 19.4 (3.1) **D2:** 18.9 (2.8)	Sig improvement was seen in patients treated with CIT compared to placebo ($P < 0.05$)	NR	**Overall attrition rate:** 13.6% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Barrett et al., 2001 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundation	**Research objective:** To compare PAR vs. placebo vs. behavioral treatment for dysthymia and minor depression in primary care patients **Duration of study:** 11 wks **Study design:** RCT **Overall study N:** 241 **Intervention:** **D1:** Paroxetine 10-40 mg/d, individually titrated **D2:** placebo	**Inclusion criteria:** • Adults 18 to 59 • Minimum HAM-D score of 10 • Dysthymia **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies • Current depression treatment	**Mean age (yrs):** **D1:** 45.2 **D2:** 42.6 **Sex (% female):** **D1:** 57.5 **D2:** 66.7 **Race (% white):** **D1:** 90 **D2:** 89 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	ITT analysis: mean decrease in HSCL-D-20; PAR: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no sig diffs between arms Remission by HAM-D-17 score < 6: PAR: 80%, placebo: 44.4%; behavior therapy: 56.8% (*P* = 0.008 for diff among all 3 arms) Minor depression: PAR 60.7%, placebo 65.6%; behavior therapy 65.5% (*P* = 0.906 for diff among all 3 arms)	NR	**Overall attrition rate:** 20.7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Blumenfield et al., 1997 **Country and setting:** United States (New York) 2 inpatient centers **Funding:** Lilly Research Laboratories	**Research objective:** To test safety and efficacy of FLUO in patients with renal failure on dialysis **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 14 **Intervention:** **D1:** Fluoxetine: 20mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Concomitant condition: renal failure **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Investigational drug use within last 4 wks • Suicidal tendencies	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	At wk 4 sig improvements in depression were seen in BDI and BSI ($P < 0.05$) At endpoint, wk 8, there were no longer any diffs between fluo and placebo in depression scores No withdrawals due to AEs	**Cardiovascular adverse events:** **D1:** 67 **D2:** 14 **Constipation:** **D1:** 0 **D2:** 14 **Diarrhea:** **D1:** 17 **D2:** 14 **Dizziness:** **D1:** 17 **D2:** 0 **Headache:** **D1:** 50 **D2:** 0 **Insomnia:** **D1:** 33 **D2:** 14 **Nausea:** **D1:** 83 **D2:** 29	**Overall attrition rate:** 7.1% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Burt et al., 2005 **Country and setting:** US; multicenter **Funding:** Eli Lilly and Co	**Research objective:** To assess efficacy of DUL in depressed women ages 40 to 55 yrs **Duration of study:** 9 wks **Study design:** Post-hoc analysis of pooled data from 2 identical, but independent, randomized, double-blind studies **Overall study N:** 114 **Intervention:** **D1:** Duloxetine: 60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to no max given • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 • CGI-S ≥ 4 at 2 consecutive screening visits **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Treatment-resistant depression; lack of response of current depression episode to 2+ adequate treatment courses	**Mean age (yrs):** **D1:** 47.7 **D2:** 46.4 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 80.0 **D2:** 72.6 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 21.3 (4.4) **D2:** 21.5 (3.5)	Using LOCF, response rates were 58.2% in DUL vs. 32.2% in placebo group (P = 0.003, cell = 1, 1, P = 0.008). Remission rates were 34.6% in DUL and 18.6% in placebo group (P = 0.027, cell = 1, 1, P = 0.006). Magnitude of treatment effect was similar in women aged 40-55 compared to older and younger women	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A Post-hoc analysis **Quality rating:** Fair Post-hoc analysis

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cassano et al., 2002 **Country and setting:** Italy Multicenter (38 centers) **Funding:** SmithKline, Beecham	**Research objective:** To assess efffects of PAR and FLUO on mood and cognitive function in depressed non-demented geriatric patients **Duration of study:** 1 yr **Study design:** RCT **Overall study N:** 242 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Minimum HAM-D score of 18 • ICD-10, mini mental state, Raskin, Covi Anxiety **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 75.6 **D2:** 74.9 **Sex (% female):** **D1:** 61 **D2:** 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Both treatment groups showed sig improvements in cognitive performance on all test scales No sig diffs between treatment groups and cognitive performance except for Buschke test at wk 3 and 6 where PAR showed a sig greater improvement on a number of tests Both treatment groups sig improved HAM-D total scores but overall no diffs in HAM-D improvement between treatment groups Kaplan Meier analysis evaluating percentage of responders (HAM-D < 10) over time showed a sig diff in favor of PAR ($P < 0.03$) No sig diffs on CGI scores	**Overall adverse events:** **D1:** 27.6 **D2:** 32.8 **Cardiovascular adverse events:** **D1:** 6.5 **D2:** 7.5	**Overall attrition rate:** 39.3% **ITT Analysis** No another type of analysis was used (define): Observed case **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Devanand, 2005 **Country and setting:** United States Outpatient clinic **Funding:** NIMH	**Research objective:** FLUO vs. placebo for treatment of dysthymia in patients over 60 **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg (individually titrated by protocol according to response) **D2:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 8, max score 25 • Dysthymia • Adults at least 60 yrs old • CGI-s score ≥ 3 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Active suicidal ideation or plan • MDD during current dysthymia episode • Lack of response of current episode to prior trial of any SSRI • Major neurologic disorder • MMSE <24	**Mean age (yrs):** **D1:** 69.0 **D2:** 70.8 **Sex (% female):** **D1:** 32.6 **D2:** 40.9 **Race (% white):** **D1:** 86.4 **D2:** 89.1 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 15.3 (5.1) **D2:** 14.4 (3)	No sig differences in response rates between treatment groups Responders: FLUO: 27.3%, placebo: 19.6% (*P* = 0.4) No sig differences in QOL measures on Q-LES-Q	NR	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ferrando et al., 1997 **Country and setting**: US appears to be a university outpatient clinic (outpatients referred from Northwestern Memorial Hospital) **Funding:** Chicago Consortium for Psychiatric Research	**Research objective:** To assess effectiveness and tolerability of SER, PAR, and FLUO in treatment of depressed patients with medically symptomatic HIV or AIDS **Duration of study:** 6 wks **Study design:** Other: open-label medication trial **Overall study N:** 33 **Intervention:** **D1:** Sertraline: 50 mg/d to a maximum of 150 mg/d as tolerated **D2:** Paroxetine: 20 mg/d to a maximum of 40 mg/d **D3:** Fluoxetine: 20 mg/d to a maximum of 40 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Symptomatic HIV infection (CDC stage B2, or B3) or AIDS (CDC stage C2 or C3) as determined by CD4 count, physical exam by physician, and medical records review • BDI ≥ 20 **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Actively suicidal • Had been treated with other psychotropics in past mo • Unable to sign informed consent	**Mean age (yrs):** Overall: 38 **Sex (% female):** Overall: 18 **Race (% white):** Overall: 73 **Baseline (HAM-A):** NR **Baseline HAM-D:** Overall: 23.3 (4.8)	Clinical response (response = CGI of much or very much improved) Overall = 83% SER = 71% PAR = 86% FLUO = 90% Subjects who completed 6 wks of SSRI treatment experienced sig reductions in both affective and somatic symptoms (as measured by HAM-D, BDI, HAM-D affective, BDI cognitive subscale, HAM-D vegetative, and BDI somatic subscale scores among completers), many of the latter having been attributed to HIV rather than depression Nine subjects dropped out early due to AEs	**Diarrhea:** Overall: 9 **Headache:** Overall: 21 **Insomnia:** Overall: 21 **Nausea:** Overall: 15	**Overall attrition rate**: 27.3% **ITT Analysis** No- completer analysis **Quality rating:** Poor: open-label, no ITT

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating

Author: Glassman et al., 2002
 	
Country and setting: multinational, conduceted in 40 outpatient cardiology centers and psychiatry clinics
 	
Funding: Pfizer
	Research objective: To evaluate safety and efficacy of SER treatment of MDD in patients hospitalized for acute MI or unstable angina free of other life-threatening medical conditions
	
	Duration of study: 24 wks
	
	Study design: RCT
	
	Overall study N: 369
	
	Intervention:
	D1: Sertraline: 50-200 mg/d
	D2: Placebo
		Inclusion criteria:
		• Adults
		• Diagnosed with MDD according to DSM-III or -IV
		• Acute MI or hospitalization for unstable angina in past 30 days
		
		Exclusion criteria:
		• Concomitant psychotheraputic or psychotropic medications
		• Additional mental illnesses or organic mental disorder
		• Illicit drug and alcohol abuse
		• Clinically sig medical disease
		• Sig suicide risk
		• Women of childbearing potential not on adequate contraception
		• Current use of antiarrythmic medications
			Mean age (yrs):
			D1: 56.8
			D2: 57.6
			
			Sex (% female):
			D1: 37
			D2: 36
			
			Race (% white):
			D1: 74
			D2: 79
			
			Baseline (HAM-A): NR
			
			Baseline HAM-D:
			D1: 19.6 (5.3)
			D2: 19.6 (5.4)
				HAM-D mean score (SD) and mean score change:
				All randomized patients:
				SER = 19.6 (5.3) and -8.4 (0.41)
				Placebo = 19.6 (5.4) and -7.6 (0.41)
				
				Any recurrent depression:
				SER = 20.6 (5.1) and -9.8 (0.59)
				placebo = 20.8 (5.6) and -7.6 (0.61)
				
				Patients with 2 prior episodes, plus HAM-D score $\geq$ 18:
				SER = 22.9 (3.6) and -12.3 (0.88)
				Placebo = 24.5 (4.4) and -8.9 (0.98)
				
				# CGI responders total sample:
				SER = 125 (67%)
				Placebo = 97 (53%)
				(P = 0.01)
				
				Any recurrent MDD:
				SER = 69 (72%)
				Placebo = 46 (51%)
				(P = 0.003)
				
				Patients with more severe (2 prior episodes plus HAM-D score ≥ 18):
				SER = 39 (78%)
				Placebo = 18 (45%)
				(P = 0.001)
					Cardiovascular adverse events:
					D1: 52.7
					D2: 59.0
					
					Diarrhea:
					D1: 18.8
					D2: 7.7
					
					Dizziness:
					D1: 15.6
					D2: 12.0
					
					Headache:
					D1: 20.4
					D2: 16.4
					
					Insomnia:
					D1: 18.8
					D2: 18.8
					
					Nausea:
					D1: 19.9
					D2: 10.9
					
					Somnolence (fatigue):
					D1: 14.5
					D2: 13.7
						Overall attrition rate: 26.8%
						
						ITT Analysis Yes
						
						Quality rating: Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Goldstein et al., 1997 **Country and setting:** United States multicenter, outpatient trial **Funding:** Lilly	**Research objective:** To assess effect of FLUO 20 mg/d on weight loss in older patients **Duration of study:** 6 wks (after a 1-wk placebo lead-in) **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Adults 60+ **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Clinically sig medical disease • Suicidal tendencies • Score less than 25 on MMSE • History of allergic reaction to FLUO • History of nonresponse to at least 2 antidepressants at usual doses	**Mean age (yrs):** **D1:** 68 **D2:** 68 **Sex (% female):** **D1:** 55 **D2:** 55 **Race (% white):** **D1:** 94 **D2:** 94 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Mean change (SD) in body weight: Low/normal BMI: FLUO -0.88 (2.11) Placebo 0.11 (1.96) (P < 0.001) High BMI: FLUO -1.14 (1.99) Placebo 0.04 (1.72) (P < 0.001) Pooled: FLUO -1.01 (2.05) Placebo 0.08 (1.85) (P < 0.001) % with weight loss of at least 5% low/normal BMI: FLUO 2.4 Placebo 1.1 (P = 0.225) High BMI: FLUO 3.7 Placebo 0 (P = 0.021) Pooled: FLUO 3.1 Placebo 0.6 (P = 0.017)	**Cardiovascular adverse events:** **D1:** 2.7 **D2:** 3.3 **Changes in weight (decrease):** **D1:** 3.3 **D2:** 1.2	**Overall attrition rate:** NR **ITT Analysis** No another type of analysis was used (define): included patients with complete data only **Quality rating:** Fair for AE reporting

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gual et al, 2003 **Country and setting:** Spain, single-center, hospital **Funding:** Pfizer	**Research objective:** To evaluate efficacy and safety of SER at achieving stable maintenance, at amerliorating depressive symptoms, and at improving QOL in patients with alcohol dependence and current depressive symptoms **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 83 **Intervention:** **D1:** Placebo **D2:** Sertraline: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to no upper limit • Diagnosed with MDD according to DSM-III or -IV • Alcohol dependence (according to DSM-IV and ICD10) • Dysthymia • MDD according to DSM-IV and ICD-10 • Abstinent from alcohol for at least 2 wks following detoxification **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 6 mos • Suicidal tendencies • ECT within 3 mos	**Mean age (yrs):** **D1:** 47.3 **D2:** 46.1 **Sex (% female):** **D1:** 46.1 **D2:** 47.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 12.8 (4.0) **D2:** 13.9 (5.6)	Treatment response (≧ 50% improvement in MADRS score), % SER = 44% placebo = 39% No sig diff in SF-36 physical component score, mean (SD) SER = 48.6 (9.6); change from baseline ~ 2.5 points Placebo = 47.0 (11.0); change from baseline ~ 4 points	**Diarrhea:** **D1:** 7.7 **D2:** 9.1 **Dizziness:** **D1:** 12.8 **D2:** 11.4 **Headache:** **D1:** 28.2 **D2:** 27.3 **Nausea:** **D1:** 7.7 **D2:** 9.1	**Overall attrition rate:** 61% **ITT Analysis** Yes **Quality rating:** Fair:

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **Country and setting:** United States University **Funding:** Organon, Inc	**Research objective:** To assess clinical efficacy and safety of "Org 3770" (MIR) and TRA in treatment of elderly outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Age 55+ • Able to complete Zung Self Rating Depression Scale (SDS) • Chloral hydrate (500 mg) at bedtime was permitted **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos of baseline • Suicidal tendencies • Rapid placebo responders (reduction of 20%+ in total HAM-D score)	**Mean age (yrs):** **D1:** 63 **D2:** 61 **D3:** 62 **Sex (% female):** **D1:** 42.9 **D2:** 60.4 **D3:** 59.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.6 **D3:** 23.5	On 21-item HAM-D, diffs between MIR and placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig)	**Cardiovascular adverse events:** **D1:** 2% Tachycardia; 4% Palpitations **D2:** 12% Tachycardia; 12% Palpitations **D3:** 2% Tachycardia; 2% Palpitations **Constipation:** **D1:** 18 **D2:** 24 **D3:** 16 **Dizziness:** **D1:** 22 **D2:** 27 **D3:** 8 **Headache:** **D1:** 14 **D2:** 20 **D3:** 20 **Nausea:** **D1:** 10 **D2:** 14 **D3:** 14 **Somnolence (fatigue):** **D1:** 54 **D2:** 55 **D3:** 22	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hernandez-Avila et al., 2003 **Country and setting:** United States Outpatient **Funding:** Bristol-Meyers Squibb NIH Grants	**Research objective:** To compare NEF or placebo in a sample of alcohol dependant subjects with current major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 41 **Intervention:** **D1:** Nefazodone: 200-600 mg/d (412.9) **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Alcoholism • Age 21 to 65 • Spoke english **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Suicidal tendencies • Drug dependance other than alcohol • Major mental illness other than depression or anxiety	**Mean age (yrs):** **D1:** 43.1 **D2:** 42.7 **Sex (% female):** **D1:** 52.4 **D2:** 50.0 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 16.33 (2.31) **D2:** 17.35 (1.98)	NEF group showed greater reductions in depression, effects did not reach statistical significance (P = 0.82); however, NEF subjects showed sig greater reduction in heavy drinking days (P = 0.01)	NR	**Overall attrition rate:** 31.7 **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper et al., 2005 **Country and setting:** Multinational (11 countries) Multicenter (76 general practice and specialist settings) **Funding:** Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmith-Kline, Organon, Servier	**Research objective:** To compare efficacy and tolerability of ESC in a fixed dose of 10 mg with placebo in elderly patients with major depressive disorder, using FLUO at fixed dose of 20 mg as a reference drug **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 517 **Intervention:** **D1:** Placebo **D2:** Escitalopram: 10 mg **D3:** Fluoxetine: 20 mg	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Age 65+ • MADRS total score of 22-40 at screening and baseline • MMSE 22+ at screening **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Current ECT • MADRS score ≥ 5 on Item 10 (suicidal thoughts) • History of severe drug allergy or hypersensitivity • Lack of response to more than one antidepressant treatment (including CIT) during present depressive episode	**Mean age (yrs):** **D1:** 75 **D2:** 75 **D3:** 75 **Sex (% female):** **D1:** 76 **D2:** 75 **D3:** 77 **Race (% white):** **D1:** 100 **D2:** 99 **D3:** 100 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	"Responders" (≥ 50% decrease from baseline in MADRS total score) = 46% ESC group, 47% placebo group, 37% FLUO group (all NS) "Remitters" (MADRS total score < = 12): 40% ESC group, 42% placebo group, 30% FLUO group. Diff between placebo and ESC groups NS, but fewer remitters in FLUO vs. placebo groups ($P < 0.05$) ESC-treated patients experienced greater improvement than FLUO-treated patients in MADRS score at wk 8 (last observation carried forward) ($P < 0.01$); however, there was no sig diff between ESC- and placebo-treated patients	**Overall adverse events:** **D1:** 2.8 **D2:** 9.8 **D3:** 12.2 **Changes in weight (decrease):** **D1:** 1.1 **D2:** 1.2 **D3:** 2.4 **Constipation:** **D1:** 4.4 **D2:** 1.2 **D3:** 4.3 **Diarrhea:** **D1:** 5.0 **D2:** 1.7 **D3:** 4.9 **Dizziness:** **D1:** 0.6 **D2:** 2.9 **D3:** 3.7 **Headache:** **D1:** 8.3 **D2:** 5.2 **D3:** 4.3 **Insomnia:** **D1:** 2.2 **D2:** 2.3 **D3:** 1.8 **Nausea:** **D1:** 1.7 **D2:** 6.9 **D3:** 7.3 **Somnolence (fatigue):** **D1:** 0.6 **D2:** 2.3 **D3:** 0	**Overall attrition rate:** 17.6% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Kennedy et al., 2000 **Country and setting:** Canada Depression clinic **Funding:** Centre for Addiction and Mental Health Foundation	**Research objective:** To evaluate disturbances in sexual drive/desire and arousal/orgasm in depressed patients who completed 8 wks of study **Duration of study:** 14 wks (primary endpoint is 8 wks) **Study design:** Prospective cohort study **Overall study N:** 174 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Paroxetine: 10-80 mg/d **D3:** Venlafaxine: 37.5-375 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Sexual activity within past mo • Major depression with or without other secondary non-psychotic axis I disorders • No antidepressants within 2 wks (or 5 wks for FLUO) **Exclusion criteria:** • Clinically sig medical disease	**Mean age (yrs):** NR **Sex (% female):** **D1:** 84.6 **D2:** 33.3 **D3:** 61.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Men reported sig greater drug-induced impairment of drive/desire compared with women (mean [SD] = 2.26 (2.02) vs. 1.43(2.12), t = 6.23, df = 107, $P < 0.05$) No signficant diffs between antidepressants among men reporting antidepressant-induced sexual dysfunction On arousal/orgasm scale women showed lower rates of dysfunction on VEN compared to PAR and ser, however, only one item of 3 arousal/orgasm items ("difficulty achieving orgasm") reached statistical significance (chi-sq = 8.51, df = 1, $P < 0.004$). for VEN vs. PAR, VEN introduced sig less difficulty with having an orgasm than PAR (chi-sq = 2.98, df = 1, $P < 0.08$)	NR	**Overall attrition rate:** 38.5% **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Kirby et al.; 2002 **Country and setting:** Australia; inpatient **Funding:** Not reported	**Research objective:** To determine prevalence of hyponatremia associated with SSRI use vs. VEN in elderly compared to elderly not on these drugs **Duration of study:** 1 yr. (inpatients treated between 1997 to 1998) **Study design:** Observational **Overall study N:** 199 **Intervention:** Fluoxetine Fluvoxamine Paroxetine Sertraline Venlafaxine	**Inclusion criteria:** • Inpatient in North-West Hospital psychogeriatric unit between 1997 and 1998 **Exclusion criteria:** • Patients with no sodium test during admission	**Mean age (yrs):** Overall: 74.2 **Sex (% female):** Overall: 65 **Race (% white):** Overall: NR **Baseline (HAM-A):** NR **Baseline HAM-D:**	SSRIs/VEN were sig associated with hyponatremia after controlling for confounding factors (OR 3.5, 95% CI 1.4-8.9) OR adjusted for thiazide use: 2.5 (95% CI 1.1 - 5.4) VEN had a higher rate of hyponatremia than other drugs (71.4%; PAR: 32.0%; FLUO: 60.0%; SER: 28.6%)	NR	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Krishnan et al., 2001 Newhouse et al. 2000 **Country and setting:** US **Funding:** Pfizer, Inc	**Research objective:** To evaluate safety and efficacy of SER in treatment of moderate-to-severe major depression in elderly outpatients with comorbid vascular disease **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 220 **Intervention:** Fluoxetine: 50-100 mg/d Sertraline: 50-150 mg/d Other: nortriptyline **D1:** HTN **D2:** VASC **D3:** NoVasc	**Inclusion criteria:** • Adults 60 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Minimal improvement at most on CGI-I **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidal tendencies • MMSE < 23 • Current diagnosis of dysthmia • Previous history of non-response to 6-wks adequate doses of 2 or more antidepressants	**Mean age (yrs):** **D1:** 68.6 **D2:** 68.9 **D3:** 67.3 **Sex (% female):** **D1:** 69 **D2:** 44 **D3:** 62 **Race (% white):** NR **Baseline (HAM-A):** **D1:** 14.4 **D2:** 14.4 **D3:** 15.2 **Baseline HAM-D:** NR	SER found to be safe, well-tolerated, and effective as an antidepressant in elderly patients suffering from hypertension and other forms of vascular comorbidity Both completer analysis and more conservative endpoint (LOCF) analysis found similar numbers of patients achieving "responder" status by end of study treatment (responder status defined as 50% or greater reduction from baseline in HAM-D total score); SER treatment yielded comparable levels of response in all 3 groups at treatment endpoint on both completer analysis (HTN, 86%, VASC, 89%, NoVASC, 58%; $P < 0.05$)	**Constipation:** **D1:** 18 **D2:** 13 **D3:** 6 **Diarrhea:** **D1:** 21 **D2:** 19 **D3:** 22 **Headache:** **D1:** 44 **D2:** 28 **D3:** 25 **Insomnia:** **D1:** 18 **D2:** 19 **D3:** 20 **Nausea:** **D1:** 19 **D2:** 9 **D3:** 20 **Somnolence (fatigue):** **D1:** 12 **D2:** 16 **D3:** 7 **Sweating (increase):** **D1:** 17 **D2:** 6 **D3:** 8	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** US Primary care (76 physicians) **Funding:** Eli Lilly	**Research objective:** To compare efficacy of PAR, FLUO, and SER in depressed primary care patients **Duration of study:** 9 mos **Study design:** Open-label, randomized trial **Overall study N:** 573 **Intervention:** **D1:** Paroxetine: 20 mg/d **D2:** Fluoxetine: 20 mg/d **D3:** Sertraline: 50 mg/d	**Inclusion criteria:** • Adults 18 and up • Depressive disorder as determined by PCP • Home telephone **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.1 **D3:** 44.1 **Sex (% female):** **D1:** 76 **D2:** 86 **D3:** 75 **Race (% white):** **D1:** 85 **D2:** 88 **D3:** 79 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	All 3 treatment groups showed sig improvements in depression and other health related QOL domains (social function, work function, physical function) No sig diffs between treatment groups in any of 3 and 9 mos outcome measures Subgroup analysis showed no diffs in treatment effects for patients with MDD and for patients older than 60 yrs Switch rate to other medication: PAR: 22% FLUO: 14% SER: 17%	NR	**Overall attrition rate:** 24.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lyketsos et al, 2003 **Country and setting:** US, 3 psychiatric outpatient clinics **Funding:** Depression in Alzheimer's disease study from NIMH	**Research objective:** To assess efficacy and safety of SER for treatment of major depression in Alzheimer disease and to evaluate effect of depression reduction on activities of daily living, cognition, and nonmood behavioral disturbance **Duration of study:** 12 wks (after a one-wk single-blind placebo phase) **Study design:** RCT **Overall study N:** 44 **Intervention:** **D1:** Placebo **D2:** Sertraline: up to 150 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Probable alzheimer disease by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association • MMSE of 10 • Current residence in a community setting (home or assisted living) **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Use of SER contraindicated in opinion of study psychiatrist	**Mean age (yrs):** **D1:** 79.9 **D2:** 75.5 **Sex (% female):** **D1:** 50 **D2:** 83 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 21.8 (5.4) **D2:** 23.7 (6.4)	9 SER patients (38%) were full responders and 11 (46%) were partial responders compared with 3 (20%) and 4 (15%) placebo patients (P = 0.007) SER was statistically sig superior to placebo as measured by both Cornell Scale for Depression in Dementia (P = 0.002) and Hamilton Depression Rating Scale (P = 0.01)	NR	**Overall attrition rate:** 18.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Magai et al., 2000 **Country and setting:** US, nursing homes **Funding:** Pfizer Pharmaceuticals New York State Dept. of Health Dementia Grants Program; Minority Biomedical Research Support Program and National Institute on Aging	**Research objective:** To evaluate efficacy of SER in treatment of depressive symptoms and signs in late-stage dementia patients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 31 **Intervention:** **D1:** Sertraline: 25-100 mg **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Concomitant condition: dementia • Minor depression **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	**Mean age (yrs):** **D1:** 88.4 **D2:** 90.1 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 94 **D2:** 71 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	On all measures, both treatment and placebo groups improved over time, with 3 of 6 measures showing a sig time effect. "Knit-brow" facial feature approached significance for a treatment by time effect. In sum, SER had no sig benefits over placebo	**Overall adverse events:** **D1:** 11.8 **D2:** 14.3	**Overall attrition rate:** 12.9% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Moak et al., 2003 **Country and setting:** USA Single center **Funding:** National Institute on Alcohol Abuse and Alcoholism	**Research objective:** Comparison of SER and placebo in conjunction with CBT in treatment of depressed alcoholics **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 82 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Alcoholism (alcohol dependence or abuse) • Dysthymia • Primary major depression episode of dysthymic disorder or a clear family hisory of affective disorder without comorbid substance abuse in a first degree relative **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Current suicidal ideation or plan • Treatment resistant depression	**Mean age (yrs):** **D1:** 41 **D2:** 42 **Sex (% female):** **D1:** 39 **D2:** 39 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 19.4 (2.6) **D2:** 18.8 (2.4)	Subjects who received SER had fewer drinks per drinking day than subjects who received placebo, but other drinking outcomes were not different between 2 treatment groups. In female subjects, treatment with SER was associated with less depression at end of treatment compared with placebo. Less drinking during study was associated with improved depression outcomes	NR	**Overall attrition rate:** 28% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Murray et al., 2005 **Country and setting:** Sweden, outpatients (4 stroke centers) **Funding:** Pfizer AB Sweden	**Research objective:** To evaluate efficacy and safety of SER in post-stroke depression **Duration of study:** 26 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Stroke (according to WHO criteria), hospitalized during acute phase of index stroke • Minor depression according to DSM-IV and MADRS ≥ 10 and time criteria (symptoms should have been present during same 2 wk period) **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Sig risk of suicide • Severe impairment of ability to communicate • Current use of opiate analgesics	**Mean age (yrs):** **D1:** 70.7 **D2:** 70.7 **Sex (% female):** **D1:** 48.4% **D2:** 55.7% **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	HAM-D responders (percent of those who completed 26 wks of treatment) SER = 76% placebo = 78% % remission (defined as a MADRS score < 10) (percent of those who completed 26 wks of treatment) SER = 81% placebo = 87% Improvement in QOL at wk 26 was sig better in SER treated patients ($P < 0.05$)	**Changes in weight (decrease):** **D1:** 17.4 **D2:** 13.3 **Changes in weight (increase):** **D1:** 15.2 **D2:** 15.6 **Constipation:** **D1:** 14.5 **D2:** 9.3 **Diarrhea:** **D1:** 23.6 **D2:** 9.3 **Dizziness:** **D1:** 14.5 **D2:** 13.0 **Headache:** **D1:** 14.5 **D2:** 16.7 **Nausea:** **D1:** 21.8 **D2:** 14.8 **Sweating (increase):** **D1:** 16.4 **D2:** 17.0	**Overall attrition rate:** 44% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Newhouse et al., 2000 and Finkel et al., 1999 **Country and setting:** USA Multicenter **Funding:** Pfizer, Inc	**Research objective:** Examined efficacy and safety of FLUO and SER in depressed elderly outpatients **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 236 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 60 yrs or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental • Clinically sig medical disease • Failure to respond to ECT	**Mean age (yrs):** **D1:** 68 **D2:** 67 **Sex (% female):** **D1:** 63.2 **D2:** 51.3 **Race (% white):** **D1:** 95.7 **D2:** 100 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 25.1 (4.2) **D2:** 25.0 (4.7) **Subgroup analysis: Mean age (yrs):** **D1:** 74 **D2:** 75 **Sex (% female):** **D1:** 57 **D2:** 49 **Race (% white):** **D1:** 95 **D2:** 100 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.2 **D2:** 25.4	HAM-D Responders: SER: 73% FLUO: 71% *P* = NS HAM-D remitters: SER: 45% FLUO: 46% *P* = NS Q-LES-Q and other patient-rated secondary efficacy measures were similar for both treatment groups at endpoint SER-treated patients showed a greater cognitive improvement than patients on FLUO on Digit Symbol Substitution Test at endpoint (*P* = 0.037) Patients 70 yrs of age and older, HAM-D responders at endpoint in SER group (*P* = 0.027): 58.5% (SER) vs. 42.4% (FLUO)	**Diarrhea:** **D1:** 22.4 **D2:** 16.1 **Dizziness:** **D1:** 7.8 **D2:** 10.2 **Headache:** **D1:** 33.6 **D2:** 31.4 **Insomnia:** **D1:** 13.7 **D2:** 14.4 **Nausea:** **D1:** 14.7 **D2:** 18.6 **Subgroup analysis: Overall adverse events:** **D1:** 93 **D2:** 94 **Headache:** **D1:** 23.8 **D2:** 33.3 **Nausea:** **D1:** 16.7 **D2:** 15.2	**Overall attrition rate:** 32.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nyth et al., 1992 **Country and setting:** Denmark, Norway, Sweden Multicenter (7) **Funding:** NR	**Research objective:** To assess efficacy and safety of CIT vs. placebo in depressed elderly patients who might also suffer from somatic disorders and/or senile dementia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 149 **Intervention:** **D1:** Citalopram: 10-30 mg **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 14 • Mild to moderate dementia and somatic disorders acceptable but not required for inclusion **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Receipt of anti-cancer treatment; recent treatment with monoamine oxidase inhibitors; GBS geriatric rating scale with score >4	**Mean age (yrs):** **D1:** F: 77.0, M: 74.4 **D2:** F: 77.7; M: 77.8 **Sex (% female):** **D1:** 67 **D2:** 73 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 22.1 (6.2) **D2:** 21.1 (5.8)	Rate of response as measured by HAM-D was similar in CIT and placebo groups (no data given) GBS dementia rating scale indicated that intellectual function-time orientation, recent memory, and ability to increase tempo and symptoms common to dementia-anxiety, fear-panic, depressed mood all improved sig more in CIT-treated subgroup of patients with dementia than in placebo-treated subgroup ($P < 0.05$)	**Overall adverse events:** **D1:** 37 **D2:** 25 **Changes in weight (decrease):** **D1:** 9.2 **D2:** 3.9 **Constipation:** **D1:** 3.1 **D2:** 5.9 **Dizziness:** **D1:** 7.1 **D2:** 0 **Nausea:** **D1:** 5.1 **D2:** 7.8 **Somnolence (fatigue):** **D1:** 18.4 **D2:** 5.9	**Overall attrition rate:** 36.9% **ITT Analysis** Efficacy analysis; ITT done and ITT **Quality rating:** Poor Completer analysis only

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Oslin et al., 2003 **Country and setting:** US VA nursing facilities (13) **Funding:** National Institute of Mental Health; Department of Veterans Affairs	**Research objective:** To examine efficacy and tolerability of VEN and SER among nursing home residents **Duration of study:** 10 wks **Study design:** RCT **Overall study N:** 52 **Intervention:** **D1:** Sertraline: 25-100 mg/d **D2:** Venlafaxine: 18.75-150 mg/d	**Inclusion criteria:** • Age 60 or more • Diagnosed with MDD according to DSM-III or -IV • HAM-D ≤ 12 • Sig dysphoria with score ≥ 10 on GDS and/or rating >2 on depressed mood item of HAM-D • Minor depression, dementia with depression, or dysthymia • Blessed Memory Information Concentration test score < 21 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 2 wks • Suicidal tendencies	**Mean age (yrs):** **D1:** 83.8 **D2:** 81.2 Overall: 82.5 **Sex (% female):** **D1:** 56 **D2:** 33 Overall: 44.2 **Race (% white):** **D1:** 92 **D2:** 63 Overall: 76.9 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 20.2 (3.4) **D2:** 20.3 (3.7)	Mean change from baseline to endpoint: HAM-D (F 3.45, *P* 0.069) = 8.0 (SER) vs. 4.6 (VEN); GDS (F 2.13, *P* 0.151) = 3.5 (ser) vs. 0.8 (ven); Cornell (F 7.65, *P* 0.008) = 8.5 (ser) vs. 4.0 (ven). Endpoint CGI = 2.3 (ser) vs. 3.0 (ven) with F = 2.83 and *P* = 0.98. Tolerability lower for VEN	NR	**Overall attrition rate:** 38.5% **ITT Analysis** Yes **Quality rating:** Poor

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Petrakis et al., 1998 **Country and setting:** US Teaching hospital **Funding:** National Institute on Drug Abuse	**Research objective:** To evaluate efficacy of FLUO in treating depression in methadone-maintained opioid addicts **Duration of study:** 3 mos **Study design:** RCT **Overall study N:** 44 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 14 • Methadone-maintained opioid addiction • > 8 on BDI; medically healthy **Exclusion criteria:** • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** **D1:** 35.4 **D2:** 33.3 **Sex (% female):** **D1:** 39.1 **D2:** 33.3 **Race (% white):** **D1:** 91.3 **D2:** 85.7 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 14 (4.9) **D2:** 14.9 (5.8)	In entire sample, BDI and HAM-D scores decreased sig in both groups ($z = 2.37$; $P = 0.01$; $z = 5.85$, $P < 0.01$); no sig diffs between placebo and FLUO treated patients. Among subjects with major depression (n = 31), there were no sig diffs in rate of change of depressive symptoms by treatment group over time Concomitant heroin use and ASI scores decreased sig for both groups ($z = 2.92$, $P < 0.01$; $z = 2.66$, $P < 0.01$); no sig diff between groups	NR	**Overall attrition rate:** 15.9% **ITT Analysis** No **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rabkin et al., 2004 **Country and setting:** US Outpatient **Funding:** Lilly (provided tablets); Pharmacia and Upjohn (provided coded vials) National Institute of Mental Health	**Research objective:** To determine whether testosterone and FLUO is superior to placebo for depression, fatigue, or both **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Placebo Testosterone 200-400 mg biwkly	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • HIV seropositive • Dysthymia • Male • Negative PSA • Agreement of primary healthcare provider **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 5 wks • ECT • Suicidal tendencies • Psychotherapy started in last mo • Use of anabolic steroids • Current/anticipated change in ARV regimen within 4 wks • Unprotected intercourse with partners of unknown or negative HIV status	**Mean age (yrs):** **D1:** 40 **D2:** 41 **Sex (% female):** **D1:** 0 **D2:** 0 **Race (% white):** **D1:** 21.7 **D2:** 23.1 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 18.2 (4.5) **D2:** 16.8 (3.3)	No statistically different outcomes between treatment groups. HAM-D response (52% [fluox] vs. 51% [placebo] [*P* = 0.66]) and remission (50% [fluox] vs. 51% [placebo] [*P* = 0.59]) rates	**Changes in weight (decrease):** **D1:** 9 **Diarrhea:** **D1:** 4 **Headache:** **D1:** 9 **Insomnia:** **D1:** 4 **Nausea:** **D1:** 7 **Sexual dysfunctional (male ejaculation):** **D1:** 6 **Somnolence (fatigue):** **D1:** 7	**Overall attrition rate:** 26.8% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rapaport et al., 2003 **Country and setting:** US and Canada Multicenter (31) **Funding:** GlaxoSmithKline	**Research objective:** Efficacy and safety of PAR CR and IR versus placebo in late life depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** **D1:** Paroxetine CR 12.5-50 **D2:** Paroxetine IR 10-40 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults > 59 yrs • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • ECT within last 3 mos • Suicidal tendencies • History of brief depressive episodes with spontaneous remission • Neuological disorders contributing to secondary depression • Dementia • MMSE ≤ 24	**Mean age (yrs):** **D1:** 70.4 **D2:** 70.1 **D3:** 69.4 **Sex (% female):** **D1:** 48.1 **D2:** 56.6 **D3:** 63.3 **Race (% white):** **D1:** 96.2 **D2:** 95.3 **D3:** 94.5 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 22.1(3.45) **D2:** 22.3(3.15) **D3:** 22.1(3.0)	PAR CR and IR were more effective than placebo, with mean +/- SD endpoint HAM-D total scores of 10.0 +/- 7.41 (P = 0.007) and 10.0 +/- 7.10 (P = 0.003), respectively, compared with 12.6 +/- 7.34 for placebo. Response (a score of 1 or 2 on CGI-I scale) was achieved by 72% of PAR CR patients (P < 0.002 vs. placebo), 65% of PAR IR patients (P = 0.06 vs. placebo), and 52% of placebo patients. Remission, defined as HAM-D total score ≤ 7, was achieved by 43% of PAR CR patients (P = 0.009 vs. placebo), 44% of PAR IR patients (P = 0.01 vs. placebo), and 26% of placebo patients	**Insomnia:** **D1:** 9.6 **D2:** 14.2 **D3:** 8.3	**Overall attrition rate:** 24.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rocca et al., 2005 **Country and setting:** Italy University clinic **Funding:** University of Turin, Italy	**Research objective:** To compare effect of SER and CIT on depression symptoms and cognitive functions in nondemented elderly patients with minor depressive disorder or sybsyndromal depressive symptomatology **Duration of study:** 12 mos **Study design:** Nonrandomized controlled trial **Overall study N:** 138 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Sertraline: 50 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 10 • Nondemented elderly (65 or older) • Minor depressive disorder or subsyndromal depressive disorder according to SCID **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Any other current Axis I or II psychiatric disorder • Impairment and decline of global cognitive functions on MMSE • Score of at least 12 on Alzheimer's Disease Assessment Scale-Cognitive Subscale	**Mean age (yrs):** **D1:** 72.4 **D2:** 71.9 **Sex (% female):** **D1:** 24.2 **D2:** 31.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 12.9 **D2:** 12.9	Both treatments induced a sig, sustained, comparable improvement in depressive symptoms and in social functioning Change from baseline to endpoint on HAM-D CIT and SER groups decrease 55% vs. 52.7%; *(P* = NR) or GDS Remission observed at any timepoint between treatment groups 12 mos: 53% vs. 42%; *P* = 0.25 Sig within-group improvements seen in all cognitive measures for both SER and CIT WMS, TMT-A, TMT-B, VF, and MMSE)	**Dizziness:** **D1:** 15.2 **D2:** 9.7 **Headache:** **D1:** 10.1 **D2:** 9.7 **Nausea:** **D1:** 24.2 **D2:** 18.1	**Overall attrition rate:** 27.5 **ITT Analysis:** Yes **Quality rating:** N/A

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Roose et al., 2004 **Country and setting:** US, multicenter **Funding:** Forest Laboratories	**Research objective:** To evaluate efficacy of CIT for treatment of depression in "old-old" **Duration of study:** 8 wks (after a single-blind placebo lead-in) **Study design:** RCT **Overall study N:** 184 **Intervention:** **D1:** Citalopram: 10-40 mg/d **D2:** Placebo	**Inclusion criteria:** • Age 75 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 (HAM-D 24) **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Current suicide intent or serious suicide attempt within past yr • Probable Alzheimer's disease or probable vascular dementia • MMSE score ≤ 18 • Parkinson's disease • Failure to respond to either a trial of an SSRI for at least 4 wks, or trials of 2 or more different classes of antidepressants other than SSRIs	**Mean age (yrs):** **D1:** 79.8 **D2:** 79.3 **Sex (% female):** **D1:** 53.6 **D2:** 62.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.4 (4.3) **D2:** 24.2 (3.9)	Number of responders (reduction of ≥ 50% in HAM-D score) CIT = 34 placebo = 34 f = 0.97 (*P* = 0.32) Number of remitters (HAM-D ≤ 10) CIT = 29 placebo = 30 f = 0.29 (*P* = 0.59) CGI improvement of 1 or 2 CIT = 37 placebo = 39 f = 1.53 (*P* = 0.22) Higher rate of response, CIT vs. placebo, in high severity group: chi-square = 4.03, df = 1 (*P* = 0.04) Patients with onset of major depression before 60 yrs of age had poorer outcome when treated with placebo than any other 3 subgroups (*P* < 0.05)	**Constipation:** **D1:** 11.5 **D2:** 4.4 **Diarrhea:** **D1:** 14.9 **D2:** 6.7 **Dizziness:** **D1:** 9.2 **D2:** 7.8 **Headache:** **D1:** 11.5 **D2:** 4.4 **Insomnia:** **D1:** 3.4 **D2:** 5.6 **Nausea:** **D1:** 6.9 **D2:** 6.7 **Somnolence (fatigue):** **D1:** 5.7 **D2:** 4.4	**Overall attrition rate:** 16.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Roscoe et al., 2005 **Country and setting:** US University medical center **Funding:** SmithKline Beecham (supplied medication), Department of Defense	**Research objective:** To evaluate effect of PAR on fatigue and depression in breast cancer patients receiving chemotherapy **Duration of study:** Undefined (visits conducted 7 days after each of 4 on-study treatments) PAR: 20 mg/d placebo **Study design:** RCT **Overall study N:** 122 **Intervention:** **D1:** Paroxetine **D2:** Placebo	**Inclusion criteria:** • Breast cancer • Beginning or currently receiving treatment for breast cancer • Females **Exclusion criteria:** • Concurrent radiation, interferon, history of seizures or mania, treatment cycles less than 2 wks apart, radiation okay if occurs between chemo cycles (it was regarded as a treatment cycle) • Concomitant psychotherapeutic or psychotropic medications	**Mean age (yrs):** **D1:** 52.2 **D2:** 52.2 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 93 **D2:** 86 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Controlling for cycle 1, PAR was more effective in reducing depression during chemotherapy as measured by CESD (P = 0.006) [mean (SD) at cycle 4 for PAR and placebo: 8.8 (1.11) vs. 12.6 (1.24)] No sig diff between PAR and placebo on all 4 fatigue scales MAF question 1, Fatigue/Inertia Scale, Fatigue Symptom Checklist, and Interference with Daily Activities Sub-Scale from MAF (Interference)]; mean at cycle 4: MAF 4.6 vs. 5.0; Fatigue/Inertia Scale 6.0 vs. 7.1, Fatigue Symptom Checklist 44.6 vs. 48.0, Interference 3.1 vs. 3.8) (all Ps >0.27)	NR	**Overall attrition rate:** 23% **ITT Analysis** No **Quality rating:** Poor: Appears to be completer analysis only, study length is not defined

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rossini et al., 2005 Study has 13-20% bipolars **Country and setting:** Italy One inpatient center **Funding:** Not reported	**Research objective:** To compare efficacy and tolerability of FLUV and SER in elderly patients **Duration of study:** 7 wks (after a 7-day single-blind placebo washout) **Study design:** RCT **Overall study N:** 93 **Intervention:** **D1:** Fluvoxamine: 200 mg/d (100mg twice daily) **D2:** Sertraline: 150 mg/d (75mg twice daily)	**Inclusion criteria:** • Age 59 or more • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • MDD diagnosed by MD using unstructured interviews and medical records according to DSM-IV, and after best estimate procedure **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • MMSE score <23 • Nonreversible MAOI or slow release neuroleptics within 1 mo of study • Bipolar patients had to be on mood stabilizers • Depression or bipolar disorder due to a medical condition or induced by a substance • No psychotic features	**Mean age (yrs):** **D1:** 67.80 **D2:** 68.24 **Sex (% female):** **D1:** 61.5 **D2:** 82.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 31.23 (5.12) **D2:** 29.23 (3.45)	No sig diff in final response rates was found between 2 treatment groups, 55.6% (25/45) and 71.8% (28/39) for SER and FLUV, respectively (P = 0.12). A repeated-measures analysis of variance on Hamilton Rating Scale for Depression scores revealed a sig different decrease of depressive symptoms between 2 treatment groups, favoring FLUV (P = 0.007)	NR	**Overall attrition rate:** 4.5% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schatzberg et al, 2002 **Country and setting:** US Mutli-center (recruited from advertising, private practice, routine intake at clinics and other healthcare facilities) **Funding:** Organon Pharmacueticals	**Research objective:** To compare efficacy and tolerability of MIR with PAR in elderly patients with MDD **Duration of study:** 8 wk acute phase, optional 16 wk continuation phase **Study design:** RCT **Overall study N:** 255 **Intervention:** **D1:** MIR: 15 mg/d up to 45 mg/d **D2:** Paroxetine: 20 mg/d up to 40 mg/d	**Inclusion criteria:** • Adults 65 or older • MDD diagnosis according to DSM-III or -IV • HAM-D ≥ 18 • MMSE above 25% for age and educational level **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicide attempts • MAOIs within 14 days, other psychotropic drugs or herbals within 7 days • PAR or MIR for current depressive episode • Patients requiring drugs for memory deficit • Patients who did not respond to or tolerate MIR or PAR during a previous depressive episode	**Mean age (yrs):** **D1:** 71.7 **D2:** 72.0 **Sex (% female):** **D1:** 50 **D2:** 53 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.2 (3.5) **D2:** 22.4 (3.5)	CGI-I responders (CGI-I of much or very much improved) At endpoint MIR = (80) 64.0% PAR = (68) 56.7% chi square = 1.23 *P* = 0.267 Greater early efficacy for mirtazapine, similar number of CGI responders at end of continuation phase	**Overall adverse events:** **D1:** 79.7 **D2:** 82.5 **Changes in weight (increase):** **D1:** 10.9 **D2:** 0 **Constipation:** **D1:** 11.7 **D2:** 11.1 **Diarrhea:** **D1:** 14.8 **D2:** 17.5 **Dizziness:** **D1:** 15.6 **D2:** 14.3 **Headache:** **D1:** 15.6 **D2:** 24.6 **Insomnia:** **D1:** 11.7 **D2:** 11.1 **Nausea:** **D1:** 6.3 **D2:** 19.0 **Somnolence (fatigue):** **D1:** 30.5 **D2:** 29.4 **Sweating (increase):** **D1:** 6.3 **D2:** 13.5	**Attrition:** 26.8% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schmitz et al., 2001 **Country and setting:** US **Funding:** National Institute on Drug Abuse and Department of Pscyhiatry and Behavioral Sciences, University of Texas-Houston	**Research objective:** To test hypothesis that FLUO would produce favorable effects onoutcome measures of retention, depression, and cocaine use compared with placebo for treatment of comorbid cocaine dependence and depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 68 **Intervention:** **D1:** Fluoxetine: 40 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 50 • Diagnosed with MDD according to DSM-III or -IV • Diagnosed dually with MDD and cocaine dependence • BDI score > 10 • English speaking • Free of serious legal and medical problems **Exclusion criteria:** • Current dependence on alcohol or any other psychoactive substance (except nicotine or cannabis) • Met criteria for current primary Axis I disorders other than depression	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No sig diff in response among depressed cocaine abusers	NR	**Overall attrition rate:** 52.9% **ITT Analysis:** NR **Quality rating:** Poor High LTF

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schneider et al., 2003 and Sheikh et al., 2004 **Country and setting:** US; psychiatric and primary care **Funding:** Pfizer	**Research objective:** To confirm results of non-placebo controlled efficacy trials of SER for treating late-life derpession and to report on efficacy, safety, and tolerability of SER in treatment of elderly depres-sed patients with and without comorbid medical illness **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 752 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Age 60 or more • Diagnosed with MDD according to DSM-III or -IV • HAM-D > 17 • Community-dwelling • Episode ≥ 4 wks • HAM-D depressed mood score ≥ 2 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses • Illicit drug and alcohol abuse • Investigational drug in last 2 wks • Any need for ECT • Suicidal tendencies • Psychotic features, dementia, seizure disorder • Previous nonresponse/ hypersensitivity • Clinically sig unstable medical disease • Psychotherapy within 3 mos	**Mean age (yrs):** **D1:** 70 **D2:** 69.6 **Overall**: 69.8 **Sex (% female):** **D1:** 54 **D2:** 58 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 21.4 (2.7) **D2:** 21.4 (2.6)	Mean changes in HAM-D = -7.4 (SD 6.3) for SER and -6.6 (SD 6.4) for placebo with $P = 0.01$ HAM-D responders = 35% for SER vs. 26% for placebo ($P = 0.007$) CGI responders = 45% for SER vs. 35% for placebo (chi sq = 7.8, df = 1, $P = 0.005$) SER was superior to placebo on all three primary outcome measures, HAM-D, and overall clinical severity and change (CGI-S/CGI-I). Furthermore, therapeutic response to SER was comparable in those with or without medical comorbidity, and there were no treatment by comorbidity group interactions	**Diarrhea:** **D1:** 19 **Dizziness:** **D1:** 8 **Headache:** **D1:** 17 **Insomnia:** **D1:** 9 **Nausea:** **D1:** 16 **Somnolence (fatigue):** **D1:** 10	**Overall attrition rate:** 20.9% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schone et al., 1993 and Geretsegger et al., 1994 **Country and setting:** NR (but assume Germany, based on authors' affiliations), inpatient and outpatient clinics **Funding:** Not reported	**Research objective:** To compare efficacy of PAR vs. FLUO in treatment of depression among elderly clients, and to assess drugs' effects on clients' cognitive and behavioral function **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 106 **Intervention:** **D1:** Paroxetine: 20-40 mg **D2:** Fluoxetine: 20-60 mg	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Serious risk of suicide • Improvement of more than 20% on HAM-D during placebo run-in period (3-7 days)	**Mean age (yrs):** **D1:** 74.3 **D2:** 73.7 **Sex (% female):** **D1:** 83.3 **D2:** 90.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.2 **D2:** 26.0	Wk 6 (endpoint) mean changes from baseline, PAR vs. FLUO, respectively: (1) SCAG total score = -14.5 vs. -8.9. (2)SCAG Cognitive dysfunction factor scores = -2.9 vs. -0.6. (3) HAM-D cognitive factor scores = -1.5 vs. -1.0. (4)MMS total scores = 2.3 vs. 1.1 Sig higher proportion of responders (reduction of 50% or more in HAM-D [37.5% vs. 17.5%, *P* = 0.03] or MADRS [*P* = 0.04] total scores) at end of treatment in PAR group. No sig diff between treatment groups in proportion of responders on CGI-S	**Overall adverse events:** **D1:** 61 **D2:** 77 **Constipation:** **D1:** 10 **D2:** 0 **Dizziness:** **D1:** 0 **D2:** 7	**Overall attrition rate:** 17% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Strik et al., 2000 **Country and setting:** Netherlands Hospitals (2) **Funding:** Eli Lilly Dutch Prevention Fund; Maastricht University Hospital Research Fund	**Research objective:** To investigate efficacy and safety of FLUO in patients with depression after their first MI **Duration of study:** Maximum of 25 wks (acute phase 9 wks; continuation phase 16 wks) **Study design:** RCT **Overall study N:** 54 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • 3 to 12 mos post-MI **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Right ventricular filling pressure > 30 mmHG; ATVI < 20 cm	**Mean age (yrs):** **D1:** 54.1 **D2:** 58.7 **Sex (% female):** **D1:** 22.2 **D2:** 37.0 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 22.0 (3.5) **D2:** 21.2 (3.7)	At 9 wks mean HAM-D-17 score FLUO - 8.34(5.87) vs. placebo 5.84(5.92) (P = 0.06) but mildly depressed patients in FLUO group had endpoint HAM-D scores sig different (by 5.4 points) than placebo (P = 0.01). At wk 25- responder rates 48% (fluox) vs. 26% (placebo) (P = 0.05) and remission rates 26% (fluox) vs. 14.8% (placebo)(P = 0.60)	**Cardiovascular adverse events:** **D1:** 18.5 **D2:** NR	**Overall attrition rate:** 25.9% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tollefson et al., 1993 Tollefson et al., 1995 Small et al., 1996 and Heiligenstein et al., 1995 **Country and setting:** US Mulitcenter **Funding:** Not reported	**Research objective:** To compare HAM-D scores of FLUO-treated vs. placebo-treated elderly depressed patients (not explicitly stated) **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 60 yrs or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • MMSE < 25 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUO had sig better rates of response and remission than placebo. Response of FLUO group was 36% versus 27% placebo (P = 0.014) and remission of FLUO group was 21% versus 13% for placebo (P = 0.008) FLUO was statistically sig more efficacious than placebo in overall response (43.9% vs. 31.6%, P = 0.002) and remission (31.6% vs. 18.6%, P < 0.001) Number of physical illnesses did not affect treatment response, though historic illness was associated with greater fluoxetine repsone and poorer placebo repsonse	**Overall adverse events:** **D1:** 11.6% discontinuation rate **Dizziness:** **D1:** 0.3% discontinuation rate **Insomnia:** **D1:** 0.9% discontinuation rate **Suicidality:** **D1:** n = 4	**Overall attrition rate:** 20.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2000 **Country and setting:** US Multicenter **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and safety of BUP and PAR with PAR in treatment of MDD in elderly **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 10-40 mg/d (22)	**Inclusion criteria:** • Adults 60+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 69.2 **D2:** 71.0 **Sex (% female):** **D1:** 54 **D2:** 60 **Race (% white):** **D1:** 98 **D2:** 90 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in any outcome measures between treatment groups (LOCF and observed) Response rates ≥ 50% reduction in HAM-D) were similar in both groups: BUP sr: 71% PAR: 77% No sig diffs in QOL scales (QLDS, SF-36) between treatment groups at endpoint; overall sig improvement in QLDS and QOL at day 42 ($P < 0.0001$)	**Constipation:** **D1:** 4 **D2:** 15 **Diarrhea:** **D1:** 6 **D2:** 21 **Dizziness:** **D1:** >10 **D2:** >10 **Headache:** **D1:** 35 **D2:** 19 **Insomnia:** **D1:** >10 **D2:** >10 **Nausea:** **D1:** >10 **D2:** >10 **Somnolence (fatigue):** **D1:** 6 **D2:** 27	**Attrition:** 16% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Williams et al., 2000 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundations	**Research objective:** To compare effectiveness of PAR vs. placebo vs. behavioral treatment for dysthymia or minor depression in primary care patients older than 60 yrs **Duration of study:** 11 wk **Study design:** RCT **Overall study N:** 415 **Intervention:** **D1:** Paroxetine: 10-40, individually titrated **D2:** placebo	**Inclusion criteria:** • Minimum HAM-D score of 10 • Dysthymia • Age 60+ **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Severe Suicidal tendencies • MMSE <24 • Current depression treatment	**Mean age (yrs):** **D1:** 71 **D2:** 71 **Sex (% female):** **D1:** 39 **D2:** 45 **Race (% white):** **D1:** 82.5 **D2:** 75.7 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Mean decrease in HSCL-D-20: PAR: 0.61 (P = 0.05) placebo: 0.40 (P = 0.05) Behavior Therapy 0.52 (P = 0.05) P = 0.004 for PAR vs. placebo PAR only statistically and clinically sig better than placebo for subjects with dysthymia and high baseline mental health function HAM-D results NR for ITT population	NR	**Overall attrition rate:** 25.1% **TT Analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Wilson et al, 2003 **Country and setting:** UK, outpatient clinic(s) **Funding:** Not reported	**Research objective:** To examine efficacy of SER in preventing recurrence of depression in older people living in community **Duration of study:** 8 wk treatment phase and a 16-20 wk continuation phase (open-label SER) 100 wk randomized, double-blind phase (SER and placebo) (article focuses on results of this maintenance phase) **Study design:** RCT **Overall study N:** 113 (randomised to double-blind phase) **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 65+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Geriatric Mental State AGECAT depression level 3 or greater **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medicationsIllicit drug and alcohol abuse • Clinically sig medical diseaseSuicidial tendencies: sig suicidal or delusional experiences • MMSE ≤ 11 • Concomitant drugs excluded include psychotropic drugs, warfarin, and anticonvulsants	**Mean age (yrs):** **D1:** 76.6 **D2:** 76.8 **Sex (% female):** **D1:** 66.1 **D2:** 75.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 20.7 (3.7) **D2:** 20.3 (3.3)	Analysis of recurrence Kaplan Meier analysis, SER vs placebo, log rank test = 1.55, df = 1 (*P* = 0.21) Cumulative survival function SER = 39%, median survival 92 wks; placebo = 31%, median survival 48 wks Reduction in risk of recurrence: 8.4% over 100 wks (SER vs. placebo) % with recurrence in first 26 wks and wks 27-52, respectively: SER = 57%, 16% placebo = 60%, 32% Cox regression model predicting recurrence: hazard ratio (95% CI) included variables: SER vs. placebo = 1.21 (0.704, 2.082)	NR	**Overall attrition rate:** 72.6% **ITT Analysis** Not applicable: recurrence trial **Quality rating:** Fair

Evidence Table 7. KQ5: Systematic reviews and meta-analyses on antidepressants in subpopulations

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Bush et al., 2005 **Country and setting:** Multinational **Funding:** AHRQ **Research objective:** To examine role of depression post-MI	**Study design:** Systematic review **Number of Patients:** NR **Studies Included:** Studies (86) have examined depression or depressive symptoms in patients after MI and focuses on prevalence, clinical significance, treatment, and methods of evaluating condition	**Included Studies:** See above **Included Populations** Patients suffering from myocardial infarction and depression **Interventions:** SSRIs and therapy	**Study Results:** In post-MI patients with depression, selective serotonin reuptake inhibitors improve depression and some surrogate markers of cardiac risk, but no studies of sufficient power address question of whether treatment improves survival	**Adverse Events:** NR	**Publication Bias:** Yes **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** MEDLINE®, Cochrane CENTRAL Register of Controlled Trials (Issue 1, 2003), Cochrane Database of Methodology Reviews (CDMR®), Cumulative Index of Nursing and Allied Health Literature (CINAHL®), Psychological Abstracts (PsycINFO®), and EMBASE **Quality Rating:** Fair

Evidence Table 7. KQ5: Systematic reviews and meta-analyses on antidepressants in subpopulations (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Entsuah et al., 2001 Thase et al., 2005 **Country and setting:** Multinational **Funding:** NR **Research objective:** To compare response and remission rates in different sub-populations	**Study design:** Pooled analysis **Number of Patients:** 2,045 **Studies Included:** 8 double-blind, active controlled	**Included Studies:** Studies that compared VEN to FLUO or PAR **Included Populations** • 18 yrs of age or more • HAM-D of 20 or more or MADRS of 25 or more **Interventions:** • **D1:** Venlafaxine 75-225 mg/d • **D2:** Fluoxetine 20-50 mg/d • **D3:** Paroxetine 20-40 mg d	**Study Results:** No sig age by treatment; gender by treatment; or age-by-gender by treatment interactions (all *P* -values >0.1) Among women, but not men, there was a sig interaction reflecting poorer SSRI response in older age group (*P* = 0.04). HRT appeared to eliminate this diff. Diff among older women taking and not taking HRT was 23% Remission (HAMD at endpoint ≤ 7): VEN = 45% SSRI = 35% placebo = 25% (VEN vs SSRI, *P* < 0.0001; SSRI vs placebo, *P* = 0.0003)	**Adverse Events:** Women on VEN had more nausea than other groups	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Table E-1. Characteristics of Studies with Poor Internal Validity

Study	Design	Sample Size	Intervention	Reason for Exclusion
Aguglia et al., 1993[1]	RCT	108	Fluoxetine vs. sertraline	High LTF
Amini et al., 2005[2]	RCT	36	Mirtazapine vs. fluoxetine	No ITT analysis
Clerc et al., 1994[3]	RCT	68	Fluoxetine vs. venlafaxine	High differential attrition
Falk et al., 1989[4]	RCT	27	Trazadone vs. fluoxetine	High LTF
Ferrando et al., 1997[5]	RCT	33	Sertraline vs. paroxetine vs. fluoxetine	No ITT analysis
Flament et al., 2001[6]	RCT	286	Sertraline vs. fluoxetine	No ITT analysis
Goldstein et al., 2004[7]	RCT	353	Duloxetine vs. paroxetine	High LTF
Grigoriadis et al., 2003[8]	Observational	201	Citalopram vs. fluoxetine	No ITT analysis (completer analysis only)
Gülseren et al., 2005[9]	RCT	25	Fluoxetine vs. paroxetine	No ITT analysis; high rate of post-randomization exclusions
Mesters et al., 1993[10]	RCT	308	Fluoxetine	No ITT analysis
Oslin et al., 2003[11]	RCT	52	Sertraline vs. venlafaxine IR	High attrition
Roscoe et al., 2005[12]	RCT	94	Paroxetine vs. placebo	No ITT analysis
Rosenbaum et al., 1998[13]	Observational	242	Sertraline, fluoxetine, paroxetine	No ITT analysis
Schmitz et al., 2001[14]	RCT	68	Fluoxetine vs. placebo	High LTF
Stahl et al., 2000[15]	RCT	323	Citalopram vs. sertraline	High attrition
Thase et al., 2001[16]	Pooled analysis	2,045	Venlafaxine vs. SSRIs	No systematic literature search
Tollefson et al., 1994[17] and Beasley et al., 1991[18]	Meta-analysis	3,065	Fluoxetine vs. placebo	No systematic literature search
Wade et al., 2003[19]	RCT	197	Mirtzapine vs paroxetine	High LTF; high post-randomization exclusions
Wagner et al., 1998[20]	RCT	118	Fluoxetine vs. placebo	No ITT analysis
Winokur et al., 2003[21]	RCT	21	Fluoxetine vs. mirtazapine	No ITT analysis, small sample size
Zanardi et al., 1996[22]	RCT	46	Paroxetine vs. sertraline	High LTF (41%)

ITT, intent to treat analysis; LTF, loss to followup; RCT, randomized controlled trial.

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Placebo Studies Included in Meta-Regression

Study	Design	Sample Size	Intervention	Quality Rating
Addington et al., 2002[1]	RCT	48	Sertraline vs. placebo	Fair
Brannan et al., 2005[2]	RCT	282	Duloxetine vs. placebo	Fair
Burke et al., 2001[3]	RCT	70	Fluoxetine vs. placebo	Fair
Claghorn et al., 1992[4]	RCT	71	Paroxetine vs. placebo	Fair
Claghorn et al., 1992[5]	RCT	341	Paroxetine vs. placebo	Fair
Cohn et al., 1996[6]	RC	81	Nefazodone vs. placebo	Fair
Cunningham et al., 1997[7]	RCT	268	Venlafaxine vs. placebo	Fair
Detke et al., 2002[8]	RCT	267	Duloxetine vs. placebo	Fair
Detke et al., 2002[9]	RCT	236	Duloxetine vs. placebo	Fair
Feighner et al., 1999[10]	RCT	650	Citalopram vs. placebo	Fair
Fontaine et al., 1994[11]	RCT	135	Nefazodone vs. placebo	Fair
Hypericum Depression Trial Study Group, 2002[12]	RCT	227	Sertraline vs. placebo	Good
Khan et al., 1991[13]	RCT	93	Venlafaxine vs. placebo	Fair
Kocsis et al., 1997[14,15]	RCT	416	Sertraline vs. placebo	Fair
Lineberry et al., 1990[16]	RCT	224	Bupropion vs. placebo	Fair
Lydiard et al., 1989[17]	RCT	36	Fluvoxamine vs. placebo	Fair
Lydiard et al., 1997[18]	RCT	234	Sertraline vs. placebo	Fair
Mendels et al., 1993[19]	RCT	312	Venlafaxine vs. placebo	Fair
Mendels et al., 1995[20]	RCT	240	Nefazodone vs. placebo	Fair
Olie et al., 1997[21]	RCT	258	Sertraline vs. placebo	Fair
Reimherr et al., 1990[22]	RCT	290	Sertraline vs. placebo	Fair
Reimherr et al., 1988[23]	RCT	77	Sertraline vs. placebo	Fair
Rickels et al., 1989[24]	RCT	102	Paroxetine vs. placebo	Fair
Shrivastava et al., 1992[25]	RCT	69	Paroxetine vs. placebo	Fair
Strik et al., 2000[26]	RCT	54	Fluoxetine vs. placebo	Fair
Thase et al., 1997[27]	RCT	197	Venlafaxine vs. placebo	Fair
Tollefson et al., 1993[28]	RCT	534	Fluoxetine vs. placebo	Fair
Tollefson et al., 1995[29,30]	RCT	671	Fluoxetine vs. placebo	Fair
Trivedi et al., 2004[31]	RCT	459	Paroxetine vs. placebo	Fair
Wade et al., 2002[32]	RCT	380	Escitalopram vs. placebo	Fair
Walczak et al., 1996[33]	RCT	577	Fluvoxamine vs. placebo	Fair

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Placebo Studies Excluded from Meta-Regression

Study	Design	Sample Size	Intervention	Reason for Exclusion
Brown et al., 2005[1]	RCT	90	Citalopram vs. placebo	High attrition
Byerley et al., 1988[2]	RCT	97	Fluoxetine vs. placebo	No ITT analysis
Claghorn et al., 1995[3]	RCT	90	Mirtazapine vs. placebo	No ITT analysis
Claghorn et al., 1996[4]	RCT	150	Fluvoxamine vs. placebo	No ITT analysis
Claghorn, 1992[5]	RCT	72	Paroxetine vs. placebo	No ITT analysis
Cohn et al., 1990[6]	RCT	120	Paroxetine vs. placebo	No ITT analysis
Cohn et al., 1992[7]	RCT	120	Paroxetine vs. placebo	No ITT analysis; high rate of post-randomization exclusions
Corrigan et al., 2000[8]	RCT	70	Fluoxetine vs. placebo	No ITT analysis
Croft et al., 2002[9]	RCT	432	Bupropion vs. placebo	High LTF
Dunbar et al., 1991[10]	RCT	480	Paroxetine vs. placebo	High Attrition
Dunbar et al., 1993[11]	RCT	273	Paroxetine vs. placebo	High Attrition
Elliot et al., 1998[12]	RCT	75	Paroxetine vs. placebo	High LTF; no ITT analysis
Evans et al., 1997[13]	RCT	82	Fluoxetine vs. placebo	High Attrition
Fabre et al., 1996[14]	RCT	100	Fluvoxamine vs. placebo	High Attrition
Fabre et al., 1995[15]	RCT	369	Sertraline vs. placebo	No ITT analysis
Fabre et al.,1992[16]	RCT	74	Paroxetine vs. placebo	High Attrition
Fabre et al., 1987[17]	RCT	84	Fluoxetine vs. placebo	No ITT analysis
Fava et al., 2005[18]	RCT	90	Fluoxetine vs. placebo	High Attrition
Fava et al., 1997[19]	RCT	20	Venlafaxine vs. placebo	No ITT analysis
Feighner et al., 1989[20]	RCT	45	Nefazodone vs. placebo	Not enough data
Feighner et al., 1992[21]	RCT	430	Paroxetine vs. placebo	High Attrition
Feighner et al., 1992[22]	RCT	76	Paroxetine vs. placebo	High Attrition
Feighner et al., 1993[23]	RCT	480	Paroxetine vs. placebo	High Attrition
Feighner et al., 1998[24]	RCT	117	Nefazodone vs. placebo	High Attrition
Gilaberte et al., 2001[25]	RCT	140	Fluoxetine vs. placebo	High attrition
Lapierre et al., 1987[26]	RCT	63	Fluvoxamine vs. placebo	No ITT analysis
March et al., 1990[27]	RCT	54	Fluvoxamine vs. placebo	No ITT analysis

Study	Design	Sample Size	Intervention	Reason for Exclusion
McGrath et al., 2000[28]	RCT	154	Fluoxetine vs. placebo	High rate of post-randomization exclusions
Montgomery et al., 1992[29]	RCT	199	Citalopram vs. placebo	High rate of post-randomization exclusions
Muijen et al., 1988[30]	RCT	81	Fluoxetine vs. placebo	No ITT analysis
Petracca et al., 2001[31]	RCT	41	Fluoxetine vs. placebo	No ITT analysis
Ravindram et al., 1995[32]	RCT	103	Sertraline vs. placebo	High attrition; no ITT analysis
Reimherr et al., 1998[33]	RCT	362	Bupropion vs. placebo	High Attrition
Rickels et al., 1994[34]	RCT	191	Nefazodone vs. placebo	High Attrition
Rickels et al., 1982[35]	RCT	202	Trazadone vs. placebo	No ITT analysis
Rickels et al., 1992[36]	RCT	111	Paroxetine vs. placebo	No ITT analysis
Roth et al., 1990[37]	RCT	90	Fluvoxamine vs. placebo	No ITT analysis
Roy-Byrne et al., 2000[38]	RCT	64	Nefazodone vs. placebo	High Attrition
Rudolph et al., 1998[39]	RCT	358	Venlafaxine vs. placebo	High Attrition
Schweizer et al., 1991[40]	RCT	60	Venlafaxine vs. placebo	High Attrition
Smith et al., 1990[41]	RCT	150	Mirtazapine vs. placebo	No ITT analysis
Smith et al., 1992[42]	RCT	77	Paroxetine vs. placebo	No ITT analysis
Sramek et al., 1995[43]	RCT	144	Fluoxetine vs. placebo	Not enough data
Vartiainen et al., 1994[44]	RCT	114	Mirtazapine vs. placebo	High Attrition
Wernicke et al., 1987[45]	RCT	345	Fluoxetine vs. placebo	High Attrition
Wernicke et al., 1988[46]	RCT	363	Fluoxetine vs. placebo	Not enough data

ITT, intent to treat; RCT, randomized controlled trial; LTF, lost to follow-up

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Discontinuation Rates

Background

Presented in this appendix are relative risk meta-analyses that compare selective serotonin reuptake inhibitors (SSRIs) with individual drugs with respect to discontinuation. The specific comparisons with SSRIs are shown below: bupropion, duloxetine, mirtazapine; nefazodone; trazodone, and venlafaxine The first six figures are for overall discontinuation. The two sets of figures following those are for discontinuation specifically for adverse events and then for discontinuation for lack of efficacy. All are random effects models.

Relative Risk of Overall Discontinuation

Figure H-1. Bupripion vs. SSRIs

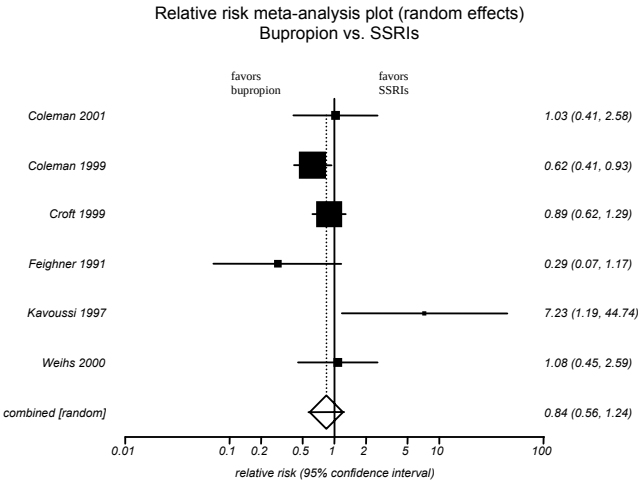


Figure H-2. Duloxetine vs. SSRIs

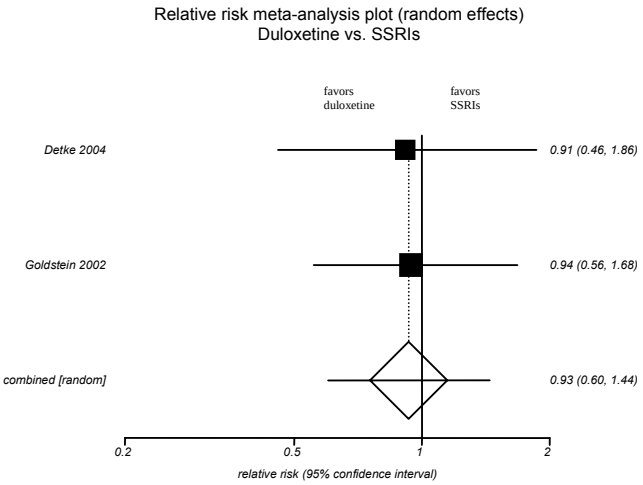


Figure H-3. Mirtazapine vs. SSRIs

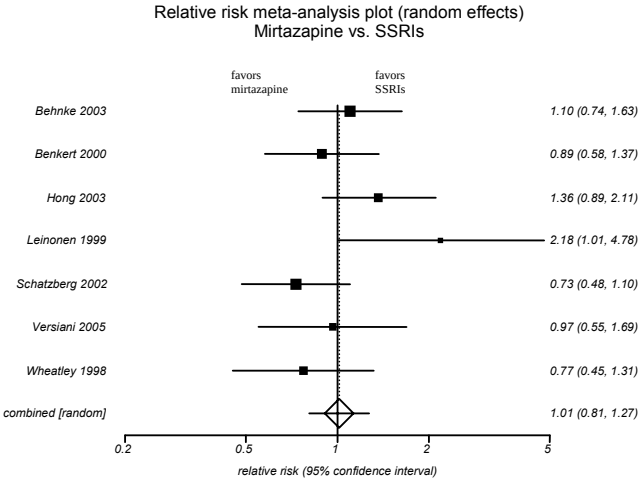


Figure H-4. Nefazodone vs. SSRIs

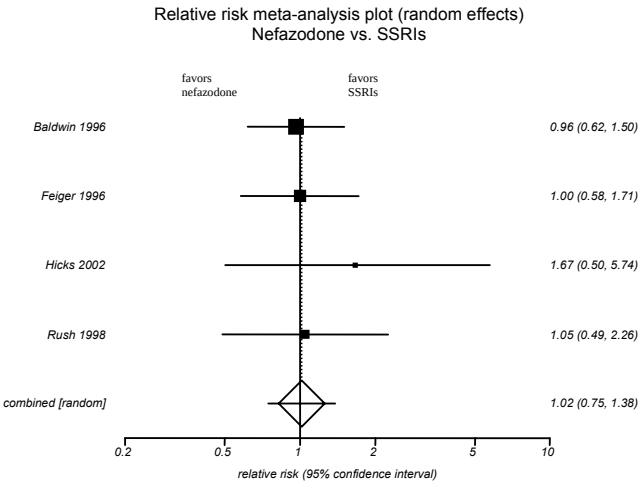


Figure H-5. Trazadone vs. SSRIs

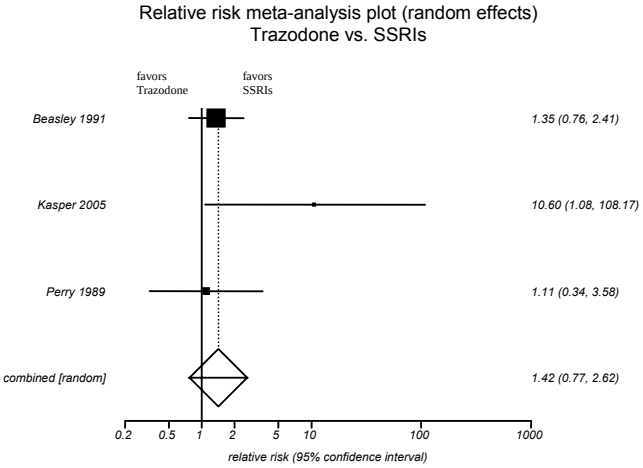
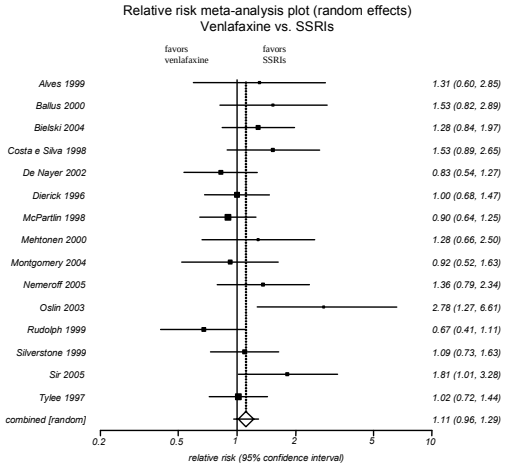


Figure H-6. Venlafaxine vs. SSRIs



Relative Risk of Discontinuation because of Adverse Events

Figure H-7: Bupropion vs. SSRIs: Adverse Events

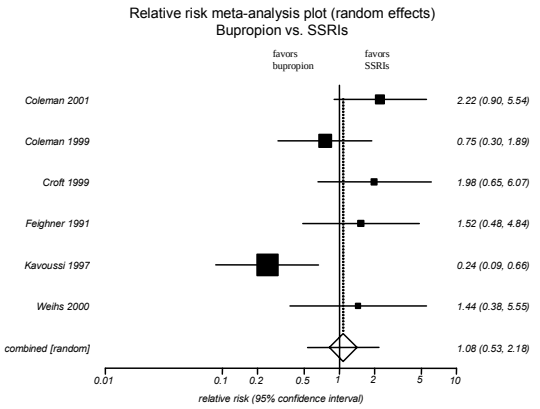


Figure H-8: Duloxetine vs. SSRIs: Adverse Events Only

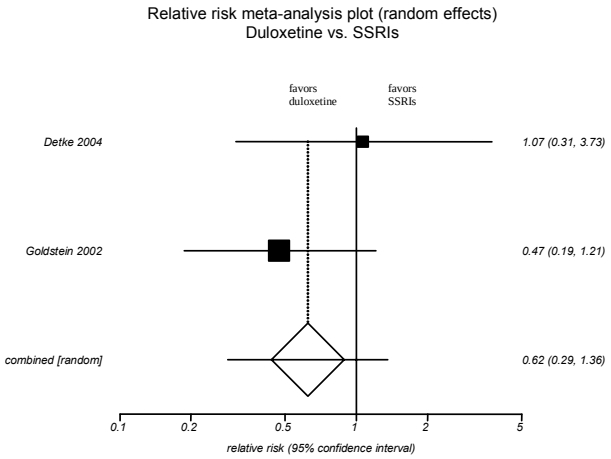


Figure H-9: Mirtzapine vs SSRIs: Adverse Events Only

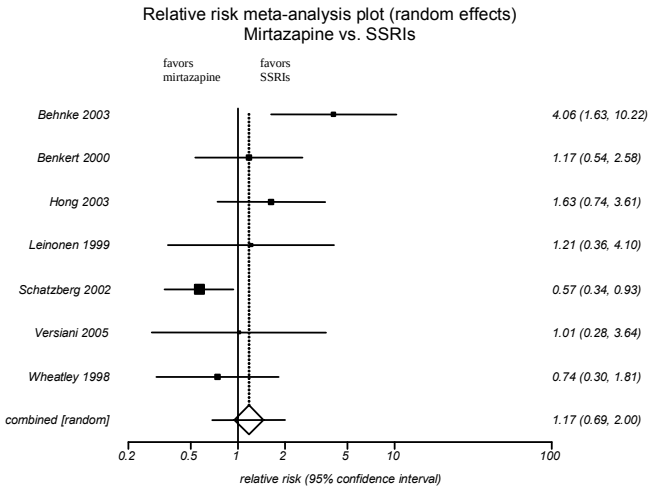


Figure H-10: Nefazodone vs SSRIs: Adverse Events Only

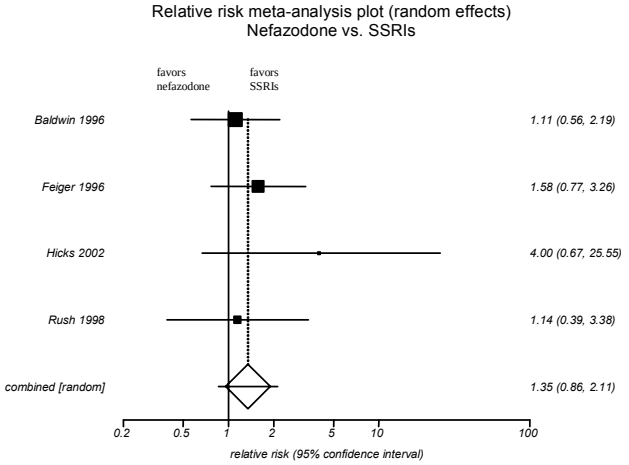


Figure H-11: Trazodone vs SSRIs: Adverse Events Only

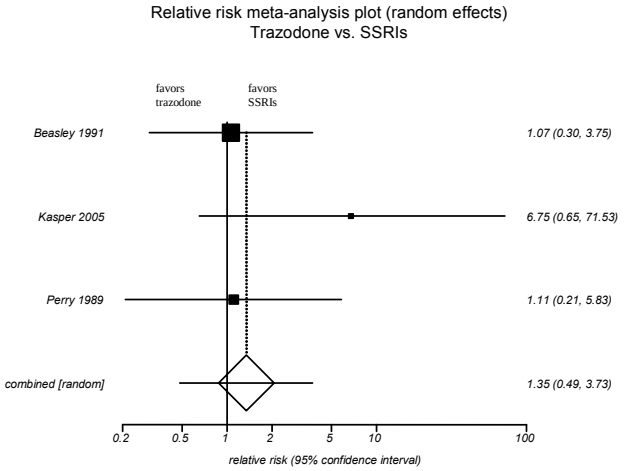
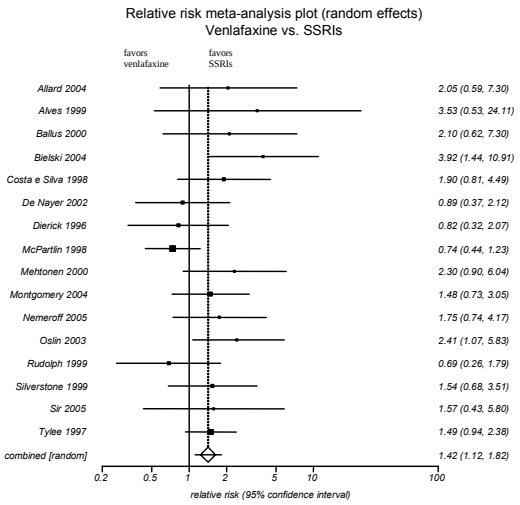


Figure H-12: Venlafaxine vs SSRIs: Adverse Events Only



Relative Risk of Discontinuation because of Lack of Efficacy

Figure H-13. Bupropion vs. SSRIs: Lack of Efficacy

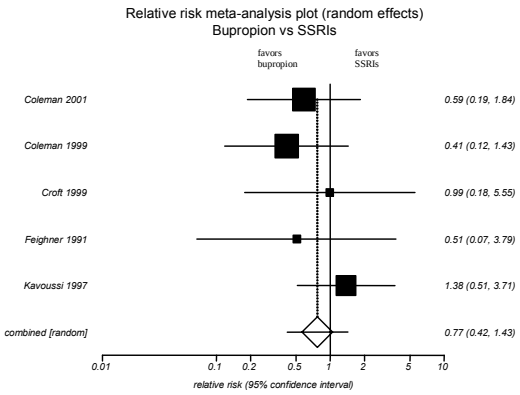


Figure H-14: Mirtzazpine vs. SSRIs: Lack of Efficacy

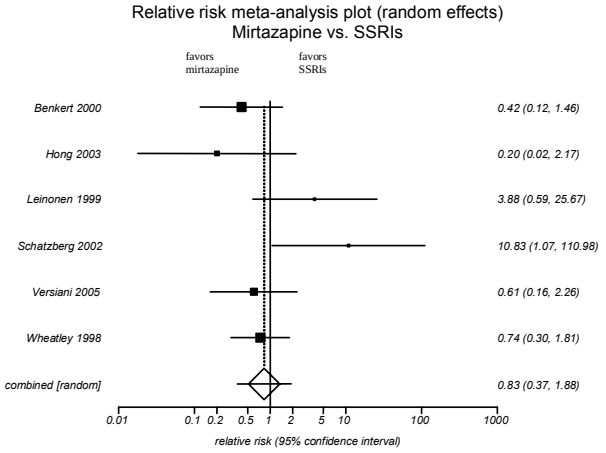


Figure H-15: Nefazodone vs SSRIs: Lack of Efficacy

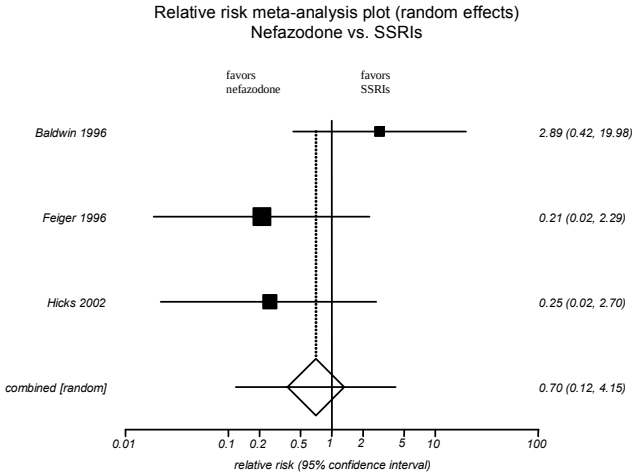
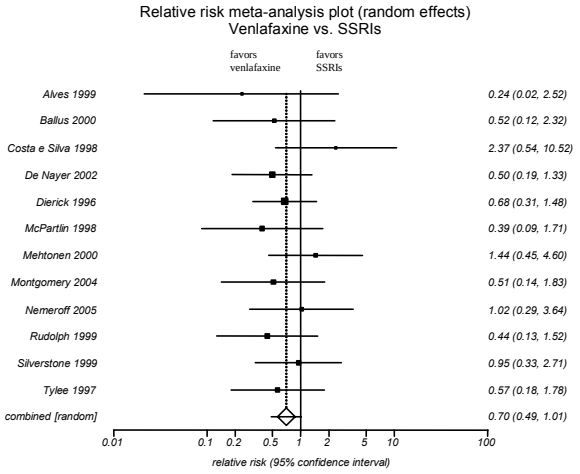


Figure H-16: Venlaxafine vs SSRIs: Lack of Efficacy



Appendix I. Publications Appearing Only as Abstracts

1. Ansseau M, Gabriels A, Loyens J, Bartholome F, Evrard J, Linhart R, et al. A double-blind comparison of paroxetine and fluvoxamine in major depression. Eur Neuropsychopharmacol 1993;3(3):323-324.

2. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file at Forest Laboratories. 2004.

3. Skinner EP, Cantrell R, Chaffin J, et al. Adherence with once-daily bupropion XL versus twice-daily bupropoion SR. J Am Pharm Assoc 2005;45:265.

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