The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.
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**Evidence Table 1**  
**Major Depressive Disorder Adults**

| STUDY:  
Authors: Aberg-Wistedt A, et al.  
Year: 2000  
Country: Sweden |  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING: Pfizer, Inc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| DESIGN: Study design: RCT  
Setting: Multi-center  
Sample size: 353 |  
| INTERVENTION:  
Drug:  
Dose:  
Duration:  
Sertraline  
50-150 mg/d  
24 weeks  
Paroxetine  
20-40 mg/d  
24 weeks |  
| INCLUSION: Age 18 and over; met DSM-III-R criteria for MDD; MADRS score of ≥ 21 at baseline with less than 25% improvement during washout |  
| EXCLUSION: Negative pregnancy test and stable use of oral contraceptive for 3 months; current or past history of mania; hypomania; alcoholism; substance abuse; dementia; epilepsy; presence of psychotic depression or organic affective illness; history of suicide attempts or high risk; current use of psychotropic meds; treatment with lithium or MAOI in the month prior to screening; history of intolerance or allergic reaction to either study drug; clinically evidence of hepatic or renal disease or other acute or unstable medical condition; use of any meds that would interfere with safe conduct of the study |  
| OTHER MEDICATIONS/INTERVENTIONS: Nitrazepam, oxazepam, flunitrazepam |  
| POPULATION CHARACTERISTICS: Groups similar at baseline: Yes  
Mean age: 43  
Gender (% Female): 67.4%  
Ethnicity: Not reported  
Other population characteristics: 8% over 65 years, 53% less than 45 years, 33% married or live with significant other |
**Authors:** Aberg-Wistedt A, et al.  
**Year:** 2000  
**Country:** Sweden

### OUTCOME ASSESSMENT:

| Measures: MADRS, CGI-S, Secondary Battelle Quality of Life Measure (BQOL), SCID-II before and after treatment |
| Timing of assessments: Primary measures at baseline and weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 |

### RESULTS:

- Response-LOCF at 24 weeks: sertraline: 72%, paroxetine 69%
- Response-Observed Cases at 24 weeks: sertraline 89%, paroxetine 89%
- No significant difference at endpoint or at any other study point measures
- No significant difference in CGI severity change score or improvement score
- Relapse during weeks 9-24: paroxetine 8.6%, sertraline 1.9% (no p value reported)
- No significant differences on QOL measures

### ANALYSIS:

| ITT: LOCF  |
| Post randomization exclusions: Yes |

### ATTRITION:

| Loss to follow-up: 35.4%; sertraline 36.4%, paroxetine 34.5%  |
| Withdrawals due to adverse events: Not reported  |
| Loss to follow-up differential high: No  |

### ADVERSE EVENTS:

- Diarrhea: sertraline 35.2%, paroxetine 15.2% (p < 0.01)
- Constipation: sertraline 5.7%, paroxetine 16.4% (p < 0.01)
- Fatigue: sertraline 21.0%, paroxetine 45.8% (p < 0.01)
- Decreased libido female: sertraline 1.8%, paroxetine 8.8% (p < 0.05)
- Micturition problems: sertraline 0.6%, paroxetine 6.2% (p < 0.05)

### QUALITY RATING:

| Fair |
### Evidence Table 1  
**Major Depressive Disorder**

| STUDY: | Authors: Allard P, et al.  
Year: 2004  
Country: Sweden and Denmark |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: 12 centers  
Sample size: 151 |
| INTERVENTION: |  
| Drug: |  
| Dose: |  
| Duration: |  
| Sample size: |  
| Venlafaxine ER | 37.5-150 mg/day  
6 months | 73 |
| Citalopram | 10-30 mg/day  
6 months | 75 |
| INCLUSION: | Male or female outpatients 65 years or older; DSM-IV for major depression; MADRS greater than 20 with less than a 20% decrease from pre-study to baseline visits (one week) |
| EXCLUSION: | Cognitive impairment; alcohol or drug abuse; psychotic disorder not associated with depression; psychiatric inpatient treatment within the last year; acute suicidal tendencies; anti-psychotic drug, ECT or sumatriptan within last 30 days; bipolar, clinically evident or diagnosed dementia; mental disorders due to medical conditions; history of seizure, significant CVD, cerebrovascular disorder or uncontrolled hypertension |
| OTHER MEDICATIONS/INTERVENTIONS: | Zopiclone 7.5 mg/day or less; zolpidem 5 mg/day or less for sleep; medications for the treatment of somatic disorders provided they were not expected to be associated with significant toxicity |
| POPULATION CHARACTERISTICS: | Groups similar at baseline:  
Mean age: venlafaxine: 73.6, citalopram: 72.5  
Gender (% female): venlafaxine: 73.6%, citalopram 72.7%  
Ethnicity: NR  
Other population characteristics: Baseline MDRS: venlafaxine: 27.6, citalopram: 27.0 |
**Authors:** Allard P, et al.  
**Year:** 2004  
**Country:** Sweden and Denmark

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>MADRS at 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>MADRS responders and remitters, time to sustained response using MADRS and CGI-I; CGI-S and GDS-20 scores at weeks 8 and 22</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Pre-study, baseline and weeks 2,4,6,8,16,22,24</td>
</tr>
</tbody>
</table>

### RESULTS:

- No statistical differences between groups in MADRS, CGI-S, CGI-I, and GDS-20 were observed
- At week 22 both groups had a 93% response rate
- MADRS remission rate was 19% for venlafaxine and 23% for citalopram

### ANALYSIS:

| ITT: | Yes |
| Post randomization exclusions: | Yes (3) |

### ATTRITION:

<table>
<thead>
<tr>
<th>Overall</th>
<th>Venlafaxine</th>
<th>Citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.2%</td>
<td>(6) 8%</td>
<td>(3) 4%</td>
</tr>
</tbody>
</table>

| Withdrawals due to adverse events: | 6% |
| Withdrawals due to lack of efficacy: | |
| Loss to follow-up differential high: | |

### ADVERSE EVENTS:

- Spontaneously reported adverse events venlafaxine: 62%, citalopram: 43%
- Tremor more common during citalopram; nausea/vomiting during venlafaxine treatment

### QUALITY RATING:

| Fair |
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | **Authors:** Alves C, et al.³  
**Year:** 1999  
**Country:** Portugal |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst International</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center (3 centers)  
**Sample size:** 87 |
| INTERVENTION: Drug: Dose: Duration: | Venlafaxine  
75-150 mg/day  
12 weeks | Fluoxetine  
20-40 mg/day  
12 weeks | Doses could be increased from day 15 if needed |
| INCLUSION: | 18-65 yrs; DSM-IV criteria for major depression; ≥ 20 on HAM-D-21 |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; history of seizures, mental or neurological disorders; alcohol or substance abuse; existing suicidal risk; use of study drugs, sumatriptan, or antipsychotic drugs within 30 days; fluoxetine within 21 days; anxiolytic or sedative within 7 days; stable dose of 3 months for drugs with psychotropic effects like b-blockers; clinically relevant medical disease; known sensitivity to venlafaxine or fluoxetine |
| OTHER MEDICATIONS/ INTERVENTIONS: | Diazepam |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** venlafaxine: 45.4, fluoxetine: 42.3  
**Gender (% female):** venlafaxine: 92.5%, fluoxetine: 91.5%  
**Ethnicity:** Not reported  
**Other population characteristics:** CGI diagnosis:  
- Moderately ill: venlafaxine: 45%, fluoxetine: 50%.  
- Markedly ill: venlafaxine: 33%, fluoxetine: 38%.  
- Severely ill: venlafaxine: 15%, fluoxetine: 6%.  
- Previous antidepressant treatment: venlafaxine: 45%, fluoxetine: 55% |
Authors: Alves C, et al.  
Year: 1999  
Country: Portugal

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Measures:</th>
<th>HAM-D, MADRS, CGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Baseline, days 7, 14, 21, 28, 42, 56, 70, 84</td>
</tr>
</tbody>
</table>

### RESULTS:

- There were no significant differences between study groups in any outcome measures at endpoint.
- Venlafaxine showed a faster onset with significant differences in various outcome measures during weeks 1 to 4: mean decreases of HAM-D and MADRS scores were significantly greater with venlafaxine ($p < 0.05$) during weeks 1-4.
- Suicide ideation scores at week 6 were significantly lower for venlafaxine on MADRS and HAM-D scales.
- Remission (HAM-D < 8) at week 3 was found in 30% of venlafaxine treated patients and 11% of fluoxetine treated patients ($p = 0.03$).

### ANALYSIS:

- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** 21.8%; venlafaxine: 25%, fluoxetine: 19%  
- **Withdrawals due to adverse events:** venlafaxine: 7%, fluoxetine: 2%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- There were no significant differences between study groups in the frequency of adverse events.
- At least one adverse event was recorded in 56% of the venlafaxine group and 51% of the fluoxetine group.
- Nausea was the most common adverse event: venlafaxine: 33.3%, fluoxetine: 27.7%.
- No clinically significant changes in laboratory parameters, body weight, heart rate, or blood pressure were recorded in either treatment group.

### QUALITY RATING:

- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:** | *Authors:* Baldwin DS, et al.*4,5*
*Year:* 1996, 2001 (continuation phase)
*Country:* UK, Ireland |
| **FUNDING:** | Bristol Myers Squibb |
| **DESIGN:** | *Study design:* RCT
*Setting:* Multi-center, 20 psychiatric outpatient clinics
*Sample size:* 206 |
| **INTERVENTION:** | |
| *Drug:* | Nefazodone
200-600 mg/d
Mean dose: 472.0 mg
8 weeks, twice a day |
| *Dose:* | Paroxetine
20-40 mg/d
Mean dose: 32.7 mg
8 weeks, twice a day |
| *Duration:* | Continuation Phase:
from week 8 to
to month 6
dose was
gradually reduced wherever possible |
| **INCLUSION:** | 18 years or older; non-psychotic depression; HAM-D score of ≥ 18; moderately ill on CGI-S scale
Continuation Phase: patients who responded to treatment during the 8 weeks acute treatment phase |
| **EXCLUSION:** | Pregnancy, lactation, or lack of adequate contraception; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; electroconvulsive therapy within last 6 months; previously failed to respond to at least 2 antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication |
| **OTHER MEDICATIONS/INTEGRATIONS:** | Benzodiazepines, antipyretics, analgesics, supportive psychological treatment |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes
Mean age: 38; Continuation phase mean age: 38.8
Gender: (female %) nefazodone: 60%, paroxetine: 50%
Continuation phase: nefazodone: 51%, paroxetine: 55%
Ethnicity: Not reported
Other population characteristics: Not reported |
**Authors:** Baldwin DS, et al.
**Year:** 1996, 2001
**Country:** UK, Ireland

**OUTCOME ASSESSMENT:**

| Measures and timing of assessments: | HAM-D, CGI-S, CGI-I, Patient’s Global Assessment: Baseline, weeks 1, 2, 3, 4, 6, 8, HAM-A: weeks 2 and 8, MADRS: weeks 4 and 8 | Continuation Phase: weeks 12, 16, 20, and 24 |

**RESULTS:**

- Both groups showed significant improvements from baseline HAM-D, HAM-A, and MADRS scores
- There were no significant differences between the treatment groups
- The proportion of CGI responders was also similar between treatment groups
- **Continuation Phase:**
  - No statistically significant differences between study groups regarding efficacy
  - Clinical improvement either maintained or improved in continuation phase

**ANALYSIS:**

| ITT: | Yes |
| Post randomization exclusions: | Not reported |

**ATTRITION:**

| Loss to follow-up: | 27.2 %; nefazodone: 26.7%, paroxetine: 27.7%. |
| Continuation Phase: | 32.4 %; nefazodone: 33%, paroxetine: 32.7% |

| Withdrawals due to adverse events: | 13.5%; nefazodone: 14%, paroxetine: 13%. |
| Continuation Phase: | nefazodone: 7%, paroxetine: 8% |

| Loss to follow-up differential high: | No |

**ADVERSE EVENTS:**

- 84% of nefazodone treated patients and 78% of paroxetine treated patients reported side effects
- Frequencies among adverse events were similar except a higher frequency of somnolence in the paroxetine group (24% vs. 16%) and higher frequencies of headache (35% vs. 25%) and dizziness (17% vs. 9%) in the nefazodone group
- **Continuation Phase:** 75% of nefazodone treated patients and 81% of paroxetine treated patients reported side effects
- Most common adverse events in paroxetine group were nausea (34% vs. 16% in nefazodone group) and somnolence (27% vs. 20%)
- Most common adverse event in nefazodone group was headache (31% vs. 28% in paroxetine group)

**QUALITY RATING:**

| Fair |
Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Baldwin D et al.\textsuperscript{1}  
| Year: 2006  
| Country: Multinational (6 countries) |
| FUNDING: | H Lunbeck A/S |
| DESIGN: | Study design: RCT  
| Setting: Multicenter  
| Sample size: 323 |
| INTERVENTION: | Drug:  
| Dose:  
| Duration:  
| Sample size: |
| Paroxetine | Escitalopram  
| 20-40 mg | 10-20 mg  
| 8 (27) weeks | 8 (27) weeks  
| 158 | 165 |
| INCLUSION: | Either sex, aged at least 18 years or older, fulfilled DSMIV criteria for a current episode of MDD, and had a baseline MADRS total score between 22 and 40 |
| EXCLUSION: | Another Axis I disorder previous 6 months; if they had a DSM-IV diagnosis of alcohol or drug abuse, schizophrenia/other psychotic disorder, mania or hypomania, eating disorders, OCD, bipolar disorder; had a learning disability or other cognitive disorder; a serious risk of suicide; previously not responded to or had a known hypersensitivity to citalopram and/or paroxetine, had a history of severe drug allergy or hypersensitivity; lactose intolerance. taken a psychoactive drug (including tryptophan, benzodiazepines unless the dose had been stable for the previous 6 months and remained fixed during the study), antipsychotics and psychoactive herbal remedies, MAOIs, or prophylactic treatment (lithium, valproate, or carbamazepine) dopamine antagonists, antidepressants within 2 weeks [5 weeks for fluoxetine], triptans, oral anticoagulants, sildenafil citrate, cimetidine, type 1c anti-arrhythmics, cardiac glycosides, narcotic analgesics, an investigational drug within 3 months, or if they were receiving (or planning to initiate) formal psychotherapy. |
| OTHER MEDICATIONS/ INTERVENTIONS: | See above |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: Paroxetine 45.1 Escitalopram 44.9  
| Gender (female %): Paroxetine 74.7 Escitalopram 72.7  
| Ethnicity (Caucasian %): Paroxetine 99.4 Escitalopram 98.8  
<p>| Other population characteristics: MADRS Paroxetine 29.7 Escitalopram 29.6 |</p>
<table>
<thead>
<tr>
<th>Authors: Baldwin et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2006</td>
</tr>
<tr>
<td>Country: Multinational (6 countries)</td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**
- **Primary Outcome Measures:** Change at week 8 in MADRS
- **Secondary Outcome Measures:** Moderately ill vs severely ill, responders and remitters
- **Timing of assessments:** Baseline, week 8

**RESULTS:**
- Acute period baseline to week 8
- Change in MADRS paroxetine -18.31 escitalopram -17.16
- Responders paroxetine 71.2% escitalopram 67.9%
- Remitters paroxetine 61.5% escitalopram 56.4%

**ANALYSIS:**
- ITT: yes
- Post randomization exclusions: 2

**ATTRITION:**
- Loss to follow-up: 7.0% paroxetine 8.5% escitalopram
- Withdrawals due to adverse events: 3.2% paroxetine 4.2% escitalopram
- Withdrawals due to lack of efficacy: 0 escitalopram
- Loss to follow-up differential high: No

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>25 (7.7%)</td>
<td></td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**
- Patients with adverse events 131 (82.9) vs. 135 (81.8)
- Headache 21 (13.3) vs. 33 (20.0)
- Nausea 22 (13.9) vs. 19 (11.5)
- Rhinitis 15 (9.5) vs. 18 (10.9)
- Diarrhoea 10 (6.3) vs. 17 (10.3)
- Bronchitis 9 (5.7) vs. 14 (8.5)
- Insomnia 7 (4.4) vs. 11 (6.7)
- Accidental injury 8 (5.1) vs. 10 (6.1)
- Back pain 7 (4.4) vs. 10 (6.1)
- Dizziness 10 (6.3) vs. 10 (6.1)
- Myalgia 4 (2.5) vs. 10 (6.1)
- Pharyngitis 7 (4.4) vs. 10 (6.1)
- Anxiety 9 (5.7) vs. 9 (5.5)
- Somnolence 10 (6.3) vs. 8 (4.8)
- Constipation 13 (8.2) vs. 6 (3.6)
- Fatigue 9 (5.7) vs. 6 (3.6)
- Upper resp tract infection 17 (10.8) vs. 6 (3.6)*
- Abdominal pain 8 (5.1) vs.5 (3.0)
- Sweating increased 12 (7.6) vs. 5 (3.0)
- Ejaculation failure (men) 3 (7.5) vs. 0
QUALITY RATING: Fair
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Ballus C, et al.  
Year: 2000  
Country: Spain |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported (several authors have affiliations with Wyeth)</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 84 |
| INTERVENTION: | Drug: Venlafaxine  
Dose: 75-150 mg/day  
Duration: 24 weeks  
Paroxetine  
Dose: 20-40 mg/day  
Duration: 24 weeks  
Initial dose of each drug could be increased after 4 weeks |
| INCLUSION: | Age 18-70 years; ICD-10 criteria for mild to moderate depression or dysthymia; minimum score of 17 on the 21 item HAM-D; less than a 20% decrease in HAM-D score between screening and baseline |
| EXCLUSION: | Sensitivity to either study drug; history of significant illness; pregnant or breastfeeding; suicidal tendencies; psychotic disorder not associated with depression; drug or alcohol dependence; use of investigational drugs or treatments shortly before the study |
| OTHER MEDICATIONS/ INTERVENTIONS: | Yes |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: venlafaxine: 44, paroxetine: 45.1  
Gender (% female): venlafaxine: 88%, paroxetine: 88%  
Ethnicity: Not reported  
Other population characteristics: Both groups have similar clinical characteristics; mild to moderate depression; dysthymia diagnosis not differentiated |
**Authors:** Ballus C, et al.  
**Year:** 2000  
**Country:** Spain

### OUTCOME ASSESSMENT:
- **Measures:** 21 item HAM-D, MADRS, CGI scale  
- **Timing of assessments:** Baseline, weeks 1, 2, 4, 6, 8, 12, 16, 24

### RESULTS:
- No significant differences between groups on the HAM-D, MADRS, or CGI scales at 24 weeks or endpoint  
- At week 12 the percent of patients with a HAM-D score $\leq 8$ was significantly greater in the venlafaxine group than the paroxetine group (57% vs. 33%; $p = .011$)  
- More patients exhibited a drug response ($\geq 50\%$ decrease in HAM-D) on venlafaxine than paroxetine at week 6 ($p = 0.03$)

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Not reported

### ATTRITION:
- **Loss to follow-up:** 32%, venlafaxine: 39%, paroxetine: 26%  
- **Withdrawals due to adverse events:** 11%, venlafaxine: 15%, paroxetine: 8%  
- **Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:
- Venlafaxine: nausea: 28%, headache: 18%, dry mouth: 15%  
- Paroxetine: headache: 40%, constipation: 16%

### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING: Organon NV</td>
</tr>
<tr>
<td>DESIGN: Study design: RCT Setting: Multi-center Sample size: 346</td>
</tr>
<tr>
<td>INTERVENTION: Drug: Sertraline 50-150 mg/day 8 weeks Mirtazapine 30-45 mg/day 8 weeks</td>
</tr>
<tr>
<td>INCLUSION: DSM IV criteria for major depression; HAM-D score ≥ 18; age 18-70 yrs</td>
</tr>
<tr>
<td>EXCLUSION: Other psychiatric disorders; epilepsy or history of seizures; pregnancy, lactation, childbearing potential; substance abuse; chronic and unstable physical disease; current episode ≥ 12 months or 2 ≤ weeks; lack of response to at least 2 prior antidepressant therapies; previous hypersensitivity; use of sildinafil</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS: Oxazepam, temazepan, zolpidem, zopiclone</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS: Groups similar at baseline: Yes Mean age: 41.5 yrs; mirtazapine 42, sertraline: 41 Gender (% female); sertraline: 61.5%, mirtazapine: 55.7% Ethnicity: Not reported Other population characteristics: Previous episodes of major depression: sertraline: 69.8%, mirtazapine: 73.3%</td>
</tr>
<tr>
<td>Authors: Behnke K, et al.</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Year: 2003</td>
</tr>
<tr>
<td>Country: Multinational</td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**

*Measures and timing of assessment:* HAM-D, MADRS, CGI at baseline, and days 4, 7, 10, 14, 28, 42, 56 or on premature withdrawal, changes in sexual function questionnaire at baseline and biweekly thereafter.

**RESULTS:**

- Onset of action was faster in the mirtazapine group.
- At all assessments during the first two weeks the mean change of HAM-D from baseline was significantly greater in the mirtazapine group than in the sertraline group ($p < 0.05$).
- After week 2 the difference remained greater with mirtazapine but lacked statistical significance.
- Reduction in sleep disturbance was significantly greater in the mirtazapine group at all assessments ($p \leq 0.01$).
- CGI scores did not show significant differences throughout the study.
- Changes in sexual function scores did not show significant differences although the mirtazapine group showed greater improvements.

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Yes

**ATTRITION:**

- **Loss to follow-up:** 20.8%; sertraline: 18%, mirtazapine: 23%
- **Withdrawals due to adverse events:** mirtazapine: 11.9%, sertraline: 3%
- **Loss to follow-up differential high:** Loss to follow up: 20.8%, sertraline: 23%, mirtazapine: 18%

**ADVERSE EVENTS:**

- Percentage of patients reporting at least one adverse event was similar in both groups (mirtazapine: 64%, sertraline: 68%)
- A significantly higher number of patients withdrew from the mirtazapine group (21 vs. 5 in sertraline group; $p = NR$).
- Significantly more patients reported nausea (38 vs. 13; $p < 0.01$), libido decrease (10 vs. 2; $p < 0.01$) and diarrhea (16 vs. 7; $p < 0.01$) in the sertraline-treated group.
- Somnolence was significantly higher in the mirtazapine group (35 vs. 13; $p < 0.01$).
- Weight increase higher in the mirtazapine group (16 vs. 3; $p = 0.01$).

**QUALITY RATING:**

Fair
<table>
<thead>
<tr>
<th><strong>Evidence Table 1</strong></th>
<th><strong>Major Depressive Disorder Adults</strong></th>
</tr>
</thead>
</table>
| **STUDY:**           | *Authors:* Benkert O, et al.²  
  *Year:* 2000  
  *Country:* Germany |
| **FUNDING:**         | Organon, GmBH, Munich, Germany |
| **DESIGN:**          | *Study design:* RCT  
  *Setting:* Multi-center (50 centers)  
  *Sample size:* 275 |
| **INTERVENTION:**    |  
  **Drug:** Mirtazapine  
  **Dose:** 15-45 mg/d  
  **Duration:** 6 weeks  
  Paroxetine  
  **Dose:** 20-40 mg/d  
  **Duration:** 6 weeks |
| **INCLUSION:**       | 18-70 years of age; DSM-IV criteria for major depression; > 18 on HAM-D-17 |
| **EXCLUSION:**       | Depressive episode longer than 12 months; other psychiatric or psychotic disorder; alcohol or substance abuse; suicidal risk; significant physical illness; non-responders to antidepressants; recent medication with similar drugs; pregnancy |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate for sleep |
| **POPULATION CHARACTERISTICS:** | *Groups similar at baseline:* Yes  
  *Mean age:* mirtazapine: 47.2, paroxetine: 47.3  
  *Gender:* (% female): mirtazapine: 63%, paroxetine: 65%  
  *Ethnicity:* Not reported  
  *Other population characteristics:* Not reported |
<table>
<thead>
<tr>
<th>Authors: Benkert O, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2000</td>
</tr>
<tr>
<td>Country: Germany</td>
</tr>
</tbody>
</table>

### OUTCOME ASSESSMENT:

**Measures:** HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36  
**Timing of assessments:** Screening, baseline, weeks 1, 2, 3, 4, 6

### RESULTS:

- Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%)  
- Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% (p < 0.002).

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 23%; mirtazapine: 21.6%, paroxetine: 24.2%  
**Withdrawals due to adverse events:** 8%; mirtazapine: 8.6%, paroxetine: 7.4%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Significantly more mirtazapine patients experienced weight increase (p < 0.05)  
- At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4%  
- Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2%  
- Headache: mirtazapine: 9.6%, paroxetine: 10.4%  
- Nausea: mirtazapine: 4.4%, paroxetine: 11.2%  
- Flu like symptoms: mirtazapine: 9.6%, paroxetine: 3.7%  
- Differences all p < 0.1

### QUALITY RATING:

Fair
## Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Bennie EH, et al.  
| Year: 1995  
| Country: UK |
| --- | --- |
| FUNDING: | Pfizer |
| DESIGN: | Study design: RCT  
| Setting: Multi-center (20 centers)  
| Sample size: 286 |
| INTERVENTION: | **Drug:**  
| Sertraline  
| Dose: 50-100 mg/d  
| Duration: 6 weeks |
| Fluoxetine  
| Dose: 20-40 mg/d  
| Duration: 6 weeks |
| INCLUSION: | 18 yrs or older; DSM-III-R criteria for major depression; ≥ 18 on HAM-D-17; higher score on the Raskin scale than on the Covi anxiety scale |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; previous treatment with sertraline or fluoxetine; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapy; clinically relevant progressive disease; hypersensitivity to study drug class |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate (500-1000 mg), temazepam (10-20 mg) |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
| **Mean age:** sertraline: 49.9, fluoxetine: 49.9  
| **Gender (% female):** sertraline: 57.7%, fluoxetine: 64.6%  
| **Ethnicity:** Not reported  
| **Other population characteristics:** Recurrent episode: sertraline: 53.5%, fluoxetine: 53.5%; duration of current episode: sertraline: 5.4 mo., fluoxetine: 5.2 mo. |
**Authors:** Bennie, et al.  
**Year:** 1995  
**Country:** UK

### OUTCOME ASSESSMENT:

**Measures:** HAM-D, HAM-A, CGI-I, CGI-S, Covi Anxiety Scale, Raskin Depression Scale, Leeds Sleep Questionnaire  
**Timing of assessments:** Baseline, weeks 1, 2, 4, 6

### RESULTS:

- There were no significant differences between treatment groups in any of the outcome measures at any point in time (changes in HAM-D, HAM-A, CGI, Raskin, Covi scales)  
- Both groups showed significant improvements from baseline  
- Response rate (≥ 50% improvement on HAM-D): sertraline: 59%, fluoxetine: 51%  
- Both treatment groups showed significant improvement in the Leeds Sleep Questionnaire

### ANALYSIS:

**ITT:** No  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 13.3%  
**Withdrawals due to adverse events:** sertraline: 14%, fluoxetine: 13%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No significant difference between treatment groups in the occurrence of adverse events  
- Incidence of adverse events: sertraline: 56%, fluoxetine: 60%  
- Most common adverse events: nausea: sertraline: 21%, fluoxetine: 25%; headache: sertraline: 14.1%, fluoxetine: 14.6%; agitation: sertraline: 4.9%, fluoxetine: 5.6%  
- 3 patients in each treatment group experienced severe drug related adverse events

### QUALITY RATING:

**Fair**
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Bielski RJ, et al.  
Year: 2004  
Country: US |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Forest Laboratories</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (8 sites)  
Sample size: 198 |
| INTERVENTION: | Drug: Escitalopram  
Dose: 20 mg/d  
Duration: 8 weeks  
Sample size: 98  
Venlafaxine XR  
Dose: 225 mg/d  
Duration: 8 weeks  
Sample size: 100 |
| INCLUSION: | Male and female patients 18 to 65 years of age; met DSM-IV criteria for MDD; minimum score of 20 on the HAM-D-24 at screening and baseline |
| EXCLUSION: | Pregnant or lactating women; patients with a primary diagnosis for other Axis I disorder; history of schizophrenia or other psychotic disorder; severe personality disorder; history of substance abuse; suicidal risk; unstable significant medical illness |
| OTHER MEDICATIONS/INTERVENTIONS: | No psychoactive drugs allowed except zolpidem or zaleplon as needed for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No (more women in escitalopram group)  
Mean age: Escitalopram: 37.3; venlafaxine: 37.5  
Gender (% female): Escitalopram: 69.4%; venlafaxine: 47.0%  
Ethnicity (% white): Escitalopram: 77.6 %; venlafaxine: 73.0 %  
Other population characteristics: Not reported |
**Outcomes Assessment:**

- **Primary Outcome Measures:** MADRS
- **Secondary Outcome Measures:** HAM-D-24; HAM-D somatic subscale; HAM-A; CGI-S; CES-D; Q-LES-Q; CGI-I
- **Timing of assessments:** Evaluations were conducted at baseline and weeks 1, 2, 4, 6, and 8 for the MADRS, HAM-D-24, CGI-I, and CGI-S. Anxiety symptoms were measured at baseline and weeks 2 and 8.

**Results:**

- No significant differences between treatment groups observed in the LOCF analysis for any of the outcome measures.
- Response rates favored escitalopram (MADRS: 58.8% vs. 48.0%; Ham-D: 61% vs. 48%); no statistical significance was reached.
- No significant differences in remission rates between escitalopram and venlafaxine XR.

**Analysis:**

- **ITT:** Yes
- **Post randomization exclusions:** Yes

**Attrition:**

- **Loss to follow-up:** 30% (60); escitalopram: 27% (26); venlafaxine XR: 34% (34)
- **Withdrawals due to adverse events:** 10% (20); escitalopram: 4% (4); venlafaxine XR: 16% (16)
- **Loss to follow-up differential high:** No

**Adverse Events:**

- Significantly more patients in the venlafaxine XR than in the escitalopram group (16% vs. 4%; p < 0.01) group withdrew due to adverse events.
- Significantly more patients in the venlafaxine XR group than in the escitalopram group (24% vs. 6.1%; p < 0.05) reported nausea.
- Significantly more patients had ejaculation disorders in the venlafaxine XR than in the escitalopram group (22.6% vs. 6.7%; p < 0.05).

**Quality Rating:** Fair
### Evidence Table 1

#### Major Depressive Disorder Adults

| STUDY: | Authors: Boulenger J.-P et al.\textsuperscript{12}  
Year: 2006  
Country: Multinational (Europe) |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter (49)  
Sample size: 454 |
| INTERVENTION: |  
**Drug:** Escitalopram  
Dose: 20 mg  
Duration: 24 weeks  
Sample size: 229  
**Paroxetine**  
Dose: 40 mg  
Duration: 24 weeks  
Sample size: 225 |
| INCLUSION: | Male and female outpatients, 18 to 75 years with MDD; duration more than 2 weeks and MADRS > 30. |
| EXCLUSION: | Schizophrenia/other psychotic disorder, mania or hypomania, eating disorders, OCD, bipolar disorder, alcohol or drug abuse within 1 year; formal or systemic psychotherapy; pregnant or lactating; history of use of paroxetine, citalopram or escitalopram, lactose intolerance; ECT within 6 months; current use of MAOIs, RIMA, SSRIs, SNRIs, tricyclics, tryptophan herbal ADs, anxiolytics, anti-manic or antipsychotic drugs. |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem, zolpidem or zaleplon for periodic insomnia |
| POPULATION CHARACTERISTICS: |  
**Groups similar at baseline:** Yes  
**Mean age:** Escitalopram 43.8  
Paroxetine 44.7  
**Gender (female %):** Escitalopram 52  
Paroxetine 50.6  
**Ethnicity (Caucasian %):** Escitalopram 98.8  
Paroxetine 99.6  
**Other population characteristics:** MADRS Escitalopram 35.2  
Paroxetine 34.8  
HAM-D 17/24  
Escitalopram 24.7/31.9  
Paroxetine 24.3/31.5 |
<table>
<thead>
<tr>
<th>Authors: Boulenger et al.</th>
<th>Primary Outcome Measures: MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2006</td>
<td>Secondary Outcome Measures: HAM-D, CGI-I and CGI-S, HAM-A</td>
</tr>
<tr>
<td>Country: Multinational</td>
<td></td>
</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Timing of assessments: Baseline weeks 1,2,4,8,12,16,20,24,28 (2 week follow up after end)</td>
</tr>
<tr>
<td>RESULTS:</td>
<td></td>
</tr>
<tr>
<td>• Escitalopram vs. paroxetine change from baseline</td>
<td></td>
</tr>
<tr>
<td>• MADRS week 12 -23.2 vs. -21.2 P = 0.019 week 24 -25.2 vs. -23.1 P = 0.021</td>
<td></td>
</tr>
<tr>
<td>• HAMD17 -16.9 vs. -15.0 P = 0.006 HAMD24 -22.5 vs. -20.0 P = 0.005</td>
<td></td>
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<tr>
<td>• HAMA -15.1 vs. -13.2 P = 0.008 CGI-S -2.8 vs. -2.6 P = 0.020</td>
<td></td>
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<tr>
<td>• Remission: 75% vs. 67%</td>
<td></td>
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<tr>
<td>• CGI-I 2.0 vs. 2.2 P = 0.032</td>
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<tr>
<td>ANALYSIS:</td>
<td></td>
</tr>
<tr>
<td>ITT: Yes</td>
<td></td>
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<tr>
<td>Post randomization exclusions:</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td></td>
</tr>
<tr>
<td>ATTRITION:</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Loss to follow-up:</td>
<td>19%</td>
</tr>
<tr>
<td>Withdrawals due to AEs:</td>
<td>7.9%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>4.4%</td>
</tr>
<tr>
<td>Overall 116 (26%)</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Escitalopram vs. paroxetine (%)</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>AEs 66.8 vs. 72.0</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea 24.9 vs. 25.8</td>
<td>15.6%</td>
</tr>
<tr>
<td>Headache 24.5 vs. 20.4</td>
<td>6.2%</td>
</tr>
<tr>
<td>Dizziness 9.2 vs. 8.9</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis 8.7 vs. 12.4</td>
<td></td>
</tr>
<tr>
<td>Insomnia 7.4 vs. 8.0</td>
<td></td>
</tr>
<tr>
<td>Dry mouth 7.0 vs. 9.8</td>
<td></td>
</tr>
<tr>
<td>Diarrhea 6.6 vs. 10.2</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction 5.3 vs. 5.9</td>
<td></td>
</tr>
<tr>
<td>Ejaculation delayed 2.7 vs. 8.8</td>
<td></td>
</tr>
<tr>
<td>Constipation 2.2 vs. 5.3</td>
<td></td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Second generation antidepressants

Final Report Update 4

Drug Effectiveness Review Project
## Evidence Table 1: Major Depressive Disorder Adults

| STUDY:                  | Authors: Boyer P, et al.13  
|                        | Year: 1998  
|                        | Country: France  
| FUNDING:               | At least 1 author is affiliated with Pfizer  
| DESIGN:                | Study design: RCT  
|                        | Setting: Multi-center, primary care settings (57 general practitioners)  
|                        | Sample size: 242  
| INTERVENTION:          |  
| Drug:                  | Fluoxetine  
| Dose:                  | 50-150 mg/d  
| Duration:              | 180 days  
|                       | Sertraline  
|                       | 20-60 mg/d  
|                       | 180 days  
|                       | Mean daily dose: Fluoxetine -26 mg/d, Sertraline - 55 mg/d  
| INCLUSION:             | 18-65 yrs; DSM-IV criteria for major depression; ≥ 20 on MADRS  
| EXCLUSION:             | Pregnancy, lactation, or lack of adequate contraception; concurrent major psychiatric disorders; alcohol or substance abuse; existing suicidal risk; previous course of antidepressant treatment ≤ 3 weeks; clinically severe medical illness; history of allergy to related drugs  
| OTHER MEDICATIONS/     | Allowed medications for medical diseases  
| INTERVENTIONS:         |  
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                        | Mean age: fluoxetine: 43.7, sertraline: 43.0  
|                        | Gender (% female): fluoxetine: 79.1%, sertraline: 77.6%  
|                        | Ethnicity: Not reported  
|                        | Other population characteristics: Previous depression: fluoxetine: 38.3 %, sertraline: 34.5%; concomitant medical conditions: fluoxetine: 72%, sertraline: 78%  

Second generation antidepressants
| Authors: Boyer P, et al.  
Year: 1998  
Country: UK |
|---|---|
| **OUTCOME ASSESSMENT:** | **Measures:** MADRS, CGI, FSQ (Functional Status Questionnaire)  
**Timing of assessments:** Baseline, 120, 180 days |
| **RESULTS:** | • No significant differences in changes in MADRS, FSQ, CGI-I, and CGI-S scores between treatment groups  
• No significant differences in response rates (improvement of MADRS ≥ 50%) between the treatment groups  
• Day 120: fluoxetine: 54.3%, sertraline: 49%  
• Day 180: fluoxetine: 42.6%, sertraline: 47.4% |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 4.5%; fluoxetine: 4.2%, sertraline: 4.9%  
**Withdrawals due to adverse events:** fluoxetine: 8.6%, sertraline: 7.7%  
**Loss to follow-up differential high:** No |
<p>| <strong>ADVERSE EVENTS:</strong> | No significance between group differences in the numbers of patients who experienced adverse events, fluoxetine: 51.3%, sertraline: 57.8% |
| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Burke WJ, et al. Year: 2002</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Forest Pharmaceuticals</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT Setting: Multi-center (35 US centers) Sample size: 491</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td><em>Drug:</em></td>
<td>Placebo N/A 8 weeks</td>
</tr>
<tr>
<td><em>Dose:</em></td>
<td>Escitalopram 10 mg/day 8 weeks</td>
</tr>
<tr>
<td><em>Duration:</em></td>
<td>Escitalopram 20 mg/day 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Citalopram 40 mg/day 8 weeks</td>
</tr>
<tr>
<td>Fixed dose trial (patients in escitalopram 20 mg/d &amp; citalopram group were started at half dose &amp; titrated up to randomized dose.)</td>
<td></td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Outpatients 18-65 yrs; DSM-IV criteria for major depression; ≥ 22 score on MADRS; ≥ 2 score on item 1 of the HAM-D scale</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>DSM-IV Axis I disorder; history of substance abuse; suicide attempt past year; active suicidal ideation; pregnant or lactating women; women childbearing age without contraception; psychotropic medication</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Zolpedim 3 times/week</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: placebo: 40.1, escitalopram 10 mg: 40.7, escitalopram 20 mg: 39.6, citalopram 40 mg: 40.0</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): placebo: 60, escitalopram 10 mg: 70, escitalopram 20 mg: 68, citalopram 40 mg: 62</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
</tbody>
</table>
**Authors:** Burke WJ, et al.  
**Year:** 2002  
**Country:** US

### OUTCOME ASSESSMENT:
- **Measures:** MADRS, HAM-D, CGI-I, CGI-S at weeks 1, 2, 4, 6, 8, HAM-A, CES-D, QOL  
- **Timing of assessments:** Baseline and week 8

### RESULTS:
- There were no significant differences in the mean change of MADRS and CGI-S from baseline to endpoint between escitalopram 20 mg and citalopram 40 mg  
- Escitalopram 10 mg was equally effective as citalopram 40 mg on the majority of outcome measures (MADRS, HAM-D, CGI-I, CGI-S)  
- No further treatment group comparisons reported  
- All treatment groups were significantly more efficacious than the placebo group  
- Observed case analysis was consistent with ITT analysis

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes (6)

### ATTRITION:
- **Loss to follow-up:** 24%  
- **Withdrawals due to adverse events:** placebo 2.5%, escitalopram 10 mg: 4.2%; escitalopram 20 mg: 10.4%; citalopram 40 mg: 8.8%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Nausea, diarrhea, insomnia, dry mouth ejaculatory disorder occurred in more than 10% of the treatment population  
- No statistical difference in adverse events between placebo and escitalopram 10 mg  
- Escitalopram 10 mg and citalopram had significantly higher incidence of nausea than placebo but not different from each other

### QUALITY RATING:
- **Fair**
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Cassano GB, et al.  
Year: 2002  
Country: Italy |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>SmithKline Beecham, Ravizza Farmaceutici</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (38)  
Sample size: 242 |
| INTERVENTION: | **Drug:** Paroxetine  
Dose: 20-40 mg/day  
Duration: 1 year  
Fluoxetine  
Dose: 20-60 mg/day  
Duration: 1 year |
| INCLUSION: | 65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score |
| EXCLUSION: | History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months |
| OTHER MEDICATIONS/INTERVENTIONS: | Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: paroxetine: 75.6, fluoxetine: 74.9  
Gender (% female): paroxetine: 61%, fluoxetine: 50%  
Ethnicity: Not reported  
Other population characteristics: Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%, 40% had already been treated for present episode |
Authors: Cassano GB, et al.  
Year: 2002  
Country: Italy

### OUTCOME ASSESSMENT:

**Measures and timing of assessments:** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52  
**Cognitive tests:** Buschke Selective Reminding Test; Blessed Information and Memory Test; Clifton Assessment Schedule; Cancellation Task Test; Wechsler Paired Word Test; MMSE at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52

### RESULTS:

**Cognitive function:**  
- Both treatment groups showed significant improvements in cognitive performance on all test scales  
- There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests

**Depressive symptoms:**  
- Both treatment groups significantly improved the HAM-D total scores  
- Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: p < 0.05; week 6: p < 0.002), otherwise there were no differences between the treatment groups  
- A Kaplan Meier analysis evaluating the percentage of responders (HAM-D ≤ 10) over time showed a significant difference in favor of paroxetine (p < 0.03)  
- No significant differences on CGI scores

### ANALYSIS:

**ITT:** No  
**Post randomization exclusions:** Not reported

### ATTRITION:

**Loss to follow-up:** 39.3%; paroxetine: 40.6%, fluoxetine:37.8%  
**Withdrawals due to adverse events:** 15%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- At least 1 adverse event: paroxetine: 27.6%, fluoxetine: 32.8%  
- Fluoxetine had significantly more severe adverse events than paroxetine (22 vs. 9; p < 0.02)

### QUALITY RATING:

Fair
## Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: FDA Center for Drug Evaluation & Research (Unpublished study SCT-MD-02)  
Year: 2000  
Country: USA |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Forest Laboratories, Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter (22)  
Sample size: 375 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
**Sample size:**  
Escitalopram  
10-20 mg/day  
8 weeks  
124  
Citalopram  
20-40 mg/day  
8 weeks  
119  
Placebo  
N/A  
8 weeks  
125 |
| INCLUSION: | Adults 18 to 80; MDD diagnosis according to DSM III or IV; MADRS ≥ 22 |
| EXCLUSION: | Pregnant; additional mental illnesses or organic mental disorder; illicit drug and alcohol abuse; suicidal tendencies |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 42 (escitalopram: 41.4, citalopram: 42.0, placebo: 42.3)  
Gender (female %): 53% (escitalopram: 52%, citalopram: 48%, placebo 58%)  
Ethnicity (% white): 83% (escitalopram: 82%, citalopram: 86%, placebo 82%)  
Other population characteristics:  
Mean HAM-D score: escitalopram: 24.8, citalopram: 25.0, placebo: 25.0  
<table>
<thead>
<tr>
<th>Authors: FDA</th>
<th>Year: 2000</th>
<th>Country: USA</th>
</tr>
</thead>
</table>

**OUTCOME ASSESSMENT:**
- **Primary Outcome Measures:** MADRS
- **Secondary Outcome Measures:** HAM-D, CGI-S, CGI-I
- **Timing of assessments:** Baseline and week 8

**RESULTS:**
- Mean change from baseline in HAM-D score (escitalopram vs. citalopram vs. placebo; p-values vs. placebo): 10.4 (p=0.506) vs. 11.4 (p=0.068) vs. 9.6
- Mean change from baseline in MADRS score (escitalopram vs. citalopram vs. placebo; p-values vs. placebo): escitalopram: 12.9 (p=0.251) vs. 13.0 (p=0.151) vs. 11.2
- MADRS response rate (escitalopram vs. citalopram vs. placebo; p-values NR): 16 vs. 52 vs. 41

**ANALYSIS:**
- ITT: Yes
- Post randomization exclusions: Yes
- Loss to follow-up differential high: No

**ATTRITION:**
- **Loss to follow-up:**
  - Escitalopram: 29 (23.2%)
  - Citalopram: 24 (19.5%)
  - Placebo: 22 (17.3%)
- **Withdrawals due to adverse events:**
  - Escitalopram: 8.8%
  - Citalopram: 4.1%
  - Placebo: 3.1%
- **Withdrawals due to lack of efficacy:**
  - Escitalopram: 1.6%
  - Citalopram: 0.8%
  - Placebo: 0.8%

**ADVERSE EVENTS:**
- Treatment emergent adverse events (escitalopram vs. citalopram vs. placebo):
  - At least 1 TEAE: 79.2% vs. 81.3% vs. 76.6%
  - Headache: 21.6% vs. 22.8% vs. 18.1%
  - Nausea: 16.0% vs. 14.6% vs. 12.6%
  - Ejaculation disorder: 15.0% vs. 15.9% vs. 0
  - Insomnia: 13.6% vs. 11.4% vs. 6.3%
  - Fatigue: 12.0% vs. 4.1% vs. 2.4%
  - Mouth Dry: 10.4% vs. 6.5% vs. 11.8%
  - Somnolence: 10.4% vs. 7.3% vs. 4.7%
  - Diarrhea: 9.6% vs. 14.6% vs. 8.7%

**QUALITY RATING:**
- Fair
**Evidence Table 1**  
**Major Depressive Disorder Adults**

| STUDY: | **Authors:** Chouinard G, et al.  
**Year:** 1999  
**Country:** Canada |
| FUNDING: | One author is employee of SmithKline Beecham |
| DESIGN: | **Study design:** RCT, double blind  
**Setting:** Multicenter  
**Sample size:** 203 |
| INTERVENTION: | **Drug:** Paroxetine  
**Dose:** 20-50 mg/d  
**Duration:** 12 weeks  
**Fluoxetine:**  
**Dose:** 20-80 mg/d  
**Duration:** 12 weeks |
| INCLUSION: | Meeting DSM IIIR criteria for MDD with symptoms for at least 1 month prior to screening; min. score on HAM-D₂₁ of 20 and score of “2” on the first item |
| EXCLUSION: | Significant coexisting illness including renal, hepatic, GI, neurological, non-stabilized diabetes; other current Axis I disorders; organic brain syndrome; past or present abuse of alcohol or other illicit drugs; significant suicide risk; pregnant or lactating; ECT or continuous lithium therapy in the prior 2 months; MAOI or oral neuroleptics use in prior 21 days; any antidepressant or sedative hypnotic in prior 7 days; fluoxetine in prior 35 days or current therapy with an anticoagulant or type 1C anti-arrhythmic; subjects with clinically significant abnormalities on physical examination, ECG, or lab |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate for hypnotic |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** 40.9; paroxetine: 40.6, fluoxetine: 41.2  
**Gender (% female):** paroxetine: 63.7%, fluoxetine: 59.4%  
**Ethnicity:** 96.5% white, 1.5 % Asian  
**Other population characteristics:**  
2 or more depressive episodes: paroxetine 76.5%, fluoxetine 59.5% |
**Authors:** Chouinard G, et al.  
**Year:** 1999  
**Country:** Canada

### OUTCOME ASSESSMENT:

**Measures:** HAM-D_{21} measured at baseline, weeks 1-6, 8, 10 and 12. Response ≥ 50% reduction from baseline, remission score < 10 (HAMD)  
**Timing of assessments:** Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12

### RESULTS:

- No statistically significant differences in response rates: (Observed cases at 12 weeks) paroxetine 85.7%, fluoxetine 88.4%; (LOCF endpoint) paroxetine 67.0%, fluoxetine 68.4%  
- No statistically significant differences in remission rates: (Observed cases at 12 weeks) paroxetine 77.8%, fluoxetine 81.2%; (LOCF endpoint) paroxetine 58.0%, fluoxetine 59.2%

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes (5)

### ATTRITION:

**Loss to follow-up:** 36%; paroxetine: 39.2%, fluoxetine: 32.67%  
**Withdrawals due to adverse events:** Not reported  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

No significant differences between groups

### QUALITY RATING:

Fair
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Clayton A. et al.  
Year: 2006  
Country: USA |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: 2 pooled RCTs  
Setting: Multicenter  
Sample size: 830 |
| INTERVENTION: | Drug:  
Bupropion XL  
Dose: 300-450 mg  
Duration: 8 weeks  
Sample size: 276  
Escitalopram  
Dose: 10-20 mg  
Duration: 8 weeks  
Sample size: 281  
Placebo  
Dose: NA  
Duration: 8 weeks  
Sample size: 273 |
| INCLUSION: | Men and women > 18 years old, MDD; HAMD17 > 19; current episode duration 12 weeks to 2 years; sexually active. |
| EXCLUSION: | Other sexual disorders; past or present anorexia nervosa, bulimia, seizure disorder, or brain injury; diagnosis of panic disorder, OCD, PTSD or acute stress disorder within 12 months: bipolar I or II, schizophrenia or other psychotic disorders; attempted suicide within 6 months; any drug that may effect sexual functioning. |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem, zaleplon and and non-prescription sleep aids were allowed in 1st 10 days only. |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Bupropion XL 37 Escitalopram 37 Placebo 36  
Gender (female %): Bupropion XL 58 Escitalopram 57 Placebo 60  
Ethnicity: White Bupropion XL 70% Escitalopram 68% Placebo 70%  
Black Bupropion XL 20% Escitalopram 19% Placebo 17%  
Other population characteristics: NR |
| Authors: Clayton A et al.  
Year: 2006  
Country: USA |
|---|
| **OUTCOME ASSESSMENT:** Primary Outcome Measures: % patients w/orgasm dysfunction at week 8  
Secondary Outcome Measures: CSFQ, HAMD17, CGI-S and CGI-I and HAD  
Timing of assessments: Baseline, weeks 1,2,3,4,6 and 8 |
| **RESULTS:**  
- % patients w/orgasm dysfunction at week 8: Bupropion XL 15  
  Escitalopram 30  
  Placebo 9  
- Change in HAMD17: Bupropion XL -13.2 (0.5)  
  Escitalopram -13.6 (0.5)  
  Placebo -12.0 (0.5)  
- HAMD response: Bupropion XL 62%  
  Escitalopram 65%  
  Placebo 52%  
- HAMD remission: Bupropion XL 43%  
  Escitalopram 45%  
  Placebo 34%  
- Change in CGI-S: Bupropion XL -1.9 (0.1)  
  Escitalopram -1.9 (0.1)  
  Placebo -1.6 (0.1)  
- CGI-I response: Bupropion XL 67%  
  Escitalopram 67%  
  Placebo 57% |
| **ANALYSIS:** ITT: Yes  
Post randomization exclusions: 45  
Loss to follow-up differential high: No |
| **ATTRITION:**  
Loss to follow-up:  
Withdrawals due to adverse events:  
Withdrawals due to lack of efficacy: |
| Bupropion XL 68 (25%)  
Escitalopram 71 (25%)  
Placebo 66 (24%)  
6%  
4%  
5% |
| **ADVERSE EVENTS:**  
Bupropion XL vs. Escitalopram vs. Placebo %  
- Dry mouth: 22 vs. 13 vs. 11  
- Fatigue: 4 vs. 14 vs. 6  
- Insomnia: 14 vs. 10 vs. 8  
- Constipation: 9 vs. 3 vs. 6  
- Somnolence: 3 vs. 8 vs. 5  
- Decreased appetite: 5 vs. 6 vs. 4  
- Nasopharyngitis: 5 vs. 5 vs. 3  
- Irritability: 5 vs. 1 vs. 4  
- Yawning: <1 vs. 5 vs. 1 |
<p>| <strong>QUALITY RATING:</strong> Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| STUDY:           | Authors: Coleman CC, et al.\textsuperscript{19}  
                    Year: 1999  
                    Country: US |
| FUNDING:         | Glaxo Wellcome                  |
| DESIGN:          | Study design: RCT  
                    Setting: Multi-center (9 centers)  
                    Sample size: 364 |
| INTERVENTION:    | Drug:  
                    Sertraline  
                    50-200 mg/d  
                    8 weeks  
                    Bupropion SR  
                    150-400 mg/d  
                    8 weeks  
                    Placebo  
                    N/A  
                    8 weeks |
| INCLUSION:       | DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; >18 years of age; be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 weeks; currently experiencing recurrent major episode of duration 2-24 months |
| EXCLUSION:       | Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of an eating disorder; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or 4 weeks for fluoxetine) |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate for sleep (first 2 weeks only) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: sertraline: 38.3, bupropion SR: 38.1, placebo: 38.5  
Gender (% female): 59%; sertraline: 54%, bupropion SR: 56%, placebo: 59%  
Ethnicity: sertraline: white: 92%, black: 8%; bupropion SR: white: 87%, black: 11%, other: 2%; placebo: white: 88%, black: 9%, other: 3%  
Other population characteristics: No significant differences at baseline |
| Authors: Coleman CC, et al.  
Year: 1999  
Country: US |
|---|
| OUTCOME ASSESSMENT: | Measures: 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function  
Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, and 8 |
| RESULTS: | • Mean HAM-D scores in the buproprion SR but not the sertraline group were statistically better than placebo (by day 28 p < 0.05)  
• There was no significant difference between the buproprion SR and sertraline groups  
• CGI-I and CGI-S for buproprion SR significantly better than placebo but not better than sertraline  
• Sertraline not statistically better than placebo  
• No differences in HAM-A; significantly fewer buproprion SR patients had sexual desire disorder than sertraline patients (p < 0.05)  
• There was no significant difference between either active treatment group and placebo  
• Orgasm dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion SR patients (p < 0.05)  
• Diagnosed with at least one sexual dysfunction: sertraline: 39%, buproprion SR: 13%, placebo: 17% |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION: | Loss to follow-up: 30%; sertraline: 36%, buproprion SR: 22%, placebo: 32%  
Withdrawals due to adverse events: 5%; sertraline: 8%, buproprion SR: 6%, placebo: 2%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | • Headache was the most commonly reported event in all treatment groups  
• Nausea, diarrhea, dyspepsia occurred more frequently in sertraline patients than buproprion SR or placebo  
• Insomnia and agitation were reported more frequently in buproprion SR patients than sertraline or placebo |
| QUALITY RATING: | Fair |
## Evidence Table 1  
### Major Depressive Disorder Adults

| STUDY: | Authors: Coleman CC, et al.  
Year: 2001  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (15 centers)  
Sample size: 456 |
| INTERVENTION: | **Drug:** | **Dose:** | **Duration:** |
| Bupropion SR | 150-400 mg/d | 8 weeks |
| Fluoxetine | 20-60 mg/d | 8 weeks |
| Placebo | N/A | 8 weeks |
| INCLUSION: | DSM-IV criteria for major depression; minimum score of 20 on the 21 item HAM-D; >18 years of age; have sexual activity at least once every 2 weeks; currently experiencing episode lasting 2-24 months; currently in a stable relationship |
| EXCLUSION: | Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of anorexia or bulimia; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with bupropion SR or fluoxetine; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or any investigational drug; non-responders to antidepressant treatment |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: fluoxetine: 37.1, bupropion SR: 36.6, placebo: 36.7  
Gender (% female): fluoxetine: 66%, bupropion SR: 63%, placebo: 61%  
Ethnicity: fluoxetine: white 82%, black 11%, other 7%; bupropion SR: white 83%, black 11%, other 5%; placebo: white 82%, black 14%, other 4%  
Other population characteristics: More patients in the fluoxetine and bupropion SR groups had sexual desire disorder than at baseline the placebo group |
### OUTCOME ASSESSMENT:

**Measures:** 21 item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale)

**Timing of assessments:** Assessments made at baseline and weeks 1, 2, 3, 4, 5, 6, 7, and 8

### RESULTS:

- Mean HAM-D scores were not statistically different between the three groups (in ITT analysis)
- No difference in responders (≥ 50 decrease in HAM-D), remitters (HAMD < 8)
- More bupropion SR remitters (47%) compared to placebo (32%).
- Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or bupropion SR patients (p < 0.001)
- At endpoint, more fluoxetine treated patients had sexual desire disorder than bupropion SR treated patients (p < 0.05).
- More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 (p < 0.05)

### ANALYSIS:

**ITT:** Yes

**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 34%; fluoxetine: 37%, bupropion SR: 37%, placebo: 33%

**Withdrawals due to adverse events:** 6%; fluoxetine: 4%, bupropion SR: 9%, placebo: 3%

**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Headache was the most commonly reported event in all treatment groups
- Headache, diarrhea, and somnolence occurred more frequently in fluoxetine patients than bupropion SR or placebo
- Dry mouth, nausea, and insomnia were reported more frequently in bupropion SR patients than fluoxetine or placebo
- Bupropion SR group had mean increases in DBP (1.7 mm Hg) and fluoxetine group (0.3 mm Hg) and heart rate (3.8 beats/min), authors state these were not clinically significant
- Bupropion SR group had mean increases in heart rate (3.8 beats/min) and fluoxetine group had a mean decrease in heart rate (-2.8 beats/min), authors state these were not clinically significant

### QUALITY RATING:

Fair
**Evidence Table 1**

**Major Depressive Disorder**

| STUDY: | Authors: Colonna L, et al.\(^{21}\)  
Year: 2005  
Country: Europe |
| FUNDING: | H Lundbeck A/S |
| DESIGN: | Study design: RCT  
Setting: 66 primary care centers  
Sample size: 357 |
| INTERVENTION: | Drug: Escitalopram  
Dose: 10 mg/day  
Duration: 24 weeks  
Sample size: 181 (ITT=165)  
Citalopram  
Dose: 20 mg/day  
Duration: 24 weeks  
Sample size: 177 (ITT=174) |
| INCLUSION: | Outpatients; 18-65 years old; MDD according to the DSM-IV; baseline MADRS of 22 - 39 |
| EXCLUSION: | Pregnant; breast-feeding; adequate contraception; DSM-IV criteria for bipolar disorder, schizophrenia, psychotic disorder, OCD, or eating disorders; mental retardation; score of 5 or more on MADRS item 10 (suicidal thoughts); receiving treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, barbiturates, chloral hydrate, 5 HT receptor agonists; ECT CBT or psychotherapy; investigational drug within 30 days; history of drug abuse; lack of response to more than one antidepressant in current episode |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 46  
Gender (% female): escitalopram: 73%, citalopram: 76%  
Ethnicity: NR  
Other population characteristics:  
Mean MADRS (SD): escitalopram 29.5 (4.3), citalopram 30.2 (4.7)  
Mean CGI-S (SD): escitalopram 4.2 (0.8), citalopram 4.3 (0.8)  
Moderately depressed patients (MADRS < 30) n (%): escitalopram: 85 (51.5), citalopram: 85 (48.9)  
Severely depressed patients (MADRS of 30 or more) n(:,): escitalopram: 80 (48.5)m, citalopram: 89 (51.1) |
## Authors: Colonna L, et al.  
Year: 2005

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>MADRS total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>CGI-S, Responders (50% reduction in MADRS) and remitters (MADRS total score 12 or less)</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Screening, baseline weeks 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24. Final safety assessment 30 days after last assessment</td>
</tr>
</tbody>
</table>

### RESULTS:

All results are escitalopram vs. citalopram at 24 weeks
- No significant differences in changes of MADRS scores from baseline to endpoint 8.3 vs. 9.3  p = NR
- CGI-S mean 1.75 vs. 2.00  p < 0.05
  - Moderately depressed 1.57 vs. 1.95  p < 0.05
  - Severely depressed 2.02 vs. 2.13
    - Responders: 80% vs. 78%  p = NR
    - Remitters: 76% vs. 71%  p = NR
- Overall, statistically significantly fewer withdrawals in the escitalopram than in the citalopram group
  - 13% vs. 22%  p < 0.05
  - Total withdrawals in the moderately depressed was 10 (11.8%) vs. 26 (30.6%)  p < 0.01
  - Total withdrawals in the severely depressed was 11 (13.8%) vs. 13 (14.6%)  p = NR

### ANALYSIS:

ITT: Yes  
Post randomization exclusions: Yes (18)

### ATTRITION (%):

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Escitalopram</th>
<th>Citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>17.7</td>
<td>12.7</td>
<td>22.4</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>8.3</td>
<td>6.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>1.5</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:

- All results are escitalopram versus citalopram n(%)  
  - Patients with AEs: 110 (62.9) vs. 131 (72.0)
  - Nausea: 28 (16.0) vs. 18 (9.9), Rhinitis: 17 (9.7) vs. 12 (6.6), Headache: 12 (6.9) vs. 16  (8.8), Back pain: 11 (6.3) vs. 15 (8.2), Accidental injury: 10 (5.7) vs. 8 (4.4), Bronchitis: 10 (5.7) vs. 7 (3.8), Weight increase: 2 (1.1) vs. 12 (6.6)

### QUALITY RATING:

Fair
### Evidence Table 1: Major Depressive Disorder Adults

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Lilly Research Laboratories</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT Setting: Multicenter Sample size: 483 of which 119 are of interest</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Fluoxetine 25 or 50 mg (mean 37.5) 12 weeks 60</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>MDD</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Current or past diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar I disorder, bipolar II disorder, posttraumatic stress disorder, major depressive disorder with seasonal pattern, or dissociative disorders (as defined in DSM-IV); female patients who were pregnant or nursing. Concomitant medications with primary central nervous system activity were not allowed</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>benzodiazepines as permitted at doses up to an equivalent of 4mg of lorazepam per day</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes according to authors Mean age: 45.7 Gender (female %): 72.5 Ethnicity: Caucasian 89.9% Other population characteristics: MADRS 30.0 (SD 6.8)</td>
</tr>
</tbody>
</table>
Authors: Corya et al.  
Year: 2006  
Country: Multinational

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** baseline to end point mean change in the MADRS  
**Secondary Outcome Measures:** CGI Severity of Depression, HAM-A; Brief Psychiatric Rating Scale (BPRS); Clinical response was defined as a ≥ 50% decrease in MADRS total score at end point. Remission was defined as MADRS total score ≤ 8 for any two consecutive visits.  
**Timing of assessments:** Baseline and visits

### RESULTS:

- Baseline to endpoint change fluoxetine vs. venlafaxine  
  - MADRS: -11.7 (1.14) vs. -13.73 (1.16)  
  - CGI-Depression: -1.26 (0.15) vs. -1.49 (0.14)  
  - HAM-A: -5.30 (1.01) vs. -5.89 (0.94)  
  - BPRS: -4.82 (0.88) vs. -4.76 (0.98)

**Response** fluoxetine, 33.9% (n=19); venlafaxine, 50.0% (n=29),  
**Remission** fluoxetine, 17.9% (n=10); venlafaxine, 22.4% (n=13),

### ANALYSIS:

- ITT: Yes  
- Post randomization exclusions:

### ATTRITION:

- Loss to follow-up: 27 (23%) fluoxetine 12 (20%) venlafaxine 15 (25%)  
- Withdrawals due to adverse events: Fluoxetine 5% venlafaxine 1.7%  
- Withdrawals due to lack of efficacy: Fluoxetine 6.7% venlafaxine 11.9%  
- Loss to follow-up differential high: No

### ADVERSE EVENTS:

- fluoxetine vs. venlafaxine (%)  
  - Weight gain 13 vs. 5  
  - Somnolence 5 vs. 8  
  - Increased appetite 7 vs. 5  
  - Dizziness 10 vs. 5  
  - Dry mouth 7 vs. 5  
  - Asthenia 8 vs. 8  
  - Peripheral edema 0 vs. 2  
  - Headache 17 vs. 17

### QUALITY RATING:

Fair
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | **Authors:** Costa e Silva JC, et al.  
**Year:** 1998  
**Country:** South America |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst International</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 382 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:** |
| | Venlafaxine  
75-225 mg/d  
8 weeks |
| | Fluoxetine  
20-40 mg/d  
8 weeks |
| INCLUSION: | 18-60 yrs; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21; symptoms for at least 1 month |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; investigational drugs within 30 days; clinically relevant cardiac, hepatic, or renal disease; abnormalities on screening examination; known sensitivity to venlafaxine or fluoxetine |
| OTHER MEDICATIONS/INTERVENTIONS: | Zopiclone 7.5 mg |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** venlafaxine: 40.5, fluoxetine: 39.8  
**Gender (% female):** venlafaxine: 80.1%, fluoxetine: 77.4%  
**Ethnicity:** Not reported  
**Other population characteristics:** Previous history of depression: venlafaxine: 79.6%, fluoxetine: 76.3%, CGI: Moderately ill: venlafaxine: 33.7%, fluoxetine: 36.3%.  
Markedly ill: venlafaxine: 43.0%, fluoxetine: 43.4%.  
Severely ill: venlafaxine: 20.2%, fluoxetine: 17.0% |
**Authors:** Costa e Silva JC, et al.  
**Year:** 1998  
**Country:** South America

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures and timing of assessments: HAM-D, MADRS, CGI at baseline, days 7, 14, 21, 28, 42, 56. SCL-61 or SCL-90 administered baseline, days 28 and 56</th>
</tr>
</thead>
</table>
| RESULTS:            | • HAM-D and MADRS scores decreased significantly in both treatment groups (p < 0.05)  
                      • There were no significant differences between treatment groups in any 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 the venlafaxine group and 82% in the fluoxetine group (p = 0.074)  
                      • Remission was observed in 60.2% of patients in each group  
                      • In patients who increased their dose to venlafaxine 150 mg and fluoxetine 40 mg after 3 weeks significantly more achieved a CGI score of 1 in the venlafaxine group (p < 0.05)  
                      • There was no significant difference in remission rates between treatment groups |
| ANALYSIS:           | **ITT:** Yes  
                      **Post randomization exclusions:** No |
| ATTRITION:          | **Loss to follow-up:** 12.3%; venlafaxine: 14.8%, fluoxetine: 9.7%  
                      **Withdrawals due to adverse events:** venlafaxine: 7.2%, fluoxetine: 3.8%  
                      **Loss to follow-up differential high:** No |
| ADVERSE EVENTS:     | • There were no significant differences between groups for specific adverse events  
                      • At least one adverse event: venlafaxine: 69.4%, fluoxetine: 65%  
                      • There were no clinically significant changes in laboratory parameters, ECG, or blood pressure in either group  
                      • Nausea: venlafaxine: 28.9%, fluoxetine: 18.9%  
                      • Headache: venlafaxine: 11.3%, fluoxetine: 7% |
| QUALITY RATING:     | Fair |
### Evidence Table 1: Major Depressive Disorder Adults

| STUDY:          | Authors: Croft H, et al.  
|                 | Year: 1999  
|                 | Country: US  
| FUNDING:        | Glaxo Wellcome  
| DESIGN:         | Study design: RCT (active and placebo control)  
|                 | Setting: Multi-center (8 centers)  
|                 | Sample size: 360  
| INTERVENTION:   | Drug:  
|                 | Dose:  
|                 | Duration:  
|                 | Sertraline  
|                 | 50-200 mg/d  
|                 | 8 weeks  
|                 | Buproprion  
|                 | 150-400 mg/d  
|                 | 8 weeks  
|                 | Placebo  
|                 | N/A  
|                 | 8 weeks  
| INCLUSION:      | DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; ≥ 18 years of age; in a stable relationship; have normal sexual functioning and sexual activity at least once every 2 weeks; current depressive episode of 8 weeks to 24 months  
| EXCLUSION:      | Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of eating disorder; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or 4 weeks for fluoxetine or any investigational drug)  
| OTHER MEDICATIONS/  
| INTERVENTIONS:  | Not reported  
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                 | Mean age: sertraline: 36.0, buproprion: 35.9, placebo: 37.4  
|                 | Gender (% female): sertraline: 50%, buproprion: 51%, placebo: 50%  
|                 | Ethnicity: sertraline: white: 87%, black: 8%, other: 4%; buproprion: white: 86%, black: 9%, other: 5%; placebo: white: 88%, black: 8%, other: 3%  
|                 | Other population characteristics: Not reported  

---

Second generation antidepressants
### Authors: Croft H, et al.  
**Year:** 1999  
**Country:** US

### Outcome Assessment:

- **Measures:** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview—sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation, overall patient satisfaction with sexual functioning, vital signs  
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, and 8

### Results:

- Mean HAM-D scores in both the buproprion and sertraline group were statistically better than placebo ($p < 0.05$)  
- No significant difference in HAM-D scores between the buproprion and sertraline groups  
- CGI-S and CGI-I improvement compared to placebo but no differences between drugs at any week  
- No difference in changes of HAM-A scores for any group  
- By day 42 significantly fewer buproprion sr treated patients had sexual desire disorder than sertraline or placebo-treated patients ($p < 0.05$)  
- At day 56, both buproprion and sertraline had higher sexual arousal disorder ($p < 0.05$) than placebo  
- Orgasmic dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients ($p < 0.001$)  
- At day 56 no difference in overall satisfaction with sexual function between treatment groups

### Analysis:

- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### Attrition:

- **Loss to follow-up:** 32%  
- **Withdrawals due to adverse events:** (12); sertraline: 3%, buproprion sr: 3%, placebo: 7%  
- **Loss to follow-up differential high:** Yes

### Adverse Events:

- Headache was the most commonly reported event in all treatment groups  
- Somnolence and insomnia occurred more frequently in sertraline patients than buproprion patients  
- Nausea and diarrhea occurred more frequently with sertraline than buproprion or placebo

### Quality Rating:

- Quality Rating: Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Dalery J, et al. 25</td>
</tr>
<tr>
<td></td>
<td>Year: 2003</td>
</tr>
<tr>
<td></td>
<td>Country: Europe</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Solvay Pharmaceuticals</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center</td>
</tr>
<tr>
<td></td>
<td>Sample size: 184</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td>Fluvoxamine 100 mg/day 6 weeks</td>
</tr>
<tr>
<td>Dose:</td>
<td>Fluoxetine 20 mg/day 6 weeks</td>
</tr>
<tr>
<td>Duration:</td>
<td></td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>18-70 years; DSM-III-R criteria for major depression; ≥ 17 on HAM-D</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Pregnancy, lactation, or lack of adequate contraception; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to SSRI therapy; clinically relevant progressive disease; concomitant warfarin, lithium, insulin, theophylline, carbamazepine</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Oxazepam, nitrazepam</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: fluvoxamine: 42.0, fluoxetine: 42.1</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): fluvoxamine: 63.3%, fluoxetine: 62.7%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
</tbody>
</table>
**Authors:** Dalery J, et al.  
**Year:** 2003  
**Country:** Europe  

### OUTCOME ASSESSMENT:

*Measures and timing of assessments:* HAM-D-17 Weeks 1, 2, 4, 6, CGI, CAS (Clinical Anxiety Scale), IDAS (irritability, depression and anxiety scale), SSI (Beck's scale for suicidal ideation) at all visits

### RESULTS:

- Both treatment groups resulted in significant improvements of symptoms
- There were no significant differences between the study groups in changes of HAM-D scores from baseline at any point in time
- After 2 weeks of treatment, the percentage of patients who responded was significantly higher in the fluvoxamine group (29% vs. 16%; p ≤ 0.05), as was the improvement of CGI-I scores (p ≤ 0.05). This significant difference was not evident after week 2
- Improvement in sleep disturbance sub scores (HAM-D) was significantly greater in the fluvoxamine group at week 4 and at the endpoint (p ≤ 0.05)
- Overall sleep evaluation was not significantly different

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 20.9%; fluvoxamine: 23.3%, fluoxetine: 18.7%  
**Withdrawals due to adverse events:** Not reported  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No significant differences
- No clinically significant changes in vital signs or body weights in either group
- Most common adverse events: nausea: fluvoxamine, 24%; fluoxetine, 20%; headache: fluvoxamine-13%, fluoxetine-14%

### QUALITY RATING:

Fair
# Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Detke MJ, et al.  
Year: 2004  
Country: US |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (number of centers NR)  
Sample size: 367 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
**Acute phase:**  
**Continuation:**  
**Sample size:** |
| | Duloxetine (low dose)  
80 mg/d  
8 weeks  
95 |
| | Duloxetine (high dose)  
120 mg/d  
8 weeks  
93 |
| | Paroxetine  
20 mg/d  
8 weeks  
86 |
| | Placebo  
N/A  
8 weeks  
93 |
| INCLUSION: | Patients ≥ 18 yrs old; met DSM-IV and MINI criteria for MDD; CGI-S rating ≥ 4; HAM-D-17 score ≥ 15 at entry |
| EXCLUSION: | Pregnant, Current primary DSM-IV diagnosis other than MDD; any anxiety disorder as a primary diagnosis; previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder; history of substance abuse; failed to respond to two courses of antidepressant therapy; serious suicidal risk; serious medical illness |
| OTHER MEDICATIONS/INTERVENTIONS: | Nonprescription analgesic medications allowed; no prescription analgesics |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** Duloxetine 80: 43.1, Duloxetine 120: 44.7, Paroxetine 20: 42, placebo: 42  
**Gender (% female):** Duloxetine 80: 70%, Duloxetine 120: 70%, Paroxetine 20: 58%, placebo: 58%  
**Ethnicity (% white):** Duloxetine 80: 95%, Duloxetine 120: 92%, Paroxetine 20: 86%, placebo: 86%  
**Other population characteristics:** Mean baseline HAM-D: Duloxetine 80: 19.9, Duloxetine 120: 20.2, Paroxetine: 20.3, placebo: 19.9; Mean baseline HAM-A: Duloxetine 80: 17.8, Duloxetine 120: 18, Paroxetine 20: 18.5, placebo: 17.9 |
<table>
<thead>
<tr>
<th>Authors: Detke MJ, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2004</td>
</tr>
<tr>
<td>Country: US</td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**

- **Primary Outcome Measures:** HAM-D-17
- **Secondary Outcome Measures:** HAM-D-17 subscales; MADRS; HAM-A; Visual Analog Scales for pain; CGI-S; PGI; Sheehan Disability Scale; Somatic Symptom Inventory
- **Timing of assessments:** HAM-D-17 administered at baseline and weeks 1, 2, 4, 6 and 8.

**RESULTS:**

- Response and remission rates did not differ significantly among duloxetine 120 mg (71%; 52%), duloxetine 80 mg (65%; 46%) and paroxetine (74%; 44%)
- No significant differences in HAM-D-17 score reduction found between the duloxetine groups and the paroxetine group
- 120 mg/d duloxetine had significantly greater improvement on MADRS than 80 mg/d duloxetine ($p < 0.05$)
- PGI score significantly superior in patients receiving paroxetine than patients receiving 80 mg/d duloxetine ($p < 0.05$)

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Not reported

**ATTRITION:**

- **Loss to follow-up:** 13.3%; duloxetine, low-dose: 12.6%; duloxetine, high-dose: 9.7%; paroxetine: 11.6%; placebo 19%
- **Withdrawals due to adverse events:** Duloxetine, low-dose: 4.2%; duloxetine, high-dose: 3.2%; paroxetine: 3.5%; placebo: 3.2%
- **Loss to follow-up differential high:** Not reported

**ADVERSE EVENTS:**

- **Acute Phase:**
  - At endpoint, diastolic blood pressure was significantly elevated in the duloxetine 120mg group compared to the paroxetine group (+0.7 mm Hg; $p < 0.05$)
  - No statistically significant differences in other adverse events
- **Continuation Phase:**
  - No significant between group differences were found

**QUALITY RATING:**

- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | **Authors:** De Wilde J, et al.  
                    **Year:** 1993  
                    **Country:** Belgium |
| **FUNDING:**     | SmithKline, Beecham Pharma.      |
| **DESIGN:**      | **Study design:** RCT  
                    **Setting:** Multi-center  
                    **Sample size:** 100 |
| **INTERVENTION:**| **Drug:** Paroxetine  
                     **Dose:** 20-40 mg/day  
                     **Duration:** 6 weeks  
                     Fluoxetine  
                     **Dose:** 20-60 mg/day  
                     **Duration:** 6 weeks |
| **INCLUSION:**   | Age 18-65; MDD by DSM III criteria; HAM-D 21 score ≥ 18 |
| **EXCLUSION:**   | Pregnancy or lactation; severe concomitant disease; alcohol or substance abuse; severe suicide risk; ECT within 3 months; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks; lithium |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Temazapam, other short-acting benzodiazepines, stable doses of long-acting benzodiazepines |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
                        **Mean age:** paroxetine: 44.6, fluoxetine: 44.1  
                        **Gender (female%):** paroxetine: 57%, fluoxetine: 66%  
                        **Ethnicity:** Not reported  
                        **Other population characteristics:** 65% of paroxetine group and 70% group of fluoxetine had prior depression |
| Authors: De Wilde J, et al.  
Year: 1993  
Country: Belgium |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
</tr>
</tbody>
</table>
| **Measures:** HAM-D21, MADRS, HSCL58, CGI  
**Timing of assessments:** Baseline, weeks 1, 3, 4 & 6 |
| **RESULTS:** |
| Responders at week 6 (i.e., reduction > 50% from baseline HAM-D21): paroxetine: ~67%, fluoxetine: ~62%, not significantly different |
| **ANALYSIS:** |
| **ITT:** Not reported  
**Post randomization exclusions:** Yes |
| **ATTRITION:** |
| **Loss to follow-up:** 21.2%  
**Withdrawals due to adverse events:** paroxetine: 4%, fluoxetine: 8%  
**Loss to follow-up differential high:** Not reported |
| **ADVERSE EVENTS:** |
| • No significant differences  
• No vital sign or laboratory changes reported  
• Paroxetine: n = 3 had weight gain > 7%, fluoxetine: n = 2 had weight gain > 7% |
| **QUALITY RATING:** |
| Fair |
## Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: De Nayer A, et al.  
Year: 2002  
Country: Belgium |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported (author affiliation with Wyeth)</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center; 14 psychiatric practices  
Sample size: 146 |
| INTERVENTION: |  
**Drug:**  
Venlafaxine  
Fluoxetine  
**Dose:**  
75-150 mg/day  
20-40 mg/day  
12 weeks  
12 weeks  
**Duration:** |
| INCLUSION: | Age 18-70 yrs; HAM-D-21 score 18-25; ≥ 8 Covi Anxiety scale |
| EXCLUSION: | Concomitant psychiatric disease; history of substance abuse; suicide attempt past year; active suicidal ideation;  
pregnant or lactating women, childbearing age without contraception; psychotropic medication; fluoxetine within 21 days  
of baseline; MAOI within 14 days; non-psychotropic within 7 days of baseline unless dose stable for 1 month |
| OTHER MEDICATIONS/ INTERVENTIONS: | 2 mg lormetazepam at bedtime |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: venlafaxine: 41.6, fluoxetine: 43.9  
Gender (% female): venlafaxine: 71.2%, fluoxetine: 65.8%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
**Authors:** De Nayer A, et al.  
**Year:** 2002  
**Country:** Belgium

| OUTCOME ASSESSMENT: | Measures: HAM-D, MADRS, Covi Anxiety Scale, CGI  
Timing of assessments: Baseline, weeks 1, 2, 4, 8, 12 (inferred from table) |
|--------------------|-----------------------------------------------|
| RESULTS: | - The venlafaxine group showed significantly 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 the fluoxetine group  
- Venlafaxine treated patients also showed significantly greater improvements in the Covi Anxiety scores (p = 0.0004) and the CGI scores (p = 0.016)  
- MADRS and HAM-D scores at week 2 improved significantly more in the venlafaxine group  
- (HAM-D, p = 0.0058)  
- At the final visit 59.4% of venlafaxine patients were in remission vs. 40.3% of fluoxetine patients (p = 0.028)  
- Fewer venlafaxine patients required a dose increase (37.1% vs. 52.9%) |
| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| ATTRITION: | **Loss to follow-up:** 36.3%; venlafaxine: 32.9%, fluoxetine: 39.7%  
**Withdrawals due to adverse events:** venlafaxine: 11%, fluoxetine: 12.3%  
**Loss to follow-up differential high:** Yes |
| ADVERSE EVENTS: | - No significant differences  
- Overall most common adverse event: nausea (28.6% in venlafaxine group vs. 21.4% in fluoxetine group)  
- 55.7% in the venlafaxine group and 67.1% in the fluoxetine group experienced at least one adverse event  
- Most common adverse events that lead to withdrawal: venlafaxine: headache, diarrhea, nausea; fluoxetine: insomnia, dyspepsia, nausea, anxiety, nervousness |
<p>| QUALITY RATING: | <strong>Fair</strong> |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td><strong>Authors:</strong> Dierick M, et al. 1996</td>
</tr>
<tr>
<td></td>
<td><strong>Year:</strong> 1996</td>
</tr>
<tr>
<td></td>
<td><strong>Country:</strong> France</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td></td>
<td><strong>Setting:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Sample size:</strong> 314</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td><strong>Drug:</strong> Venlafaxine</td>
</tr>
<tr>
<td></td>
<td><strong>Dose:</strong> 75-150 mg/d</td>
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<tr>
<td></td>
<td><strong>Duration:</strong> 8 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>Drug:</strong> Fluoxetine</td>
</tr>
<tr>
<td></td>
<td><strong>Dose:</strong> 20 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Duration:</strong> 8 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>Mean daily dose for venlafaxine:</strong> 109-122 mg/d from day 15 forward</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td><strong>18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21</strong></td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td><strong>Pregnancy, lactation, or lack of adequate contraception; history of seizures; organic mental disorder; personality disorders; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; use of investigational drug; MAO inhibitor; ECT within 14 days; clinically relevant progressive disease; concomitant warfarin, lithium, insulin, theophylline, carbamazepine; hypersensitivity to or use of antidepressant within 14 days; use of anxiolytic that could not be withdrawn</strong></td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td><strong>Oxazepam, chloral hydrate</strong></td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td><strong>Groups similar at baseline:</strong> Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Mean age:</strong> venlafaxine: 43.7, fluoxetine: 43.2</td>
</tr>
<tr>
<td></td>
<td><strong>Gender (% female):</strong> venlafaxine: 65%, fluoxetine: 64%</td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong> Not reported</td>
</tr>
<tr>
<td></td>
<td><strong>Other population characteristics:</strong> Not reported</td>
</tr>
<tr>
<td>Authors: Dierick M, et al.</td>
<td></td>
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<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Year: 1996</td>
<td></td>
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<tr>
<td>Country: France</td>
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<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: HAM-D, MADRS, CGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Baseline, days 7, 14, 21, 28, 56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Both treatment groups improved significantly in efficacy outcomes from baseline</td>
</tr>
<tr>
<td>• Response rate on HAM-D scale was significantly higher in the venlafaxine group at week 6: venlafaxine: 72%, fluoxetine: 60% (p = 0.023)</td>
</tr>
<tr>
<td>• No differences between groups on MADRS</td>
</tr>
<tr>
<td>• In a low dose comparison there were no significant differences between groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT: Yes</td>
</tr>
<tr>
<td>Post randomisation exclusions: Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: 24.8%; venlafaxine: 25%, fluoxetine: 25%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: venlafaxine: 9%, fluoxetine: 4%</td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significantly more patients reported nausea in the venlafaxine group: 28% vs. 14% (p = 0.003)</td>
</tr>
<tr>
<td>• Anticholinergic side effects greater in venlafaxine group: 15% vs. 7%</td>
</tr>
<tr>
<td>• No clinically significant changes in vital signs, ECG or lab parameters</td>
</tr>
<tr>
<td>• 1 patient on fluoxetine committed suicide after 1 week treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Evidence Table 1</td>
</tr>
<tr>
<td>------------------</td>
</tr>
</tbody>
</table>
| **STUDY:**       | Authors: Eckert L, et al.*7  
                     Year: 2006  
                     Country: France |
| **FUNDING:**     | H. Lundbeck A/S           |
| **DESIGN:**      | Study design: Meta-analysis  
                     Number of patients: 3212 |
| **AIMS OF REVIEW:** | Using direct comparisons of escitalopram versus venlafaxine extended release (XR), the differences between the two compounds through indirect comparisons is examined |
| **STUDIES INCLUDED IN REVIEW** | Head to head studies (2)- Montgomery 2004, Bielski, 2004,  
| **TIME PERIOD COVERED:** | NR |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Short-term RCTs |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult outpatients 18 years or more diagnosed with MDD, categorized as moderate to severe and treated for an episode during its acute phase |
| Authors: Eckert  
| Year: 2006  
| CHARACTERISTICS OF INTERVENTIONS: | Escitalopram to venlafaxine XR or one of the 2 drugs to placebo  
| MAIN RESULTS: | • Escitalopram is non-inferior to venlafaxine XR  
| | • Direct (via Bielski 2004) escitalopram vs. venlafaxine effect size mean 0.23 (95% CI -0.01 to infinity)  
| | • Indirect (10 studies used) escitalopram vs. venlafaxine effect size mean -0.03 (95% CI -0.17 to infinity)  
| ADVERSE EVENTS: | NR  
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | CENTRAL, Medline and Embase databases were interrogated  
| STANDARD METHOD OF APPRAISAL OF STUDIES: | NR  
| QUALITY RATING: | Fair |
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Ekselius L, et al.  
Year: 1997  
Country: Sweden |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Swedish Medical Research Council, Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (general physicians)  
Sample size: 400 |
| INTERVENTION: |  
**Drug:**  
Sertraline  
50-100 mg/d  
24 weeks  
Citalopram  
20-60 mg/d  
24 weeks |
| INCLUSION: | 18-70 yrs; DSM-III-R criteria for major depression; ≥ 21 on MADRS |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; therapy refractory depression; previous failure on sertraline or citalopram; psychotropic medication; clinically significant hepatic or renal disease; concomitant warfarin, lithium, cimetidine, or tryptopan |
| OTHER MEDICATIONS/INTERVENTIONS: | All other medications except: psychotropic medication, warfarin, and cimetidine  
Patients instructed to minimize use of nitrazepam, flunitrazepam, and oxazepam. |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** sertraline: 47.0, citalopram: 47.2  
**Gender (% female):** sertraline: 71%, citalopram 72.5%  
**Ethnicity:** Not reported  
**Other population characteristics:** Concomitant medications: sertraline: 55%, citalopram: 44.5%  
Recurrence depression: sertraline: 56%, citalopram: 65% |
**Authors:** Ekselius L, et al.  
**Year:** 1997  
**Country:** Sweden

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Measures:</th>
<th>CGI-S, MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Weeks 2, 4, 8, 12, 16, 20, 24</td>
</tr>
</tbody>
</table>

### RESULTS:

- Both treatment groups showed significant decreases in MADRS and CGI scores from baseline at all weeks starting at week 2  
- There were no significant differences between treatment groups in any primary outcome variables at any time  
- Response rates week 12: sertraline: 69.5%; citalopram: 68.0%; week 24: sertraline: 75.5%; citalopram: 81.0%  
- **Subgroup analysis:** There were no significant differences between treatment groups in any primary outcome variables in patients with recurrent depression

### ANALYSIS:

**ITT:** Yes. LOCF  
**Post randomization exclusions:** Yes

### ATTRITION:

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
<th>22%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>sertraline: 12.5%, citalopram: 9.0%</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:

- No significant differences between treatment groups  
- At least one adverse event: sertraline: 90%, citalopram: 85.5%  
- Nausea: sertraline: 6%, citalopram: 2.5%  
- Diarrhea: sertraline: 8.5%, citalopram: 5.5%  
- Increased sweating: sertraline: 13%, citalopram 17%  
- Dry mouth: sertraline: 18.5%, citalopram: 16%  
- Headache: sertraline: 9%, citalopram: 6.5%  
- Sexual dysfunction was experienced in 8% of the sertraline group and 13.5% of the citalopram group

### QUALITY RATING:

**Good**
**Evidence Table 1**  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Fava M, et al.  
Year: 1998  
Country: US |
| FUNDING: | SmithKline Beecham Pharmaceuticals |
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 128 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
20-50 mg/d (Initial dosage of 20 mg/d could be increased weekly by 10 mg/d up to 50 mg/d)  
12 weeks  
Paroxetine  
Fluoxetine  
(Initial dosage of 20 mg/d could be increased weekly by 20 mg/d up to 80 mg/d)  
12 weeks  
Placebo  
N/A  
12 weeks |
| Duration: |  
**Raskin Depression score of > 8** (and larger in value than the Covi anxiety scale) score of ≥ 18 on the 21 item HAM-D |
| INCLUSION: |  
EXCLUSION: |  
Serious concomitant medical illness; suicidal risk; alcohol or drug abuse; patients previously treated with paroxetine; hypersensitive to fluoxetine; diagnosed with another primary psychiatric disorder; other psychotropic drugs within 14 days; ECT within 3 months; pregnancy or no acceptable contraception |
| OTHER MEDICATIONS/INTERVENTIONS: | Chlora hydrate for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 41.3  
Gender (% female): 50%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
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</tbody>
</table>

**OUTCOME ASSESSMENT:**

- **Measures:** 21 item HAM-D, Covi Anxiety Scale, vital signs at weeks 1, 2, 3, 4, 6, 9, 12
- **Timing of assessments:** Laboratory evaluations at weeks 3, 6, 9, 12

**RESULTS:**

No significant differences among the three treatment groups in the degree of depression and anxiety improvement

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Not reported

**ATTRITION:**

- **Loss to follow-up:** 28%; paroxetine: 29%, fluoxetine: 31%, placebo: 21%
- **Withdrawals due to adverse events:** 12%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- Gastrointestinal effects were reported in 47% of paroxetine patients, 48% fluoxetine patients
- 25% of paroxetine patients reported sexual dysfunction; this was significantly more than the fluoxetine (7%) or placebo groups (0%)

**QUALITY RATING:** Fair
### Evidence Table 1

<table>
<thead>
<tr>
<th></th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**     | Authors: Fava M, et al.\(^\text{33}\)  
                 | Year: 2002  
                 | Country: US |
| **FUNDING:**   | Eli Lilly Research               |
| **DESIGN:**    | Study design: RCT  
                 | Setting: Multi-center  
                 | Sample size: 284 |
| **INTERVENTION:** | Drug:  
                 | Dose:  
                 | Duration: |
|                | Fluoxetine  
                 | 20-60 mg/day  
                 | 10-16 weeks |
|                | Sertraline  
                 | 50-200 mg/day  
                 | 10-16 weeks |
|                | Paroxetine  
                 | 20-60 mg/day  
                 | 10-16 weeks |
| **INCLUSION:** | > 18 years of age; DSM-IV for atypical MDD; HAM-D-17 ≥ 16; episode ≥ 1 month |
| **EXCLUSION:** | Pregnancy or lactation; lack of adequate contraception; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication; serious comorbid illness not stabilized; anxiolytic or psychotropic within 7 days; MAOI within 2 weeks |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Thyroid medications, chloral hydrate |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                 | Mean age: fluoxetine: 42.1, sertraline: 44.0, paroxetine: 42.5  
                 | Gender (female%): fluoxetine: 63.0, sertraline: 57.3, paroxetine: 58.3  
                 | Ethnicity: Not reported  
                 | Other population characteristics: Not reported |
**Authors:** Fava M, et al.  
**Year:** 2002  
**Country:** US

### OUTCOME ASSESSMENT:

**Measures:** HAM-D-17, CGI-S, HAM-D sleep disturbance  
**Timing of assessments:** Not reported

### RESULTS:

- No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures  
- Response rate: 64.8%, 72.9%, and 68.8% respectively  
- Remission rates: 54.4%, 59.4%, and 57.0% respectively  
- No statistical differences in sleep disturbance factor scores. No significant differences of treatment groups in patients with high or low insomnia  
- **Subgroup analysis (Fava 2000): Anxious depression**  
  - No significant differences between treatment groups and changes over time  
  - Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405  
  - Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588  
  - Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Not reported

### ATTRITION:

**Loss to follow-up:** 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1%  
**Withdrawals due to adverse events:** fluoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients, and the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients  
- Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%)  
- There was a significant increase in weight for the paroxetine group, fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint  
- **Subgroup analysis (Fava 1999)**  
  - Adverse events were similar among treatments; only “flu syndrome” was significantly higher in the sertraline treated group overall (p = 0.021)

### QUALITY RATING:

**Fair**
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Feiger A, et al.  
Year: 1996  
Country: Europe |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Bristol-Myers Squibb</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 160 |
| INTERVENTION: |  
**Drug:**  
Nefazodone  
100-600 mg/d  
6 weeks  
Sertraline  
50-200 mg/d  
6 weeks |
| INCLUSION: | 18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-17 after washout period |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; Axis I diagnosis; history of seizures; alcohol or substance abuse; existing suicidal risk; previous nefazodone trial; sertraline treatment within 1 year; clinically relevant progressive disease; known hypersensitivity to study drugs; psychotropic medication within 6 months; participation in other trial within 3 months; use of any other antidepressant within 3 weeks |
| OTHER MEDICATIONS/INTERVENTIONS: | Concomitant medications |
| POPULATION CHARACTERISTICS: |  
**Groups similar at baseline:** sertraline group had a significantly higher rate of recurring illness than the nefazodone group (73% vs. 57%; p = 0.01)  
**Mean age:** 43.7; sertraline: 43, nefazodone: 44.5  
**Gender** (% female): 51%; sertraline: 48%, nefazodone: 55%  
**Ethnicity:** white: 84%, black: 11%, Hispanic: 7%, Asian: 1%, other: 1%; sertraline: white: 79%, nefazodone: 90% white  
**Other population characteristics:** Concomitant medication taken by 85% in the nefazodone group and 78% in the sertraline group; recurrent illness: sertraline: 57%, nefazodone: 73% |
**Authors:** Feiger A, et al.  
**Year:** 1996  
**Country:** Europe

| OUTCOME ASSESSMENT: | Measures: HAM-D-17, CGI, sexual function questions  
Timing of assessments: Weekly |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>RESULTS:</td>
<td>There were no statistically significant differences between treatment groups; response rates: nefazodone: 59%, sertraline: 57%</td>
</tr>
</tbody>
</table>
| ANALYSIS:           | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION:          | Loss to follow-up: 24.4%; nefazodone: 24.4%, sertraline: 24.4%  
Withdrawals due to adverse events: nefazodone: 19.2%, sertraline: 12.2%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS:     |  
- Reported at least one adverse event: sertraline: 95%, nefazodone: 96%  
- Overall satisfaction with sexual function was significantly higher in the nefazodone group (p < 0.1)  
- 67% of men in the sertraline group reported difficulty with ejaculation vs. 19% in the nefazodone group (p < 0.01)  
- No significant differences in other adverse events  
- No clinically significant effects on the cardiovascular system in either group; no differences in withdrawals due to adverse events.  
- Headache: sertraline: 55%, nefazodone: 55%  
- Nausea: sertraline: 27%, nefazodone: 32%  
- Dizziness: sertraline: 7%, nefazodone: 32% |
| QUALITY RATING:     | Fair |
## Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | **Authors:** Feighner JP, et al.  
**Year:** 1991  
**Country:** US |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Burroughs Wellcome Co.</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center (2 centers)  
**Sample size:** 123 |
| INTERVENTION: | **Drug:**  
**Bupropion**  
225-450 mg/d  
6 weeks  
**Fluoxetine**  
20 mg for 3 weeks, then 20-80 mg  
6 weeks |
| INCLUSION: | At least 18 years; DSM-III criteria for nonpsychotic depression; current depressive episode for at least 4 weeks but less than 2 yrs; ≥ 20 on HAM-D scale; considered clinically appropriate for bupropion or fluoxetine treatment |
| EXCLUSION: | Predisposition to seizures; hepatic or renal dysfunction; thyroid disorder; anorexia; bulimia; other unstable medical condition; pregnant, lactating, no acceptable contraception method; history of alcohol or substance abuse; psychoactive drugs; MAO inhibitors within 1 week before treatment; four weeks of investigational drugs; suicidal ideation; current treatment with tryptophan, warfarin, digoxin, or thyroid preparations; unable to conduct meaningful conversation |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** bupropione: 40.9, fluoxetine: 42.9  
**Gender** (female%): bupropione: 62%, fluoxetine: 61%  
**Ethnicity:** Not reported  
**Other population characteristics:** Not reported |
| Authors: Feighner JP, et al.  
Year: 1991  
Country: US |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D (21), CGI-S, CGI-I, HAM-A  
**Timing of assessments:** Weekly |
| **RESULTS:** | • No significant differences in changes of the HAM-D score between treatment groups  
• No significant differences in percentage of clinical responders (more than 50% HAM-D scale reduction) between treatment groups, bupropion: 62.7%, fluoxetine: 58.3%  
• No significant differences in changes of CGI-S, CGI-I, and HAM-A scores |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomisation exclusions:** Yes, 3 patients |
| **ATTRITION:** | **Loss to follow-up:** 7.3%; bupropion: 3.3%, fluoxetine: 11.3%  
**Withdrawals due to adverse events:** Bupropion: 10%, fluoxetine: 7%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | No significant differences of adverse events between treatment groups |
| **QUALITY RATING:** | Fair |
### Evidence Table 1 Major Depressive Disorder Adults

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>Authors: Finkel SI, et al.³⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year: 1999</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>Two authors are affiliated with Pfizer, Inc.</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT, subgroup analysis</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center</td>
</tr>
<tr>
<td></td>
<td>Sample size: 75</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Dose:</td>
<td>50-100 mg/day</td>
</tr>
<tr>
<td></td>
<td>20-40 mg/day</td>
</tr>
<tr>
<td>Duration:</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>DSM III-R criteria for major depression; HAM-D: ≥ 18; age 70 or older</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Significant medical problems; Axis I psychiatric disorders; cognitive impairment; suicidal risk; drug abuse or dependence; failure to respond to antidepressant treatment</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/</td>
<td>Chloral hydrate, temazepam</td>
</tr>
<tr>
<td>INTERVENTIONS:</td>
<td></td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: No-Fluoxetine group had higher rate of prior episodes of depression.</td>
</tr>
<tr>
<td></td>
<td>Mean age: sertraline: 74, fluoxetine 75</td>
</tr>
<tr>
<td></td>
<td>Gender: (female%): sertraline: 57%, fluoxetine 49%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: 97% white, 3% black; sertraline 95%, fluoxetine: 100%</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Prior depressive episodes: sertraline: 45%, fluoxetine 61%</td>
</tr>
</tbody>
</table>
**Authors:** Finkel SI, et al.  
**Year:** 1999  
**Country:** US

| OUTCOME ASSESSMENT: | Measures and timing of assessments: HAM-D, Baseline (pre & post washout), weeks 2, 4, 6, 8, 10, 12, 3  
POMS (baseline, weeks 2, 4, 8, 12), 2. Q-Les-Q (baseline, week 12), cognitive tests: 1. DSST from the WAIS-R, 2. shopping list task, both given, Mini-Mental SE (baseline and week 12) |
| RESULTS: | • Overall no significant differences between treatment groups on endpoint scores  
• Significantly more patients in the sertraline group achieved a clinical response on HAM-D (reduction from baseline of 50% or greater) between weeks 6 to 12  
• Changes in the Vigor Subscale of POMS, and 2 subscales of the Q-LES-Q (physical health, psychological health) showed significant differences favoring sertraline (p = 0.04; p = 0.03; p = 0.03) |
| ANALYSIS: | ITT: Yes  
*Post randomization exclusions:* Yes. 1 person excluded from ITT because lack of measures |
| ATTRITION: | Loss to follow-up: 37.3%; sertraline: 36%, fluoxetine: 39%  
Withdrawals due to adverse events: sertraline: 9%, fluoxetine: 30%  
Loss to follow-up differential high: Yes |
| ADVERSE EVENTS: | • Sertraline-treated patients reported “shaking” to a greater degree (14.3%) than did fluoxetine treated patients (0%) (p = 0.03)  
• Fluoxetine-treated patients lost more weight than sertraline-treated patients (week 12: 2.8 vs. 0.6 pounds; p = 0.05) |
| QUALITY RATING: | Fair |
**Evidence Table 1**

**Major Depressive Disorder Adults**

| STUDY: | Authors: Franchini L, et al.37, 38  
Year: 1997, 2000  
Country: Italy |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 64 (4-year follow-up: enrolled 47) |
| INTERVENTION: | **Drug:** Sertraline  
Dose: 100-200 mg/d  
Duration: 24/48 months  
Fluvoxamine  
Dose: 200-300 mg/d  
Duration: 24/48 months |
| INCLUSION: | Asymptomatic patients; unipolar patients with prior episodes; depressive episode within past 18 months; at least 4 months of remission confirmed by absence of symptoms according to DSM-IV; absence of other Axis I diagnosis  
4-year follow-up: patients who remained without recurrence after 2 years of prophylactic treatment (HAMD >15) |
| EXCLUSION: | Other Axis I diagnosis; low compliance with past treatments; mania or hypomania; prior long-term maintenance treatment; recurrence cycle not longer than 18 months |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: sertraline: 47.3, fluvoxamine: 49.0  
Gender (% female): sertraline: 78%, fluvoxamine: 75%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
**Authors:** Franchini L, et al.  
**Year:** 1997, 2000  
**Country:** Italy

| OUTCOME ASSESSMENT: | Measures: HAM-D  
Timing of assessments: Monthly |
|---------------------|-----------------------------|

**RESULTS:**
- 21.9% of sertraline-treated patients and 18.7% of fluvoxamine-treated patients had a single recurrence ($z = 0.14; p = 0.88$)
- **4-year follow-up:**  
  - No significant difference in recurrences between the treatment groups; sertraline: 13.6%, fluvoxamine: 20%

**ANALYSIS:**
- **ITT:** No but not necessary since 100% completed trial with outcome assessments  
- **Post randomization exclusions:** No

**ATTRITION:**
- **Loss to follow-up:** 0  
- **Withdrawals due to adverse events:** 0  
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- No significant differences in adverse events.  
- Most common adverse events:  
  - Sertraline: nausea (6.2%), abnormal ejaculation (12.5%)  
  - Fluvoxamine: nausea: (9.4%), anorexia (9.4%)  
- **4-year follow-up:** Not reported

**QUALITY RATING:** Fair
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY:       | Authors: Gagiano CA<sup>39</sup>  
|             | Year: 1993  
|             | Country: South Africa |
| FUNDING:     | Not reported |
| DESIGN:      | Study design: RCT  
|             | Setting: Single center (University hospital)  
|             | Sample size: 90 |
| INTERVENTION:| Fluoxetine  
| Drug:       | Paroxetine  
| Dose:       | 20-60 mg/d  
| Duration:   | 6 weeks  
| Duration:   | 20-40 mg/d  
| Duration:   | 6 weeks  
| INCLUSION:  | Age 18-65 years; met DSM-III-R criteria for MDD; HAM-D (21-item scale) score of $\geq 18$ |
| EXCLUSION:  | Pregnant or lactating women; underlying renal, hepatic, neurological, gastrointestinal or severe cardiovascular disease, schizophrenia, organic brain syndrome and unstable diabetes; recent treatment with MAOIs or neuroleptics, lithium therapy, ECT in the previous three months and alcohol or drug abuse; patients considered to be at severe risk of suicide; any patient with 20% improvement in their HAMD score over one-week placebo washout period was not randomized to active treatment |
| OTHER MEDICATIONS/ INTERVENTIONS: | Short-acting benzodiazepines such as temazepam; any other concomitant therapy already being employed prior to treatment was to be continued where possible |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age:  | fluoxetine: 39.6, paroxetine: 37.8  
| Gender (% female): | fluoxetine: 80%, paroxetine: 80%  
| Ethnicity: | Not reported  
| Other population characteristics: | Previous depression fluoxetine: 60%, paroxetine: 53% |
**Authors:** Gagiano CA  
**Year:** 1993  
**Country:** South Africa

| OUTCOME ASSESSMENT: | Measures: Physical exam, HAM-D, MADRS, CGI, HAM-A, routine hematology and biochemistry on blood samples at baseline and end of week 6  
**Timing of assessments:** Baseline and weekly intervals except week 5 |

| RESULTS: | • No significant differences between treatment groups in HAM-D subfactor scores at any time point  
• No significant differences in mean total scores for HAM-D, HAM-A, and MADRS at endpoint or at any other study point measures  
• No significant difference in CGI severity change score or improvement score  
• No significant difference in patients responding (at least 50% improvement of HAM-D) between treatment groups (paroxetine: 70%, fluoxetine: 63%; no p value reported)  
• No significant differences in groups on HAMD (item 3) measure for suicidal ideation, both groups showed reduction over six-week period |

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** No |

| ATTRITION: | **Loss to follow-up:** 21%; fluoxetine 22%, paroxetine 14%  
**Withdrawals due to adverse events:** 6.7%  
**Loss to follow-up differential high:** No |

| ADVERSE EVENTS: | • Fluoxetine-treated patients experienced a statistically significant weight loss from baseline to endpoint (-1.46 kg; p = 0.001)  
• Headache: fluoxetine 47.0%, paroxetine 53.0%  
• Nausea: fluoxetine 33.0%, paroxetine 36.0%  
• Diarrhea: fluoxetine 13.0%, paroxetine 13.0%  
• Insomnia: fluoxetine 20.0%, paroxetine 11.0%  
• Vomiting was noted for only four (8.9%) patients in each group |

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Gartlehner G et al. <sup>40</sup>  
                     Year: 2007  
                     Country: Multinational |
| **FUNDING:**     | AHRQ |
| **DESIGN:**      | Study design: Systematic review and meta-analysis  
                     Number of patients: NR |
| **AIMS OF REVIEW:** | To compare the benefits and harms of second-generation antidepressants for the treatment of depressive disorders in adults |
| **STUDIES INCLUDED IN REVIEW** | 187 studies |
| **TIME PERIOD COVERED:** | 1980-February 2006 |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | For efficacy and effectiveness: double-blinded, placebo controlled or head-to-head RCTs of at least 6 weeks duration.  
 For harms, also included observational studies with N ≥ 100 and follow up ≥ 12 weeks |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult inpatients and outpatients with MDD, dysthymia or subsyndromal depression |
**Authors:** Gartlehner G et al.  
**Year:** 2007

### CHARACTERISTICS OF INTERVENTIONS:
Bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine

### MAIN RESULTS:
- No substantial differences in comparative efficacy and effectiveness of second-generation antidepressants for treatment of MDD. This pertains to acute, continuation, and maintenance phases, to patients with accompanying symptom clusters, and to subgroups defined by age, ethnicity, sex, or comorbidities (only sparse evidence for subgroups).
- Overall, 38% of patients did not respond during 6-12 weeks of treatment; 54% did not achieve remission.
- Quality of life or functional capacity was infrequently assessed; 18 studies (4,050 patients) indicated no statistical differences in efficacy with respect to health related QoL.
- Seven studies reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine and sertraline.

### ADVERSE EVENTS:
- Overall, second-generation antidepressants have similar adverse events profiles.
- Constipation, diarrhea, dizziness, headache, insomnia, nausea and somnolence were commonly and consistently reported AEs.
- Venlafaxine associated with higher incidence of nausea and vomiting than SSRIs as a class.
- Mirtazapine led to higher weight gains than fluoxetine, paroxetine, venlafaxine and trazodone.
- Sertraline led to higher rates of diarrhea than comparator drugs.

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
MEDLINE®, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts from 1980 to April 2007, limited to English language. We manually searched reference lists of pertinent review articles and explored the Center for Drug Evaluation and Research database to identify unpublished research.

### STANDARD METHOD OF APPRAISAL OF STUDIES:
Yes

### QUALITY RATING:
Good
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Goldstein DJ, et al.41</td>
</tr>
<tr>
<td></td>
<td>Year: 2002</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Eli Lilly</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center (8 sites)</td>
</tr>
<tr>
<td></td>
<td>Sample size: 173</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>Dose:</td>
</tr>
<tr>
<td></td>
<td>Duration:</td>
</tr>
<tr>
<td></td>
<td>Sample size:</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Male and female outpatients 18-65 years; met DSM-IV and MINI criteria for MDD; CGI-S score of at least 4 at visit 1; HAM-D-17 score of at least 15 at visits 1 and 2</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Any primary DSM-IV Axis I disorder diagnosis other than MDD; anxiety disorder as primary diagnosis within the past year; history of substance abuse or dependence; failed two or more courses of antidepressant therapy</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age:</td>
</tr>
<tr>
<td></td>
<td>Gender (% female):</td>
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<tr>
<td></td>
<td>Ethnicity:</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
<tr>
<td>Authors: Goldstein DJ, et al.</td>
<td>Year: 2002</td>
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</tbody>
</table>

**OUTCOME ASSESSMENT:**  
*Primary Outcome Measures:* HAM-D-17  
*Secondary Outcome Measures:* MADRS; CGI; HAM-A; PGI  
*Timing of assessments:* HAM-D-17 measured at baseline and weekly

**RESULTS:**  
- No statistically significant differences between duloxetine and fluoxetine in response (49% vs. 45%) and remission (43% vs. 30%) rates  
- Duloxetine showed a significantly greater mean change from baseline in HAM-D-17 than placebo at week 8 ($p = 0.009$)  
- Duloxetine showed a greater change from baseline in HAM-D-17 than placebo at week 8 but the difference was not statistically different  
- Duloxetine patients showed significantly greater improvement on the MADRS ($p = 0.047$), CGI-S ($p = 0.007$), CGI-I ($p = 0.005$), and PGI ($p = 0.006$) than placebo

**ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes

**ATTRITION:**  
*Loss to follow-up:* 35% (60); duloxetine: 34.3% (24); fluoxetine: 36.4% (12); placebo: 34.3% (24)  
*Withdrawals due to adverse events:* 6.4% (11); duloxetine: 10% (7); fluoxetine: 3% (1); placebo 4.3% (3)  
*Loss to follow-up differential high:* No

**ADVERSE EVENTS:**  
- Significantly more duloxetine patients experienced asthenia (17.1% vs. 4.3%; $p = 0.026$), and insomnia (20.0% vs. 7.1%; $p = 0.046$) than placebo  
- Most common adverse events (duloxetine vs. fluoxetine): dry mouth: 30.0% vs. 21.2%; headache: 20% vs. 33.3%; insomnia: 20% vs. 9.1%; nausea: 12.9% vs. 18.2%; diarrhea: 14.3% vs. 30.3%

**QUALITY RATING:** Fair
### Evidence Table 1

#### Major Depressive Disorder Adults

| STUDY: | Authors: Hong CJ, et al.  
Year: 2003  
Country: Taiwan |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>NV Organon, Oss, the Netherlands</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 133 |
| INTERVENTION: | Drug:  
Dose:  
Duration: |
| Mirtazapine: | 15 mg-45 mg/d  
6 weeks |
| Fluoxetine | 20 mg-40 mg/d  
6 weeks |
| INCLUSION: | 18-75 years; DSM-IV diagnosis of major depression; ≥ 15 HAM-D score (17); current episode between 1 week and 1 year |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; actual suicide risk; bipolar disorder or history of psychotic disorders; alcohol or substance abuse; DSM-IV of anxiety; history of seizures; clinically relevant progressive disease; psychotropic medication |
| OTHER MEDICATIONS/INTERVENTIONS: | Lorazepam, estazolam, supportive psychotherapy, medication for mild physical illness |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 47.2  
Gender (% female): 63%; mirtazapine 62%, fluoxetine 64%  
Ethnicity: Chinese  
Other population characteristics: Not reported |
**Authors:** Hong CJ, et al.  
**Year:** 2003  
**Country:** Taiwan

### OUTCOME ASSESSMENT:

**Measures:** HAM-D, CGI  
**Timing of assessments:** Days 7, 14, 28, 42

### RESULTS:

- No significant differences in HAM-D scores reduction between treatment groups  
- No significant differences in HAM-D responders (mirtazapine: 58% vs. fluoxetine: 51%)  
- Mirtazapine had more remitters and responders at all time points, however no statistical significance in differences was reached

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 39.4%; mirtazapine: 45.5%, fluoxetine: 33.3%  
**Withdrawals due to adverse events:** Mirtazapine: 19.7%, fluoxetine: 12.1%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No statistically significant differences between treatment groups  
- 71.2% of mirtazapine and 57.6% of fluoxetine treated subjects reported adverse events  
- Mirtazapine: dizziness 19.7%, constipation 15.2%, weight increase 13.6%, somnolence 12.1%  
- Fluoxetine: dizziness 13.6%, influenza-like symptoms 13.6%, constipation 9.1%

### QUALITY RATING:

Fair
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY:            | Authors: Kasper S, et al.  
|                   | Year: 2005  
|                   | Country: Multinational (11 countries) |
| FUNDING:          | H. Lundbeck A/S |
| DESIGN:           | Study design: RCT  
|                   | Setting: Multicenter (general practice and specialists)  
|                   | Sample size: 518 |
| INTERVENTION:     | Drug:  
|                   | Dose:  
|                   | Duration:  
|                   | Sample size:  
|                   | escitalopram  
|                   | 10 mg/day  
|                   | 8 weeks  
|                   | 174  
|                   | fluoxetine  
|                   | 20 mg/day  
|                   | 8 weeks  
|                   | 164  
|                   | placebo  
|                   | NA  
|                   | 8 weeks  
|                   | 180  
| INCLUSION:        | ≥ 65 years of age; fulfilled DSM-IV criteria for MDD; had a MADRS total score ≥ 22 and ≤ 40 at both screening and baseline; MMSE score of 22 at screening |
| EXCLUSION:        | DSM-IV criteria for mania or any bipolar disorder, schizophrenia, or any psychotic disorder, OCD, eating disorders, or mental retardation or any pervasive developmental or cognitive disorder; had a MADRS score ≥ 5 on Item 10 (suicidal thoughts); were receiving treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, AEDs, barbiturates, chloral hydrate, antiparkinsonian drugs, diuretics, 5-HT receptor agonists; ongoing prophylactic treatment with Lithium, sodium valproate, or carbamazepine; ECT; were receiving treatment with behavior therapy or psychotherapy; had received any investigational drug within 30 days of entry; history of schizophrenia, psychotic disorder, or drug abuse; history of severe drug allergy or hypersensitivity (including citalopram); had a lack of response to more than one antidepressant treatment (including citalopram) during the present depressive episode |
| OTHER MEDICATIONS/INTERVENTIONS: | Oxazepam (max 30 mg/day), temazepam (max 20 mg/day), zopiclone (max 3.75 mg/day), zolpidem (max 5 mg/day) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                   | Mean age: 75 (overall and for each treatment group)  
|                   | Gender (female %): escitalopram: 75%; fluoxetine: 77%; placebo: 76%  
|                   | Ethnicity (% white): escitalopram: 99%; fluoxetine: 100%; placebo: 100%  
|                   | Other population characteristics:  
|                   | Baseline mean MADRS score: escitalopram: 28.2; fluoxetine: 28.5; placebo: 28.6  
<p>|                   | Baseline mean CGI-S score: 4.3 (overall and for each treatment group) |</p>
<table>
<thead>
<tr>
<th>Authors: Kasper S, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2005</td>
</tr>
<tr>
<td>Country: Germany</td>
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</tbody>
</table>

**OUTCOME ASSESSMENT:**

**Primary Outcome Measures:** Change from baseline to endpoint in MADRS total score

**Secondary Outcome Measures:** CGI-S change/visit, MADRS response and remission at endpoint

**Timing of assessments:** baseline and weekly

**RESULTS:**

- No statistically significant difference between escitalopram and placebo in mean change from baseline in MADRS total score; placebo was statistically significantly superior to fluoxetine ($p<0.01$)
- MADRS responders at last assessment (LOCF) (escitalopram vs. fluoxetine vs. placebo): 46% vs. 37% vs. 47% ($p=NS$)
- MADRS remission: at last assessment (LOCF): 40% vs. 30% vs. 42%; No significant difference between placebo and escitalopram
- Significantly fewer remitters remitters in fluoxetine vs. placebo ($p<0.05$)
- Statistically significant difference between placebo and fluoxetine in adjusted change in mean CGI-S (2.70 vs. 3.02; $p<0.05$); no significant difference between placebo and escitalopram (2.64); $p=NS$

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** yes (4)
- **Loss to follow-up differential high:** No

**ATTRITION:**

<table>
<thead>
<tr>
<th></th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>16.8%</td>
<td>25.6%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Withdrawals due to AEs:</td>
<td>9.8%</td>
<td>12.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Withdrawals lack of efficacy:</td>
<td>1.7%</td>
<td>1.8%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

<table>
<thead>
<tr>
<th>TEAEs (escitalopram vs. fluoxetine vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall: 50.9% vs. 56.7% vs. 53.3%</td>
</tr>
<tr>
<td>Nausea: 6.9%* vs. 7.3%* vs. 1.7% ($p&lt;0.01$ escitalopram vs. fluoxetine)</td>
</tr>
<tr>
<td>Abdominal pain: 6.4% vs. 6.1% vs. 3.9%</td>
</tr>
<tr>
<td>Headache: 5.2% vs. 4.3% vs. 8.3%</td>
</tr>
<tr>
<td>Hypertension: 2.3% vs. 2.4% vs. 6.1%</td>
</tr>
<tr>
<td>Diarrhea: 1.7% vs. 4.9% vs. 5.0%</td>
</tr>
<tr>
<td>Back pain: 4.6% vs. 2.4% vs. 3.9%</td>
</tr>
<tr>
<td>Anxiety: 2.9% vs. 3.7% vs. 2.8%</td>
</tr>
<tr>
<td>Dizziness: 2.9% vs. 3.7% vs. 0.6%</td>
</tr>
<tr>
<td>Dyspepsia: 2.3% vs. 4.3% vs. 4.4%</td>
</tr>
<tr>
<td>Insomnia: 2.3% vs. 1.8% vs. 2.2%</td>
</tr>
<tr>
<td>Somnolence: 2.3% vs. 0% vs. 0.6%</td>
</tr>
<tr>
<td>Anorexia: 1.2% vs. 2.4% vs. 1.1%</td>
</tr>
<tr>
<td>Constipation: 1.2% vs. 4.3% vs. 4.4%</td>
</tr>
<tr>
<td>Depression aggravated: 1.2% vs. 2.4% vs. 0.6%</td>
</tr>
<tr>
<td>Dry mouth: 0.6% vs. 2.4% vs. 0.6%</td>
</tr>
<tr>
<td>Orthostatic hypotension: 1.2% vs. 0.6% vs. 0.6%</td>
</tr>
</tbody>
</table>
Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Katzman MA, et al.  
Year: 2007  
Country: Multinational |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>GlaxoSmithKline Canada</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Systematic review  
Number of patients: NR |
| AIMS OF REVIEW: | To compare paroxetine with placebo and other antidepressants across multiple efficacy and tolerability outcomes |
| STUDIES INCLUDED IN REVIEW | 62 trials |
| TIME PERIOD COVERED: | 1966-Feb 2004 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs comparing paroxetine with placebo or other antidepressants |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Adult in and outpatients with primary diagnosis of MDD or other depressive disorder |
**Authors:** Katzman M, et al.  
**Year:** 2007

### CHARACTERISTICS OF INTERVENTIONS:
Paroxetine vs. placebo (11 studies); paroxetine vs. other antidepressants (51 studies). Comparative antidepressants included amitriptyline (13 studies), fluoxetine (12 studies), mirtazapine (4 studies), imipramine (4 studies), clomipramine (3 studies), sertraline (3 studies), venlafaxine (3 studies), maprotiline (2 studies), and nefazodone (2 studies).

### MAIN RESULTS:
- Paroxetine was consistently and significantly more efficacious than placebo with respect to remission (RD: 10% [95% CI 6 to 14]), clinical response (RD: 17% [95% CI 7 to 27]) and change score (ES: 0.2 [95% CI 0.1 to 0.3])
- Clinical response with paroxetine was significantly lower than with venlafaxine (RD: -21% [95% CI -34 to -81]); however, no difference between drugs with respect to remission (RD: -12% [95% CI -29 to 5]) and change score (ES: -0.07 [95% CI -0.24 to 0.10])
- Remission and change score with paroxetine were significantly lower than with mirtazapine (RD: -9% [95% CI -16 to -21]; ES: -0.24 [95% CI -0.40 to -0.09]); however, no difference between paroxetine and mirtazapine with respect to clinical response (RD: -7% [95% CI -14 to 1])
- Clinical response with paroxetine was significantly higher than with fluoxetine (RD: 7% [95% CI 0.7 to 13]); no difference between drugs with respect to change scores (ES: 0.10 [95% CI -0.05 to 0.24]) and remission (RD: 3% [95% CI -2 to 9])

### ADVERSE EVENTS:
Paroxetine associated with significantly more dropouts due to AEs than treatment with placebo (RD: 8% [95% CI -4 to 13])

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
Yes-MEDLINE, EMBASE, CINAHL, all Evidence-Based Medicine Reviews, HealthSTAR, BIOSIS, and PsycINFO

### STANDARD METHOD OF APPRAISAL OF STUDIES:
Yes

### QUALITY RATING:
Good
### Evidence Table 1  
**Major Depressive Disorder Adults**

<table>
<thead>
<tr>
<th>STUDY:</th>
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</thead>
</table>
| **Authors:** Kavoussi et al.  
**Year:** 1997  
**Country:** US |

<table>
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<tr>
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<table>
<thead>
<tr>
<th>DESIGN:</th>
</tr>
</thead>
</table>
| **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 248 |

<table>
<thead>
<tr>
<th>INTERVENTION:</th>
</tr>
</thead>
</table>
| **Drug:**  
**Dose:**  
**Duration:** |
| Bupropion SR  
100-300 mg/d  
16 weeks | Sertraline  
50-200 mg/d  
16 weeks |

<table>
<thead>
<tr>
<th>INCLUSION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18-76; DSM-IV criteria for MDD with current episode ≥ 4 weeks but ≤ 24 months; in a stable relationship with normal sexual functioning</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant, lactating; history of bulimia or anorexia; predisposition to seizures; actively suicidal; no prior treatment with buproprion sr or sertraline; no psychoactive drug within 1 week; (2 weeks for MAOI or protryptyline, 4 weeks for fluoxetine)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER MEDICATIONS/ INTERVENTIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlora hydrate allowed, no other psychoactive agents, allowed non-psychoactive agents not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POPULATION CHARACTERISTICS:</th>
</tr>
</thead>
</table>
| **Groups similar at baseline:** Yes  
**Mean age:** 39.5; buproprion SR: 39, sertraline: 40  
**Gender** (female%): 48%, buproprion SR: 48%, sertraline: 48%  
**Ethnicity:** 93.5 % white, 4.5 % black, 2% other; buproprion 93% white, sertraline 94% white  
**Other population characteristics:** Prior antidepressant use for current episode: buproprion SR: 22%, sertraline: 21% |
### Authors: Kavoussi et al.
**Year:** 1997  
**Country:** US

### OUTCOME ASSESSMENT:
- **Measures:** HAM-D21, HAM-A, CGI  
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16

### RESULTS:
- HAM-D21: similar changes in scores over study, no differences at any point in study  
- CGI, CGI-S, HAMA: no differences between groups

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 31.5%; bupropion SR: 28.7%, sertraline: 34.1%  
- **Withdrawals due to adverse events:** bupropion SR: 3%, sertraline: 13% (p = 0.004)  
- **Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:
- Significant differences (p < 0.05):  
  - Nausea: bupropion SR: 10%, sertraline: 30%  
  - Diarrhea: bupropion SR: 3%, sertraline: 22%  
  - Somnolence: bupropion SR: 2%, sertraline: 13%  
- Sexual dysfunction: bupropion SR: 10%, sertraline: 61%  
- Orgasm failure or delay: men – bupropion SR: 10%, sertraline: 61% (p < 0.001); women – bupropion SR: 7%, sertraline: 41% (p < 0.001)

### QUALITY RATING:
- Fair
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Keller M et al.  
Year: 2007  
Country: USA |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth Research</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 1047 (715) |
| INTERVENTION: | 
**Drug:** Venlafaxine  
**Dose:** 37.5-225 mg  
**Duration:** 10 (36) weeks  
**Sample size:** 781 (530)  
**Fluoxetine:**  
**Dose:** 10-60 mg  
**Duration:** 10 (36) weeks  
**Sample size:** 266 (185) |
| INCLUSION: | men or women aged 18 years or older who met DSM-IV criteria for MDD, had experienced depressive symptoms for at least 1 month prior to the start, and had recurrent depression: a history of at least three episodes of major depression, with at least two episodes in the past 5 years, and an interval of at least 2 months between the end of the previous episode and the beginning of the current episode. A total score \( \geq 20 \) on the 17-item Hamilton Depression Rating Scale at screening and \( \geq 18 \) at randomization |
| EXCLUSION: | Failed an adequate trial of fluoxetine, venlafaxine, or venlafaxine ER during the current episode of major depression or who were treatment-resistant; known hypersensitivity to venlafaxine or fluoxetine; history or presence of a serious medical disease, cancer, seizure disorder, bipolar disorder, eating disorder (if not remitted for 5 years), significant Axis II disorder, any psychotic disorder, or current postpartum depression; serious suicide risk; those who had clinically significant abnormalities on prestudy medical assessments; or were women of childbearing age who were pregnant, breastfeeding, or not using a medically acceptable method of birth control; any investigational drug, antipsychotic drug, fluoxetine, or monoamine oxidase inhibitor within 30 days or any other antidepressant within 14 days; ECT within 3 months; any anxiolytic, sedative-hypnotic drug (except chloral hydrate or zaleplon), sumatriptan (and similar agents), or any other psychotropic drug or substance within 7 days; or any nonpsychopharmacologic drug with psychotropic effects within 7 days of randomization, unless a stable dose of the drug had been maintained for \( \geq 1 \) month. |
| OTHER MEDICATIONS/INTERVENTIONS: | See above |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Venlafaxine 39.6 (40.4)  
Fluoxetine 40.0 (40.9)  
Gender (female %): Venlafaxine 65 (61)  
Fluoxetine 67 (61)  
Ethnicity: NR  
Other population characteristics: HAMD Venlafaxine 22.6 (22.4)  
Fluoxetine 23.0 (22.7) |
<table>
<thead>
<tr>
<th>Authors: Keller et al.</th>
<th>Year: 2007</th>
<th>Country: USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td><strong>Primary Outcome Measures:</strong> HAMD (HAMD)</td>
<td><strong>Secondary Outcome Measures:</strong> CGI-I, CSI-S, Q-LES-Q, HAMA, SF-36</td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong> baseline weeks 1,2,3,4,6,8,10 (days 100,130,160,190,220 and 250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>Venlafaxine vs. fluoxetine 10 weeks (36 weeks)</td>
<td><strong>Timing of assessments:</strong> baseline weeks 1,2,3,4,6,8,10 (days 100,130,160,190,220 and 250)</td>
</tr>
<tr>
<td></td>
<td>HAMD Total, LS Mean (SE) 9.2 (.3) vs. 8.9 (.4)</td>
<td>(6.2 (.2) vs. 6.0 (.4))</td>
</tr>
<tr>
<td></td>
<td>Response, 612 (79%) vs. 210 (79%)</td>
<td>((449 (90%) vs. 163 (92%))</td>
</tr>
<tr>
<td></td>
<td>Remission, 380 (49%) vs. 132 (50%)</td>
<td>((358 (72%) vs. 123 (69%))</td>
</tr>
<tr>
<td></td>
<td>CGI-S, LS Mean (SE) 2.3 (.05) vs. 2.3 (.07)</td>
<td>(1.7 (.05) vs. 1.7 (.07))</td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>ITT:</strong> 1047 (676)</td>
<td><strong>Post randomization exclusions:</strong> Cannot determine</td>
</tr>
<tr>
<td><strong>Loss to follow-up differential high:</strong> No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Overall</strong></td>
<td><strong>Loss to follow-up:</strong> 27% (34%)</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events:</strong></td>
<td>NR</td>
<td><strong>NR</strong></td>
</tr>
<tr>
<td><strong>Withdrawals due to lack of efficacy:</strong></td>
<td>NR</td>
<td><strong>NR</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>Venlafaxine vs. fluoxetine 10 weeks %</td>
<td>36 weeks %</td>
</tr>
<tr>
<td></td>
<td>Headache 28 vs. 29</td>
<td>34 vs. 32</td>
</tr>
<tr>
<td></td>
<td>Insomnia 22 vs. 20</td>
<td>25 vs. 22</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth 25 vs. 16</td>
<td>25 vs. 17</td>
</tr>
<tr>
<td></td>
<td>Nausea 20 vs. 19</td>
<td>22 vs. 20</td>
</tr>
<tr>
<td></td>
<td>Somnolence 16 vs. 17</td>
<td>18 vs. 19</td>
</tr>
<tr>
<td></td>
<td>Dizziness 12 vs. 13</td>
<td>17 vs. 16</td>
</tr>
<tr>
<td></td>
<td>Sweating 13 vs. 12</td>
<td>17 vs. 15</td>
</tr>
<tr>
<td></td>
<td>Constipation 14 vs. 7</td>
<td>16 vs. 7</td>
</tr>
<tr>
<td></td>
<td>Upper Respiratory Infection 9 vs. 7</td>
<td>14 vs. 14</td>
</tr>
<tr>
<td></td>
<td>Asthenia 11 vs. 9</td>
<td>14 vs. 12</td>
</tr>
<tr>
<td></td>
<td>Nervousness 10 vs. 10</td>
<td>11 vs. 11</td>
</tr>
<tr>
<td></td>
<td>Anorexia 10 vs. 5</td>
<td>11 vs. 5</td>
</tr>
<tr>
<td></td>
<td>Libido Decreased 8 vs. 6</td>
<td>10 vs. 10</td>
</tr>
<tr>
<td></td>
<td>Accidental Injury 3 vs. 4</td>
<td>7 vs. 11</td>
</tr>
<tr>
<td></td>
<td>Infection 4 vs. 7</td>
<td>7 vs. 11</td>
</tr>
<tr>
<td></td>
<td>Tremor 4 vs. 7</td>
<td>5 vs. 8</td>
</tr>
<tr>
<td></td>
<td>Tinnitus 3 vs. 7</td>
<td>4 vs. 7</td>
</tr>
<tr>
<td></td>
<td>Yawn 4 vs. 7</td>
<td>4 vs. 7</td>
</tr>
<tr>
<td></td>
<td>Gastroenteritis 2 vs. 1</td>
<td>4 vs. 1</td>
</tr>
<tr>
<td></td>
<td>Impotence 3 vs. 1</td>
<td>4 vs. 1</td>
</tr>
<tr>
<td></td>
<td>Weight Loss 2 vs. 4</td>
<td>2 vs. 4</td>
</tr>
</tbody>
</table>

Second generation antidepressants
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY:</td>
<td>Authors: Khan A et al.⁴⁷&lt;br&gt;Year: 2007&lt;br&gt;Country: USA</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>National Institutes of Health Center Grant P30 MH 68638 and Forest Research Institute Jersey City, NJ, USA.</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT&lt;br&gt;Setting: Multicenter&lt;br&gt;Sample size: 278</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Drug: Escitalopram&lt;br&gt;Dose: 10-20 mg&lt;br&gt;Duration: 8 weeks&lt;br&gt;Sample size: 137 safety&lt;br&gt;Duloxetine&lt;br&gt;Dose: 60 mg&lt;br&gt;Duration: 8 weeks&lt;br&gt;Sample size: 133 safety</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Male or female outpatients; 18-80 years; MDD for at least 12 weeks; MADRS &gt; 26 and CGI-S &gt; 4; normal or clinically insignificant labs, physical exams and ECG and negative pregnancy test</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Another Axis I disorder; alcohol or drug abuse, schizophrenia/other psychotic disorder, mania or hypomania, eating disorders, OCD, bipolar disorder; had a learning disability or other cognitive disorder; a serious risk of suicide; had a history of seizure disorder; pregnant or breastfeeding; clinically significant medical condition, or if they were receiving (or planning to initiate) formal psychotherapy; depot antipsychotic in 6 months; benzodiazepine within 4 weeks, or any anti-psychotic, antidepressant or anxiolytic medication within 2 weeks (5 weeks for fluoxetine); previous treatment with study meds; investigational drug w/in 1 month or ECT within 3 months</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Zolpidem or zaleplon for sleep</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes&lt;br&gt;Mean age: Escitalopram 41.8 Duloxetine 43.0&lt;br&gt;Gender (female %): Escitalopram 59.1 Duloxetine 63.9&lt;br&gt;Ethnicity (white %): Escitalopram 78.8 Duloxetine 81.2&lt;br&gt;Other population characteristics: MADRS Escitalopram 31.0 Duloxetine 31.6</td>
</tr>
</tbody>
</table>
### Authors: Khan A et al.
Year: 2007
Country: USA

#### OUTCOME ASSESSMENT:

| Primary Outcome Measures: | change from baseline in MADRS |
| Secondary Outcome Measures: | HAM-D24, CGI-S, CGI-I |
| Timing of assessments: | Baseline, weeks 1,2,4,6,8 and 9 |

#### RESULTS:
- Escitalopram vs. duloxetine change at week 8
- MADRS: -18.0(9.4) vs. -15.9(10.3) *p* < 0.05
- HAMD24: -14.5(8.8) vs. -12.7(9.5)
- HAMD17: -11.1(6.9) vs. -9.6(7.6) *p* < 0.05
- CGI-S: -2.0(1.2) vs. -1.7(1.4)
- MADRS responders: escitalopram 68% vs. duloxetine 50%, *p* < 0.05

#### ANALYSIS:
- ITT: yes
- Post randomization exclusions: 8+8

#### ATTRITION:

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
<th>Escitalopram</th>
<th>Duloxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 (13%)</td>
<td></td>
<td>41 (31%)</td>
</tr>
<tr>
<td>3 (2.2%)</td>
<td>1 (0.7%)</td>
<td>17 (12.8%)</td>
</tr>
<tr>
<td>1 (0.7%)</td>
<td>2 (1.5%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Withdrawals due to adverse events:</th>
<th>Escitalopram</th>
<th>Duloxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea 15 vs. 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia 9 vs. 20 (P &lt; 0.05)</td>
<td></td>
<td></td>
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<tr>
<td>Headache 12 vs. 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejaculation disorder 9 vs. 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence 12 vs. 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth 9 vs. 11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### ADVERSE EVENTS:
- Escitalopram vs. Duloxetine (%)
- Nausea 15 vs. 23
- Insomnia 9 vs. 20 (P < 0.05)
- Headache 12 vs. 15
- Ejaculation disorder 9 vs. 15
- Somnolence 12 vs. 8
- Dry mouth 9 vs. 11

#### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1 Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Kiev A, et. al. 43  
**Year:** 1997  
**Country:** US |
| **FUNDING:** | Solvay Pharma, Upjohn |
| **DESIGN:** | **Study design:** RCT  
**Setting:** Multi-center (2 centers)  
**Sample size:** 60 |
| **INTERVENTION:** |  
**Drug:**  
**Dose:**  
**Duration:**  
| Fluvoxamine | 50-150 mg/d | 7 weeks |
| Paroxetine | 20-50 mg/d | 7 weeks |
| **INCLUSION:** | Age 18-65; DMS-IIIR criteria for single or recurrent MDD; minimum score of 20 on HAM-D21 (incl min score of 2 on depressed mood item) |
| **EXCLUSION:** | Not fluent in written or oral English; history of medication non-compliance; demonstration of placebo response during run-in; history of substance abuse; severe suicide risk or auto-aggressive behavior; used a drug within 30 days with anticipated major organ toxicity; pregnancy or lactation; hypersensitivity to SSRIs; participation in previous fluvoxamine studies; other significant organic disease; clinically significant lab abnormalities; other primary psychiatric diagnoses; transportation difficulties |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
**Mean age:** fluvoxamine: 42.7; paroxetine: 39.9  
**Gender** (% female): fluvoxamine: 53%; paroxetine: 53%  
**Ethnicity:** fluvoxamine: white 87%, non-white 13%; paroxetine: white: 93%, non-white: 7%  
**Other population characteristics:** (mean weight) fluvoxamine: 180.1 lbs; paroxetine: 175.8 lbs (mean height) fluvoxamine: 67.2 in; paroxetine: 65.8 in |
**Authors:** Kiev A, et. al.  
**Year:** 1997  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: HAM-D-21  
Timing of assessments: Baseline and weeks 1,2,3,5,7 |
<table>
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<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>RESULTS:</td>
<td>There was a mean change in HAM-D score for fluvoxamine: -13.45 and for paroxetine: -12.86, p = 0.763</td>
</tr>
</tbody>
</table>
| ANALYSIS:           | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION:          | Loss to follow-up: 31%; fluvoxamine: 34.5%; paroxetine: 27.6%  
Withdrawals due to adverse events: fluvoxamine: 6.8%; paroxetine: 13.8%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS:     | Significant differences in sweating was reported: fluvoxamine 10% and paroxetine 33% (p = 0.028)  
Treatment-emergent adverse events were reported by 97% of fluvoxamine patients and 100% of paroxetine patients  
One trend that was reported although not statistically significant: fluvoxamine patients reported more sleep-related side effects and paroxetine patients reported more GI side effects |
| QUALITY RATING:     | Fair |
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Kroenke K, et al.  
Year: 2001  
Country:  
Trial name: ARTIST (A randomized trial investigating SSRI treatment) |
| FUNDING: | Eli Lilly |
| DESIGN: | Study design: RCT (open label)  
Setting: Multi-center (76 primary care physicians)  
Sample size: 601 |
| INTERVENTION: | Drug:  
Dose:  
Duration: |
| | Paroxetine  
20 mg/day  
9 months |
| | Fluoxetine  
20 mg/day  
9 months |
| | Sertraline  
50 mg/day  
9 months |
| Mean dose at 9 months:  
Paroxetine: 23.5mg  
Fluoxetine: 23.4mg  
Sertraline: 72.8mg |
| INCLUSION: | 18 years or older; depressive disorder as determined by the primary care physician (PCP); had home telephone |
| EXCLUSION: | Cognitive impairment; lack of reading/writing skills; terminal illness; nursing home resident; actively suicidal; SSRI within past 2 months; other antidepressant therapy; bipolar disorder; pregnancy; lactation |
| OTHER MEDICATIONS/ INTERVENTIONS: | Yes |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: paroxetine: 47.2, fluoxetine: 47.1, sertraline: 44.1  
Gender (% female): paroxetine: 76; fluoxetine: 86; sertraline: 75  
Ethnicity: (white) paroxetine: 85%; fluoxetine: 88%; sertraline: 79%; (black) paroxetine: 13%; fluoxetine: 9%; sertraline: 17% (other) paroxetine: 2%; fluoxetine: 3%; sertraline: 4%  
Other population characteristics: (MDD) total: 74%, paroxetine: 71%, fluoxetine: 74%; sertraline: 73%; (dysthymia) total: 18%, paroxetine: 22%, fluoxetine: 17%, sertraline: 18%; (minor depression) total: 8%, paroxetine: 7%, fluoxetine: 9%, sertraline: 9% |
<table>
<thead>
<tr>
<th>Authors: Kroenke K, et al.</th>
<th>Year: 2001</th>
</tr>
</thead>
</table>

### OUTCOME ASSESSMENT:

**Measures:** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS): patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire  

**Timing of assessments:** Months 1, 3, 6, 9

### RESULTS:

- All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function)
- There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures
- Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years
- Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17%

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 24.3% (numbers provided are conflicting); paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7%  
**Withdrawals due to adverse events:** paroxetine: 30%, fluoxetine: 23%, sertraline: 24%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

No significant differences in adverse events between treatment groups

### QUALITY RATING:

Fair
### Evidence Table 1

#### Major Depressive Disorder

| **STUDY:** | **Authors:** Lader M, et al.<sup>30</sup>  
|            | **Year:** 2005  
|            | **Country:** UK and Denmark (meta-analysis) US and Europe (included trials) |
| **FUNDING:** | H. Lundbeck A/S; Forest Laboratories Inc |
| **DESIGN:** | **Study design:** Meta-analysis  
|            | **Number of patients:** 1,321 |
| **AIMS OF REVIEW:** | To investigate the effect of escitalopram on sleep seen in clinical trials in the treatment of patients with depression based on single item scores of the Montgomery Asberg depression rating scale (MADRS) and reported treatment-emergent adverse effects, such as sedation and insomnia |
| **STUDIES INCLUDED IN META-ANALYSIS** | US: Burke et al., 2002; Rapaport et al., 2004  
|            | Europe: Lepola et al., 2003 |
| **TIME PERIOD COVERED:** | NR |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blind; RCT; placebo-controlled; 8 week studies; 1 week single-blind placebo run-in; primary efficacy measure MADRS |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | DSM-IV criteria for MDD; minimum MADRS score of 22 for inclusion; patients aged 18-65 (2 studies) or 18-80 (Rapaport) |
### Authors: Lader M, et al.
Year: 2005
Country: UK and Denmark

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Patients randomized to escitalopram, citalopram, or placebo; no concomitant psychotropic medication allowed except zolpidem or benzodiazepines for insomnia</th>
</tr>
</thead>
</table>

| MAIN RESULTS:                  | • Mean change from baseline in total MADRS score was -11.2 for placebo, -13.1 citalopram, and -13.8 for escitalopram; not a significant difference between the active drug groups in the LOCF analysis  
• Escitalopram patients with sleep problems shows statistically greater improvement ($p < 0.05$) in item 4 of the MADRS (sleep disturbance) than citalopram patients at weeks 1,4,6, 8, and endpoint (LOCF analysis) |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------|

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>8.6%</td>
<td>9.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.7%</td>
<td>6.9%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | NR |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Fair |
### Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Lee P et al.\(^1\)  
| Year: 2007  
| Country: China, Korea, Taiwan and Brazil |
| FUNDING: | Eli Lilly |
| DESIGN: | Study design: RCT  
| Setting: Multicenter  
| Sample size: 478 |
| INTERVENTION: |  
| Drug: | Duloxetine  
| Dose: 60 mg  
| Duration: 8 weeks  
| Sample size: 238 |
| Paroxetine  
| Dose: 20 mg  
| Duration: 8 weeks  
| Sample size: 240 |
| INCLUSION: | Men and non-pregnant women must have been at least 18 years of age and met the DSM-IV diagnostic criteria for non-psychotic major depression (single episode or recurrent). Baseline severity of symptoms also had to be at least moderate as determined by scores of ≥15 on the HAMD17 and ≥4 on the Clinical Global Impressions–Severity (CGI-S) scale |
| EXCLUSION: | Current DSM-IV diagnosis other than MDD, previous psychotic disorder diagnosis, dysthyemic disorder within the past 2 years, anxiety disorder as a primary diagnosis within the past year, axis II disorder that would interfere with protocol compliance, history of substance abuse, lack of response of the current episode to two or more adequate courses of antidepressant therapy, history of a lack of response to an adequate trial of paroxetine; serious suicidal risk, serious medical illness, history of hepatic dysfunction, current jaundice, or positive hepatitis B surface antigen (Dane particle; HBsAg) or positive hepatitis C, alanine aminotransaminase level > 2-fold the upper limit of normal, ECT within the past year, psychotherapy, started light therapy or phototherapy within 6 weeks, taking any excluded medications or abnormal thyroid-stimulating hormone concentrations. |
| OTHER MEDICATIONS/INTERVENTIONS: | Anti-hypertensive and other cardiovascular medications were permitted only if the patient had been on a stable dose for at least 3 months prior to the study and remained on the medication for the duration |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: Duloxetine 39.0  Paroxetine 38.0  
| Gender (female %): Duloxetine 65.5  Paroxetine 73.8  
| Ethnicity: East Asian Duloxetine 90.8%  Paroxetine 91.3%  Caucasian Duloxetine 7.1%  Paroxetine 4.6%  Hispanic Duloxetine 0.8  Paroxetine 2.1  West Asian Duloxetine 0.4  Paroxetine 2.1  African Duloxetine 0.8  Paroxetine 1.7  
| Other population characteristics: HAMD Duloxetine 21.1  Paroxetine 21.2 |
## Authors: Lee P et al.  
**Year:** 2007  
**Country:** China, Korea, Taiwan and Brazil

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** change in HAMD17 over 8 weeks  
- **Secondary Outcome Measures:** CSI-S, HAMA  
- **Timing of assessments:** Screening, baseline weeks 1, 2, 4, 6, 8

### RESULTS:
- HAMD17 Duloxetine 11.73 (0.296) vs. Paroxetine 11.94 (0.283)  
- Change in HAMD duloxetine: -14.19 vs. Paroxetine -13.52, *P* = 0.218  
- HAMA Duloxetine 11.17 (0.294) vs. Paroxetine 11.25 (0.280)  
- CGI-S Duloxetine 2.89 (0.51) vs. Paroxetine 2.95 (0.49)  
- Response Duloxetine 60.5% vs. Paroxetine 64.5%  
- Remission Duloxetine 49.2% vs. Paroxetine 50.4%

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** No  
- **Loss to follow-up differential high:** No

### ATTRITION:  
- Loss to follow-up:  
  - Duloxetine: 72 (30.3%)  
  - Paroxetine: 57 (23.8%)  
- Withdrawals due to adverse events:  
  - Duloxetine: 8.4%  
  - Paroxetine: 7.1%  
- Withdrawals due to lack of efficacy:  
  - Duloxetine: <1%  
  - Paroxetine: <1%

### ADVERSE EVENTS:  
- Duloxetine vs. Paroxetine n (%)  
  - Nausea: 88 (37.1) vs. 59 (24.7) *P* = 0.004  
  - Dizziness: 50 (21.1) vs. 44 (18.4)  
  - Dry mouth: 41 (17.3) vs. 29 (12.1)  
  - Constipation: 35 (14.8) vs. 27 (11.3)  
  - Headache: 27 (11.4) vs. 29 (12.1)  
  - Somnolence: 27 (11.4) vs. 27 (11.3)  
  - Palpitations: 22 (9.3) vs. 10 (4.2) *P* = 0.029  
  - Anorexia: 21 (8.9) vs. 17 (7.1)  
  - Vomiting: 19 (8.0) vs. 14 (5.9)  
  - Decreased appetite: 18 (7.6) vs. 19 (7.9)  
  - Vision blurred: 16 (6.8) vs. 16 (6.7)  
  - Asthenia: 13 (5.5) vs. 9 (3.8)  
  - Fatigue: 12 (5.1) vs. 14 (5.9)  
  - Hyperhidrosis: 12 (5.1) vs. 11 (4.6)

### QUALITY RATING:  
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Lepola, et al. (^{52})</td>
</tr>
<tr>
<td></td>
<td>Year: 2003</td>
</tr>
<tr>
<td></td>
<td>Country: Europe, Canada</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>H. Lundbeck A/S</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center (primary care)</td>
</tr>
<tr>
<td></td>
<td>Sample size: 471</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>Citalopram</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>20-40 mg/d</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
</tr>
<tr>
<td></td>
<td>10-20 mg/d</td>
</tr>
<tr>
<td></td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Age 18 to 65 years; met DSM-IV criteria for MDD; MADRS score of ≥ 22 at baseline</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Negative pregnancy test and stable use of oral contraceptive for 3 months; current or past history of mania; hypomania; alcoholism; substance abuse; dementia; epilepsy; presence of psychotic depression or organic affective illness; history of suicide attempts or high risk; current use of psychotropic meds; behavior therapy; psychotherapy</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTEVENTIONS:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 43</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): citalopram: 69.4%, escitalopram 74.8%, placebo 72.1%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
</tbody>
</table>
**Authors:** Lepola et al.  
**Year:** 2003  
**Country:** Europe, Canada

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: MADRS, CGI-S, CGI-I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of assessments:</strong></td>
<td>(Primary measures) baseline, weeks 1, 2, 3, 4, 6, 8</td>
</tr>
</tbody>
</table>

| RESULTS: |  
|-----------|------------------------------------------------|
| • Significantly more escitalopram patients responded to treatment at study endpoint on the MADRS scale than citalopram patients (63.7% vs. 52.6%; p =0.009)  
• Significantly more escitalopram than citalopram-treated patients were in remission at endpoint (52.1% vs. 42.8%; p < 0.036)  
• Escitalopram was numerically better than citalopram at all time points on all 3 efficacy scales  
• Analysis of time to response showed that escitalopram–treated patients were responders 8.1 days faster than citalopram-treated patients |

| ANALYSIS: |  
|-----------|---------------------------------|
| **ITT:** | Yes |
| **Post randomization exclusions:** | Yes |

| ATTRITION: |  
|-----------|---------------------------------|
| **Loss to follow-up:** | 7%; citalopram 5%, escitalopram 6%, placebo 10% |
| **Withdrawals due to adverse events:** | citalopram 3.8%, escitalopram 2.6%, placebo 2.6% |
| **Loss to follow-up differential high:** | No |

| ADVERSE EVENTS: |  
|----------------|------------------------------------------------|
| • No significant differences between study groups  
• Nausea the most common adverse event: citalopram 14.4%, escitalopram 17.4% |

| QUALITY RATING: | Fair |
# Evidence Table 1

| **STUDY:** | **Authors:** Lepola UA, et al.  
**Year:** 2004  
**Country:** Multi-national (Canada, Europe, US) |
| **FUNDING:** | Not reported |
| **DESIGN:** | Study design: Pooled analysis  
**Number of patients:** 977 |
<p>| <strong>AIMS OF REVIEW:</strong> | Compare efficacy of escitalopram (10-20 mg/d) versus citalopram (20-40 mg/d) by pooling the data from two published clinical trials |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | Burke et al. (2002) and Lepola et al. (2003) |
| <strong>TIME PERIOD COVERED:</strong> | 8 weeks |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | RCTs of escitalopram versus citalopram |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Outpatients male or female 18-65 years old who met DSM-IV criteria for major depressive episode; MADRS score of 22 or higher; Burke study et al., 2002 HAMD-17 score of 2 on item 1 was an additional requirement in the fixed dose study |</p>
<table>
<thead>
<tr>
<th>Authors: Lepola UA, et al.</th>
<th>Year: 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></td>
<td>Escitalopram 10-20 mg/d for 8 weeks; citalopram 20-40 mg/d for 8 weeks</td>
</tr>
</tbody>
</table>
| **MAIN RESULTS:** | • Statistically significantly greater proportion of patients responded to escitalopram than to citalopram (56.8% vs. 48.9%; p = 0.033)  
• Remission rates favored escitalopram but did not reach statistical significance (46.4% vs. 40.8%; p = 0.123).  
• Escitalopram-treated patients had a significant reduction in HAMD-17 total score compared to citalopram-treated patients (estimated difference 1.62; p = 0.034, LOCF) |
<p>| <strong>ADVERSE EVENTS:</strong> | Headache (placebo 20%, escitalopram 16%, citalopram 19%); nausea (placebo 8%, escitalopram 16% (p &lt; 0.05 vs placebo); citalopram 18% (p &lt; 0.05 vs placebo) were reported by ≥10% of the patients in any treatment group in the pooled analysis |
| <strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong> | Analysis includes the only 2 published studies. Authors state that data of a third, unpublished trial were not included |
| <strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong> | No |
| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | **Authors:** McPartlin GM, et. al.⁵⁴  
 | **Year:** 1998  |
| **Country:** UK  |  |
| **FUNDING:**     | Wyeth-Ayerst            |
| **DESIGN:**      | **Study design:** RCT  
 | **Setting:** Multi-center (43 general practice sites)  
 | **Sample size:** 361  |
| **INTERVENTION:** | **Drug:** Venlafaxine XR  
 | **Dose:** 75 mg/day  
 | **Duration:** 12 weeks  
 | **Drug:** Paroxetine  
 | **Dose:** 20 mg/day  
 | **Duration:** 12 weeks  |
| Fixed dose trial |  |
| **INCLUSION:**   | **At least 18 yrs; DSM-IV criteria for major depression; ≥ 19 on MADRS; symptoms for at least 14 days**  |
| **EXCLUSION:**   | Pregnancy, lactation, or lack of adequate contraception; history of seizures; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; use of investigational drug or antipsychotic drug within 30 days; clinically relevant medical disease or abnormalities in ECG or laboratory parameters; sumatriptan; MAOI; anxiolytic or sedative hypnotic within 30 days  |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Temazepam, zopiclone  |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
 | **Mean age:** venlafaxine xr: 45, paroxetine: 44  
 | **Gender (% female):** venlafaxine xr: 68.3%, paroxetine: 68.5%  
 | **Ethnicity:** Not reported  
 | **Other population characteristics:** CGI severity:  
 | - Moderately ill-venlafaxine xr: 68%, paroxetine: 66%  
 | - Markedly ill-venlafaxine xr: 25%, paroxetine: 24%  
 | - Severely ill-venlafaxine xr: 3%, paroxetine: 3%  |
### Authors: McPartlin GM, et al.
**Year:** 1998  
**Country:** UK

#### OUTCOME ASSESSMENT:
- **Measure and timing of assessments:** MADRS, HAM-D-17, CGI at days 7, 14, 21, 28, 42, 56, 84, quality of life questionnaire at day 84

#### RESULTS:
- Mean MADRS and HAM-D scores decreased significantly in both treatment groups (p < 0.05)
- There were no significant differences in outcome measures between treatment groups
- Global response (HAM-D, CGI, MADRS rates were at 76% for both treatment groups
- Remission rates (≤ 6 on MADRS) were 48% for venlafaxine XR and 46% for paroxetine
- Both treatment groups produced significant improvements on the quality of life scale without showing differences between groups

#### ANALYSIS:
- **ITT:** Yes  
  **Post randomization exclusions:** Yes

#### ATTRITION:
- **Loss to follow-up:** 27.4%; venlafaxine XR: 26%, paroxetine: 29%
- **Withdrawals due to adverse events:** Overall: 14.1%; venlafaxine XR: 12%, paroxetine: 16%
- **Loss to follow-up differential high:** No

#### ADVERSE EVENTS:
- There were no significant differences in the frequency of adverse events between the treatment groups
- 70% of patients in each group experienced at least 1 adverse event
- Most common adverse events: nausea: venlafaxine XR: 25.4%, paroxetine: 24.9%; headache: venlafaxine XR: 8.8%, paroxetine: 11.9%; dizziness: venlafaxine XR: 16.6%, paroxetine: 9.6%
- 3 patients in the paroxetine group experienced clinically significant increases in blood pressure vs. 1 patient in the venlafaxine group
- No significant changes in weight or ECG findings were observed

#### QUALITY RATING:
- **Fair**
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | **Authors**: Mehtonen OP, et al.  
**Year**: 2000  
**Country**: Scandinavia |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst International</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design**: RCT  
**Setting**: Multi-center  
**Sample size**: 147 |
| INTERVENTION: | **Drug**:  
**Dose**:  
**Duration**:  
Venlafaxine  
75-150 mg/d  
8 weeks  
Sertraline  
50-100 mg/d  
8 weeks |
| INCLUSION: | 18-65 years; ≥ 18 on HAM-D-21 |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; known sensitivity to venlafaxine or sertraline; history of seizures; dementia; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease (cardiac, hepatic, renal); investigational drugs within 30 days |
| OTHER MEDICATIONS/INTERVENTIONS: | Oxazepam, temazepam |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline**: Yes  
**Mean age**: venlafaxine: 44.1, sertraline: 41.0  
**Gender (% female)**: venlafaxine: 65%, sertraline: 67%  
**Ethnicity**: Not reported  
**Other population characteristics**: Majority moderately or markedly ill on CGI scale |
**Authors:** Mehtonen OP, et al.<br>**Year:** 2000<br>**Country:** Scandinavia

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: HAM-D, CGI, MADRS&lt;br&gt;Timing of assessments: Baseline, days 7, 14, 28, 42, 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response: 50% reduction in HAMD or MADRS and a CGI response&lt;br&gt;Remission: HAMD score &lt; 10</td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS:**
- Both treatment groups showed significant reductions of MADRS, CGI, and HAM-D scores from baseline to week 8
- No significant differences between groups were observed at any point in time
- Response rates (decrease ≥ 50% on HAM-D) were higher for venlafaxine at week 6 (74% vs. 59%; p = 0.04) and at the endpoint (83% vs. 68%; p = 0.05)
- Remission rates (HAMD ≤ 10) at endpoint were higher for the venlafaxine treated group (68% vs. 45%; p = 0.008)
- No significant differences were noted in response rates on MADRS and CGI scales
- Remission rates for patients who increased their dose was higher for the venlafaxine group (67% vs. 36%; p < 0.05)

**ANALYSIS:**
- **ITT:** Yes<br>- **Post randomization exclusions:** Not reported

**ATTRITION:**
- **Loss to follow-up:** 19%; venlafaxine: 21%, sertraline: 17%
- **Withdrawals due to adverse events:** 11.5%; venlafaxine: 16%, sertraline: 7%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- No significant differences were observed between treatment groups for adverse events
- Most common adverse events: nausea: venlafaxine: 36.0%, sertraline: 29.2%; headache: venlafaxine: 28.0%, sertraline: 29.2%; diarrhea: venlafaxine: 8.0%, sertraline: 13.9%; sexual dysfunction: venlafaxine: 8.0%, sertraline: 5.6%
- No clinically relevant changes in pulse, blood pressure or weight in either group

**QUALITY RATING:** Good
<table>
<thead>
<tr>
<th><strong>Evidence Table 1</strong> Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:** Authors: Montgomery SA, et al.  
Year: 2004  
Country: Multinational (8 European countries) |
| **FUNDING:** H. Lundbeck A/S |
| **DESIGN:** Study design: RCT  
Setting: Multicenter (44 sites)  
Sample size: 293 |
| **INTERVENTION:**  
**Drug:**  
**Dose:** Escitalopram  
10-20 mg/d  
8 weeks  
148  
Venlafaxine XR  
75-150 mg/d  
8 weeks  
145 |
| **INCLUSION:** 18-85 years of age; DSM-IV diagnosis of MDD; score of at least 18 on the MADRS |
| **EXCLUSION:** History of mania or bipolar disorder; schizophrenia or any psychotic disorder; currently suffering from OCD, eating disorders, mental retardation, any pervasive development disorder, or cognitive disorder; alcohol or drug abuse; treatment with antipsychotics, antidepressants, psychotropics, serotonin receptor agonists, lithium, carbamazepine, valproate, valpromide, electroconvulsive treatment; pregnant or breastfeeding |
| **OTHER MEDICATIONS/INTERVENTIONS:** Medications thought to interfere with the study were excluded. |
| **POPULATION CHARACTERISTICS:** Groups similar at baseline: Yes  
Mean age: 48  
Gender (% female): 72%  
Ethnicity: Not reported  
Other population characteristics: MADRS score: 28.8; HAM-D-17 score: 20.1 |
| Outcome Assessment | Primary Outcome Measures: MADRS total score  
| Secondary Outcome Measures: HAM-D-17; response and remission rates  
| Timing of assessments: Baseline, weeks 1,2,3,4,6, and 8.  
| Results: | No statistically significant differences between escitalopram and venlafaxine XR in response (77.4% vs. 79.6%) and remission (69.9% vs. 69.7%)  
| In the LOCF analysis there was no difference between groups in total MADRS or HAM-D-17 scores  
| Survival analysis of the ITT group showed that escitalopram patients achieved sustained remission 6.6 days faster than the venlafaxine XR patients (p < 0.01)  
| Analysis: | ITT: Yes  
| Post randomization exclusions: Yes  
| Attrition: | Loss to follow-up: 13.7%; escitalopram: 14%; venlafaxine XR: 13%  
| Withdrawals due to adverse events: Escitalopram: 7.5%; venlafaxine XR: 11.2%  
| Loss to follow-up differential high: No  
| Adverse Events: | Nausea: venlafaxine XR: 26%; escitalopram: 17% (p < 0.05).  
| Increased sweating: venlafaxine XR: 12.5%; escitalopram: 6% (p < 0.05).  
| Constipation: venlafaxine XR: 6%; escitalopram: 2% (p < 0.05)  
| Quality Rating: | Fair  

Authors: Montgomery SA, et al.  
Year: 2004  
Country: Multinational
### Evidence Table 1  Major Depressive Disorder

| STUDY: | Authors: Moore N, et al.  
Year: 2005  
Country: NR |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Clinic and general practice  
Sample size: 280 |
| INTERVENTION: | | |
| Drug: | Escitalopram | Citalopram |
| Dose: | 20 mg  
8 weeks | 40 mg  
8 weeks |
| Sample size: | 138 | 142 |
| INCLUSION: | Outpatients, age 18-65 years; DSM IV MDD; MADRS of at least 30 |
| EXCLUSION: | Other primary diagnosis of Axis 1 disorders or a history of; substance abuse within 12 months; use of a depot antipsychotic within 6 months or any antipsychotic, anxiolytic or anticonvulsant within 2 weeks before start |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Escitalopram: 44.1; citalopram: 46.2  
Gender (% female): escitalopram: 81.7%, citalopram: 72%  
Ethnicity: NR  
Other population characteristics:  
Baseline MADRS: escitalopram: 16.6, citalopram: 15.7  
Baseline CGI-S: escitalopram: 5.1, citalopram: 5.1 |
Authors: Moore N, et al.  
Year: 2005  
Country: NR

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th><strong>Primary Outcome Measures:</strong> MADRS; CGI-S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Secondary Outcome Measures:</strong> MADRS-S</td>
</tr>
<tr>
<td></td>
<td><strong>Timing of assessments:</strong> Baseline, weeks 1, 4 and 8</td>
</tr>
</tbody>
</table>

**RESULTS:**
- MADRS adjusted for baseline MADRS and investigator specialty: Esc -22.4, Cit -20.3 (p < 0.05), between groups mean difference 2.1 (95% CI 0.01-4.21; p < 0.05)
- 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 significantly higher in the Cit (10.6%) than in the Esc (4.3%) group (p = 0.005)

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** Yes, 14 (11 protocol violations and 3 GCP violations)

**ATTRITION:**
- **Loss to follow-up:**
  - Escitalopram: 6 (4.3%)
  - Citalopram: 15 (10.6%)
- **Withdrawals due to adverse events:**
  - Escitalopram: 4 (2.9%)
  - Citalopram: 9 (6.3%)
- **Withdrawals due to lack of efficacy:**
  - Escitalopram: 1 (0.7%)
  - Citalopram: 4 (2.8%)

**ADVERSE EVENTS:**
- 46 patients had adverse events: escitalopram: 21 (14.8%), citalopram: 25 (16.4%) (p = 0.70)
- No significant difference was reported between treatment groups

**QUALITY RATING:** Fair
## Evidence Table 1  
### Major Depressive Disorder Adults

| STUDY: | Authors: Nemeroff CB, et al.  
Year: 1995  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Solvay Pharmaceuticals</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 95 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:** |
| Fluvoxamine | Sertraline |  
50-150 mg/day | 50-200 mg/day |  
Mean dose: 123.75 mg | Mean dose: 137.10 mg |  
7 weeks | 7 weeks |
| INCLUSION: |  
18-65 years; DSM-III-R criteria for major depression; HAM-D ≥ 20; minimum score of 2 on depressed mood item of HAMD; ≥ 8 Raskin Depression Scale; Covi anxiety score less than Raskin score; depressive symptoms for more than 2 weeks |
| EXCLUSION: |  
Use of study drugs within 1 month; history of psychosis; lack of English fluency; response during washout; suicidal; psychoactive drugs, electroconvulsive therapy within 2 weeks; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities; history of noncompliance; drug use within 30 days that could have toxic effects on organs; patients intolerant to SSRI side effects |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate for sleep, meds to treat GI disturbances and headache |
| POPULATION CHARACTERISTICS: |  
*Groups similar at baseline:* No. Fluvoxamine group had a significantly higher rate of severe depression at baseline; sertraline group had significantly more non-caucasians.  
*Mean age:* fluvoxamine: 38.5, sertraline: 41.2  
*Gender (female%):* fluvoxamine: 61.2%, sertraline: 60.9%  
*Ethnicity:* non-caucasian: fluvoxamine: 2.0%; sertraline: 15.2%  
*Other population characteristics:* Recurrent episode: fluvoxamine: 61.0%, sertraline: 56.5%, more melancholic patients in fluvoxamine group (77.6% vs. 58.7%) |
**Authors:** Nemeroff CB, et al.  
**Year:** 1995  
**Country:** US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures and timing of assessments: HAM-D (primary), HAM-A, Covi scale, Raskin scale, CGI-I, CGI-S, Hopkins symptom checklist: baseline, weeks 1, 2, 3, 5, 7, MSSI and clinical laboratory evaluation at week 7 only</th>
</tr>
</thead>
</table>
| RESULTS:            | • Both treatment groups resulted in significant improvements of depression scores compared to baseline  
                      • Mean decrease in HAMD: sertraline: -10.98, fluvoxamine: -10.61  
                      • There was no significant difference in efficacy between the treatment groups |
| ANALYSIS:           | **ITT:** Yes  
                      **Post randomization exclusions:** Yes |
| ATTRITION:          | **Loss to follow-up:** 30.9%; fluvoxamine: 42.9%, sertraline: 18.5%  
                      **Withdrawals due to adverse events:** fluvoxamine: 18.4%, sertraline: 2.2% (p-value not reported)  
                      **Loss to follow-up differential high:** Yes |
| ADVERSE EVENTS:     | • Significantly more patients withdrew due to adverse events in the fluvoxamine group (n = 9) than in the sertraline group (n = 1) (p = 0.016)  
                      • Significantly greater sexual dysfunction was reported in the sertraline group (28%) than in the fluvoxamine group (10%); p = 0.047  
                      • Most common adverse events: sertraline: insomnia (34.8%), headache (32.6%), diarrhea (23.9%), ejaculatory abnormality (22.2%); fluvoxamine: nausea (30.6%), headache (26.5%), insomnia (26.5%), somnolence (24.5%) |
| QUALITY RATING:     | Fair |
### Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Nemeroff et al.\(^{39}\)  
| Year: 2007  
| Country: USA |
| FUNDING: | Wyeth Research, Collegeville, PA |
| DESIGN: | Study design: RCT  
| Setting: Multicenter (13 university and private research clinics)  
| Sample size: 308 |
| INTERVENTION: | **Drug:**  
| **Dose:**  
| **Duration:**  
| **Sample size:**  |
| Venlafaxine | 75-225 mg/day | 6 weeks | 102 |
| Fluoxetine | 20-60 mg/day | 6 weeks | 104 |
| Placebo | N/A | 6 weeks | 102 |
| INCLUSION: | 18 years or older; met DSM-IV criteria for MDD; had symptoms present for at least 1 month before study entry and HAM-D-21 score > 20; ≤ 20% decrease in HAM-D-21 during run-in period |
| EXCLUSION: | History or presence of bipolar disorder or any psychotic disorder; history of alcohol or substance abuse within the past year; any clinically significant medical disorders or abnormalities detected during the presudy physical screening that might compromise study participation; were acutely suicidal to the degree that precautions against suicide were needed; history of nonresponse to venlafaxine or fluoxetine; had received any of the following treatments: electroconvulsive therapy within 3 months; any investigational drug or antipsychotic drug within 30 days; astemizole, cisapride, sumatriptan, terfenadine, any monoamine oxidase inhibitor, paroxetine, or sertraline within 14 days; any other antidepressant, anxiolytic, sedative-hypnotic drug (except chloral hydrate), or any other psychotropic drug within 7 days of the start of double-blind treatment; or any other drug with psychotropic effects within 7 days of the start of the double-blind treatment period unless a stable dose of the drug had been maintained for at least 1 month (3 months for thyroid or hormonal medications) before study day 1; pregnant or lactating |
| OTHER MEDICATIONS/INTerventions: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| **Mean age:** venlafaxine: 40.1, fluoxetine: 37.9, placebo: 40.4  
| **Gender (female %):** venlafaxine: 65%, fluoxetine: 69%, placebo: 56%  
| **Ethnicity (% white):** venlafaxine: 91%, fluoxetine: 93%, placebo: 92%  
| Other population characteristics: |
### Authors: Nemeroff
Year: 2007  
Country: USA

#### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>HAM-D-21, MADRS, CGI-S, CGI-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>Response (HAMD-21, MADRS, CGI-I, PGI), remission (HAM-D-21)</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Weeks 1, 2, 3, 4, and 6</td>
</tr>
</tbody>
</table>

#### RESULTS:

- Overall differences among treatment groups on HAM-D at week 6 did not reach statistical significance ($p = 0.051$); difference between venlafaxine and placebo groups was statistically significant ($p=0.016$); differences between fluoxetine and placebo ($p=0.358$) and between venlafaxine and fluoxetine ($p=0.130$) not statistically significant.
- Difference on HAM-D depressed mood item was statistically significant among treatment groups at week 6 ($p<0.001$); venlafaxine ($p<0.001$) and fluoxetine ($p=0.024$) significantly more effective than placebo; difference between venlafaxine and fluoxetine not statistically significant ($p=0.117$).
- HAM-D response (venlafaxine vs. fluoxetine vs. placebo): 53% (51/96) vs. 45% (45/100) vs. 37% (37/101); $p=0.067$.
- MADRS response: 52% (50/96) vs. 44 (44/100) vs. 34% (34/101); $p=0.032$.
- CGI response: 61% (59/96) vs. 53% (54/101) vs. 38% (38/101); $p=0.003$.
- Remission <8: 32% (31/96) vs. 32% (32/101) vs. 22% (22/101); $p=0.181$.
- Remission based on HAM-D17 <7: 32% (31/96) vs. 28 (28/101) vs. 22% (22/101); $p=0.250$.
- Statistically significant difference observed on only 1 of the 5 QoL measures (general life functioning) where there was a greater improvement in venlafaxine group compared with fluoxetine and placebo groups ($p=0.033$ for venlafaxine vs. fluoxetine).

#### ANALYSIS:

- ITT: Yes
- Post randomization exclusions: Yes (11)
- Loss to follow-up differential: No

#### ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine</th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>12%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

#### ADVERSE EVENTS:

- % of patients reporting TEAEs (venlafaxine vs. fluoxetine vs. placebo)
  - Nausea: 40% vs. 22% vs. 8%; $p<0.001$ (venlafaxine vs. fluoxetine, $p=0.005$)
  - Headache: 36% vs. 24% vs. 33%; $p=0.129$
  - Dry mouth: 24% vs. 16% vs. 15%; $p=0.170$
  - Insomnia: 22% vs. 15% vs. 14%; $p=0.229$
  - Dyspepsia: 9% vs. 19% vs. 16%; $p=0.138$
  - Sweating: 14% vs. 4% vs. 2%; $p<0.001$ (venlafaxine vs. fluoxetine, $p=0.012$)
  - Diarrhea: 9% vs. 13% vs. 9%; $p=0.580$
  - Dizziness: 13% vs. 8% vs. 3%; $p=0.030$
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting:</td>
<td>11% vs. 5% vs. 2%; p=0.021</td>
</tr>
<tr>
<td>Fatigue:</td>
<td>10% vs. 10% vs. 5%; p=0.325</td>
</tr>
<tr>
<td>Anxiety:</td>
<td>10% vs. 7% vs. 1%; p=0.022</td>
</tr>
<tr>
<td>Constipation:</td>
<td>10% vs. 2% vs. 5%; p=0.042 (venlafaxine vs. fluoxetine, p=0.016)</td>
</tr>
</tbody>
</table>
| Statistical difference observed for supine pulse, supine diastolic blood pressure, and weight | Rate of discontinuation due to AEs significantly different among treatment groups (p=0.049)

**QUALITY RATING:** Fair
**Evidence Table 1  Major Depressive Disorder Adults**

| STUDY: | Authors: Newhouse PA, et al. 
Year: 2000 
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer, Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT 
Setting: Multi-center 
Sample size: 236 |
| INTERVENTION: | Drug: Sertraline 
Dose: 50-100 mg/d 
Duration: 12 weeks |
| | Drug: Fluoxetine 
Dose: 20-40 mg/d 
Duration: 12 weeks |
| INCLUSION: | > 60 years of age; DSM-III-R criteria for major depression; > 18 on 24 item HAM-D |
| EXCLUSION: | Other psychiatric disorder; significant physical illness; non-responders to antidepressants or ECT therapy |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate, temazepam for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes 
Mean age: sertraline: 68, fluoxetine: 67 
Gender (% female): sertraline: 63.2%, fluoxetine: 51.3% 
Ethnicity: sertraline: 95.7% white, 3.4% black, other 0.9%, fluoxetine: 100% white 
Other population characteristics: Not reported |
### Authors:
Newhouse PA, et al.

### Year:
2000

### Country:
US

### OUTCOME ASSESSMENT:
- **Measures:** 24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT
- **Timing of assessments:** Baseline, week 1, 2, 3, 4, 6, 8, 10, 12

### RESULTS:
- Sertraline and fluoxetine were effective in the relief of depressive symptoms
- There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI)
  - HAMD Responders: sertraline: 73%, fluoxetine: 71%
  - HAMD remitters: sertraline: 45%, fluoxetine: 46%
- Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test)

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 32.2%; sertraline: 31.6%, fluoxetine: 32.8%
- **Withdrawals due to adverse events:** sertraline: 18.8%, fluoxetine: 24.4% (p = 0.5)
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018)
- Otherwise no statistically significant differences between groups
- Headache: sertraline: 33.6%, fluoxetine: 31.4%
- Dizziness: sertraline: 7.8%, fluoxetine: 10.2%
- Dry mouth: sertraline: 15.5%, fluoxetine: 7.6%
- Nausea: sertraline: 14.7%, fluoxetine: 18.6%
- Diarrhea: sertraline: 22.4%, fluoxetine: 16.1%

### QUALITY RATING:
Fair
**Evidence Table 1**  
**Major Depressive Disorder Adults**

Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING: Eli Lilly Inc</td>
</tr>
</tbody>
</table>
| DESIGN: Study design: RCT  
Setting: Multicenter  
Sample size: 684 (114 for Clayton subanalysis of CSFQ) |
| INTERVENTION: Drug: Duloxetine  
Dose: 60 mg  
Duration: 8 weeks and 8 months  
Sample size: 273  
Escitalopram  
Dose: 10 mg  
Duration: 8 weeks and 8 months  
Sample size: 274  
Placebo  
Dose: NA  
Duration: 8 weeks and 8 months  
Sample size: 137 |
| INCLUSION: 18 years old; diagnosed with MDD; MADRS > 22 and CGI-S > 4; normal or clinically unremarkable exam, lab and ECG |
| EXCLUSION: Pregnant, lactation; primary Axis 1 disorder other than MDD; previous diagnosis bipolar, schizophrenia or other psychotic disorders or Axis 2 disorder that might interfere; significant risk of suicide; substance dependence; treatment resistant; ECT. |
| OTHER MEDICATIONS/ INTERVENTIONS: Chronic use of certain prescriptions such as ACE inhibitors, alpha and beta blockers, anti-arrhythmics, and calcium channel blockers if on stable dose for at least 3 months |
| POPULATION CHARACTERISTICS: Groups similar at baseline: No  
Mean age: Duloxetine 41.1 escitalopram 43.3 placebo 42.5  
Gender (female %): overall 65.2% duloxetine 63.4% escitalopram 67.9% placebo 63.5%  
Ethnicity: Overall 77.6% Caucasian Duloxetine 75.5% escitalopram 77.4% placebo 82.5%  
Other population characteristics: Mean HAM-D Duloxetine 17.6 escitalopram 17.8 placebo 17.7 |
Authors: Nierenberg, Pigott and Clayton  
Year: 2007  
Country: USA

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Onset of efficacy HAM-D at 8 months and CSFQ  
**Secondary Outcome Measures:** HAM-D, HAM-A, CGI-S  
**Timing of assessments:** Baseline, weeks 1,2,3,4,6,8

### RESULTS:

- Mean change Duloxetine vs. escitalopram v. placebo 8 weeks and 8 months  
  - HAM-D -7.61 (0.42) vs. -7.22 (0.40) vs. -5.97 (0.58) P < 0.05 Duloxetine vs. placebo and -10.55 (0.48) vs. -10.91 (0.45) vs -8.06 (1.13)  
  - CGI-S -1.44 (0.08) vs. 1.36(0.07) vs. -1.08 (0.11) P < 0.01 Duloxetine vs. placebo and P < 0.05 Escitalopram vs. placebo and -2.17 ((0.09) vs. -2.20 (0.09) vs -2.11 (0.22)  
  - HAM-A -5.49 (0.36)) vs -5.16 (0.34) vs. -4.32 (0.50) and -7.30 (0.44) vs. -7.92 (0.41) vs. -5.73 (1.03)  
  - Response HAM-D 48.7% vs. 45.3% vs. 36.9%  
  - Remission HAM-D 37% vs. 32% vs. 27% and 70% vs. 75% vs. NR  
  - 8 week incidence of treatment-emergent sexual dysfunction duloxetine 17/51 (33.3%) escitalopram; 19/39 (48.7%) placebo  4/24 (16.7%) (P = 0.01 escitalopram vs. placebo; P = 0.13 duloxetine vs. placebo) and at 8 months duloxetine 33.3% escitalopram 43.6% placebo 25%

### ANALYSIS:

- ITT: Yes  
- Post randomization exclusions: NR

### ATTRITION:

- Loss to follow-up: 28%  
- **Withdrawals due to adverse events:** Duloxetine 7.3%, escitalopram 5.1%, placebo 5.8%  
- **Withdrawals due to lack of efficacy:** Duloxetine 3.3%, escitalopram 1.5%, placebo 5.1%  
- Loss to follow-up differential high: No

### ADVERSE EVENTS:

- **Duloxetine vs. escitalopram v. placebo (%)** 8 weeks and 8 months  
  - Nausea 23.8* ** vs. 12.0 vs. 8.8 and 29.3* vs. 14.2 vs. 10.2  
  - Dry mouth 21.6* ** vs. 10.9 vs. 10.9 and 24.2* ** vs. 11.7 vs. 11.7  
  - Headache 19.4 vs. 20.1 vs. 14.6 and 25.6* vs. 23.7 vs. 16.1  
  - Diarrhea 11.7 vs. 12.0 vs. 8.0 and 13.2 vs. 17.5* vs.9.5  
  - Dizziness 9.5 vs. 7.3 vs. 5.1 and 12.5 vs. 11.7 vs. 7.3  
  - Constipation 8.4 vs. 5.8 vs. 5.8 and 11.0 vs. 8.4 vs. 6.6  
  - Decreased appetite 8.1* vs. 4.7 vs. 2.2 and 8.1* vs. 5.1 vs. 2.2  
  - Insomnia 8.1 vs. 7.7 vs. 6.6  
  - Hyperhidrosis* 7.7 vs. 4.0 vs. 0.7 and 9.9* vs. 5.5 vs. 1.5  
  - Vomiting 7.3* ** vs. 2.2 vs. 0.7 and 9.2* ** vs. 3.6 vs. 1.5  
  - Somnolence 5.9 vs. 6.6 vs. 3.6 and 7.3 vs. 7.3 vs. 4.4  
  - Nasopharyngitis 5.5 vs. 6.6 vs. 6.6 and 8.4 vs. 10.9 vs. 8.0  
  - Yawning 5.5* ** vs. 2.2 vs. 0 and 5.9* ** vs. 2.2 vs. 0  
  - Decreased libido 5.1 vs. 4.0 vs. 2.2 and 6.6 vs. 6.6 vs. 2.9  
  - Fatigue 5.1 vs. 6.2 vs. 8.0 and 8.1 vs. 9.9 vs. 8.8
<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Duloxetine</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>4.4</td>
<td>2.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Back pain</td>
<td>NR</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>NR</td>
<td>4.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Anthralgia</td>
<td>NR</td>
<td>4.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>NR</td>
<td>5.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Anorgasmia</td>
<td>NR</td>
<td>4.8*</td>
<td>4.0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>NR</td>
<td>3.7</td>
<td>4.7*</td>
</tr>
<tr>
<td>Increased weight</td>
<td>NR</td>
<td>2.6</td>
<td>5.5*</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>NR</td>
<td>4.8*</td>
<td>1.8</td>
</tr>
<tr>
<td>Sedation</td>
<td>NR</td>
<td>4.0*</td>
<td>1.8</td>
</tr>
<tr>
<td>Night sweats</td>
<td>NR</td>
<td>3.7**</td>
<td>0</td>
</tr>
<tr>
<td>Migraine</td>
<td>NR</td>
<td>0.4</td>
<td>2.9**</td>
</tr>
<tr>
<td>* P &lt; 0.05 vs. placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>** P &lt; 0.05 duloxetine vs. escitalopram</td>
<td></td>
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</tr>
</tbody>
</table>

**QUALITY RATING:** Fair
## Evidence Table 1
### Major Depressive Disorder Adults

| STUDY: | Authors: Nieuwstraten C, et al.  
Year: 2001  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1332 |
| AIMS OF REVIEW: | To assess the benefits and risks of bupropion vs. SSRIs in major depression |
| TIME PERIOD COVERED: | 1966-1999 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs, study durations: 6-16 weeks, median 7 weeks |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8% |
**Authors** Nieuwstraten C, et al.  
**Year:** 2001  
**Country:** Canada

**Characteristics of Included Interventions:**  
Bupropion vs. sertraline (3 trials), bupropion vs. paroxetine (1 trial), bupropion vs. fluoxetine (1 trial)

**Main Results:**  
Results of HAM-D scores and CGI-I scores could not be pooled due to the unavailability of data; the weighted mean differences of CGI-S and HAM-A scores were not significantly different between bupropion and SSRIs

**Adverse Events:**  
Nausea, diarrhea, and somnolence occurred significantly less frequently in the bupropion group compared to the 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 significantly less in the SSRI group RR: 1.28 (95%CI: 1.16-1.41)

**Comprehensive Literature Search Strategy:**  
Yes

**Standard Method of Appraisal of Studies:**  
Yes

**Quality Rating:**  
Good
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Panzer MJ<sup>156</sup>  
Year: 2005  
Country: Multinational |
| **FUNDING:** | GSK |
| **DESIGN:** | Study design: Systematic review  
Number of patients: 7299 |
<p>| <strong>AIMS OF REVIEW:</strong> | To assess medication response of SSRIs to other ADs in patients suffering from MDD with secondary anxious feature |
| <strong>STUDIES INCLUDED IN REVIEW</strong> | 28 studies |
| <strong>TIME PERIOD COVERED:</strong> | Not reported |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | Double blinded, comparative trials of SSRIs to other types of ADs |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Adult in- and outpatients with MDD as the primary diagnosis with anxious tendencies but not anxiety as a comorbidity |</p>
<table>
<thead>
<tr>
<th>Authors: Panzer MJ</th>
<th>Year: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARACTERISTICS OF INTERVENTIONS:</td>
<td>SSRIs vs. bupropion (7 studies); mirtazapine vs. SSRIs or amitriptyline (5 studies including 1 meta-analysis); TCAs vs. SSRIs (3 studies); SSRIs vs. SSRIs (2 studies); bupropion vs. TCAs (3 studies); nefazadone vs. TCAs or SSRIs (4 studies); venlafaxine vs. trazadone or SSRIs (4 studies)</td>
</tr>
</tbody>
</table>
| MAIN RESULTS: | • SSRIs have not been shown to be more effective than TCAs in the treatment of anxious depression  
• Limited evidence that mirtazapine, bupropion and nefazadone may be superior to SSRIs |
| ADVERSE EVENTS: | Not reported |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes- MedLine and PsychInfo |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Not reported |
| QUALITY RATING: | Fair |
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Patris M, et al.  
Year: 1996  
Country: France |
| FUNDING: | Not specifically stated, one author is an employee of Lundbeck |
| DESIGN: | Study design: RCT  
Setting: Multi-center (general practices)  
Sample size: 357 |
| INTERVENTION: |  
**Drug:**  
**Dose:** 20 mg/d  
**Duration:** 8 weeks |
| INCLUSION: | Ages 21-73; met DSM III R criteria for unipolar depression with a score on MADRS of 22 or more |
| EXCLUSION: | Dysthymia; cyclothymia; decrease in MADRS > 20% from baseline during the run-in period; pregnancy; lactation; failure to use contraception; alcohol or drug abuse within the past year; MAOI use within 2 weeks; severe somatic disease; organic brain syndrome; schizophrenia; epilepsy; other neurological diseases; suicide risk; known hypersensitivity |
| OTHER MEDICATIONS/INTERVENTIONS: | Benzos allowed; no other psychotropics allowed; "Drug treatment for concurrent somatic illness was limited as much as possible"; high percentages of patients in both groups (83% and 81%) received concomitant medications; the use of non-psychotropic medication was similar in the two groups |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 43.5 years; citalopram: 44, fluoxetine: 43  
Gender (female%): citalopram: 79%, fluoxetine: 76%  
Ethnicity: Not reported  
Other population characteristics: Major depression single episode: citalopram: 42%, fluoxetine: 46%; recurrent episodes: citalopram: 58%, fluoxetine: 54% |
| Authors: | Patris M, et al. |
| Year: | 1996 |
| Country: | France |

**OUTCOME ASSESSMENT:**

- **Measures:** Primary outcome: MADRS, secondary outcomes: HAM-D<sub>17</sub>, CGI
- **Timing of assessments:** Baseline, 1, 2, 4, 6, 8 weeks

**RESULTS:**

No difference in mean MADRS score at endpoint or in mean change from baseline; mean change: citalopram: -20.7, fluoxetine: -19.4; responders (reduction in score from baseline > 50%) at endpoint: citalopram: 78 %, fluoxetine: 76 %; no statistical difference

**ANALYSIS:**

- **ITT:** No
- **Post randomization exclusions:** Yes

**ATTRITION:**

- **Loss to follow-up:** 12.6; citalopram: 13.9%, fluoxetine: 11.4%
- **Withdrawals due to adverse events:** citalopram: 5.7%, fluoxetine: 2.2%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- No significant differences
- Reported at least one adverse event: citalopram: 50%, fluoxetine: 52%
- No difference in the global evaluation of the interference of adverse events with the patient’s daily functioning: citalopram: 34%, fluoxetine: 33%

**QUALITY RATING:**

Fair
## Evidence Table 1  Major Depressive Disorder Adults

| **STUDY:** | Authors: Perhia et al.  
Year: 2006  
Country: Multinational (Europe) |
| **FUNDING:** | Eli Lilly and Company |
| **DESIGN:** | Study design: RCT  
Setting: Multinational  
Sample size: 392 |
| **INTERVENTION:** |  
Drug:  
Dose:  
Duration:  
Sample size: |
| Placebo | NA  
8 weeks  
99 |
| Duloxetine 80 | 80 mg  
8 weeks  
93 |
| Duloxetine 120 | 120 mg  
8 weeks  
103 |
| Paroxetine | 20 mg  
8 weeks  
97 |
| **INCLUSION:** | Male and female outpatients > 18 years with MDD; CGI-S ≥ 4; HAM-D ≥ 15 |
| **EXCLUSION:** | Axis 1 or anxiety disorder other than MDD as primary diagnosis; diagnosed with bi polar, psychosis or schizoaffective disorder; lack of response to 2 or more previous anti-depressants, during current MDD episode; serious suicide risk; substance abuse or dependence w/in last year or positive urine test; serious medical condition. |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Allowed non-prescription analgesics |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Placebo 44.7, Duloxetine80 46.5, Duloxetine120 44.0, Paroxetine 45.8  
Gender (female %): Placebo 65.7, Duloxetine80 66.7, Duloxetine120 74.8, Paroxetine 71.1  
Ethnicity (Caucasian %): Placebo 100, Duloxetine80 100, Duloxetine120 100, Paroxetine 100  
Other population characteristics: Baseline HAM-D Placebo 20.6, Duloxetine80 21.3, Duloxetine120 21.4, Paroxetine 21.0 |
## Authors: Perahia et al.
Year: 2006
Country: Multinational

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** HAM-D
- **Secondary Outcome Measures:** MADRS, HAM-A, SDS, SSI, ASEX
- **Timing of assessments:** Baseline, 1,2,4,6,8

### RESULTS:
- **At end point 8 weeks,** Placebo vs. Duloxetine80 vs. Duloxetine120 vs. Paroxetine
  - HAM-D -10.8 (0.5) vs. -12.1 (0.5) vs. -12.4 (0.5) vs. -11.9 (0.5)
  - HAM-A -9.3 (0.5) vs. -10.5 (0.5) vs. -10.5 (0.5) vs. -10.6 (0.6)
  - CGI-S -1.7 (0.1) vs. -2.0 (0.7) vs. -2.0 (0.1) vs. -2.1 (0.1)

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes 1

### ATTRITION:
- **Loss to follow-up:** Overall 43 (11%) Placebo 9 (9%) Duloxetine80 10 (10.8%) Duloxetine120 13 (12.6%) Paroxetine 9 (9.3%)
- **Withdrawals due to adverse events:** Placebo 1%. Duloxetine80 2.2% Duloxetine120 1.8%. Paroxetine 1%
- **Withdrawals due to lack of efficacy:** Placebo 4%. Duloxetine80 3.2% Duloxetine120 1.9%. Paroxetine 1%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- **TEAEs** Placebo vs. Duloxetine80 vs. Duloxetine120 vs. Paroxetine (%)
  - Nausea 1 vs. 6.5 vs. 8.7 vs. 6.2
  - Insomnia 0 vs. 3.2 vs. 5.8 vs. 6.2
  - Headache 6.1 vs. 2.2 vs. 4.9 vs. 5.2
  - Constipation 5.1 vs. 4.3 vs. 3.9 vs. 2.1
  - Dry mouth 1.0 vs. 3.2 vs. 2.9 vs. 3.1
  - Somnolence 0 vs. 1.1 vs. 2.9 vs. 5.2
  - Vomiting 0 vs. 1.1 vs. 2.9 vs. 2.1
  - Tachycardia 1.0 vs. 0 vs. 2.9 vs. 1.0

### QUALITY RATING:
- **Fair**
## Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Rapaport ME, et. al.  
Year: 1996  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Solvay Pharmaceuticals, Upjohn</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (6 sites)  
Sample size: 100 |
| INTERVENTION: | Drug: Fluvoxamine  
Dose: 100-150 mg/d  
Duration: 7 weeks  
Fluoxetine  
Dose: 20-80 mg/d  
Duration: 7 weeks |
| INCLUSION: | Male and female outpatients; 18-65 years; met DSM-III-R criteria for MDD; minimum HAM-D (21-item) score of 20; minimum score of 2 on the depressed mood item |
| EXCLUSION: | Any primary DSM-IV Axis I disorder diagnosis other than MDD; acute suicidality; unstable medical conditions; history of seizure; had been treated with study medications; history of substance abuse or dependence; pregnancy and lack of appropriate birth control for women of child-bearing age |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: fluoxetine: 38.6; fluvoxamine: 40.0  
Gender (% female): fluoxetine: 63.2; fluvoxamine: 62  
Ethnicity: 95% white; 5% other; fluvoxamine 98% white, fluvoxamine 92% white  
Other population characteristics: NR |
| **Authors:** Rapaport ME, et al.  
**Year:** 1996  
**Country:** US |
|---|
| **OUTCOME ASSESSMENT:** Measures: HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation  
**Timing of assessments:** Primary outcome measures weekly; secondary outcome measures at baseline and endpoint |
| **RESULTS:**  
- No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures  
- Both drugs significantly improved scores on HAM-D ( <10 for both groups at endpoint) |
| **ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes (7) |
| **ATTRITION:**  
**Loss to follow-up:** 16%  
**Withdrawals due to adverse events:** 4%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:**  
- Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR)  
- Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03)  
- Other frequent adverse events:  
  - headache: fluoxetine 53%, fluvoxamine 50% (p not significant)  
  - vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant)  
  - daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant) |
<p>| <strong>QUALITY RATING:</strong> Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Rudolph RL, et al.  
                  | Year: 1999  
                  | Country: US  |
| **FUNDING:**     | Wyeth-Ayerst Research  |
| **DESIGN:**      | Study design: RCT  
                  | Setting: Multi-center  
                  | Sample size: 301  |
| **INTERVENTION:**| Drug: Venlafaxine XR  
                  | Dose: 75-225 mg/d  
                  | Duration: 8 weeks  
                  | Fluoxetine  
                  | 20-60 mg/d  
                  | 8 weeks  
                  | Placebo  
                  | N/A  
                  | 8 weeks  
                  | Initial dosage could be increased after 2 weeks  |
| **INCLUSION:**   | ≥ 18 years of age; met DSM-IV criteria for MDD; symptoms of depression for one month or more before study; pre-study and baseline score of ≥ 20 on the 21 item HAM-D  |
| **EXCLUSION:**   | Known hypersensitivity to either drug; specified medical conditions; bipolar disorder; psychotic disorder not associated with depression; drug or alcohol abuse; pregnant or lactating  |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Chloral hydrate for sleep  |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                  | Mean age: 40  
                  | Gender (female%): venlafaxine: 73%, fluoxetine: 69%, placebo: 64%  
                  | Ethnicity: Not reported  
                  | Other population characteristics: No statistically significant differences between groups in baseline mean 21-HAMD scores, mean MADRS scores, or duration of the current episode of depression; 24% used fluoxetine in past and 2% used venlafaxine in past  |
### Authors: Rudolph RL, et al.
**Year:** 1999  
**Country:** US

#### OUTCOME ASSESSMENT:
**Measures:** HAMD-21, MADRS, CGI, HAM-A)  
**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 8

#### RESULTS:
- No significant difference between venlafaxine and fluoxetine treatment on the 21-HAMD or MADRS at endpoint in the LOCF analysis
- At endpoint in the LOCF analysis, venlafaxine patients showed a significant difference from placebo in the MADRS, CGI, and HAM-D depressed mood item
- Fluoxetine patients only showed a significant difference in the HAM-D depressed mood item

#### ANALYSIS:
**ITT:** Yes  
**Post randomization exclusions:** Yes

#### ATTRITION:
- **Loss to follow-up:** 23%; venlafaxine: 19%, fluoxetine: 28%, placebo: 21%
- **Withdrawals due to adverse events:** venlafaxine: 6%, fluoxetine: 9%
- **Loss to follow-up differential high:** No

#### ADVERSE EVENTS:
- Venlafaxine patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients (p < 0.05)
- Venlafaxine and fluoxetine patients experienced significantly more asthenia and tremor than placebo patients

#### QUALITY RATING:
Fair
### Evidence Table 1  
#### Major Depressive Disorder Adults

| STUDY:                      | Authors: Rush AJ, et al.  1998  
|                            | Year: 1998  
|                            | Country: US and Canada  
| FUNDING:                   | Bristol Myers Squibb, Seay Center for Research (UT Southwestern), NIMH  
|                            | Setting: Multi-center  
|                            | Sample size: 125  
| INTERVENTION:              | Drug:  
|                            | **Dose:**  
|                            | Nefazodone 200-500 mg/d  
|                            | Fluoxetine 20-40 mg/d  
|                            | **Duration:**  
|                            | 8 weeks  
|                            | 8 weeks  
| INCLUSION:                 | Outpatient; ages 19-55; non-psychotic moderate to severe MDD by DSM-III-R criteria; minimum score of 18 on HAM-D  
|                            | at least one of the following sleep disturbances as part of their depression symptoms: difficulty falling asleep on a nightly basis; waking up during the night inability to fall asleep again after getting out of bed  
| EXCLUSION:                 | Engaged in shift work; independent sleep/wake disorders on polysomnography; significant concurrent general medical conditions; DSM III-R criteria for substance abuse disorders within the year prior to study; other major Axis I disorders; pregnant, lactating or not using contraception  
| OTHER MEDICATIONS/         | Not reported  
| INTERVENTIONS:             |  
| POPULATION CHARACTERISTICS:| Groups similar at baseline: No; more people in their second or more depressive episode in fluoxetine group  
|                            | **Age:** 36.5; nefazodone: 36, fluoxetine: 37  
|                            | **Gender (% female)** nefazodone: 59%, fluoxetine: 70%  
|                            | **Ethnicity:** nefazodone: 78% white, 9% black, 0% Asian, fluoxetine: 85% white, 7% black, 5% Asian  
|                            | **Other population characteristics:** Not reported  

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Second generation antidepressants

137 of 515
### Authors: Rush AJ, et al.
**Year:** 1998
**Country:** US and Canada

### OUTCOME ASSESSMENT:
**Measures:** HAM-D17, IDS-C and IDS-R, CGI, sleep quality as measured by HDRS Sleep Disturbance Factor and IDS-C and IDS-SR sleep factors and EEG measures  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:
- No difference in efficacy between groups as measured by change in HAM-D17  
- Response (< 10 on HAMD17): nefazodone: 47%, fluoxetine: 45%  
- On EEG: increased sleep efficiency, decreased awakenings and decreased % AMT (awake and moving time) for nefazodone as compared to fluoxetine  
- Also significant differences on sleep disturbance factors of the HAM-D and IDS-C and IDS-SR favoring nefazodone over fluoxetine

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 17%  
- **Withdrawals due to adverse events:** nefazodone 9%, fluoxetine 8%  
- **Loss to follow-up differential high:** Not reported

### ADVERSE EVENTS:
No statistical comparisons reported

### QUALITY RATING:
Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Schatzberg et al. \(^3\)  
                    Year: 2002  
                    Country: US |
| **FUNDING:**     | Organon Pharma                   |
| **DESIGN:**      | Study design: RCT  
                    Setting: Multi-center  
                    Sample size: 255 |
| **INTERVENTION:**| **Drug:** Mirtazapine  
                    Dose: 15-45 mg/d  
                    Duration: 8 weeks  
                    Paroxetine  
                    Dose: 20-40 mg/d  
                    Duration: 8 weeks  
                    (there was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study) |
| **INCLUSION:**   | Minimum age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score > 25% for age and education; minimum score of 18 on HAM-D\(_{17}\) |
| **EXCLUSION:**   | HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psychiatric condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazapine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chlortal hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                    Mean age: 72  
                    Gender (% female): mirtazapine: 50%, paroxetine: 53%  
                    Ethnicity: Not reported  
                    Other population characteristics: Not reported |
| Authors: Schatzberg et al.  
Year: 2002  
Country: US |
|---|
| **OUTCOME ASSESSMENT:** Measures: HAM-D 17, CGI-S, CGI-I  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8 |
| **RESULTS:**  
- Mean Ham-D17 scores significantly lower with mirtazapine at weeks 1, 2, 3, 6 but no difference at 8 week endpoint  
- Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission)  
- Time to response: mirtazapine mean 26 days, paroxetine 40 days, p = .016 for Kaplan-Meier plot comparing the two  
- No difference in CGI Improvement response |
| **ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:**  
**Loss to follow-up:** 26.8%  
**Withdrawals due to adverse events:** 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p < 0.05)  
**Loss to follow-up differential high:** Moderate |
| **ADVERSE EVENTS:**  
- Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5%  
- Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0% |
| **QUALITY RATING:** Fair |
Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Schöne W, et al.  
Year: 1993  
Country: Austria and Germany |
| FUNDING: | SmithKline, Beecham |
| DESIGN: | Study design: RCT  
Setting: Geriatric outpatients at 6 centers in Austria and Germany  
Sample size: 108 |
| INTERVENTION: | Drug: Paroxetine  
Dose: 20-40 mg/d  
Duration: 6 weeks  
Fluoxetine  
Dose: 20-60 mg/d  
Duration: 6 weeks |
| INCLUSION: | Age 65 or greater; met DSM-IIR for MDD; HAM-D21 score > 18 at baseline |
| EXCLUSION: | Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in were also excluded |
| OTHER MEDICATIONS/INTERVENTIONS: | Prohibited psychotropic meds except temazepam for sleep. Other allowed nonpsychotropic medications not specifically reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 74; paroxetine: 74.3, fluoxetine: 73.7  
Gender (% female): 87%, paroxetine: 83%, fluoxetine: 90%  
Ethnicity: Not reported  
Other population characteristics: History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27% |
<table>
<thead>
<tr>
<th>Authors: Schöne W, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 1993</td>
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<tr>
<td>Country: Germany</td>
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</table>

**OUTCOME ASSESSMENT:**

- **Measures:** HAM-D 21, MADRS, CGI
- **Timing of assessments:** Days 7, 21, 42

**RESULTS:**

- No significant difference in mean changes on HAM-D score
- HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D$_21$): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03)
- MADRS: no significant difference in mean change scores between groups
- MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5%, (p = 0.04)

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Yes

**ATTRITION:**

- **Loss to follow-up:** Not reported
- **Withdrawals due to adverse events:** 12%; paroxetine: 11.1%, fluoxetine: 13.5%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event

**QUALITY RATING:**

- Fair
**Evidence Table 1  Major Depressive Disorder Adults**

| STUDY: | Authors: Sechter D, et al.  
| Year: 1999  
| Country: France |
| FUNDING: | Pfizer France |
| DESIGN: | Study design: RCT  
| Setting: Multi-center (45 private psychiatrists)  
| Sample size: 234 |
| INTERVENTION: |  
| Drug: | Sertraline  
| Dose: | 50-150 mg/d  
| Duration: | 24 weeks |
| | Fluoxetine  
| Dose: | 20-60 mg/d  
| Duration: | 24 weeks |
| Mean daily dose: |  
| Sertraline: 76.5 mg/d  
| Fluoxetine: 33.6 mg/d |
| INCLUSION: | ≥ 18-65 yrs; DSM-III criteria for major depression; HAM-D-17 ≥ 20 |
| EXCLUSION: | History of psychosis; organic mental disorder; bipolar disorder; personality disorder; suicidal; psychoactive drugs; ECT within 1 month; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities; anticoagulant; serotonergic drugs; MAOI; lithium; alpha methylldopa; drug sensitivity or lactose intolerance; previous failure on three or more antidepressants |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: sertraline: 43.4, fluoxetine: 42.5  
| Gender (% female): sertraline: 66.7%, fluoxetine: 68.1%  
| Ethnicity: Not reported  
| Other population characteristics: Patients with first depressive episode: sertraline: 27.4%, fluoxetine: 21.0% |
**Authors:** Sechter D, et al.  
**Year:** 1999  
**Country:** France

| OUTCOME ASSESSMENT: | Measures: HAM-D, CGI-I, CGI-S, Covi, Sickness Impact Profile, HAD scores, Leeds Sleep Evaluation  
Timing of assessments: Baseline, weeks 2, 4, 8, 12, 18, 24 |
|---------------------|---------------------------------------------------------------|

| RESULTS: |  
• At study endpoint both treatment groups had significant improvements over baseline on all efficacy variables (p < 0.001)  
• There were no significant differences between study groups in outcome measures (HAM-D, CGI, Covi) at any point in time; the magnitude of changes was higher for sertraline.  
• Response was observed in 74% in sertraline patients versus 64% in fluoxetine patients on HAM-D  
• The Leeds Sleep Evaluation Scale showed a trend favoring sertraline but no significant difference compared to fluoxetine  
• Both treatments showed significant improvements in SIP  
• SIP sub scores showed significant greater improvements for sertraline relating to sleep and rest (p = 0.04), emotional behavior (p = 0.04), and ambulation (p = 0.05) |

| ANALYSIS: |  
**ITT:** Yes  
**Post randomization exclusions:** Yes |

| ATTRITION: |  
**Loss to follow-up:** 29.2%; sertraline: 24.7%, fluoxetine: 33.6%  
**Withdrawals due to adverse events:** sertraline: 6%, fluoxetine: 10%  
**Loss to follow-up differential high:** No |

| ADVERSE EVENTS: |  
• There were no significant differences in the incidence of adverse events between treatment groups  
• Most common adverse event: nausea: sertraline: 23%, fluoxetine: 17% |

| QUALITY RATING: | Fair |
## Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | **Authors:** Segraves, et al.  
**Year:** 2000  
**Country:** US |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome Inc</td>
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</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 248 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:**  
Sertraline  
50-200 mg/d  
16 weeks  
Bupropion SR  
100-300 mg/d  
16 weeks |
| INCLUSION: | DSM-IV diagnosis of moderate to severe depression with minimum duration of 4 weeks and max duration of 24 months;  
> 18 years of age; in a stable relationship, have normal sexual functioning and sexual activity at least once every 2 weeks |
| EXCLUSION: | Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of anorexia or bulimia;  
pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or 4 weeks for fluoxetine or any investigational drug); prior treatment with bupropion or sertraline |
| OTHER MEDICATIONS/INTERVENTIONS: | None reported |
| Authors: Segraves et al.  
| Year: 2000  
<table>
<thead>
<tr>
<th>Country: US</th>
</tr>
</thead>
</table>
| **POPULATION CHARACTERISTICS:**

- Groups similar at baseline: Yes
- **Mean age:** sertraline: 40 bupropion: 39
- **Gender (% female):** sertraline: 48%, bupropion SR: 48%
- **Ethnicity: (% white)** sertraline: 94%, bupropion SR: 93%
- **Other population characteristics:** No significant differences in diagnosis

| **OUTCOME ASSESSMENT:**

- **Measures:** Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation (men only), patient rated overall sexual satisfaction on 6 point Likert scale
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16

| **RESULTS:**

- Significantly more sertraline patients developed one of the following sexual dysfunctions compared to bupropion SR patients: sexual arousal disorder, orgasm dysfunction, or premature ejaculation (men only); (men: 63% and 15%, respectively, p < 0.001; women: 41% and 7%, respectively, p < 0.001)
- Beginning on day 21 and continuing throughout the study, significantly more bupropion SR-treated patients were satisfied with their overall sexual functioning compared with sertraline-treated patients

| **ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Yes

| **ATTRITION:**

- **Loss to follow-up:** 31.5%; bupropion SR: 29%, sertraline: 34%
- **Withdrawals due to adverse events:** 1.6%; bupropion SR: 0%, sertraline: 1.6%
- **Loss to follow-up differential high:** Yes

| **ADVERSE EVENTS:**

- Not reported

| **QUALITY RATING:**

- Fair
### Evidence Table 1

**Major Depressive Disorder Adults**

| STUDY: | Authors: Shelton R, et al.  
Year: 2006  
Country: USA |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 160 |
| INTERVENTION: Drug: Sertraline  
Dose: 150 mg  
Duration: 8 weeks  
Sample size: 82 | Venlafaxine XR  
Dose: 225 mg  
Duration: 8 weeks  
Sample size: 78 |
| INCLUSION: | Male and female outpatients; 18 or older; diagnosed with MDD, single episode or recurrent, w/o psychotic features; 18 or more on HAM-D; 2 or more on item 1 (depressed mood) |
| EXCLUSION: | Current or past diagnosis of bipolar; current diagnosis of dementia, delirium, substance abuse in past 6 months or schizoid, schizotypal, borderline personality; previous non-response to sertraline or venlafaxine or 2 Ads in current episode, AD within 2 weeks (fluoxetine 4 wks); score of 3 or 4 on HAM-D suicide item; ECT within 30 days; presence of serious and/or unstable medical condition; abnormal baseline lab findings; impaired hepatic function; pregnant or nursing; history of seizure disorder. |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem or zopiclone for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes except sertraline older (41.2) then Venlafaxine patients (37.2)  
Mean age: 39.3  
Gender (female %): 61  
Ethnicity: 84% white, 8% African American, 1% Asian, 7% other  
Other population characteristics: Single episode 49%, recurrent 51% |
Authors: Shelton et al  
Year: 2006  
Country: USA

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Q-LES-Q  
Secondary Outcome Measures: HAM-D, CGI-S CGI-I and HAM-A  
Timing of assessments: Baseline, weeks 1,2,3,4,6,8 and 10. |
|---|---|
| RESULTS: | Sertraline vs. Venlafaxine  
Q-LES-Q 0.69 (0.12) vs. 0.67 (0.12)  
HAM-D 10.8(6.4) vs. 9.7 (6.4)  
Response 55% vs 65%. Remission 38% vs. 49%  
CGI-S 2.6 (1.1) vs. 2.4 (1.1), CGI-I 2.3 (1.1) vs. 2.0 (1.1)  
HAMD-A 9.1 (5.4) vs. 8.2 (5.7) |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: 2 |
| ATTRITION: | Loss to follow-up: 19% overall 23% sertraline and 14% venlafaxine  
Withdrawals due to adverse events: 4 (1 sertraline, 3 venlafaxine)  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | Sertraline vs. Venlafaxine  
None 20% vs. 21%  
Headache 22% vs. 32%  
Nausea 17% vs. 17%, diarrhea 31% vs. 25%  
Insomnia 26% vs. 20%  
Sexual side effects 31 vs. 23% |
| QUALITY RATING: | Fair |
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Silverstone PH et al.74,75  
Year: 1999, 2001 (subgroup analysis)  
Country: Canada |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst Research</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 368 |
| INTERVENTION: | Drug:  
Venlafaxine XR  
75-225 mg/d (Could be increased to 150 mg/d on day 14 and 225 mg/d on day 28)  
12 weeks  
Fluoxetine  
20-60 mg/d (Could be increased to 40 mg/d on day 14 and 60 mg/d on day 28)  
12 weeks  
Placebo  
N/A  
12 weeks |
| INCLUSION: | 18 years or older; met DSM-IV criteria for major depression; score of 20 on first 17 items of the 21 item HAM-D; score of 8 on the COVI scale; depression for 1 month before the study |
| EXCLUSION: | Pregnant women; history of significant illness; suicidal tendencies; other psychiatric or psychotic disorders not associated with depression; history of drug or alcohol abuse; use of investigational drug or ECT therapy within 30 days; history of seizures; taken other antidepressant or antipsychotic within 7 days of baseline |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate or zopiclone for sleep; cisapride for nausea. |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: placebo: 41.6, venlafaxine: 41.1, fluoxetine: 43.2  
Gender (female%): venlafaxine: 64%, fluoxetine: 60%; placebo: 57.6  
Ethnicity: Not reported  
Other population characteristics: Subgroup analysis: Patients with GAD (n = 92) |
| **Authors:** Silverstone PH, et al.  
**Year:** 1999, 2001  
**Country:** Canada |
|---|
| **OUTCOME ASSESSMENT:**  
Response: 50% decrease in HAMD or HAMA score of 1 or 2 on CGI  
Remission Score < 8 on HAMD |
| **Measures:** 21 item HAM-D, HAM-A, the Covi Scale, Hospital Anxiety and Depression scale, CGI scale  
**Timing of assessments:** Baseline, days 7, 14, 21, 28, 42, 56, 84 |
| **RESULTS:**  
No statistical comparisons between fluoxetine and venlafaxine (just placebo)  
• HAM-D scores in the venlafaxine and fluoxetine groups dropped significantly when compared with placebo  
• Venlafaxine had significantly more HAM-A responders at week 12 than fluoxetine  
• The HAM-D remission rate in the venlafaxine group was significant compared to placebo at weeks 3, 4, 6, 8, 12 & final  
• The HAM-D remission rate in the fluoxetine group was significant compared to placebo at weeks 8, 12, & final  
**Subgroup analysis:**  
• There were no significant differences in outcome measures between the active treatment groups (compared to placebo)  
• Patients in the venlafaxine group but not in the fluoxetine group showed a significant decrease in HAM-D and HAM-A scores compared to placebo (p < 0.05)  
• Onset of action seemed to be slower in patients with GAD compared to patients without |
| **ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:**  
**Loss to follow-up:** 32%; venlafaxine xr: 29%, fluoxetine: 26%, placebo: 40%  
**Withdrawals due to adverse events:** venlafaxine xr: 10%, fluoxetine: 7%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:**  
Significantly more dizziness (p < 0.001) and sweating (p < 0.05) occurred with venlafaxine than with fluoxetine |
<p>| <strong>QUALITY RATING:</strong> Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | **Authors:** Sir A, et al.  
|                  | **Year:** 2005  
|                  | **Country:** Australia and Turkey |
| **FUNDING:**     | Pfizer, Inc. |
| **OBJECTIVE:**   | Test for differences between sertraline and venlafaxine XR on measures of QOL and test for efficacy differences on measures of depressive symptoms and tolerability, including discontinuation symptoms |
| **DESIGN:**      | **Study design:** RCT: 8 weeks on study drug, then up to 2 weeks discontinuation  
|                  | **Setting:** Clinics (Turkey 7 and Australia 6)  
|                  | **Sample size:** 163 |
| **INTERVENTION:**| **Drug:**  
|                  | **Dose-mean(range):** Sertraline: 105.4(50-150)mg/day  
|                  |                  | Venlafaxine XR*: 161.4(75-225)mg/day  
|                  | **Duration:** 8 weeks  
|                  |                  | 79  
|                  |                  | 8 weeks  
|                  |                  | 84 |
| **INCLUSION:**   | Outpatients; 18 years or older; HAM-D ≥ 18; MDD single or recurrent according to the DSM-IV |
| **EXCLUSION:**   | History of bipolar disorder; any psychotic disorder; delirium; dementia; pregnancy; alcohol/drug abuse/dependence in past 6 months; schizoid, schizotypal or borderline personality disorders; additional DSM IV axis I disorders were allowed if they were secondary diagnoses; history of non-response to sertraline, venlafaxine or 2 anti-depressants in the current episode |
| **OTHER MEDICATIONS/INTerventions:** | NR |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes, but there was a small differences obvious in family member diagnosis of affective disorder.  
|                  | **Mean age:** 37  
|                  | **Gender (% female):** sertraline: 72.2%, venlafaxine: 66.7%  
|                  | **Ethnicity (% white):** sertraline: 96.2%, venlafaxine: 100%  
|                  | **Other population characteristics:**  
|                  | **Baseline Q-LES-Q:** sertraline: 55.3 +/- 9.4, venlafaxine: 52.7 +/- 11.2  
|                  | **Baseline HAM-D:** sertraline: 23.4 +/-4.4, venlafaxine: 23.5 +/-4.4  
|                  | **Baseline CGI-S:** sertraline: 4.5 +/- 0.8, venlafaxine: 4.6 +/- 0.8  
|                  | **Family member diagnosed with affective disorder:** sertraline: 42 (53.2%), venlafaxine: 34 (40.5%) |

*Note: From here on venlafaxine refers to venlafaxine XR*
## Authors: Sir A, et al.
### Year: 2005

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Q-LES-Q  
**Secondary Outcome Measures:**  
- HAM-D, HAM-A, CGI-S, CGI-I, VAS for pain and depression, Endicott Work Productivity Scale (EWPS), Antidepressant Discontinuation Scale (ADDS)  
- Discontinuation emergence: any symptom present in week 9 or 10 not present in first 8 weeks or that increased in severity during weeks 9 or 10.  
**Timing of assessments:** Baseline and every week thereafter.

### RESULTS:

**Efficacy**  
- Change in Q-LES-Q: Ser 16.8 ± 1.77 Ven 17.5 ± 14.5 p = 0.74  
- Change in HAM-D: Ser -15.9 ± 0.95 Ven -14.3 ± 0.94 p = 0.17  
- Change in HAM-A: Ser -14.1 ± 0.99 Ven -12.9 ± 0.99 p = 0.32  
- Mean CGI-S: Ser 2.0 ± 1.22 Ven 2.2 ± 1.25 p = 0.45  
- No significant difference exists in terms of efficacy between venlafaxine and sertraline.

**Discontinuation**  
- Number of discontinuation-emergent symptoms with frequency of >10% vs. other drug: venlafaxine 4, sertraline 0  
- Number of discontinuation-emergent symptoms of at least moderate intensity that were more than twice as common as for the other drug: venlafaxine 8, sertraline 1  
- Discontinuation of sertraline associated with fewer discontinuation-emergent symptoms than for discontinuation of venlafaxine. (Although not all differences achieved statistical significance, there is a clear trend.)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** No

### ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>23%</td>
<td>16.5%</td>
<td>29.8%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6%</td>
<td>3.8%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:

- AE rates (n(%)) include those that were evident in taper-off period (2 additional weeks following initial 8 weeks) which results in higher rates than normally found.  
- Asthenia: Ser 21(26.6) Ven 21(25.6)  
- Headache: Ser 35(44.3) Ven 27(32.1)  
- Dry mouth: Ser 32(40.5) Ven 20(23.8)  
- Nausea: Ser 41(51.9) Ven 40(47.6)  
- Dizziness: Ser 26(32.9) Ven 22(26.2)  
- Insomnia: Ser 28(35.4) Ven 23(27.4)  
- Somnolence: Ser 17(21.5) Ven 22(26.2)  
- Yawning: Ser 24(30.4) Ven 24(28.6)  
- Sweating: Ser 25(31.6) Ven 18(21.4)

### QUALITY RATING: Good
**Evidence Table 1  Major Depressive Disorder Adults**

| STUDY: | Authors: Tylee A, et al.\(^{81}\)  
Year: 1997  
Country: UK |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (34 UK general practices)  
Sample size: 341 |
| INTERVENTION: |  
Drug: | Venlafaxine  
Dose: 75 mg/day, fixed dose  
Duration: 12 weeks + 7day post follow-up |
| | Fluoxetine  
Dose: 20 mg/day, fixed dose  
Duration: 12 weeks + 7day post follow-up |
| INCLUSION: | ≥18 yrs; DSM-IV criteria for major depression; MADRS ≥ 19; depressive symptoms for more than 2 weeks |
| EXCLUSION: | Use of study drugs within 1 month; history of psychosis; organic mental disorder; bipolar disorder; suicidal; psychoactive drugs ECT therapy within 1 month; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: venlafaxine: 43.5, fluoxetine: 45.5  
Gender (% female): venlafaxine: 67.8%, fluoxetine: 74.7%  
Ethnicity: Not reported  
Other population characteristics: CGI severity:  
Mildly ill: venlafaxine: 8%, fluoxetine: 6%.  
Moderately ill: venlafaxine: 66%, fluoxetine: 62%.  
Markedly ill: venlafaxine: 21%, fluoxetine: 28%.  
Severely ill: venlafaxine: 4%, fluoxetine: 4% |
### Authors: Tylee A, et al.  
**Year:** 1997  
**Country:** UK

### OUTCOME ASSESSMENT:
**Measures and timing of assessments:** MADRS, baseline, weeks 1, 3, 6, 8, 12, HAM-D, CGI: weeks 3, 6, 8, 12, Hospital Anxiety and Depression (HAD): weeks 3, 6, 12, patient sleep diary: first 3 weeks

### RESULTS:
- MADRS, HAM-D, and CGI scores decreased significantly for both treatment groups
- There were no significant differences between treatment groups
- Remission rate: (MADRS ≤ 6) venlafaxine: 35.4 %, fluoxetine: 34.1%
- Response rates: venlafaxine: 55.1%, fluoxetine: 62.8%
- No significant differences in effects on sleep

### ANALYSIS:
**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:
**Loss to follow-up:** 27%; venlafaxine: 27%, fluoxetine: 27%

**Withdrawals due to adverse events:** venlafaxine: 21%, fluoxetine: 14%

**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:
- No significant differences between study groups
- At least 1 adverse event: venlafaxine: 80.7%, fluoxetine: 71.8%
- Nausea: venlafaxine: 34.5%, fluoxetine: 18.2%
- Vomiting: venlafaxine: 12.9%, fluoxetine: 5.3%
- Headache: venlafaxine: 11.1%, fluoxetine: 17.1%
- Dizziness: venlafaxine: 11.1%, fluoxetine: 6.5%

### QUALITY RATING:
Fair
**Evidence Table 1**

### Major Depressive Disorder Adults

| STUDY: | Authors: Ushiroyama T, et al.
Year: 2004
Country: Japan |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT
**Setting:** University hospital clinic
**Sample size:** 105 |
| INTERVENTION: | |
| **Drug:** | Fluvoxamine
50 mg/day
3 months
53 |
| **Dose:** | Paroxetine
20 mg/day
3 months
52 |
| **Duration:** | Sample size: |
| **Sample size:** | |
| INCLUSION: | Perimenopausal women; met DSM-IV criteria for major depression; HAM-D > 13 |
| EXCLUSION: | Serious organic or neurological disorder; current psychoactive drug use; alcoholism |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes
Mean age: fluvoxamine: 51.1; paroxetine: 51.4
Gender (female %): 100
Ethnicity: 100% Japanese
Other population characteristics: Age at menopause: fluvoxamine: 50.4; paroxetine: 49.9 |
| Authors: Ushiroyama et al.  
| Year: 2004  
| Country: Japan |

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures:</th>
</tr>
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<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td></td>
</tr>
<tr>
<td>Timing of assessments:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significant reduction in HAM-D and HAM-A scores in both groups; no significant differences between groups</td>
</tr>
<tr>
<td>• HAM-D at endpoint (fluvoxamine vs. paroxetine): 9.3 vs. 10.1; p=0.45</td>
</tr>
<tr>
<td>• HAM-A at endpoint (fluvoxamine vs. paroxetine): 6.5 vs. 7.0; p=0.53</td>
</tr>
<tr>
<td>• Reduction of VAS score at endpoint (fluvoxamine vs. paroxetine): 33.1 vs. 42.8; p=0.0338</td>
</tr>
<tr>
<td>• A significant difference observed in % change for hot flashes (fluvoxamine vs. paroxetine): -81.1 vs. -66.8; p&lt;0.01</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
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</thead>
<tbody>
<tr>
<td>ITT: yes</td>
</tr>
<tr>
<td>Post randomization exclusions: NR</td>
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</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
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</thead>
<tbody>
<tr>
<td>Loss to follow-up: fluvoxamine: 18.9%; paroxetine: 30.8%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: fluvoxamine: 9.4%; paroxetine: 5.8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NR</td>
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<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
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<tbody>
<tr>
<td>Fair</td>
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</tbody>
</table>
**Evidence Table 1**  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Ventura D, et al.  
Year: 2007  
Country: USA |
| FUNDING: | Forest Labs |
| DESIGN: | Study design: RCT  
Setting: Multicenter (8)  
Sample size: 212 |
| INTERVENTION: |  
Drug: Escitalopram  
Dose: 10 mg  
Duration: 8 weeks  
Sample size: 104  
Sertraline  
50-200 mg (mean at wk 8 143.8 mg)  
8 weeks  
107 |
| INCLUSION: | Male and female outpatients; 18-80 years; diagnosed with MDD, MADRS of at least 22 with normal lab values and negative pregnancy test. |
| EXCLUSION: | Lactation; Axis disorder other than MDD, history of any psychotic disorder; bipolar; schizopherenia; OCD; mental retardation or pervasive development disorder; substance abuse or dependency; posed suicide risk; personality disorder. Depot neuroleptic w/in 6 months, any nueroleptic, antidepressant, or anxiolytic w/in 2 weeks (fluoxetine 5 weeks). Previous trmt w/ Escitalopram or sertraline; previous trmt failure with 2 antidepressants; investigational study within 1 month or psychotropic drugs |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem or zaleplon for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Escitalopram 40.6 sertraline 38.1  
Gender (female %): Escitalopram 54.8 sertraline 60.2  
Ethnicity: Escitalopram 82.7 sertraline 89.8% caucasian  
Other population characteristics: |
| Authors: Ventura et al. |
| Year: 2007 |
| Country: USA |

**OUTCOME ASSESSMENT:**
- **Primary Outcome Measures:** MADRS
- **Secondary Outcome Measures:** HAM-D, GGI-S, CGI-I, HAM-A, CES-D, and QOL scale
- **Timing of assessments:** Baseline, weeks 1,2,3,4,6,8

**RESULTS:**
- Change from baseline Escitalopram vs sertraline
  - MADRS: -19.1 (0.4) vs. -18.4 (0.9); HAM-D: -16.9 (0.7) vs. -16.1 (0.8)
  - CGI-S: -2.1 (0.7) vs. -2.1 (0.1)
  - Final CGI-I: 1.8 (0.8) vs. 1.8 (0.1)
  - Response MADRS: 75% vs. 70%; HAM-D: 72% vs. 69%; CGI-T < 2: 72% vs. 78%
  - Remission MADRS < 10: 58% vs. 58%; HAM-D < 7: 49% vs. 53%

**ANALYSIS:**
- ITT: Yes
- Post randomization exclusions: 4

**ATTRITION:**
- **Loss to follow-up:** 14.5% overall; 15% escitalopram; 14% sertraline
- **Withdrawals due to adverse events:** 2% escitalopram; 4% sertraline
- **Withdrawals due to lack of efficacy:** NR
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- Escitalopram vs. sertraline (%)
  - Diarrhea: 13 vs. 23
  - Nausea: 17 vs. 17
  - Insomnia: 14 vs. 17
  - Libido decreased: 10 vs. 14
  - Upper respiratory tract infection: 10 vs. 14
  - Dry mouth: 4 vs. 14
  - Headache: 13 vs. 10
  - Somnolence: 12 vs. 6
  - Ejaculation disorder (11/47) vs. (10/43) 23

**QUALITY RATING:** Fair
**Evidence Table 1 Major Depressive Disorder Adults**

| STUDY: | Authors: Wade A, et al.\textsuperscript{54}  
Year: 2007  
Country: Multinational (9 countries) |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter (35 general practice and psychiatric centers)  
Sample size: 295 |
| INTERVENTION: |  
Drug: Escitalopram  
Dose: 20 mg  
Duration: 24 weeks  
Sample size: 144  
Duloxetine  
Dose: 60 mg  
Duration: 24 weeks  
Sample size: 151 |
| INCLUSION: | MDD (current episode assessed with MINI) according to DSM IV-TR criteria; outpatients; aged 18-68 years; MADRS total score > 26 and CGI-S score > 4 at baseline |
| EXCLUSION: | DSM-IV-TR for bipolar disorder, psychotic disorder or features, current eating disorder, mental retardation, any pervasive developmental disorder or cognitive disorder, alcohol or drug-abuse related disorder within 12 months prior to baseline; serious suicide risk, based on investigator’s clinical judgment, or score of > 5 on item 10 of MADRS; receiving formal behavior therapy or systematic psychotherapy; pregnant or breastfeeding; history of lactose intolerance; hypersensitivity or non-response to citalopram, escitalopram or duloxetine; increased intra-ocular pressure or risk of acute narrow-angle glaucoma; taking (within 2 weeks of baseline) MAOI or RIMA, SSRIs, SNRIs, tricyclic antidepressants, tryptophan, psychoactive herbal remedies, oral antipsychotic and anti-manic drugs; ECT (within 6 months); dopamine antagonists, anxiolytics, anticonvulsants, serotonergic agonists, narcotic analgesics, cardiac glycosides, type 1c anti-arrhythmics, oral anticoagulants, cimetidine, potent inhibitors of CYP2C19, CYP1A2 |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: escitalopram: 43.3; duloxetine: 44.5  
Gender (female %): escitalopram: 74.1%; duloxetine: 70.2%  
Ethnicity: escitalopram: 94.4%; duloxetine: 97.4%  
Other population characteristics: |
| Authors: Wade A, et al.  
Year: 2007  
Country: |
|---|
| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** MADRS (adjusted mean change from baseline)  
**Secondary Outcome Measures:** MADRS total score, HAM-D-17, CGI-I, CGI-S, HAMA  
**Timing of assessments:** Baseline and after 1, 2, 4, 8, 12, 16, 20 and 24 weeks |
| **RESULTS:** | • Mean change (at week 24) from baseline in MADRS total scores (escitalopram vs. duloxetine): -23.4 vs. -21.7 (p = 0.055); mean change at week 8: -19.5 vs. -17.4 (p < 0.05)  
• After acute treatment (8 wks), 68.8% of escitalopram vs. 57.5% duloxetine patients were responders (≥50% decrease in MADRS total score); p<0.05; proportion of remitters (MADRS ≤12) was 56.0% vs. 47.9% (p=NS)  
• After 24 weeks, 81.6% vs. 76.7% were responders (p=NS); 73.0% vs. 69.9% were remitters (p=NS)  
• HAM-D-17 total scores improved steadily from baseline to week 24 for both groups with statistically significant separation (p<0.05) at weeks 1, 2, and 16 in favor of escitalopram  
• HAM-A total score at week 24 7.7 vs. 8.6 (p=NS)  
• No significant difference on any of the 8 subscales of SF-36 |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes (8)  
**Loss to follow-up differential high:** No |
<p>| <strong>ATTRITION:</strong> | Escitalopram | Duloxetine |
| Loss to follow-up: | 22.2% | 24.5% |
| Withdrawals due to adverse events: | 9% | 17.2% |
| Withdrawals due to lack of efficacy: | 4.9% | 1.3% |</p>
<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>Adverse events with incidence of ≥5% (escitalopram vs. duloxetine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall: 77.6% vs. 74.8%</td>
<td>• Nausea: 24.5% vs. 31.8%</td>
</tr>
<tr>
<td>Headache: 23.1% vs. 16.6%</td>
<td>• Dizziness: 9.1% vs. 15.9%</td>
</tr>
<tr>
<td>Dry mouth: 9.1% vs. 13.2%</td>
<td>• Fatigue: 8.4% vs. 11.3%</td>
</tr>
<tr>
<td>Insomnia: 4.9% vs. 12.6%; p&lt;0.05</td>
<td>• Nasopharyngitis: 10.5% vs. 7.3%</td>
</tr>
<tr>
<td>Diarrhea: 7.7% vs. 7.3%</td>
<td>• Hyperhidrosis: 5.6% vs. 7.3%</td>
</tr>
<tr>
<td>Vomiting: 5.6% vs. 7.3%</td>
<td>• Constipation: 2.8% vs. 8.6%; p&lt;0.05</td>
</tr>
<tr>
<td>Influenza: 6.3% vs. 3.3%</td>
<td>• Dyspepsia: 6.3% vs. 2.8%</td>
</tr>
<tr>
<td>Somnolence: 5.6% vs. 1.3%</td>
<td>• Sexual dysfunction: 4.9% vs. 6.6%; p=NS</td>
</tr>
<tr>
<td>Constipation: 2.8% vs. 8.6%; p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia: 6.3% vs. 2.8%</td>
<td>• Sexual dysfunction: 4.9% vs. 6.6%; p=NS</td>
</tr>
</tbody>
</table>

| QUALITY RATING: | Fair |
## Evidence Table 1

### Major Depressive Disorder Adults

| STUDY: | Authors: Weihs KL, et al., Doraiswamy PM, et al.\(^85, 86\)  
Year: 2000, 2001  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 100 |
| INTERVENTION: | **Drug:**  
Bupropion SR  
100-300 mg/d  
Mean daily dose: 197 mg/d  
6 weeks  
Paroxetine  
10-40 mg/d  
Mean daily dose: 22 mg/d  
6 weeks |
| INCLUSION: | 60 yrs or older; DSM-IV criteria for major depression; recurrent episode of non-psychotic depression; ≥ 18 on HAM-D-21; duration at least 8 weeks not more than 24 months |
| EXCLUSION: | History of seizures; dementia; alcohol or substance abuse; existing suicidal risk; clinically relevant; unstable medical disorder; psychoactive drugs within 1 week or investigational drugs within 4 weeks; taking other drugs known to lower seizure threshold; anorexia or bulimia; previous treatment with bupropion or paroxetine |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** bupropion SR: 69.2, paroxetine: 71.0  
**Gender (% female):** bupropion SR: 54, paroxetine: 60  
**Ethnicity:** (% white) bupropion SR: 98, paroxetine: 90  
**Other population characteristics:** Prior antidepressant use for current episode: bupropion SR: 17%, paroxetine: 12% |
| Authors: Weihs KL, et al., Doraiswamy PM et al |
| Year: 2000, 2001 |
| Country: US |

**OUTCOME ASSESSMENT:**

Measures and timing of assessments:
- HAM-D, CGI-S, CGI-I, HAM-A weekly for 6 weeks,
- Short Form 36 Health Survey (SF-36), Quality of Life Depression Scale (QLDS) at baseline and week 6

**RESULTS:**

- No significant differences in any outcome measures between the treatment groups (LOCF and observed)
- Response rates (≥ 50% reduction in HAM-D) were similar in both groups: bupropion sr: 71%, paroxetine: 77%
- CGIS, CGIi, and HAMA were all similar at each week of the study
- No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at the endpoint
- Overall significant improvement in QLDS and QOL at day 42 (p < 0.0001)

**ANALYSIS:**

- ITT: Yes
- Post randomization exclusions: Yes

**ATTRITION:**

- Loss to follow-up: 16%; bupropion sr: 16.6%, paroxetine: 15.4%
- Withdrawals due to adverse events: bupropion sr: 8.3%, paroxetine: 5.8%
- Loss to follow-up differential high: No

**ADVERSE EVENTS:**

- Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; p < 0.05), diarrhea (21% vs. 6%; p < 0.05), and constipation (15% vs. 4%; p < 0.05)
- More than 10% in both groups reported headache, insomnia, dry mouth, nausea, dizziness, and agitation
- Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects

**QUALITY RATING:**

- Fair
### Evidence Table 1

| STUDY: | Authors: Weinmann et al. 87  
Year: 2008  
Country: Multinational |
|--------|--------------------------------------------------|
| FUNDING: | German Institute for Quality and Efficiency  
in Health Care (IQWiG) |
| DESIGN: | Study design: systematic review and meta-analysis  
Number of patients: 3142 |
<p>| AIMS OF REVIEW: | Systematically review studies on the efficacy of venlafaxine vs SSRI and to evaluate the influence of methodological issues on the effect sizes. |
| TIME PERIOD COVERED: | 1966 to January 2006 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Double-blind randomized controlled trials, duration of 6 weeks to 6 months |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Adults with MDD |</p>
<table>
<thead>
<tr>
<th>Authors: Weinmann et al.</th>
<th>Year: 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARACTERISTICS OF INTERVENTIONS:</td>
<td>Venlafaxine was compared to citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline with or without a placebo control</td>
</tr>
</tbody>
</table>
| MAIN RESULTS: | • Remission rates (risk ratio \([RR]= 1.07, 95\%\text{ confidence intervals} [95\%CI]=0.99 \text{ to } 1.15\), numbers needed to treat \([NNT]=34\)  
• Response rates \(RR=1.06, 95\%CI=1.01 \text{ to } 1.12\), \(NNT= 27\) |
| ADVERSE EVENTS: | Dropout rates \(RR=1.05, 95\%CI=0.93 \text{ to } 1.2\), \(NNH=100\)  
Dropouts due to AEs \(RR\) of 1.38 (95\%CI=1.08 to 1.77, \(NNH=32\) |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Medline, EMBASE, PsycINFO, PSYNDEx, Cochrane Central Register of Controlled Trials, study registers) and the manufacturer’s database |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |
## Evidence Table 1: Major Depressive Disorder Adults

| STUDY: Authors: Yevtushenko V et al. | Year: 2007  
| Country: Russia |
| --- | --- |
| FUNDING: ARBACOM |
| DESIGN: Study design: RCT  
Setting: psychiatric outpatient clinics  
Sample size: 330 |
| INTERVENTION: Drug:  
Dose:  
Duration:  
Sample size: |
| Escitalopram  
10 mg  
6 weeks  
108 |
| Citalopram10  
10 mg  
6 weeks  
106 |
| Citalopram20  
20 mg  
6 weeks  
108 |
| INCLUSION: Age 25 to 45 years; a diagnosis of MDD; total score at least 25 on the MADRS; and, in the opinion of the treating psychiatrist, the potential to benefit from treatment with one or the other study drugs. |
| EXCLUSION: Mania or any bipolar disorder, schizophrenia, or any psychotic disorder, or displayed any psychotic features, OCD, mental retardation or any pervasive developmental disorder, eating disorder (anorexia nervosa or bulimia nervosa), dementia, or alcohol or drug abuse within the previous 12 months; history of severe drug allergy or hypersensitivity, other serious illness or sequela of serious illness, citalopram or escitalopram treatment within 60 days prior to inclusion, and/or an inability to comply with the protocol, in the investigator's opinion; if the study drugs were considered to be not clinically relevant (based on clinical judgment) or if the patient had received an oral antipsychotic drug or MAOIs within 2 weeks; a depot antipsychotic preparation within 6 months; an SSRI or SNRI, or a TCA within 1 week prior; or fluoxetine within 5 weeks; treatment with an antiparkinsonian compound, barbiturate, chloral hydrate, lithium, anticonvulsant, or hypnotic and anxiolytic; women who were pregnant or breastfeeding |
| OTHER MEDICATIONS/INTERVENTIONS: Benzodiazepines used for insomnia at a stable dose for the previous 6 months or used episodically at a lower recommended dose |
| POPULATION CHARACTERISTICS: Groups similar at baseline: Yes  
Mean age: Escitalopram 35 Citalopram10 35 Citalopram20 35  
Gender (female %): Escitalopram 61.1 Citalopram10 57.5 Citalopram20 56.5  
Ethnicity: Race white Escitalopram 100% Citalopram10 100% Citalopram20 100%  
Other population characteristics: First depressive disorder Escitalopram 85.2% Citalopram10 90.6% Citalopram20 90.7% |
**Authors:** Yevtushenko  
**Year:** 2007  
**Country:** Russia

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Change in MADRS  
|                  | Secondary Outcome Measures: MADRS subanalysis, CGI-I and CGI-S  
|                  | Timing of assessments: Baseline and weeks 1,4,6  
| RESULTS: | • Escitalopram vs. Citalopram10 vs. Citalopram20  
|           | • Response 95.4% vs. 44.3% vs. 83.3% (both, P < 0.001)  
|           | • Remission 89.8% vs. 25.5% vs. 50.9%  
|           | • Change MADRS from baseline -28.70(0.78) vs. -20.11(0.8) vs. -25.19 (0.78) (both, P < 0.001)  
| ANALYSIS: | ITT: yes  
|           | Post randomization exclusions: 8  
|           | Loss to follow-up differential high: no  
| ATTRITION: | Overall  
|           | 0  
|           | Loss to follow-up  
|           | 0  
|           | Withdrawals due to adverse events:  
|           | 0  
|           | Withdrawals due to lack of efficacy:  
|           | 0  
| ADVERSE EVENTS: | • Escitalopram vs. Citalopram10 vs. Citalopram20 n (%)  
|           | Adverse events 7 (6.5) vs. 16 (15.1) vs. 19 (17.6)  
|           | Nausea 2 (1.9) vs. 4 (4.7) vs. 7 (6.5)  
|           | Fatigue 1 (0.9) vs. 4 (3.8) vs. 0  
|           | Headache 1 (0.9) vs. 2 (1.9) vs. 4 (3.7)  
| QUALITY RATING: | Fair  

Second generation antidepressants
### Evidence Table 2  Dysthymia

| STUDY: | Authors: Barrett, et. al.  
Year: 2001  
Country: US |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Hartford Foundation, MacArthur Foundation</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT (also used a behavior therapy arm)  
Setting: Primary care settings  
Sample size: 241 |
| INTERVENTION: | Drug: Paroxetine 10-40 mg/d  
11 weeks | Placebo  
N/A  
11 weeks | Behavior Therapy  
N/A  
11 weeks |
| INCLUSION: | Age 18-59; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; illness at least 4 weeks with at least 3 symptoms; diagnosis made by research psychiatrist using PRIME-MD |
| EXCLUSION: | (from Williams et al., 2000) major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE < 23); medical illness with prognosis < 6 months to live; patients in current treatment excluded unless willing to discontinue and dose < 50 mg of amitriptyline|
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Age: Mean 44.1  
Gender (% female): 63.9%  
Ethnicity: Non-Hispanic white: 90%, Asian Pacific: 3%, African American: 3%, Native American: 3%, Hispanic: < 1%  
Other population characteristics: Comorbid anxiety disorders: 25%, employed FT: 61.3%, mean # of chronic medical conditions: 2.1, Duke Severity of Illness mean 13.3 |
| Authors: Barrett et al.  
Year: 2001  
Country: US |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
</tr>
</tbody>
</table>
| **RESULTS:** | • ITT analysis: mean decrease in HSCL-D-20: paroxetine: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no significant differences between arms;  
• remission by HAM-D-17 score ≤ 6: paroxetine: 80%, placebo: 44.4%; behavior therapy: 56.8% (p = 0.008 for difference among all three arms)  
• minor depression: paroxetine 60.7%, placebo 65.6%; behavior therapy 65.5% (p = 0.906 for difference among all three arms)  
• SF 36 results were not compared head to head, they seem to only be compared within groups over time |
| **ANALYSIS:** | ITT: Yes  
Post randomization exclusions: No |
| **ATTRITION:** | Loss to follow-up: 20.7  
Withdrawals due to adverse events: PAR: 7.5  
Loss to follow-up differential high: No |
| **ADVERSE EVENTS:** | Not reported |
| **QUALITY RATING:** | Fair |
## Evidence Table 2  
### Dysthymia

| STUDY: | Authors: Devanand DP, et al.  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH and capsules provided by Eli Lilly</td>
</tr>
<tr>
<td>OBJECTIVE:</td>
<td>To determine efficacy and side effects of fluoxetine in elderly patients with dysthymia</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Depression clinic  
Sample size: 90 |
| INTERVENTION: | **Drug:**  
Fluoxetine:  
10-60 mg/day  
12 weeks  
Sample size: 44  
Placebo:  
N/A  
12 weeks  
Sample size: 46 |
| INCLUSION: | Outpatients with a primary diagnosis dysthymia following DSM-IV criteria; at least 60 years of age; HAM-D score 8-25; and, CGI-S severity score of 3 or more |
| EXCLUSION: | MDD; allergy to fluoxetine; previous lack of response to SSRI; suicide ideation or plan; Mini-Mental State exam less than 23 out of 30; alcohol or substance abuse in last 6 months; bipolar disorder, schizophrenia or other psychotic disorder; stroke, dementia or other major neurological disorder or insult |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem (up to 10 mg/day) for insomnia and lorazepam (up to 2 mg/day) for anxiety |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Uncertain; fluoxetine group more likely to be unmarried males with comorbid anxiety disorder and have a family history of affective disorder.  
**Mean age:** fluoxetine: 69.0, placebo: 70.8  
**Gender (% female):** fluoxetine: 32.5%, placebo: 40.9%  
**Ethnicity (% white):** fluoxetine: 86.4%, placebo 89.1%  
**Other population characteristics:**  
Married: fluoxetine: 29.6%, placebo: 37%  
**Family history of affective disorder:** fluoxetine: 38.6%, placebo 21.7%  
**Comorbid anxiety disorder:** fluoxetine: 11.4%, placebo 6.5%  
**HAM-D:** fluoxetine: 15.3 (+/- 5.1), placebo: 14.4 (+/- 3.0)  
**CGI-S:** fluoxetine: 3.4 (+/- 0.5), placebo 3.2 (+/- 0.5)  
**CDRS:** fluoxetine: 28.0 (+/- 8.9), placebo 25.2 (+/- 11.5) |
| Authors: Devanand DP, et al. |
| Year: 2005 |

**OUTCOME ASSESSMENT:**

**Primary Outcome Measures:**
- HAM-D and CDRS
- Responders classified as having a ≥ 50% decrease in Ham-D scores at final assessment relative to baseline and have a CGI improvement score of 1 or 2

**Timing of assessments:**

**RESULTS:**
- Response rates: fluoxetine: 27.3%, placebo: 19.6% (p < 0.4)
- No differences between treatment groups in quality of life
- Only the CDRS scores demonstrated a significant effect for treatment group in regression analysis:
  - fluoxetine 26.2%, placebo 4.6% (p < 0.04)

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** No

**ATTRITION:**
- Loss to follow-up: Overall 21, Fluoxetine 12, Placebo 7
- Withdrawals due to adverse events: Overall 4, Fluoxetine 3, Placebo 1
- Withdrawals due to lack of efficacy: Overall 4, Fluoxetine 2, Placebo 2
- Loss to follow-up differential high: No

**ADVERSE EVENTS:**
- The only side effect that differed significantly between the 2 groups was yawning: fluoxetine baseline 2.5%, endpoint 20% vs. placebo baseline 6.3%, endpoint 7.5% (% change p < 0.03)

**QUALITY RATING:**
- Good
## Evidence Table 2: Dysthymia

| **STUDY:** | Authors: Ravindran et. al.  
Year: 2000  
Country: Canada and Europe |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| **DESIGN:** | Study design: RCT  
Setting: Multi-center  
Sample size: 310 |
| **INTERVENTION:** | Drug:  
Dose:  
Duration:  
Sertraline  
50-200 mg/day  
12 weeks  
Placebo  
N/A  
12 weeks |
| **INCLUSION:** | 18 yrs or older; DSM-III-R criteria for dysthymia disorder; duration ≥ 5yrs; ≥ 12 on HAM-D seasonal affective disorders version |
| **EXCLUSION:** | Pregnancy, lactation or lack of adequate contraception; major depression; history of psychotic disorders; bipolar disorder; previous use of sertraline; clinically relevant disease; unstable medical conditions; use of psychotropic meds |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: sertraline: 46.0; placebo: 44.2  
Gender (% female): sertraline: 65.8, placebo: 67.8  
Ethnicity: Not reported  
Other population characteristics: Early onset (before 21 yrs): sertraline: 38.0%, placebo: 40.8%  
Duration of illness: sertraline: 17 years, placebo: 15.9 years |
**Authors:** Ravindran et al.  
**Year:** 2000  
**Country:** Canada and Europe

### OUTCOME ASSESSMENT:
*Measures:* SIGH-SAD (Hamilton Depression Rating Scale, Seasonal Affective Disorders Version), HAM-A, CGI-I, CGI-S, MADRS, HAD-A, HAD-D (Hospital Anxiety and Depression scale), BQOLS (Batelle Quality of Life Scale)  
*Timing of assessments:* Weeks 1, 2, 4, 6, 8, 12

### RESULTS:
- Patients in the sertraline group had significantly greater reductions in SIGH-SAD (p = 0.03), MADRS (p = 0.02), CGI-S (p = 0.02), CGI-I (p = 0.02), HAD-A (p = 0.003), and HAD-D (p = 0.004) scores compared to placebo  
- The number of responders was significantly higher in the sertraline group  
- HAM-A: sertraline: 51.9%, placebo: 33.8%, p = 0.001  
- MADRS: sertraline: 53.2%, placebo: 37.5%, p =0.006  
- CGI-I: sertraline: 60.1%, placebo: 39.5%, p < 0.001  
- The number of remitters was also significantly higher in the sertraline group 33.8% vs. 21.6%, p = 0.02  
- BQOLS showed significantly greater improvements in 8 of 9 domains in the sertraline group

### ANALYSIS:
*ITT:* Yes  
*Post randomization exclusions:* Yes

### ATTRITION:
*Loss to follow-up:* 24.2%; sertraline: 23.4%, placebo: 25.0%  
*Withdrawals due to adverse events:* sertraline: 13.3%, placebo: 7.9%  
*Loss to follow-up differential high:* No

### ADVERSE EVENTS:
- More patients in the sertraline group experienced adverse events: 75.3% vs. 64.5% (p = 0.047)  
- Increased sweating: sertraline: 13.9%, placebo: 2%  
- Tremor: sertraline: 13.9%, placebo: 0.7%  
- Nausea: sertraline: 20.9%, placebo: 17.8%  
- Ejaculation disorder: sertraline: 9.3%, placebo: 0

### QUALITY RATING:
Fair
## Evidence Table 2: Dysthymia

| STUDY:  | Authors: Thase et. al., Kocsis et. al., Hellerstein et. al.  
| Country: US  |
| FUNDING: | Not reported  |
| DESIGN: | Study design: RCT  
| Setting: Multi-center (17 US centers)  
| Sample size: 416  |
| INTERVENTION: |  
| Drug: | Sertraline  
| Dose: | 50-200 mg/day  
| Duration: | 12 weeks  |
| | Imipramine  
| | 50-300 mg/day  
| | 12 weeks  
| | Placebo  
| | N/A  
| | 12 weeks  |
| INCLUSION: | Dysthymia for more than 5 years without depression-free period exceeding 2 consecutive months; HAM-D score ≥ 12; age 25-65 yrs.  |
| EXCLUSION: | Other Axis I disorders; pregnancy, lactation; failed to respond in previous trials; drug/alcohol dependency; suicidal risk  |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported  |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean Age: 42  
| Gender (% female): 65%  
| Ethnicity: Caucasian: 95%, black: 2%, Asian: 0.5%, other: 2%  
| Other population characteristics: Not reported  |
**Authors:** Thase, Kocsis, Hellerstein  
**Year:** 1996, 1997, 2000  
**Country:** US

### Outcome Assessment:

*Measures and timing of assessment:* CGI weekly, HAM-D, MADRS biweekly, DSM-IV, Hopkins Symptom Checklist, Inventory for Depression Symptomatology, Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction Questionnaire weeks 8 and 12.

### Results:

- Sertraline group showed significantly more responders than placebo (59.0% vs. 44.3%; p < 0.02).
- No significant differences in responders between sertraline and imipramine-treated patients.
- A significantly greater proportion of patients in the sertraline group increased in psychosocial functioning compared to placebo (61% vs. 45%; p = 0.01) as measured by the Global Assessment of Functioning Score of 71 or more.
- Significant improvements in family relationships, marital relationships, and parental role functioning.
- The harm avoidance scores (from the Tri-dimensional Personality Questionnaire) were significantly decreased in all treatment groups.
- Significantly more sertraline patients than placebo patients were classified as harm avoidance responders (p = 0.001).

### Analysis:

*ITT:* Yes  
*Post randomization exclusions:* Yes

### Attrition:

*Loss to follow-up:* 24.3%; sertraline: 15.7%; imipramine: 33.1%; placebo: 24.3%  
*Withdrawals due to adverse events:* sertraline: 6.0%; imipramine: 18.4%; placebo: 3.6%  
*Loss to follow-up differential high:* Yes

### Adverse Events:

Not reported

### Quality Rating:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 2</th>
<th>Dysthymia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td></td>
</tr>
<tr>
<td>Authors: Vanelle et al.</td>
<td></td>
</tr>
<tr>
<td>Year: 1997</td>
<td></td>
</tr>
<tr>
<td>Country: France</td>
<td></td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td></td>
</tr>
<tr>
<td>Study design: RCT</td>
<td></td>
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<tr>
<td>Setting: Psychiatric centers</td>
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<tr>
<td>Sample size: 140</td>
<td></td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Dose:</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Duration:</td>
<td>phase I: 3 months</td>
</tr>
<tr>
<td></td>
<td>phase II: 6 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>phase 1: 3 months</td>
</tr>
<tr>
<td></td>
<td>phase 2: 6 months</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Adults &gt; 18; minimum HAM-D score of 16; dysthymia not secondary to any other axis I disorder</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Additional mental illnesses or organic mental disorder; MDD or other type of depression; secondary-type dysthymia; uncontrolled serious somatic disease; fluoxetine for a depressive disorder which had not been effective; received a psychotropic drug during the previous week (except for authorized benzodiazepines); requiring one of the following during the study: neuroleptic, lithium, or other mood regulator</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/ INTERVENTIONS:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: NR</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): fluoxetine: 76.9%, placebo: 73.5%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Early onset of dysthymia: 22.9%, late onset: 77.1%</td>
</tr>
<tr>
<td>Authors: Vanelle et al.</td>
<td>Year: 1997</td>
</tr>
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<td>------------------------</td>
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</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Primary Outcome Measures: HDRS, CGI</td>
</tr>
<tr>
<td></td>
<td>Secondary Outcome Measures: HDRS, HARS, CGI, GAF-S, Paykel Life Event Questionnaire, HSCL-58, AMDP-5</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td># of responders at month 3 (&gt;50% decrease in HAM-D associated with a score of 1 (very much improved) or 2 (much improved) on the CGI-I): fluoxetine = 42, placebo = 14 (p = 0.03)</td>
</tr>
<tr>
<td></td>
<td>Remission n at month 3 (HAM-D &lt; 7): fluoxetine = 32, placebo = 10 (p = 0.07)</td>
</tr>
<tr>
<td></td>
<td># of responders at month 6: fluoxetine = 33, placebo = 9 (p = 0.48)</td>
</tr>
<tr>
<td></td>
<td>Remission n at month 6: fluoxetine = 29, placebo = 4 (p = 0.01)</td>
</tr>
<tr>
<td></td>
<td>Increase in GAF scores by month 3 significantly greater in fluoxetine (p = 0.02); mean score indicated return to functioning level compatible with normal social &amp; relational life (mean GAF score = 70)</td>
</tr>
<tr>
<td></td>
<td>No significant change in GAF scores from month 3 to 6 for either treatment group</td>
</tr>
<tr>
<td>RESULTS:</td>
<td>ANALYSIS: ITT: Yes</td>
</tr>
<tr>
<td></td>
<td>Post randomization exclusions: NR</td>
</tr>
<tr>
<td></td>
<td>ATTRITION: Loss to follow-up: Phase I: fluoxetine: 13.2%; placebo: 26.5% Phase II: fluoxetine: 7%; placebo: 31%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to adverse events: NR</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high: Yes (16.2%)</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>Phase I: reported at least one adverse event: 38.5% (fluoxetine) vs. 44.9% (placebo)</td>
</tr>
<tr>
<td></td>
<td>Phase II (responders who continued from month 3 to 6): reported at least one adverse event: 18.6% (fluoxetine) vs. 28.6% (placebo)</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 2  Dysthymia

| STUDY: | Authors: Williams JW, et. al.  
Year: 2000  
Country: US |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Hartford Foundation, MacArthur Foundation, Smith Kline Beecham supplied meds and placebo, VA (career award to lead author)</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (Community, VA, and academic primary care clinics)  
Sample size: 415 |
| INTERVENTION: |  
**Drug:** Paroxetine  
**Dose:** 10-40 mg/d, 11 weeks  
**Duration:** 11 weeks  
**Placebo:** N/A, 11 weeks  
**Behavior Therapy:** N/A, 11 weeks |
| INCLUSION: | Age 60 or older; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; symptoms for at least 4 weeks with 3-4 symptoms |
| EXCLUSION: | Major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE ≤ 23); medical illness with prognosis ≤ 6 months to live; patients in current treatment excluded unless willing to discontinue and dose ≤ 50 mg of amitriptyline |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 71  
Ethnicity: paroxetine: 82.5% white, 11.0% Latino, 6.0% black, placebo: 75.7% white, 12.1% Latino, 10.0% black  
Gender (% female): paroxetine: 39%, placebo: 45%  
Other population characteristics: Mean of 3.4 medical conditions per patient |
### Authors: Williams JW, et al.
**Year:** 2000  
**Country:** US

### OUTCOME ASSESSMENT:
**Measures:** Hopkins Symptom Checklist Depression Scale (HSCL-D-20), HDRS, and functional status, by the Medical Outcomes Study Short-Form 36 (SF-36) physical and mental components

**Timing of assessments:**

### RESULTS:
- Mean (SE) decrease in HSCL-D-20:
  - Paroxetine: 0.61 (p =0.05)
  - Placebo: 0.40 (p = 0.05)
  - Behavior Therapy 0.52 (p = 0.05)
  - p = 0.004 for paroxetine vs. placebo
- Paroxetine only statistically and clinically significantly better than placebo for subjects with dysthymia and high baseline mental health function.
- HAM-D results not reported for the ITT population

### ANALYSIS:
**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:
**Loss to follow-up:** 25.1% (for all 3 arms, including behavioral tx)  
**Withdrawals due to adverse events:** Paroxetine: 8.8%, Placebo: 5.7%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:
Not reported

### QUALITY RATING:
Fair
## Evidence Table 3

### Subsyndromal Depression

| Study: | Authors: Barrett, et. al.  
Year: 2001  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding:</td>
<td>Hartford Foundation, MacArthur Foundation</td>
</tr>
</tbody>
</table>
| Design: | Study design: RCT (also used a behavior therapy arm)  
Setting: Primary care settings  
Sample size: 241 |
| Intervention: Drug: | Paroxetine  
10-40 mg/d  
11 weeks |
| | Placebo  
N/A  
11 weeks |
| | Behavior Therapy  
N/A  
11 weeks |
| Inclusion: | Age 18-59; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; illness at least 4 weeks with at least 3 symptoms; diagnosis made by research psychiatrist using PRIME-MD |
| Exclusion: | (from Williams et al., 2000) major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE < 23); medical illness with prognosis < 6 months to live; patients in current treatment excluded unless willing to discontinue and dose < 50 mg of amitriptyline |
| Other Medications/Interventions: | Not reported |
| Population Characteristics: Groups similar at baseline: | Yes |
| Age: | Mean 44.1 |
| Gender (% female): | 63.9% |
| Ethnicity: | Non-Hispanic white: 90%, Asian Pacific: 3%, African American: 3%, Native American: 3%, Hispanic: < 1% |
| Other population characteristics: | Comorbid anxiety disorders: 25%, employed FT: 61.3%, mean # of chronic medical conditions: 2.1, Duke Severity of Illness mean 13.3 |
| **Authors:** Barrett et al.  
| **Year:** 2001  
| **Country:** US |

| **OUTCOME ASSESSMENT:** Measures and timing of assessments: Primary Outcome was 13 items from the Hopkins Symptom Check list Depression Scale (HSCL-D-20) plus 7 additional items. Timing: baseline and each treatment visit (1, 2, 4, 6, 8, 11), also measured: Ham-D-17 and SF36, mental health component and physical health component timing: baseline, 6 and 11 weeks |

| **RESULTS:** |
| ITT analysis: mean decrease in HSCL-D-20: paroxetine: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no significant differences between arms;  
| remission by HAM-D-17 score ≤ 6: paroxetine: 80%, placebo: 44.4%; behavior therapy: 56.8% (p = 0.008 for difference among all three arms)  
| minor depression: paroxetine 60.7%, placebo 65.6%; behavior therapy 65.5%(p = 0.906 for difference among all three arms)  
| SF 36 results were not compared head to head, they seem to only be compared within groups over time |

| **ANALYSIS:** |
| ITT: Yes  
| Post randomization exclusions: No |

| **ATTRITION:** |
| Loss to follow-up: 20.7  
| Withdrawals due to adverse events: PAR: 7.5  
| Loss to follow-up differential high: No |

| **ADVERSE EVENTS:** |
| Not reported |

| **QUALITY RATING:** |
| Fair |
### Evidence Table 3  Subsyndromal Depression

| STUDY: | Authors: Judd et al., 2004<sup>27</sup>  
Year: 2004  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly; NIMH grants; Roher fund of University of California, San Diego</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design:  
Setting: Multicenter  
Sample size: 162 |
| INTERVENTION: |  
Drug:  
Dose: 10-20 mg/d  
Duration: 12 weeks  
Sample size: 81 |
| Inclusion: | Fluoxetine  
Placebo  
N/A  
12 weeks  
81 |
| EXCLUSION: | Adults 18 or older; diagnosed with minor depression according to NIHMH Health Diagnostic Interview Schedule; healthy w/ normal physical exam & labs |
| OTHER MEDICATIONS/ INTERVENTIONS: | Chloral hydrate |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 43.5  
Gender (female %): 59.3  
Ethnicity (% white): 90.1 |
| Other population characteristics: | |
Authors: Judd et al.  
Year: 2004  
Country:  

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Inventory of Depressive Symptomatology  
Secondary Outcome Measures: Psychosocial functioning, overall severity of illness  
Timing of assessments: |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------|

| RESULTS: | • Significantly greater improvement on 30-item IDS for fluoxetine vs. placebo (-1.19 vs. -0.61, p < 0.02)  
• Significantly greater improvement for fluoxetine on Beck Depression Inventory (-0.75 vs. -0.29, p < 0.02)  
• Significantly greater improvement for fluoxetine on HAM-D-17 (-1.11 vs. -0.65, p < 0.05)  
• GAF score significantly greater in fluoxetine group (z = 2.10, p < 0.01)  
• At endpoint, 40.5% (fluoxetine) vs. 24.1% (placebo) patients rated as "normal/not at all depressed" on CGI-S (chi sq = 6.63, df = 1, p = 0.01)  
• No difference between groups in psychosocial functioning measures |

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: No  
Loss to follow-up differential high: No |

| ATTRITION: | Loss to follow-up: 27%  
Withdrawals due to adverse events: fluoxetine 3.7%, placebo 4.9%  
Withdrawals due to lack of efficacy: fluoxetine 7.4%, placebo 11.1% |

| ADVERSE EVENTS: | • Mean # of AEs: 5.2 (fluoxetine) vs. 4.6 (placebo)  
• Insomnia: 24.7% vs. 12.4%, p < 0.05  
• No differences in sexual side effects |

| QUALITY RATING: | Fair |
## Evidence Table 4: Seasonal Affective Disorder

| STUDY: | Authors: Lam et al.\(^98\), Michalek et al.\(^99\)  
Year: 2006, 2007  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Canadian Institute of Health Research (CIHR) &amp; CIHR/Wyeth post-doc fellowship award (Michalak)</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: multi-centre  
Sample size: 96 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:**  
**Sample size:** |
| | Light therapy  
10 000 lux  
8 weeks |
| | Fluoxetine  
20mg/d  
8 weeks |
| INCLUSION: | Out-patients aged 18-65 years  
DSM-IV criteria for major depressive episodes with a seasonal pattern  
>20 on HAMD-17 or >14 on HAMD-17 if >23 on HAMD-24 |
| EXCLUSION: | (1) pregnant or lactating women or could become pregnant  
(2) serious suicidal risk  
(3) DSM-IV diagnoses of organic mental disorders, substance use disorders, including alcohol, active within the last year, schizophrenia, paranoid or delusional disorders, other psychotic disorders, bipolar I disorder, panic disorder or generalized anxiety disorder not concurrent with major depressive episodes;  
(4) serious unstable medical illnesses;  
(5) retinal disease that precluded the use of bright light;  
(6) history of severe allergies and/or multiple drug adverse reactions;  
(7) current use of certain other psychotropic drugs (inc lithium, L-tryptophan, St John’s Wort or melatonin)  
(8) current use of beta blocking drugs;  
(9) use of antidepressants or mood-altering medications within 7 days of baseline;  
(10) previous use of fluoxetine or light therapy;  
(11) formal psychotherapy started within 3 months of baseline or initiated during the study period;  
(12) shift work or southbound travel during the protocol. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes (previous antidepressant therapy 45.8% vs. 33.3%)  
Mean age: 42.3, 44.6 Gender (female %): 66.7%  
Ethnicity: Canadian  
Other population characteristics: NR |
Authors: Lam et al., Michalek et al.
Year: 2006
Country: Canada

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Primary Outcome Measures: HAMD-24 clinical response= ≥50% reduction from baseline, clinical remission= response + scores≤8, Patient perception of Quality of Life (Q-LES-Q, SF-20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures: CGI, BDI-II</td>
</tr>
<tr>
<td>Timing of assessments: 1, 2, 4, 8 weeks</td>
</tr>
</tbody>
</table>

**RESULTS:**

- Significant effect of time, but no significant difference between light therapy and fluoxetine
- Clinical response rate: both 67%
- Clinical remission rate: light 50% vs. fluoxetine 54% p=0.84
- CGI improvement rating: 1.90 vs. 1.92
- Much/very much improved CGI: both 73%
- No difference in sub-group “severely depressed” (HAMD-24≥30): response 70% vs. 73% remission 48% vs. 50%
- Improvements in Q-LES-Q: light 20.56 vs. fluoxetine 21.77 (not sig)
- Improvements in SF-20: light 7.82 vs. fluoxetine 9.38 (not sig)
- Improvements in depression were significantly associated with improvements in QoL

**ANALYSIS:**

- ITT: yes
- Post randomization exclusions: No
- Loss to follow-up differential high: No

**ATTRITION:**

<table>
<thead>
<tr>
<th>Light therapy</th>
<th>Fluoxetine 20mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>16%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>2%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>NR</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- Light therapy vs. fluoxetine
- At least one AE: 77% vs. 75%
- Agitation 0% vs. 12.5% p<0.05
- Sleep disturbance 2.1% vs. 29.2% p<0.01
- Palpitations 0% vs. 10.4% p<0.05

Occurred more often in light therapy than fluoxetine group (though reported as not significant):
- Headache 16.7% vs. 10.4%
- Feeling faint 6.3% vs. 0

**QUALITY RATING:**

Good
<table>
<thead>
<tr>
<th>Evidence Table 4</th>
<th>Seasonal Affective Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Moscovitch et al. 100  
|                  | Year: 2004  
|                  | Country: Multinational (Canada and Europe)  |
| **FUNDING:**     | Pfizer International  |
| **DESIGN:**      | Study design: RCT  
|                  | Setting: multi-centre  |
|                  | Sample size: 187  |
| **INTERVENTION:**| Sertraline  
| Drug:            | Flexible dose 50-200mg/d  
| Dose:            | 8 weeks  |
| Duration:        | Sample size: 93  |
| Placebo          | n/a  
| Sample size:     | 8 weeks  |
|                  | Sample size: 94  |
| **INCLUSION:**   | Outpatients, older than 18,  
|                  | DSM-IIIR criteria for major depression, depressive disorder NOS, bipolar disorder depressed, or bipolar disorder NOS with a seasonal pattern.  
|                  | 12 on HAMD, plus 10 on supplementary items for SAD evaluation, 22 on 29-item HAMD, SIGH-SAD  
|                  | less than 25% improvement during washout  
|                  | enrolled during winter  |
| **EXCLUSION:**   | Very serious suicide risk, history of alcoholism, drug abuse, poor motivation or intellectual problems  |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Any necessary for other medical conditions, not psychoactive  |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: yes  
|                  | Mean age: 39.6±11.6, 40.0±11.2  
|                  | Gender (female %): 77.5%  
|                  | Ethnicity: Austria, Canada, Finland, France, UK  
|                  | Other population characteristics: NR  |
### Authors: Moscovitch et al  
### Year: 2004  
### Country: Multinational

| OUTCOME ASSESSMENT: | Primary Outcome Measures: HAMD-29, HAMD-21, HAMD-17, HAMD item 1, CGI-S, HAMA, HAD-D, HAD-A  
| | Secondary Outcome Measures: not specified  
| | Timing of assessments: 1, 2, 4, 6, 8 weeks

### RESULTS:
- Sertraline was better than placebo at endpoint (ITT population) for all of the above efficacy measures: HAMD-29 -17.90 vs. -13.39 p=0.019, HAMD-21 -10.63 vs. -7.51 p=0.016, HAMD-17 - 9.36 vs. -6.87 p=0.033, CGI-S -1.60 vs. -1.06 p=0.018, HAMA -8.99 vs. -6.52 p=0.024, HAD-D - 5.04 vs. -2.87 p=0.005, HAD-A -4.00 vs. -2.16 p=0.006.
- Significantly more patients in the sertraline group received a CGI-I rating of one or two (eg: a CGI-I response) at endpoint than placebo (62.4% vs. 46.2% p=0.04)
- There were no substantial differences in sleep factors (Leeds sleep evaluation)
- The mean final dose of sertraline was 111.3±44.9 mg

### ANALYSIS:
- ITT: Yes
- Post randomization exclusions: 1
- Loss to follow-up differential high: No

### ATTRITION:
- Loss to follow-up:
  - Sertraline: NR
  - Placebo: NR
- Withdrawals due to adverse events:
  - Sertraline: 10.8%
  - Placebo: 4.3%
- Withdrawals due to lack of efficacy:
  - Sertraline: 3.2%
  - Placebo: 14.9%

### ADVERSE EVENTS:
- Sertraline vs. placebo (%): Treatment related AEs 81.7% vs. 50.0% p=0.001  
  - Nausea 35.5% vs. 8.5% p=0.001
  - Insomnia 24.7% vs. 10.6% p= 0.01
  - Diarrhea 19.4% vs. 5.3% p= 0.004
  - Dry mouth 12.9% vs. 2.1% p=0.005
  - Ejaculation * 14.3% vs. 4.8 p=0.31
  - Abdominal pain 9.5% vs. 4.3% p=0.15
  - Sustained erection * 9.5% vs. 0 % p=0.15
  - Tremor 7.5% vs. 2.1% p=0.09
  - Vomiting 6.5% vs. 1.1% p=0.01
  - Anorexia 6.5% vs. 1.1% p= 0.053
  - Anxiety 4.3% vs. 1.1% p=0.17

### QUALITY RATING:
- Fair
### Evidence Table 5

**Major Depressive Disorder Pediatrics**

| STUDY: | Authors: Berard et al.\(^{101}\)  
Year: 2006  
Country: Multi-national (South Africa) |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>GlascoSmithKline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: multicentre  
Sample size: 286 |
| INTERVENTION: | Paroxetine  
Dose: 20-40mg/d  
Duration: 12 weeks  
Sample size: 182  
placebo  
Dose: n/a  
Duration: 12 weeks  
Sample size: 93 |
| INCLUSION: | Male and female adolescent outpatients (13–18 years of age)  
Unipolar major depression DSM-IV, diagnosis was confirmed by the K-SADS-L at baseline  
MADRS≥16 at screening and baseline and C-GAS<69 at screening. |
| EXCLUSION: | primary conduct disorder in childhood, autism or pervasive mental disorder, or obsessive compulsive disorder, panic disorder, social phobia, or posttraumatic stress disorder that preceded the diagnosis of depression.  
Current psychiatric disorder, including schizophrenia, epilepsy,  
previous response to psychotherapy as a treatment for depression or previous use of paroxetine,  
anticipated long-term formal psychotherapy substance abuse/dependence  
 concurrent psychoactive medication use  
known sensitivity to SSRIs  
pregnancy/lactation  
recent electroconvulsive therapy  
clinically significant abnormal laboratory or electrocardiogram findings  
Although a history of suicide attempt(s) was not exclusionary, patients with current serious suicidal ideation were excluded. |
| OTHER MEDICATIONS/INTERVENTIONS: | routine short-term supportive psychotherapy or family supportive therapy was permitted |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes  
Mean age: 15.5-15.8  
Gender (female %): 66.6%  
Ethnicity: approx 66% caucasian  
Other population characteristics: approx 15% co-morbidity of anxiety disorder |
Authors: Berard et al  
Year: 2006  
Country: Multi-national (South Africa)

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
</table>
| **Primary Outcome Measures:** | proportion of responders eg: ≥50% reduction in MADRS  
| | Change from baseline in K-SADS-L depression subscale score  
| **Secondary Outcome Measures:** | change from baseline in MADRS, CGI-S, BDI, Mood and feelings Questionnaire (MFQ), CGI-I  
| **Timing of assessments:** | weeks 1, 2, 3, 4, 6, 8, 12  

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| • MADRS responders paroxetine 60.5% vs placebo 58.2%, (NS p=0.702)  
| • Mean paroxetine dose 25.8mg/d  
| • K-SADS-L depression subscale decrease 9.3 vs. 8.9 (NS p=0.616)  
| • No difference in any secondary outcome measure  
| • Post hoc analysis of CGI-I responders (CGI-I=1 or 2) paroxetine 69.2% vs. placebo 57.3%, OR 1.74 (95%CI 1.01, 2.99, p=0.45)  
| • Age subgroups: patients >16 years old MADRS responders paroxetine 71.2% vs. placebo 47.1%, p=0.021 (unadjusted for co-variates)  
| • In patients ≤16 years old MADRS responders paroxetine 55.1% vs. placebo 64.9%, p = NS  

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
</table>
| ITT: Yes  
| Post randomization exclusions: 11  
| Loss to follow-up differential high: No  

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
</tr>
</tbody>
</table>
| Withdrawals due to adverse events: | Paroxetine 30.2%  
| &nbsp; | 11.0%  
| &nbsp; | 4.9%  
| Withdrawals due to lack of efficacy: | Placebo 25.8%  
| &nbsp; | 7.5%  
| &nbsp; | 6.5%  

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
</table>
| Paroxetine vs. placebo (%)  
| All AEs 65.9% vs. 59.1%  
| Nausea 1.1% vs 0%  
| Agitation 1.6% vs 0%  
| Depression 1.1% vs. 0%  
| Suicide related AE 4.4% vs. 2.1%  

| QUALITY RATING: | Fair  

---

Second generation antidepressants

Drug Effectiveness Review Project
## Evidence Table 5
**Major Depressive Disorder Pediatrics**

| STUDY: | Authors: Emslie et al.\(^{102}\)  
Year: 2006  
Country: USA |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>GlascoSmithKline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: multi-centre  
Sample size: 206 |
| INTERVENTION: | Paroxetine  
10-50mg/d  
8 weeks  
104  
placebo  
n/a  
8weeks  
102 |
| Drug: |  |
| Dose: |  |
| Duration: |  |
| Sample size: |  |
| INCLUSION: | Age 6-17 years  
DSM-IV diagnosis for MDD  
≥45 on the CDRS-R  
The diagnosis of MDD and presence of any comorbid psychiatric disorders were confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (6-18years) Present and Lifetime Version semistructured interview |
| EXCLUSION: | clinically predominant Axis I disorder other than MDD.  
history of a psychotic episode (e.g., schizophrenia), bipolar disorder, pervasive developmental disorder, substance abuse/dependence,  
prior nonresponse to SSRIs,  
suicidal/homicidal risk,  
concurrent psychotherapy  
psychotropic pharmacotherapy  
any serious medical condition or clinically significant finding in the screening or baseline evaluation that would preclude the administration of paroxetine. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes  
Mean age: 12.0 (SD=2.97) Gender (female %): 46.8%  
Ethnicity: majority white (79.3%)  
Other population characteristics: NR |
Authors: Emslie et al.  
Year: 2006  
Country: USA

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** change from baseline in CDRS-R total score  
**Secondary Outcome Measures:**  
**Responders:** CGI-I 1 or 2, **Remission:** CDRS-R ≤28 or CGI-I=1  
CGI-S; and change from baseline on the Global Assessment of Functioning scale  
Kutcher Adolescent Depression Scale (self-report instrument for 12- to 17-year-olds).  
**Timing of assessments:** week 1, 2, 3, 4, 6, 8

### RESULTS:

- no difference in CDRS-R between paroxetine and placebo (-22.58 vs. -23.38, p=.684)  
- no difference in CGI-I, CGI-S, Kutcher ADS  
- no difference in remission (CGI-I very much improved: 20.8 vs. 18.0%, p = 0.617)  
- a statistically significant treatment by age group interaction ( p = .049)  
- the adjusted mean difference in change in CDRS-R score from baseline for children (age 7-11) was 5.3 points in favor of placebo; a difference that approached statistical significance (95% CI -0.08-10.63; p = .054).  
- The adjusted mean difference for adolescents was 2.6 points in favor of paroxetine; this difference was not statistically significant (95% CI-8.23-3.13; p = .375).

### ANALYSIS:

**ITT:** yes (when at least one post-baseline assessment)  
**Post randomization exclusions:** 3  
**Loss to follow-up differential high:** no

### ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>7.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>8.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>7.7%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:

- Paroxetine vs. placebo (%)  
  - Cough 5.9% vs. 2.9%  
  - Dyspepsia 5.9% vs. 2.9%  
  - Vomiting 5.9% vs. 2.0%  
  - Dizziness 5.0% vs. 1.0%  
  - Sweating 4.0% vs. 0%  
  - Exacerbation of depression 2.9% vs. 0%  
  - Attempted suicide (suicidality) 2% vs. 1%  
  - Suicidal ideation 1% vs. 0%

### QUALITY RATING: Fair
### Evidence Table 5  
**Major Depressive Disorder Pediatrics**

| STUDY: | Authors: Hetrick  
Year: 2007  
Country: international |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>No sources of support supplied, authors report no conflict of interest</td>
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</tbody>
</table>
| DESIGN: | Study design: systemic review & meta-analysis  
Number of patients: 1972 (paroxetine 646, fluoxetine 527, sertraline 364, citalopram 435) NB: for AEs: 2240. |
| AIMS OF REVIEW: | To determine the efficacy and adverse outcomes, including definitive suicidal behavior and suicidal ideation, of SSRIs compared to placebo in the treatment of depressive disorders in children and adolescents. |
| STUDIES INCLUDED IN REVIEW | 2 RCTs on citalopram  
1 RCT on escitalopram  
4 RCTs on fluoxetine  
3 RCTs on paroxetine  
2 RCTs on sertraline |
| TIME PERIOD COVERED: | Up to October 2005 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Published and unpublished randomised controlled trials of an SSRI compared to placebo. |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Children and adolescents aged 6-18 years old, both in and outpatients, who were diagnosed by a clinician and met DSM or ICD criteria for a primary diagnosis of depressive disorder  
Children and adolescents with a co-morbid condition, an IQ<70, brain injury or serious medical condition were excluded. |
### Authors: Hetrick et al.

**Year:** 2007

### CHARACTERISTICS OF INTERVENTIONS:

fluoxetine, paroxetine, citalopram, escitalopram, and sertraline vs placebo

### MAIN RESULTS:

- Twelve trials were eligible for inclusion, with ten providing usable data. At 8-12 weeks, there was evidence that children and adolescents 'responded' to treatment with SSRIs (RR 1.28, 95% CI 1.17 to 1.41). There was also evidence of an increased risk of suicidal ideation and behaviour for those prescribed SSRIs (RR 1.80, 95% CI 1.19 to 2.72).
- Fluoxetine was the only SSRI where there was consistent evidence from three trials that it was effective in reducing depression symptoms in both children and adolescents (CDRS-R treatment effect -5.63, 95% CI -7.38 to -3.88), and 'response' to treatment (RR 1.86, 95% CI 1.49 to 2.32).
- Where rates of adverse events were reported, this was higher for those prescribed SSRIs.
- Paroxetine: no advantage in efficacy over placebo for either children or adolescents RR=1.09 (95%CI 0.95-1.26)
- Fluoxetine: significant effect in response over placebo RR 1.86, (95%CI 1.49 to 2.32) also in both children (RR 2.43 95% CI (1.30 to 4.56) and adolescents (RR 1.74, 95% CI 1.32 to 2.28)
- Sertraline, no significant benefit ( RR 1.17, 95% CI 1.00 to 1.36) except in subgroup adolescents, where depressive disorder symptom severity scores were statistically significantly lower in the group treated with sertraline (Treatment effect -4.56, 95% CI -8.79 to -0.32)
- Citalopram: significant benefit in response over placebo RR 1.30, 95% CI 1.02 to 1.67

### ADVERSE EVENTS:

- Overall, the risk of experiencing a suicide related outcome while being treated with an SSRI was 80% greater than if treated with a placebo (RR 1.80, 95% CI 1.19 to 2.72).
- Adverse events were more common for those receiving paroxetine (RR 1.14, 95% CI 1.03 to 1.27) and fluoxetine (RR 1.19, 95% CI 1.03 to 1.36)
- The percentage of participants experiencing adverse events did not differ between the citalopram and placebo groups (RR 1.09, 95% CI 0.97 to 1.22)
- AEs occurring more commonly in the SSRI group included: suicide related outcome, decreased appetite, somnolence, tremor, hostility/anger, emotional lability and nausea.

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:

CCDAN Trials Register, MEDLINE, PSYCHINFO and CENTRAL. Reference lists were checked, letters were sent to key researchers and internet databases searched. Conference abstracts for the American Academy of Child and Adolescent Psychiatry were searched.

### STANDARD METHOD OF APPRAISAL OF STUDIES:

Yes

### QUALITY RATING:

Good
### Evidence Table 5: Major Depressive Disorder Pediatrics

<table>
<thead>
<tr>
<th>STUDY: Authors: Keller, et. al.</th>
<th>Year: 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
</tr>
<tr>
<td>FUNDING: Glaxo Smith Kline</td>
<td></td>
</tr>
<tr>
<td>DESIGN: Study design: RCT</td>
<td></td>
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<tr>
<td>Setting: 10 US and 2 Canadian centers</td>
<td>Sample size: 275</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td></td>
</tr>
<tr>
<td>Paroxetine 20-40 mg/d 8 weeks</td>
<td>Imipramine 200-300 mg/d 8 weeks</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td></td>
</tr>
<tr>
<td>Ages 12-18; met DSM-IV criteria for current MDD of at least 8 weeks duration; minimum score of 12 on HAM-D17; score &lt; 60 on Children’s Global Assessment Scale and score of ≥ 80 on Peabody Picture Vocabulary Test</td>
<td></td>
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<tr>
<td>EXCLUSION:</td>
<td></td>
</tr>
<tr>
<td>Current or past history of bipolar disorder; schizoaffective disorder; eating disorder; alcohol or substance use disorder; OCD; autism/pervasive developmental disorder; organic brain disorder; diagnosis of PTSD within 12 months; suicidal ideation with intent or specific plan; history of suicide attempt by drug overdoses; current psychotropic drug use; adequate trial of antidepressant medication within 6 months; exposure to investigational drug use either within 30 days or 5 half-lives of the drug; pregnant, breastfeeding or lactating or sexually active non-contraceptive using females</td>
<td></td>
</tr>
<tr>
<td>ALLOWED OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Not reported</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td></td>
</tr>
<tr>
<td><strong>Groups similar at baseline:</strong> Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age:</strong> paroxetine: 14.8, placebo: 15.1</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong> (% female): paroxetine: 62.4%; placebo: 65.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity:</strong> paroxetine: white: 82.8%, African American: 5.4%, Asian: 1.1%, other: 10.8%, placebo: white: 80.5%, African American: 6.9%, Asian: 2.3%, other: 10.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Other population characteristics:</strong> Anxiety: 19-28%, externalizing disorder: 20-26%</td>
<td></td>
</tr>
</tbody>
</table>
**Authors:** Keller et. al.  
**Year:** 2001  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: Remission (HAM-D ≤ 8), Response (HAM-D ≥ 50% reduction from baseline), mean HAM-D change from baseline, CGI, K-SADS-L, individual HAM-D factors, SIP self-perception profile  
**Timing of assessments:** at baseline and weekly intervals weeks 1-8 |
|---|---|

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| • Mean HAM-D change: paroxetine: 10.74 (p = 0.13 vs. placebo), imipramine: 8.91 (p = 0.81 vs. placebo), placebo: 9.09;  
• HAM-D remission: paroxetine: 63.3% (p = 0.02 vs. placebo), imipramine: 50% (p = 0.57 vs. placebo), placebo: 46%;  
• HAM-D response: paroxetine: 66.7% (p = 0.11 vs. placebo), imipramine: 58.5% (p = 0.61 vs. placebo), placebo: 55.2%;  
• Mean CGI: paroxetine: 2.37 (p = 0.09 vs. placebo), imipramine 2.70 (p = 0.90 vs. placebo), placebo: 2.73  
• CGI score of 1 or 2: paroxetine: 65.6% (p = 0.02 vs. placebo), imipramine: 52.1% (p = 0.64 vs. placebo), placebo: 48.3% |

| ANALYSIS: | **ITT:** Not reported  
**Post randomization exclusions:** Yes |

| ATTRITION: | **Loss to follow-up:** 31%  
**Withdrawals due to adverse events:** paroxetine: 9.7% (p = 0.5 vs. placebo) imipramine: 31.5% (p < 0.01 vs. placebo) placebo: 6.9%  
**Loss to follow-up differential high:** Yes |

| ADVERSE EVENTS: | No p-values given for comparison  
• Side effects with > 5% difference from placebo: paroxetine: dry mouth (20.4% vs. 13.8% in placebo); nausea (23.7% vs. 19.5% in placebo); dizziness (23.7% vs. 18.4% in placebo); emotional lability (6.5% vs. 1.1% in placebo), hostility (7.5% vs. 0 in placebo); insomnia (15.1% vs. 4.6% in placebo); somnolence (17.2% vs. 3.4% in placebo); tremor (10.8% vs. 2.3% in placebo); back pain (4.3% vs. 11.5% in placebo)  
• Serious adverse effects: paroxetine: 11 (only 1 deemed to be related to medication), imipramine: 5 (2 deemed related to medication), placebo: 2 (related to medication) |

| QUALITY RATING: | Fair |
### Evidence Table 5

**Major Depressive Disorder Pediatrics**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT</td>
<td>Setting: Single center</td>
<td>Sample size: 40</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Drug: Venlafaxine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose: Age 8-12: 12.5-37.5 mg/d</td>
<td>N/A</td>
<td>Duration: 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Age 13-17: 25-75 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>6 weeks</td>
<td></td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Children and adolescents 8-18 years old; DSM-IV criteria for Major Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Female patients of childbearing age had to use oral contraceptives or depo-provera injection; Tourette's syndrome; mental retardation; seizures; schizophrenia; suicidal; medical illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHER MEDICATIONS/ INTERVENTIONS:</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Not reported</td>
<td>Mean Age: 12.8</td>
<td>Gender (% female): 24%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
<td>Other population characteristics: Not reported</td>
<td></td>
</tr>
</tbody>
</table>
**Authors:** Mandoki MW, et al.  
**Year:** 1997  
**Country:** US

### OUTCOME ASSESSMENT:
- **Measures:** Children’s Depression Inventory (CDI), Child Behavior Checklist (CBCL), 17 item HAM-D, Children’s Depression Rating Scale (CDRS)  
- **Timing of assessments:** Weekly

### RESULTS:
- Both venlafaxine and placebo patients showed significant improvement.  
- There was no difference between venlafaxine and placebo.

### ANALYSIS:
- **ITT:** No  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 7 (17.5%)  
- **Withdrawals due to adverse events:** 1 (2.5%) venlafaxine: 1 (5%), placebo: 0 (0%)  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- A higher percentage of patients in the venlafaxine group experienced side effects than in the placebo group at almost every week.  
- At week 2 more statistically more venlafaxine patients reported nausea.  
- At week 6 statistically more venlafaxine patients reported increased appetite.

### QUALITY RATING:
- Fair
Evidence Table 5  Major Depressive Disorder Pediatrics

| STUDY: | Authors: March JS<sup>108-110</sup>  
| Year: 2004 and 2006  
| Country: US  
| Trial name: TADS |

| FUNDING: | NIMH |

| DESIGN: | Study design: RCT  
| Setting: Multi-center (13 sites-academic and community clinics)  
| Sample size: 439 |

| INTERVENTION: | Drug: Placebo  
| Dose: N/A  
| Duration: 12 weeks  
| Sample Size: 112 |

| [blinded] Fluoxetine  
| 10-40 mg/d  
| 12 weeks  
| 109 |

| [unblinded] Fluoxetine and CBT  
| 10-40 mg/d  
| 12 weeks  
| 107 |

| [unblinded] CBT alone  
| N/A  
| 12 weeks  
| 111 |

| INCLUSION: | Ages 12-17; ability to receive care as an outpatient; a DSM-IV diagnosis of MDD at consent and again at baseline; a CDRS-R total score of 45 or higher at baseline; a full scale IQ of 80 or higher; not taking antidepressants prior to consent; depressive mood present in at least 2 or 3 contexts (home, school, among peers) for at least 6 wks prior to consent |

| EXCLUSION: | Current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence; pervasive developmental disorders, thought disorder; concurrent treatment with psychotropic medication or psychotherapy outside the study; 2 failed SSRI trials; a poor response to clinical treatment containing CBT for depression; intolerance to fluoxetine; confounding medical condition, non-English speaking patient or parent; pregnancy or refusal to use birth control; suicidal in the past 6 months; patients considered to be a danger to themselves or others |

| OTHER MEDICATIONS/INTERVENTIONS: | Concurrent stable psychostimulant treatment (methylphenidate or mixed amphetamine salts) for attention deficit hyperactivity disorder permitted |

| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: 14.6 (treatment-specific numbers not reported)  
| Gender (% female): 54.4% (treatment-specific numbers not reported)  
| Ethnicity: White: 73.8%; black: 12.5%; Hispanic: 8.9% (treatment-specific numbers not reported)  
| Other population characteristics: None significant |
| OUTCOME ASSESSMENT: | Measures: CDRS-R total score; CGI-I; RADS; SIQ-Jr, Functioning: Children’s Global Assessment Scale (CGAS), global health with the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA), and quality of life with the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)  
Timing of assessments: Baseline and weeks 6 and 12 |
| RESULTS: | • Fluoxetine with CBT was statistically significantly better than placebo (p = 0.001) on the CDRS-R  
• Compared to fluoxetine alone (p = 0.02) and CBT alone (p = 0.01), treatment with fluoxetine and CBT was statistically significantly superior on the CDRS-R  
• Fluoxetine alone was superior to CBT alone (p = 0.01) on the CDRS-R  
• Fluoxetine with CBT (p < 0.001) and fluoxetine alone (p < 0.001) demonstrated significant improvement on the CGI-I compared to placebo; CBT alone was not significantly better than placebo (p = 0.20)  
• Fluoxetine plus CBT were significantly better than placebo, fluoxetine alone, or CBT alone (p < 0.01) on the RADS  
• Clinically significant suicidal thinking improved significantly in all four treatment groups (SIQ-Jr), with fluoxetine plus CBT showing the greatest reduction (p = 0.02)  
• Loss of MDD diagnosis (using DSM-IV, K-SADS-P/L) at week 12: Both fluoxetine (78.6%) and fluoxetine+CBT(COMB) (85.3%) were superior to CBT alone (61.1%) and placebo (60.4%).  
• Remission rate (CDRS-R≤28): COMB was superior to all other groups (COMB 37% vs. FLX 23% vs. CBT 16% vs. PBO 17%)  
• Response rate (CGI-I≤2): COMB 71.0% vs. FLX 43.2% vs. CBT 43.2% vs. PBO 34.8%  
• Functioning and QOL: COMB was better than placebo on all measures, and better then FLX on CGAS and PQ-LES-Q. Fluoxetine was superior to both placebo and CBT on the CGAS only. CBT monotherapy was not statistically different from the placebo group on any of the measures assessed. The combination of fluoxetine and CBT was effective in improving functioning, global health, and quality of life in depressed adolescents. Fluoxetine monotherapy improved functioning.  
• LONG-TERM: 327 patients completed 36 weeks (after 12 weeks an open trial, no placebo). By week 24 all treatments converged, and remained so to 36 weeks (response rates COMB 86% vs. FLX 81% vs. CBT 81%). |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION: | Loss to follow-up: 18.2%; fluoxetine+CBT: 14%; fluoxetine: 17%; CBT: 22%; placebo: 21%  
Withdrawals due to adverse events: Not reported  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | Adverse events reported as harm-related, psychiatric, or other  
• 7.5% of patients had a harm-related adverse event; by FDA definition 69.7% of these had a serious adverse event: fluoxetine alone: 11.9%; fluoxetine with CBT: 8.4%; CBT alone: 4.5%; placebo: 5.4% |
- Psychiatric adverse events: fluoxetine+CBT: 15%; fluoxetine alone: 21%; CBT alone: 1%; placebo: 9.8%
- Headache was most common: fluoxetine+CBT 5.6%, fluoxetine alone 12%, CBT alone 0%, placebo 9%
- Sedation fluoxetine+CBT: 0.9%; fluoxetine alone: 2.8%; CBT alone: 0%; placebo: 0%
- Insomnia fluoxetine+CBT: 4.7%; fluoxetine alone: 2.8%; CBT alone: 0%; placebo: 0.9%
- Vomiting fluoxetine+CBT: 3.7%; fluoxetine alone: 1.8%; CBT alone: 0.9%; placebo: 0.9%
- Upper abdominal pain fluoxetine+CBT: 0.9%; fluoxetine alone: 5.5%; CBT alone: %; placebo: 1.8%
- Suicide related rates fluoxetine+CBT: 4.7%; fluoxetine alone: 9.2%; CBT alone: 4.5%; placebo: 2.7%
- After 36 weeks: suicidal events FLX 14.7% vs. COMB 8.4% vs. CBT 6.3%

| QUALITY RATING: | Good |
### Evidence Table 5

#### Major Depressive Disorder Pediatrics

| STUDY:       | Authors: Usula et al.  
|              | Year: 2008  
|              | Country: Italy  |
| FUNDING:     | Sardinian Public Health Secretariat  |
| DESIGN:      | Study design: systematic review & meta-analysis  
<p>|              | Number of patients: 2530  |
| AIMS OF REVIEW: | To evaluate the efficacy of SSRIs in children and adolescents with depressive disorder  |
| STUDIES INCLUDED IN REVIEW | Randomized controlled trials  |
| TIME PERIOD COVERED: | Up to January 2007  |
| CHARACTERISTICS OF INCLUDED STUDIES: | Original articles, RCTs, children/adolescents diagnosed using standardized criteria  |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Age 6-20 years, male/female ratio 1.07, mixture out- and in-patients, DSM-IIIR or DSM-IV diagnosis of depressive disorder or depressive symptoms  |</p>
<table>
<thead>
<tr>
<th>Authors: Usula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine 10-60mg/d, Paroxetine 10-50mg/d, Citalopram 10-40mg/d, Sertraline 25-200mg/d, Escitalopram 10-20mg/d Compared to placebo (or imipramine or clomipramine)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MAIN RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drop-outs: range 18.5%-39.6% (mean 26.3%), due to AEs: 25.8% (52.9% drug group vs. 29.3% placebo group), due to lack of efficacy 18.8% (37.7% drug group vs. 59.3% placebo group)</td>
</tr>
<tr>
<td>• For “primary outcome” (eg: CDRS-R, CGI-I, HAM-D) the pooled OR was 1.57 (95% CI 1.29-1.91) p&lt;0.00001</td>
</tr>
<tr>
<td>• Otherwise only fluoxetine had a significant OR of 2.39 (1.69-3.39) p&lt;0.00001</td>
</tr>
<tr>
<td>• There was a small, not significant negative association between the quality rating and the OR</td>
</tr>
<tr>
<td>• For CGI-I outcome pooled OR = 1.68 (1.38-2.03) p&lt;0.00001</td>
</tr>
<tr>
<td>• Based on CGI-I a statistically significant benefit of treatment was seen for fluoxetine (OR=2.38 [1.68-3.37]), as well as paroxetine (OR=1.49 [1.09-2.03]) and sertraline (OR=1.57 [1.04-2.37])</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of total drop-outs 25.8% due to AEs, 52.9% drug group vs. 29.3% placebo group AEs otherwise not discussed</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A hand search was performed</td>
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</tbody>
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<table>
<thead>
<tr>
<th>STANDARD METHOD OF APPRAISAL OF STUDIES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 features of a study were rated on a 1–3 scale, (total possible score of 12).</td>
</tr>
<tr>
<td>Each study was also assessed using the Jadad 5 point scale (Jadad et al., 1996). Inter-reviewer reliability for the quality of studies was measured by Kappa statistics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
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</tbody>
</table>

Second generation antidepressants
### Evidence Table 5: Major Depressive Disorder Pediatrics

| **STUDY:** | Authors: Wagner, et. al.  
Year: 2003  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Pfizer, Inc.</td>
</tr>
</tbody>
</table>
| **DESIGN:** | Study design: Pooled analysis of 2 multi-center, double-blind, placebo-controlled trials  
Setting: 53 hospital, general practice, academic centers in the US, India, Canada, Costa Rica and Mexico.  
Sample size: 376 |
| **INTERVENTION:** | **Drug:** Sertraline  
Dose: 50-200 mg/d  
Duration: 10 weeks  
Placebo  
Dose: N/A  
Duration: 10 weeks |
| **INCLUSION:** | Ages 6-17 years; met DSM-IV criteria for MDD (as determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version); current episode of at least 6 weeks duration; minimum score on CDRS-R of 45 and CGI of 4 |
| **EXCLUSION:** | Current and primary diagnoses of ADHD; conduct disorder; OCD; panic disorder; history of bipolar disorder; current psychotic features; history of psychotic disorder or autistic spectrum disorder; previous suicide attempts or high suicidal or homicidal risk; abnormal screening EKG, labs, vital signs or body weight; pregnancy; prior enrollment in a sertraline study; medical contraindications to SSRI; history of failure on SSRI; no other psychotropic meds for at least 2 weeks (4 weeks for fluoxetine) |
| **ALLOWED OTHER MEDICATIONS/INTERVENTIONS:** | Chlora hydrate, diphenhydramine as sleep aids |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Not reported  
Gender (% female): sertraline: 57.1%, placebo: 44.9%  
(p = 0.02)  
Ethnicity: sertraline: white, 71.4%; Asian, 13.8%; Hispanic, 7.9%; black, 3.7%; other, 3.2%  
placebo: white, 69.5%; Asian, 12.3%; Hispanic, 10.2%; black, 4.8%; other, 3.2%  
Other population characteristics: Comorbid psychiatric diagnosis: 38% |
**Authors:** Wagner et. al.  
**Year:** 2003  
**Country:** Multinational

### OUTCOME ASSESSMENT:

**Measures:** Change in CDRS-R, CDRS-R response > 40% change from baseline, CGI-S score, CGI-I score, and CGI-response (score of 1 or 2), MASC, CGAS, PQ-LES-Q  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 10

### RESULTS:

- **Mean CDRS-R change (ITT):** sertraline: 22.84, placebo: 20.19 (p = 0.007)  
- **Mean CDRS-R change (completers):** sertraline: 30.24, placebo: 25.83 (p = 0.001)  
- **CDRS-responder:** sertraline: 69%, placebo: 59% (p = 0.05)  
- **Mean CGI:** sertraline: 2.56, placebo: 2.75 (p = 0.009)  
- **CGI responder:** sertraline: 63%, placebo: 53% (p = 0.05)  
- **Change in CGI-S:** sertraline: 1.22, placebo: 1.01 (p = 0.005)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 20%; sertraline: 24.4%; placebo: 16.6%  
**Withdrawals due to adverse events:** 5.9%; sertraline: 9%; placebo: 2.7%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- **Adverse events that occurred in at least 5% of sertraline treated patients with an incidence at least twice that of placebo:** insomnia (19.8% vs. 8%), diarrhea (15.1% vs. 4.5%), vomiting (9.3% vs. 4.5%), anorexia (10.5% vs. 2.3%), agitation (8.1% vs. 2.3%)  
- **Serious adverse events (based on pre-defined criteria):** sertraline: 7, placebo: 6  
- **Mean change in body weight:** sertraline: -0.38 kg, placebo: 0.78 kg (p = 0.001)

### QUALITY RATING:

Fair
Evidence Table 5  Major Depressive Disorder Pediatrics

| STUDY:                  | Authors: Wagner KD, et al.  
|                        | Year: 2004  
|                        | Country: US  
| FUNDING:               | Forest Pharmaceuticals  
| DESIGN:                | Study design: RCT  
|                        | Setting: Multi-center (21)  
|                        | Sample size: 178  
| INTERVENTION:          | Drug: Citalopram  
|                        | Dose: 20-40 mg/d  
|                        | Duration: 8 weeks  
|                        | Sample size: 93  
|                        | Placebo  
|                        | N/A  
|                        | Duration: 8 weeks  
|                        | Sample size: 85  
| INCLUSION:             | Children (7-11) and adolescents (12-17) who met DSM-IV criteria for major depression; current depressive episode of 4 weeks or greater; score of at least 40 on the Children’s Depression Rating Scale; normal physical exam, laboratory tests, and ECG results.  
| EXCLUSION:             | Primary psychiatric diagnosis other than MDD; DSM-IV diagnosis of ADHD; PTSD; bipolar disorder; pervasive development disorder; mental retardation; conduct disorder; any psychotic features; history of alcohol or substance abuse; anorexia or bulimia within the past year; suicidal risk  
| OTHER MEDICATIONS/      | Certain prescription and over the counter medications prohibited (e.g., antipsychotics, anticonvulsants, sedatives, hypnotics, cardiovascular agents, among others)  
| INTERVENTIONS:         |  
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                        | Mean age: Citalopram: 12.1; placebo: 12.1  
|                        | Gender (% female): Citalopram: 52.8%; placebo: 54.1%  
|                        | Ethnicity: Citalopram: white: 80.9%; placebo: 72.9% white  
|                        | Other population characteristics: Baseline mean Children’s Depression Rating Scale: 58.8 citalopram; 57.8 placebo  

**Authors:** Wagner KD, et al.  
**Year:** 2004  
**Country:** US

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** Children’s Depression Rating Scale-Revised  
**Secondary Outcome Measures:** CGI-I; CGI-S  
**Timing of assessments:** Baseline and weeks 1, 2, 4, 6, and 8. |
| RESULTS: | • Compared to placebo, citalopram showed significantly more improvement on the Children’s Depression Rating Scale-Revised (p < 0.05)  
• 47% of citalopram-treated patients had a CGI-I rating ≤ 2 compared to 47% of placebo-treated patients (p = not reported)  
• Mean change in CGI-S was -1.3 for citalopram and -1 for placebo (p = not reported) |
| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| ATTRITION: | **Loss to follow-up:** 22% (40); citalopram: 24% (22); placebo: 21% (18)  
**Withdrawals due to adverse events:** 5.7%; citalopram: 5.6%; placebo: 5.9%  
**Loss to follow-up differential high:** No |
| ADVERSE EVENTS: | Events occurring in greater than 10% of patients (p = NR):  
• Rhinitis: Citalopram: 13.5%; placebo: 5.9%  
• Nausea: Citalopram: 13.5%; placebo: 3.5%  
• Abdominal Pain: Citalopram: 11.2%; placebo: 7.1% |
| QUALITY RATING: | Fair |
### Evidence Table 5

#### Major Depressive Disorder Pediatrics

**STUDY:**
- Authors: Wagner et al. 2006
- Year: 2006
- Country: USA

**FUNDING:**
- Forest Laboratories

**DESIGN:**
- Study design: RCT
- Setting: multicentre
- Sample size: 268

**INTERVENTION:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>10-20mg/d</td>
<td>8 weeks</td>
<td>131</td>
</tr>
<tr>
<td>Placebo</td>
<td>n/a</td>
<td>8 weeks</td>
<td>133</td>
</tr>
</tbody>
</table>

**INCLUSION:**
- 6-17 years old with DSM-IV criteria for MDD; diagnosis established with K-SADS-PL
- current depressive episode ≥4 weeks in duration.
- CDRS-R ≥40 at both the screening and baseline visits.
- normal results at screening from physical examination, laboratory tests, and electrocardiography.

**EXCLUSION:**
- any primary psychiatric diagnosis other than MDD, psychotic features, or severe personality disorder, or history of anorexia nervosa, bulimia, or substance abuse, including alcohol, within the past year
- DSM-IV criteria for ADHD, PTSD, bipolar disorder, pervasive developmental disorder, mental retardation, conduct disorder, or oppositional defiant disorder.
- Females of childbearing potential were excluded if not practicing, or not willing to practice, a reliable method of birth control or if pregnant or nursing.
- Initiation of psychotherapy or behavioral therapy during the study or within the 3 months
- suicide risk, had ever been hospitalized because of a suicide attempt, or had made a serious suicide attempt within the past year
- patients treated with any antidepressant or anxiolytic medication within 2 weeks of baseline (4 weeks for fluoxetine), patients treated with an antipsychotic or stimulant within 6 months before screening, or patients who received an investigational drug 30 days before study entry.
- Patients who had been in a previous investigational study of escitalopram or who had previously failed an adequate trial of escitalopram or citalopram or adequate trials of two other SSRIs
- certain prescription or over-the-counter medications were prohibited per protocol.

**OTHER MEDICATIONS/ INTERVENTIONS:**
- Zolpidem, zaleplon allowed

**POPULATION CHARACTERISTICS:**
- Groups similar at baseline: yes
- Mean age: 12.3 ±3.0 years
- Gender (female %): 51.9%
- Ethnicity: NR
- Other population characteristics: NR
<table>
<thead>
<tr>
<th>Authors: Wagner et al</th>
<th>Year: 2006</th>
<th>Country: USA</th>
</tr>
</thead>
</table>

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** change from baseline in CDRS-R
- **Secondary Outcome Measures:** CGI-S, CGI-I, CGAS, response is CDRS-R ≤ 28 and CGI-I ≤ 2
- **Timing of assessments:** 1, 2, 4, 6, 8 weeks

### RESULTS:
- change in CDRS-R escitalopram -21.9 vs. placebo -20.2, p=0.310 (NS)
- no significant differences in secondary outcome measures
- post hoc subgroup analysis of adolescents (age 12-17) showed significant improvements in CGI-S (-1.5 vs. -1.0, p=0.02), CGI-I (2.4 vs. 2.8, p=0.038) and CGAS (15.7 vs. 10.0, p=0.005) but not the CDRS-R.
- escitalopram and placebo results in children (6-11) equivocal
- authors note a high placebo response rate of 52.3% (as in other JMDD trials)

### ANALYSIS:
- **ITT:** yes (all patients who had at least one post-baseline assessment)
- **Post randomization exclusions:** 7
- **Loss to follow-up differential high:** no

### ATTRITION:
- **Loss to follow-up:**
  - Escitalopram: 22.1%
  - Placebo: 13.6%
- **Withdrawals due to adverse events:**
  - Escitalopram: 1.5%
  - Placebo: 1.5%
- **Withdrawals due to lack of efficacy:**
  - Escitalopram: 3.0%
  - Placebo: 3.1%

### ADVERSE EVENTS:
- Escitalopram vs. placebo (%):
  - At least 1 AE: 68.7% vs. 67.7%
  - Potential suicide related event: 0.8% vs. 1.5%
  - Abdominal pain: 10.7% vs. 5.3%

### QUALITY RATING:
- **Fair**
Evidence Table 5  
Major Depressive Disorder Pediatrics

| STUDY: | \textbf{Authors}: Whittington CJ, et. al.  
\textbf{Year}: 2004  
\textbf{Country}: UK |
| FUNDING: | NICE (National Institute for Clinical Excellence) |
| DESIGN: | \textbf{Study design}: Systematic review, SSRI versus placebo  
\textbf{Number of patients}: 2145 |
<p>| AIMS OF REVIEW: | To evaluate the risk versus benefit of SSRI’s when used to treat childhood depression |
| STUDIES INCLUDED IN META-ANALYSIS | Emslie GJ et al., 1997, Emslie GJ et al., 2002, Keller MB et al., 2001, Wagner, KD et al., 2003 ; unpublished results included in a report by the Committee on Safety of Medicines (UK) |
| TIME PERIOD COVERED: | All studies up to 2003 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Patients randomized to either an SSRI or placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Included trials had patients aged 5-18 years old; no other population information given |</p>
<table>
<thead>
<tr>
<th>Authors: Whittington CJ, et. al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2004</td>
</tr>
<tr>
<td>Country: UK</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</strong></td>
</tr>
<tr>
<td><strong>MAIN RESULTS:</strong></td>
</tr>
<tr>
<td>• Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile</td>
</tr>
<tr>
<td>• Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response</td>
</tr>
<tr>
<td>• One paroxetine study reported an increased risk of serious adverse events (11.8% vs 2.3%; NNTH 10 [95% CI 6-50]) and suicidal ideation or attempting suicide (5.4% vs 0%; NNTH 20 [10 to ∞])</td>
</tr>
<tr>
<td>• Unpublished data on sertraline in children indicate it is not as effective as reported in published trials</td>
</tr>
<tr>
<td>• One unpublished study of citalopram suggested a negative risk-benefit profile</td>
</tr>
<tr>
<td>• Combined, published and unpublished data of venlafaxine suggested a negative risk-benefit profile</td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
</tr>
<tr>
<td>Paroxetine, sertraline, citalopram, and venlafaxine all indicated an increased risk of adverse events</td>
</tr>
<tr>
<td><strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
</tr>
<tr>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 6  General Anxiety Disorder

| STUDY: | Authors: Allgulander et. al.  
Year: 2004  
Country: Australia, Canada, Denmark, Norway, and Sweden |
| FUNDING: | Not reported |
| DESIGN: | Study design: RCT  
Setting: Multi-center (21)  
Sample size: 378 |
| INTERVENTION: |  
**Drug:** Sertraline  
**Dose:** 50-150 mg/d (mean 95 mg/d)  
**Duration:** 12 weeks  
**Sample size:** 190  
**Placebo:** N/A  
**Duration:** 12 weeks  
**Sample size:** 188 |
| INCLUSION: | Outpatients (18 years or older) with a primary diagnosis of DSM-IV defined anxiety disorder based on clinical assessments and structured interview; screening and baseline scores > 18 on the Hamilton Anxiety Rating Scale and scores > 2 on Hamilton Anxiety Scale item 1 and item 2 |
| EXCLUSION: | No current use of medically accepted contraception in fertile women; current or past history of bipolar, schizophrenic, psychotic, or OCD; current history of MDD; score > 16 on MADRS; concurrent psychotherapy for GAD; unstable medical condition; positive drug test; suicidal risk; previous failure to respond to adequate trial on antidepressant drug treatment |
| OTHER MEDICATIONS/ INTERVENTIONS: | Drugs with psychotropic activity |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Sertraline: 40.3; placebo 42.4  
Gender (% female): Sertraline 59% female; placebo 51% female  
Ethnicity (% white): Sertraline 98%; placebo 97%  
Other population characteristics: 44% of sertraline patients had partial/full high school education vs. 40% for placebo |
**Authors:** Allgulander, et al.  
**Year:** 2004  
**Country:** Multi-country (Australia, Canada, Denmark, Norway, and Sweden)

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th><strong>Primary Outcome Measures:</strong></th>
<th>HAM-A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Outcome Measures:</strong></td>
<td>CGI-I, CGI-S, MADRS, HADS, QoL enjoyment and satisfaction questionnaire, Endicott Work Productivity Scale, VAS for perceived health</td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong></td>
<td>Baseline, weeks 1, 2, 4, 6, 8, and 12</td>
</tr>
</tbody>
</table>

### RESULTS:

- Mean change in HAM-A total score significantly greater among sertraline-treated patients (-11.7) compared to placebo-treated patients (-8.0); (p < 0.0001)
- Significantly greater improvement for sertraline in the anxiety and depression component of the HADS (p < 0.0001)
- Sertraline significantly better than placebo as assessed by change in the MADRS, CGI-I, CGI-S, QoL, and Endicott Work Productivity Scales
- VAS not reported

### ANALYSIS:

| **ITT:** | Yes |
| **Post randomization exclusions:** | Yes |

### ATTRITION:

| **Loss to follow-up:** | 23%; sertraline: 20%; placebo: 26% |
| **Withdrawals due to adverse events:** | 9%; sertraline: 8%; placebo: 10% |
| **Loss to follow-up differential high:** | No |

### ADVERSE EVENTS:

Discontinuations due to adverse events were 8% for sertraline and 10% for placebo; the incidence of severe adverse events was ≥3% with sertraline for the following: sweating (3.8% vs 0.0% for placebo), headache (3.3% vs 4.8%), nausea (4.3% vs 1.6%), insomnia (4.3% vs 3.7%), anxiety (3.3% vs 4.2%), and decreased libido in women (4.6% vs 0.0%); Significantly more nausea (28% vs. 13%), insomnia (20% vs. 15%), decreased libido in men (17% vs. 5%), diarrhea (11% vs. 5%), and fatigue (10% vs. 5%)

### QUALITY RATING:

Fair
### Evidence Table 6 Generalized Anxiety Disorder Adults

| STUDY: | Authors: Baldwin et al.\(^{117}\)  
Year: 2006  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 681 |
| INTERVENTION: |  
**Drug:** Placebo  
**Dose:** NA  
**Duration:** 12 weeks  
**Sample size:** 139  
**Escitalopram**  
**Dose:** 5 mg/day  
**Duration:** 12 weeks  
**Sample size:** 134  
**Escitalopram**  
**Dose:** 10 mg/day  
**Duration:** 12 weeks  
**Sample size:** 136  
**Escitalopram**  
**Dose:** 20 mg/day  
**Duration:** 12 weeks  
**Sample size:** 133  
**Paroxetine**  
**Dose:** 20 mg/day  
**Duration:** 12 weeks  
**Sample size:** 139 |
| INCLUSION: | aged 18–65 years old with a Hamilton Anxiety Scale (HAMA; Hamilton, 1959) total score > 20, and a score of ≥ 2 on both HAMA item 1 (anxious mood) and item 2 (tension) at screening and at baseline |
| EXCLUSION: | MDD, panic disorder, social anxiety disorder, PTSD, bipolar disorder, OCD, eating disorders, body dysmorphic disorder, substance misuse disorder, any personality disorder that could jeopardize the evaluation of the treatment for primary generalised anxiety, and any current or previous psychotic disorder at risk of suicide; receiving CBT, ECT, cognitive therapy or problem-solving treatment, or planned to initiate such therapy; unstable serious illness and/or serious sequelae; psychoactive substances, anxiolytics, antidepressants, MAOIs, benzodiazepines, b-blockers, tryptophan, oral antipsychotics, narcotic analgesics (except intermittent use of codeine-based analgesics), warfarin sodium, digitalis, cardiac glycosides, type 1c antiarrhythmics, phenytoin, cimetidine, regular daily therapy with any hypnotic psychoactive herbal remedies, antiepileptics, ongoing prophylactic treatment with lithium, valproate or carbamazepine, and triptans within the 2 weeks; any investigational drug or depot antipsychotics within 6 months. |
| OTHER MEDICATIONS/INTERVENTIONS: | use of anti-hypertensives other than b-blockers was permitted as long as the dose had been stable for 6 months and remained fixed during the study; zolpidem, zopiclone, or zaleplon for insomnia, but not more than 3 times per week |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 41  
Gender (female %): 64.2  
Ethnicity: 99% caucasian |

*Final Report Update 4  
Second generation antidepressants*
Authors: Baldwin et al.
Year: 2006
Country: Multinational

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Mean change in HAM-A  
Secondary Outcome Measures:  
Timing of assessments: Baseline and weeks 1,2,4,6,8,10,12,13,14 |
|---------------------|------------------------------------------------------------------|

| RESULTS: |  
PBO vs. ESC5 vs. ESC10 vs. ESC20 vs. PAR  
Mean change in HAM-A (P vs. PBO) -14.20 vs. -15.49 (p = 0.165) vs. -16.76 (p = 0.006) vs. -16.35 (p = 0.022) vs. -14.71 (p = 0.585)  
Rest of data NR or is in graphs |
|-----------|------------------------------------------------------------------|

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: 7 |
|-----------|------------------------------------------------------------------|

| ATTRITION: | Loss to follow-up: Overall 14% PBO 10% ESC5 13% ESC10 12% ESC20 16% PAR 16%  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |
|-----------|------------------------------------------------------------------|

| ADVERSE EVENTS: |  
PBO vs. ESC5 vs. ESC10 vs. ESC20 vs. PAR  
Patients with adverse events, n (%) 88 (63.3) vs. 88 (65.7) vs. 94 (69.1) vs. 94 (70.7) vs. 101 (72.7)  
Fatigue 4 (2.9) vs. 11 (8.2) vs. 14 (10.3)* vs. 22 (16.5)* vs. 12 (8.6)  
Insomnia 3 (2.2) vs. 12 (9.0)* vs. 17 (12.5)* vs. 14 (10.5)* vs. 15 (10.8)*  
Diarrhoea 4 (2.9) vs. 13 (9.7)* vs. 13 (9.6)* vs. 13 (9.8)* vs. 11 (7.9)  
Sweating increased 4 (2.9) vs. 4 (3.0) vs. 11 (8.1) vs. 12 (9.0)* vs. 12 (8.6)  
Somnolence 3 (2.2) vs. 10 (7.5)* vs. 5 (3.7) vs. 10 (7.5)* vs. 10 (7.2)  
Yawning 1 (0.7) vs. 1 (0.7) vs. 7 (5.3)* vs. 3 (2.2)  
Anorgasmia 2 (1.5) vs. 6 (4.4)* vs. 2 (1.5) vs. 9 (6.5)* |
|-----------|------------------------------------------------------------------|

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Fair</th>
</tr>
</thead>
</table>
## Evidence Table 6

### General Anxiety Disorder

| STUDY: | Authors: Ball SG, et al.\textsuperscript{18}  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer Inc, NY</td>
</tr>
<tr>
<td>OBJECTIVE:</td>
<td>To test hypothesis that paroxetine and sertraline are similar in their effectiveness and tolerability for the treatment of adult GAD</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 55 |
| INTERVENTION: | \begin{itemize}  
- **Drug:**  
  - Paroxetine  
  - 10-40 mg/d  
  - 8 weeks  
  - 25  
  - Sertraline  
  - 25-100 mg/d  
  - 8 weeks  
  - 28  
- **Sample size:** |
| INCLUSION: | 18 years or older; primary DSM-IV diagnosis of GAD; HAM-A score of 18 or greater; good physical health |
| EXCLUSION: | HAM-D score greater than 20 at baseline; history of substance abuse/dependence within 6 months of baseline; history of psychotic or bipolar disorders; prior non-response to sertraline or paroxetine; pregnancy |
| OTHER MEDICATIONS/INTERVENTIONS: | Concomitant medication for sleep disturbance was not allowed |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No  
Mean age: paroxetine: 35.6, sertraline: 42.9  
Gender (% female): paroxetine: 84%, sertraline: 71%  
Ethnicity: paroxetine: 84% white, 12% black, 4% Asian; sertraline: 93% white, 7% black, 0% Asian |
| Other population characteristics: | Baseline HAM-A: paroxetine: 20.8, sertraline: 21.4  
Baseline: CGI-S: paroxetine: 4.2, sertraline: 4.4  
Baseline Q-LES-Q: paroxetine: 62, sertraline: 64 |
### Authors: Ball SG, et al.  
**Year:** 2005  
**Country:** US

#### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** HAM-A; Remission rate (defined as CGI-S score of 1)  
- **Secondary Outcome Measures:** IU-GAMS (Indiana University Generalized Anxiety Measurement Scale); BAI (Beck Anxiety Inventory); Q-LES-Q  
- **Timing of assessments:** Baseline and weekly during the study

#### RESULTS:
- There was no significant difference between SR and PX patients in HAM-A score reduction ($F= 0.37$, df=1,51)  
- There was no significant difference between SR and PX patients in remission rate ($\chi^2= 0.22$, df=1)  
- Quality of life scores did not differ significantly between treatment groups

#### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes (2)

#### ATTRITION:
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Paroxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>12 (22%)</td>
<td>5 (20%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6 (11%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>1 (2%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

#### ADVERSE EVENTS:
- Paroxetine: dizziness, nausea, sexual dysfunction, and constipation  
- Sertraline: sexual dysfunction, diarrhea

#### QUALITY RATING:  
Fair
## Evidence Table 6

**Generalized Anxiety Disorder Adults**

| STUDY: | Authors: Brawman-Mintzer et al.119  
Year: 2006  
Country: United States |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter (9)  
Sample size: 326 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
**Sample size:**  
Placebo  
NA  
10 weeks  
163  
Sertraline  
50-200 mg  
10 weeks  
165 |
| INCLUSION: | Male and female outpatients, 18 years or more; met DSM-IV criteria for primary diagnosis of GAD; HAM-A 20 or more; 2 or more on anxiety item 1 (anxious mood) and Covi Anxiety score greater than Raskin Depression Scale score |
| EXCLUSION: | MDD, panic disorder, OCD, PTSD or substance abuse; additional DSM-IV axis 1 disorders, MADRS > 18: using psychotropic medicines; ECT; pregnancy; current use of benzodiapine; failure to respond to at least 1 SSRI for 4 weeks; CBT or other forms of psychotherapy. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** Placebo 40.8  
Sertraline 40.1  
**Gender (female %):** Placebo 56.8  
Sertraline 59.8  
**Ethnicity (% white):** Placebo 75.3  
Sertraline 76.2  
Other population characteristics: |
**Authors:** Brawman-Mitzer  
**Year:** 2006  
**Country:** USA

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** HAM-A  
- **Secondary Outcome Measures:** HADS, MADRS, Sheehan Disability Scale and Q-LES-Q  
- **Timing of assessments:** Baseline, weeks 1,2,3,4,6,8,10 and 11

### RESULTS:
- HAM-A change from baseline Placebo -11.15 (7.32) vs. Sertraline -12.71 (7.17) p = 0.032  
- HADS change from baseline Placebo -6.02 (7.22) Sertraline -9.12 (7.77) p < 0.001  
- CGI-S change from baseline Placebo -1.39 (1.28) Sertraline -1.67 (1.29) p = 0.223  
- **HAM-A responders** Placebo 48.2  Sertraline 59.2  p = 0.05

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** 2

### ATTRITION:
- **Loss to follow-up:** 26.5% Placebo 23.3% Sertraline 28.5%  
- **Withdrawals due to adverse events:** Placebo 1.8% Sertraline 5.5%  
- **Withdrawals due to lack of efficacy:** Placebo 3.1% Sertraline 1%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Sertraline vs placebo  
- Diarrhea/loose stools 17.6 vs. 11.7  
- Insomnia 17.0 vs. 14.7  
- Nausea 21.8 vs 14.1  
- Dry mouth 13.9 vs. 8.6  
- Libido decrease loss 17.6 vs. 2.4 p < 0.001

### QUALITY RATING:
- **Fair**
**Evidence Table 6  General Anxiety Disorder**

| STUDY: | Authors: Dahl AA, et al.\textsuperscript{120}  
          | Year: 2005  
          | Country: Multinational |
| FUNDING: | Pfizer, Inc. |
| DESIGN: | Study design: RCT  
          | Setting: Multinational, outpatient “investigational sites”  
          | Sample size: 373 |
| INTERVENTION: only for RCT | | |
| Drug: | Sertraline  
          | Placebo |
| Dose: | 50-150 mg/d  
          | N/A |
| Duration: | 12 wks  
          | 12 wks |
| Sample size: | 184  
          | 189 |
| INCLUSION: | Adult outpatients; DSM-IV diagnosis of GAD; screening & baseline HAM-A scores $\geq 18$; score $\geq 2$ on HAM-A item 1 (anxious mood) & item 2 (tension) at baseline |
| EXCLUSION: | Current or history of bipolar, schizophrenia, or OCD; dysthymia, social anxiety, substance abuse or major depressive / panic / eating / body dysmorphic / or post-traumatic stress disorders within last 6 months; MADRS score $>16$; psychotropic drug treatment within 2 wks of randomization |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes, except significantly later mean onset of GAD symptoms in placebo (25.6y) vs. sertraline (22.9y) ($p = 0.04$).  
          | Mean age (sd): sertraline: 40.3 (11.1), placebo: 42.4 (11.5) placebo  
          | Gender (% female): sertraline: 59%, placebo: 51%  
          | Ethnicity(% white): sertraline: 98%, placebo: 97%  
          | Other population characteristics: Both groups similar in highest education level achieved, current marital status, and current employment status |
Authors: Dahl AA, et al.  
Year: 2005  
Country: Multinational

| OUTCOME ASSESSMENT: | Primary Outcome Measures: HAM-A  
| | Secondary Outcome Measures: CGI-S & CGI-I, MADRS, Q-LES-Q  
| Timing of assessments: Screening, baseline, and weeks 1, 2, 4, 6, 8, and 12 |
| --- | --- |

**RESULTS:**

- Sertraline group improved significantly more than placebo group across both primary & secondary measures, including HAM-A somatic and psychic anxiety factors.
- From week 4 to endpoint, HAM-A psychic factor improved at somewhat faster rate (slope -0.39+/− 0.05 [95% CI: -0.48 to -0.29]) than somatic factor (slope -0.25+/− 0.05 [95% CI: -0.34 to -0.15]) (F=12.51; d.f = 1,170;p = 0.005)
- LOCF endpoint mean HAM-A total score (sd) = -11.7(0.6) in sertraline vs. -8.0(0.6) in placebo; p < 0.001
- LOCF endpoint mean CGI-S score (sd) = -1.6(0.1) in sertraline vs. -0.9(0.1) in placebo; p < 0.001
- LOCF endpoint mean CGI-I score (sd) = 2.3(0.1) in sertraline vs. 3.0(0.1) in placebo; p < 0.001
- LOCF endpoint mean MADRS score (sd) = -4.8(0.4) in sertraline vs. -1.1(0.4) in placebo; p < 0.001
- 51% of sertraline group compared to 35% of placebo group had a QLESQ score within normal range.
- LOCF endpoint mean QLESQ score (sd) = 9.1(1.0) in sertraline vs. 2.4(0.9) in placebo; p < 0.001

**ANALYSIS:**

- ITT: yes (defined as patients who took at least one dose of double-blind medication and had a baseline and at least 1 post-baseline HAM-A assessment)
- **Post randomization exclusions:** Cannot tell

**ATTRITION:**

- Loss to follow-up: NR
- Withdrawals due to adverse events: NR
- Withdrawals due to lack of efficacy: NR
- Loss to follow-up differential high: NR

**ADVERSE EVENTS:**

- NR

**QUALITY RATING:**

- Fair
### Evidence Table 6  Generalized Anxiety Disorder Adults

| STUDY: | Authors: Hartford et al.121  
Year: 2007  
Country: USA |
| --- | --- |
| FUNDING: | Eli Lilly and Company and  
Boehringer Ingelheim |
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 487 |
| INTERVENTION: | Drug:  
Dose:  
Duration:  
Sample size: |
| Duloxetine | 60-120 mg/day | 10 weeks | 162 |
| Venlafaxine | 75-225 mg/day | 10 weeks | 164 |
| Placebo | NA | 10 weeks | 161 |
| INCLUSION: | Male and female outpatients of at least 18 years of age who met criteria for GAD as defined by the DSM-IV. disease severity of at least moderate intensity as defined by a HADS anxiety subscale score ≥ 10, a Covi Anxiety Scale score ≥ 9, and no item in the Raskin Depression Scale >3 at visit 1. The Covi Anxiety Scale score must have been greater than the Raskin Depression Scale score at visit 1; CGI-S score ≥ 4 at visit 1 and visit 2. |
| EXCLUSION: | Any current primary DSM-IV Axis I diagnosis other than GAD including MDD within the past 6 months; panic disorder, PTSD or an eating disorder, within the past year; or OCD, bipolar disorder, psychosisis, factitious disorder, or somatoform disorders during their lifetime; an Axis II disorder or history of antisocial behavior; benzodiazepine use in the 2 weeks; judged clinically to be at serious suicidal risk; previous treatment with duloxetine; history of alcohol or any psychoactive substance abuse or dependence within the past 6 months; a serious medical illness; initiation of psychotherapy, change in intensity of psychotherapy or other nondrug therapies within 6 weeks before enrollment or at any time during the study; treatment with a MAOI or fluoxetine within 30 days of visit 2; uncontrolled narrow-angle glaucoma; and lack of response of the current episode of GAD to two or more adequate studies of antidepressants, benzodiazepines, or other anxiolytics at a clinically appropriate dose for a minimum of 4 weeks. |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 40.8  
Gender (female %): 62.2  
Ethnicity: 705 Caucasian  
Other population characteristics: |
| Authors: Hartford et al.  
| Year: 2007  
| Country: USA |

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>HAM-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>HAMA Psychic Anxiety Factor Score, Somatic Anxiety Factor Score, mood item, and tension item; the HADS Anxiety and Depression subscales scores the CGI-I and PGI-I; the Sheehan Disability Scale Impairment scores. Response, remission, and sustained improvement rates also were determined.</td>
</tr>
</tbody>
</table>

**Timing of assessments:** Baseline and weeks 1,2,4,7,10

**RESULTS:**

- The mean decrease in the HAMA total scores was 11.8 for duloxetine (46% improvement from baseline) and 12.4 for venlafaxine XR (50% improvement from baseline) compared with 9.2 (37% improvement from baseline) in the placebo group. Duloxetine, P=0.007; venlafaxine XR, P < 0.001
- Treatment response HAM-A 47% for duloxetine, 54% for venlafaxine XR, and 37% for placebo (venlafaxine vs. placebo, P < 0.001).

**ANALYSIS:**

- ITT: Yes
- Post randomization exclusions: NR

**ATTRITION:**

- Loss to follow-up: Duloxetine 45.7% venlafaxine 37.8% placebo 38.5%
- Withdrawals due to adverse events: Duloxetine 14.2% venlafaxine 11.0% placebo 1.9%
- Withdrawals due to lack of efficacy: Duloxetine 1.2% venlafaxine 1.2% placebo 3.7%
- Loss to follow-up differential high: No

**ADVERSE EVENTS:**

- Duloxetine vs. venlafaxine vs. placebo
- One or more adverse events 136 (84.0)* vs. 140 (85.4)** vs. 117 (72.7)
- Nausea 51 (31.5)*** vs. 38 (23.2)* vs. 22 (13.7)
- Constipation 23 (14.2)** vs. 22 (13.4)** vs. 7 (4.3)
- Dry mouth 19 (11.7) vs. 29 (17.7)** vs. 10 (6.2)
- Somnolence 19 (11.7)* vs. 22 (13.4)** vs. 6 (3.7)
- Fatigue 12 (7.4) vs. 19 (11.6)* vs. 6 (3.7)
- Decreased appetite 16 (9.9)** vs. 14 (8.5)* vs. 4 (2.5)
- Insomnia 12 (7.4)* vs. 15 (9.1)** vs. 3 (1.9)
- Decrease in libido 11 (6.8)** vs. 5 (3.0) vs. 1 (0.6)
- Yawning 12 (7.4)*** vs. 5 (3.0) vs. 0 (0.0)

  *P < 0.05, **P < 0.01, ***P < 0.001, vs. placebo

**QUALITY RATING:**

- Poor – attrition >40%
### Evidence Table 7

#### Obsessive-compulsive Disorder

| STUDY: | Authors: Ackerman, et al.  
Year: 2002  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: Meta-analysis (meta regression)</td>
</tr>
<tr>
<td>AIMS OF REVIEW:</td>
<td>Meta-analysis with meta regression for treatment of OCD to explain the apparent discrepancy in the literature that makes it seem that CMI is superior to SSRI's in placebo trials vs. in head/head comparison</td>
</tr>
<tr>
<td>TIME PERIOD COVERED:</td>
<td>Not explicitly reported, studies included spanned 1992-1997 for head to head comparisons and 1989-1999 for placebo comparisons</td>
</tr>
<tr>
<td>CHARACTERISTICS OF INCLUDED STUDIES:</td>
<td>RCTs, double-blinded; 8 weeks or longer; efficacy assessed with Y-BOCS; point estimates and SD(or SE) provided or calculable from report</td>
</tr>
<tr>
<td>CHARACTERISTICS OF INCLUDED POPULATIONS:</td>
<td>Not reported</td>
</tr>
<tr>
<td>Authors: Ackerman, et al.</td>
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<td>--------------------------</td>
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<tr>
<td>Year: 2002</td>
<td></td>
</tr>
<tr>
<td>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</td>
<td></td>
</tr>
<tr>
<td>Clomipramine, fluvoxamine, fluoxetine, sertraline, paroxetine, placebo</td>
<td></td>
</tr>
<tr>
<td>MAIN RESULTS:</td>
<td></td>
</tr>
<tr>
<td>• Result reported as mean difference in change from baseline on Y-BOCS scale support equal efficacy for clomipramine and all SSRIs; pooled difference between clomipramine and all SSRIs was 0.15 (95% CI -8.86, 9.16), where a number significantly greater than 1.00 would represent greater efficacy for the SSRIs</td>
<td></td>
</tr>
<tr>
<td>• Effect size was estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo. Negative pooled difference represents greater improvement (greater decrease in Y-BOCS) across studies for the active drug compared to placebo</td>
<td></td>
</tr>
<tr>
<td>• Pooled Difference:</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine vs. placebo (4 studies): -4.84 (-7.78, -1.83)</td>
<td></td>
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<tr>
<td>Fluoxetine vs. placebo (3 studies): -1.61 (-2.18, -1.04)</td>
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<tr>
<td>Sertraline vs. placebo (4 studies): -2.47 (-6.13, 1.20)</td>
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<tr>
<td>Paroxetine vs. placebo (1 study): -3.00 (-4.91, -1.09)</td>
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<tr>
<td>ADVERSE EVENTS:</td>
<td></td>
</tr>
<tr>
<td>None reported</td>
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<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
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<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td></td>
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<tr>
<td>No</td>
<td></td>
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<tr>
<td>QUALITY RATING:</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 7  Obsessive-compulsive Disorder

| STUDY: (Authors: Bergeron, et al.) | Year: 2002  
| Country: Canada |
| FUNDING: | Pfizer |
| DESIGN: | Study design: RCT  
| Setting: Multi-center  
| Sample size: 150 |
| INTERVENTION: | Drug: Sertraline  
| Dose: 50-200 mg/d  
| Duration: 24 weeks  
| Fluoxetine  
| 20-80 mg/d  
| 24 weeks |
| INCLUSION: | Ages 18-65; primary diagnosis of OCD for at least 6 months using Structured Clinical Interview based on DSM-IV criteria; baseline minimum scores of > 17 on Y-BOCS; > 7 on NIMH-OC; and CGI-S ≥ 4 and HAM-D17 ≤ 17; females had to have negative pregnancy test at baseline and using medically acceptable form of contraception for at least 3 months |
| EXCLUSION: | Primary Axis I disorder other than OCD including presence of major depressive episode; >25% reduction in Y-BOCS or NIMH-OC or > 2 point improvement in CGI-S during washout; suicidal; history of seizure disorder; organic brain disorder; anorexia; bulimia; purgative abuse; drug or alcohol abuse or dependence within 6 months prior; psychotropic medication within the previous week; 2 weeks for antidepressants requiring concomitant treatment with any psychotropic (other than exception as previously noted); requiring concurrent ECT, cognitive-behavioral therapy or formal structured psychotherapy or a likelihood that such therapy might be required; acute or unstable medical condition or used any meds known to interact with either study drug; reported previous adequate treatment > 4 weeks with either study drug or known or suspected intolerance or allergy; participated in a clinical research study within the prior 4 months; pregnancy or lactation |
| OTHER MEDICATIONS/INTERVENTIONS: | Zopiclone or chloral hydrate as hypnotics |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
| Mean age: 36; sertraline: 36.6; fluoxetine: 36.5  
| Gender (female%): 54%  
| Ethnicity: Not reported  
| Other population characteristics: Approximately 20% of the sample had a history of a prior episode of depression; OCD > 10 years in 79% of patients |
**Authors:** Bergeron  
**Year:** 2002  
**Country:** Canada

### OUTCOME ASSESSMENT:

**Measures:** Primary efficacy measures: Y-BOCS, NIMH-OC, CGI-S, response (CGI-I ≤ 2), remission (CGI-I ≤ 2 and YBOCS ≤ 11); Secondary measures: HAM-D, CAS, Yale schedule for multiple tics and tourettes, Battelle QOL  

**Timing of assessments:** Screening, baseline, weeks 1, 2, 4, 6, 8, 12, 16, 20, 24 or final visit if patients withdrew before study end

### RESULTS:

- No significant differences in mean Y-BOCS change at endpoint  
- Sertraline showed statistically significant improvement at some of the early assessment times (weeks 4, 8, 12)  
- No difference in CGI-S or CGI-I between groups at week 24  
- Median time to response not significantly different  
  - Sertraline: 16 weeks  
  - Fluoxetine: 20 weeks (p = 0.703)  
- Remission (combined CGI and YBOCS):  
  - Week 12: Sertraline: 20%, Fluoxetine: 8% (p = 0.045)  
  - Week 24: Sertraline: 36%, Fluoxetine: 22% (p = 0.075)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** 29.3%; sertraline: 29%; fluoxetine: 30%  
- **Withdrawals due to adverse events:** Sertraline: 19%; fluoxetine: 14% (p = 0.342)  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No significant differences in incidence of side effects between groups  

### QUALITY RATING:

Fair
| STUDY: | Authors: Denys D, et al.¹²⁴, ¹²⁵  
Year: 2003  
Country: US |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth and Glaxo-Smith-Kline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 150 |
| INTERVENTION: |  
**Drug:**  
Venlafaxine  
Paroxetine  
**Dose:**  
75-300 mg/d  
15-60 mg/d  
12 weeks  
12 weeks  
**Duration:**  
12 weeks  
12 weeks |
| INCLUSION: | DSM-IV criteria for OCD; > 18 on the Y-BOCS or > 12 if only obsessions or compulsions were present; 18-65 years of age |
| EXCLUSION: | Organic mental disorders; epilepsy; CNS disorder; DSM-IV diagnosis of major depression; psychotic illness or bipolar disorder; personality disorder; severe somatic symptoms; pregnancy; suicidal; use of antidepressants 1 month before study |
| OTHER MEDICATIONS/INTERVENTIONS: | Oxazepam, maximum of 30 mg/d, was permitted on an intermittent basis |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 35; venlafaxine: 36, paroxetine: 34  
Gender (female%): venlafaxine: 63%, paroxetine: 61%  
Ethnicity: Not reported  
Other population characteristics: Patients assigned to venlafaxine had a significantly greater number of previous medication trials |
### Authors: Denys D, et al.
#### Year: 2003
#### Country: Canada

**OUTCOME ASSESSMENT:**
- **Measures:** Yale-Brown Obsessive Compulsive scale (Y-BOCS), Hamilton Anxiety Scale (HAS), HAM-D-17, Global Assessment of Functioning, Lancashire Quality of Life Profile (LQoLP)
- **Timing of assessments:** Baseline, weeks 1, 3, 5, 8, 10, 12

### RESULTS:
- Paroxetine showed significantly greater improvement in HAM-D at endpoint (p < 0.05)
- Both treatment groups had a significant improvement in Y-BOCS score but there was no significant difference between treatment groups; no differences in HAS
- Paroxetine and venlafaxine groups improved on all QoL measures
- Paroxetine and venlafaxine were equally effective based on LQoLP improvement scores

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 16 (11%)
- **Withdrawals due to adverse events:** 5%; venlafaxine: 2%, paroxetine: 6%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Somnolence, sweating, insomnia, nausea, dry mouth, dizziness, constipation, sexual dysfunction
- No differences reported

### QUALITY RATING:
- Fair
### Evidence Table 7: Obsessive-compulsive Disorder

| STUDY: | Authors: Denys D, et al.\(^{126}\)  
Year: 2004  
Country: The Netherlands |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth and GlaxoSmithKline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 43 (of 150) continued in switch study |
| INTERVENTION: | **Drug:** Paroxetine  
**Dose:** 60 mg/d  
**Duration:** 12 weeks (switch study)  
**Sample Size:** 27  
**Drug:** Venlafaxine XR  
**Dose:** 300 mg/d  
**Duration:** 12 weeks (switch study)  
**Sample Size:** 16 |
| INCLUSION: | Outpatients ages 18-65 with a primary OCD according to DSM-IV criteria; only patients with a score of at least 18 on the Y-BOCS or at least 12 if only obsessions or compulsions were included; nonresponse in the first phase of the study defined as less than a 25% decrease in Y-BOCS |
| EXCLUSION: | Patients with significant depression as determined by a total score of 15 or more on the HAM-D on admission were excluded; pregnant women, childbearing potential not using adequate methods of contraception; patients with organic mental disorders, epilepsy, any structural central nervous system disorder or stroke within the last year; primary DSM–IV diagnoses of major depression, bipolar disorder, schizophrenia, or any other psychotic condition; substance-related disorders within the past 6 months; primary anxiety disorders or obvious personality disorders; use of antidepressants or antipsychotics 1 month before screening visit; use of a concomitant psychotropic drug, behavioral or cognitive therapy 3 months prior to the screening visit |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** 35  
**Gender (% female):** 54.5%  
**Ethnicity:** Not reported  
**Other population characteristics:** YBOCS total score 27.7; HAM-A score 11.0; HAM-D score 7.6 |
| Authors: Denys D, et al.  
Year: 2004  
Country: The Netherlands |
|---|
| **OUTCOME ASSESSMENT:** | Measures: Y-BOCS; HAM-D; HAM-A; GAF  
Timing of assessments: 0, 1, 3, 5, 8, 10, 12 weeks |
| **RESULTS:** |  
- LOCF analysis demonstrated a mean decrease of 1.8 (+/-3.5) in the venlafaxine XR group and 6.5 (+/-7.1) in the paroxetine group as measured by the reduction in total Y-BOCS scores; significant decrease in total Y-BOCS score from baseline was found in the paroxetine group (t=4.7, df=26, p < 0.0001) but not in the venlafaxine group (t = 2.0, df = 15, p = .065)  
- No significant differences between baseline and endpoint for venlafaxine XR- or paroxetine-treated patients on the HAM-D or HAM-A  
- GAF not reported |
| **ANALYSIS:** |  
ITT: Yes  
Post randomization exclusions: Not reported |
| **ATTRITION:** | Loss to follow-up: Paroxetine 0 (0%); Venlafaxine XR 1 (6%) (numbers reported for 43 patients switching)  
Withdrawals due to adverse events: Yes  
Loss to follow-up differential high: No |
| **ADVERSE EVENTS:** |  
- 98% of patients reported adverse events;  
- Paroxetine: somnolence 54%, sweating 25%, headache 21%, constipation 21%, insomnia 18%, nausea 18%, change in mood 18%, loss of libido 18%  
- Venlafaxine: somnolence 38%, sweating 31%, constipation 31%, dry mouth 19%, headache 13%, insomnia 13%, nausea 13%, loss of libido 13%  
- p-values not reported |
| **QUALITY RATING:** | Fair |
## Evidence Table 7  
### Obsessive-compulsive Disorder

| STUDY: | Authors: Montgomery SA, et. al.  
Year: 2001  
Country: Europe, South Africa |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 401 |
| INTERVENTION: | Drug:  
Dose:  
Duration: |
| | Citalopram  
20 mg/d  
12 weeks | Citalopram  
40 mg/d  
12 weeks | Citalopram  
60 mg/d  
12 weeks | Placebo  
N/A  
12 weeks |
| INCLUSION: | 18-65 years; DSM-IV criteria for OCD; Y-BOCS ≥ 20; symptoms stable for the preceding 6 months |
| EXCLUSION: | MADRS ≥ 22; other Axis I disorders; suicidal risk; recent treatment with fluoxetine or MAOI; hypersensitivity to SSRIs; hepatic impairment; drug/alcohol dependence; pregnancy/lactation; Tourette’s syndrome in family; concomitant therapy with anticonvulsive and psychoactive drugs |
| OTHER MEDICATIONS/INTERVENTIONS: | 55.4% received concomitant medication |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean Age: 38; citalopram: 37.6, placebo: 38.6  
Gender (% female): citalopram: 55%, placebo: 50.1%  
Ethnicity: Not reported  
Other population characteristics: Mean duration of illness greater than 15 years for all groups |
**Authors:** Montgomery SA, et al.  
**Year:** 2001  
**Country:** Europe, South Africa

| OUTCOME ASSESSMENT: | Measures: Y-BOCS, MADRS, CGI-I, NIMH-OC  
Timing of assessments: Baseline, weeks 1, 3, 5, 7, 9, 12 |
| --- | --- |

| RESULTS: |  
- A significant reduction in Y-BOCS scores for all 3 citalopram groups (p < 0.01) compared to placebo  
- Citalopram 60 mg reached statistical significance at week 3, citalopram 20 mg and 40 mg at week 7  
- Changes in NIMH-OC scores were also significantly greater in the citalopram groups (p < 0.001)  
- All 3 treatment groups had significantly more responders than placebo |

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Not reported |

| ATTRITION: | Loss to follow-up: 16%; citalopram 20 mg: 16%; citalopram 40 mg: 15%; citalopram 60 mg: 15%; placebo: 17%  
Withdrawals due to adverse events: 4%; citalopram 20 mg: 4%; citalopram 40 mg: 6%; citalopram 60 mg: 4%; placebo: 2%  
Loss to follow-up differential high: No |

| ADVERSE EVENTS: |  
- Treatment emergent adverse events: citalopram 20 mg: 73%; citalopram 40 mg: 68%; citalopram 60 mg: 72%; placebo: 58%  
- The incidence of nausea, insomnia, fatigue, increased sweating, dry mouth, ejaculation failure, and diarrhea was significantly higher in one or more citalopram groups compared to placebo |

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 7</th>
<th>Obsessive-compulsive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Pallanti S, et al.¹²⁸</td>
</tr>
<tr>
<td></td>
<td>Year: 2004</td>
</tr>
<tr>
<td></td>
<td>Country: Italy</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Not reported</td>
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<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Single center</td>
</tr>
<tr>
<td></td>
<td>Sample size: 49</td>
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<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Citalopram and placebo</td>
</tr>
<tr>
<td>Drug:</td>
<td>citalopram</td>
</tr>
<tr>
<td>Dose:</td>
<td>20-80 mg/d and N/A</td>
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<tr>
<td>Duration:</td>
<td>12 weeks</td>
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<td>Sample size:</td>
<td>28</td>
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<tr>
<td></td>
<td>Citalopram and Mirtazapine</td>
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<tr>
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<td>citalopram and mirtazapine</td>
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<td>20-80 mg/d and 15-30 mg/d</td>
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<td></td>
<td>12 weeks</td>
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<tr>
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<td>21</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Diagnosis of OCD with co-morbid depression by structured clinical interview for DSM-IV Axis I and II disorders; OCD symptoms for 1 year; at least moderate severity on the CGI; SRI naive</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Any of the following conditions: organic mental disorder, psychotic mental disorders, mental retardation, current depressive episode; substance or alcohol abuse; history of bipolar disorder; personality disorders; pregnant or nursing women</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: citalopram/placebo 30.4; citalopram/mirtazapine 28.1</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): citalopram/placebo 43%; citalopram/mirtazapine 43%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: HAM-D total score: 8.7; CGI-S score: 5.4</td>
</tr>
</tbody>
</table>
**Authors:** Pallanti S, et al.  
**Year:** 2004  
**Country:** Italy

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** Yale-Brown Obsessive Compulsive Scale (YBOCS)  
**Secondary Outcome Measures:** HAM-D19; CGI-I, Arizona Sexual Experience Scale  
**Timing of assessments:** At baseline and weekly thereafter. |
|---|---|

| RESULTS: |  
• The citalopram/mirtazapine group showed an earlier response than the citalopram/placebo on reduction in mean YBOCS score; a significant between group difference was observed during weeks 2 through 6 ($p < 0.05$)  
• No significant between group difference in YBOCS score observed at endpoint.  
• No differences in CGI-I at endpoint  
• HAM-D not reported |
|---|---|

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** No |
|---|---|

| ATTRITION: | **Loss to follow-up:** 8.2% (4): Citalopram/placebo: 7.1% (2); citalopram/mirtazapine: 9.5% (2)  
**Withdrawals due to adverse events:** 2% (1); citalopram/placebo: 3.6% (1); citalopram/mirtazapine: 0%  
**Loss to follow-up differential high:** No |
|---|---|

| ADVERSE EVENTS: |  
• Mean Arizona Sexual Experience Scale score at endpoint was significantly worse in citalopram/placebo group than the citalopram/mirtazapine ($p < 0.01$)  
• Significantly greater weight gain among citalopram/mirtazapine group. |
|---|---|

| QUALITY RATING: | Fair |
## Evidence Table 7  
### Obsessive-compulsive Disorder

| STUDY:            | Authors: Piccinelli M, et. al.,
|                  | Year: 1995
|                  | Country: Italy
| FUNDING:         | University of Verona
| DESIGN:          | Study design: Meta-analysis
|                  | Number of patients: 1076
| AIMS OF REVIEW:  | Efficacy of drug treatment in OCD; subgroup analysis: SSRIs vs. placebo
| TIME PERIOD COVERED: | 1975-1994
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs, double-blind placebo-controlled
| CHARACTERISTICS OF INCLUDED POPULATIONS: | DSM-III-R diagnosis of OCD; adult patients not refractory to standard treatments with OCD; no comorbid Tourette’s syndrome, phobia, depression or obsessive compulsive neurosis
### Authors: Piccinelli M, et al.
**Year:** 1995  
**Country:** Italy

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>13 trials of SSRI vs. placebo (fluoxetine, fluvoxamine, sertraline)</th>
</tr>
</thead>
</table>
| MAIN RESULTS:                           | • Effect size calculated using Hedge’s $g$; a measure of the difference between the means of active treatment and placebo control; difference measures (Y-BOCS and NIMH-OC) abstracted from trials as the weighted mean $g$; positive values for Hedge’s $g$ indicate greater improvement in the active treatment group, compared to placebo  
• Fluvoxamine vs. placebo:  
  Y-BOCS: 0.57 (95% CI: 0.37-0.77)  
  NIMH-OC: 0.29 (95% CI 0.07-0.51)  
• Fluoxetine vs. placebo:  
  Y-BOCS: 0.57 (95% CI: 0.33-0.81)  
  NIMH-OC: N/A  
• Sertraline vs. placebo:  
  Y-BOCS: 0.52 (95% CI: 0.27-0.77)  
  NIMH-OC: 0.55 (95% CI: 0.30-0.80)  
• Improvement rate over placebo (binominal effect size display, Rosenthal 1984):  
  Fluvoxamine: 28.2%  
  Fluoxetine: 28.5%  
  Sertraline: 21.6%  
• No statistically significant differences between study drugs |

<p>| ADVERSE EVENTS: | Not reported |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 7</th>
<th>Obsessive-compulsive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Soomro et al.¹³⁹</td>
</tr>
<tr>
<td></td>
<td>Year: 2008</td>
</tr>
<tr>
<td></td>
<td>Country: Multinational</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Cochrane</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: Systematic review and meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Number of patients: 3097</td>
</tr>
<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
<td>To examine the efficacy and adverse effects of serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD) in adults</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
<td>Until December 2007</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
<td>RCTs and quasi-RCTs</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
<td>Adults with OCD</td>
</tr>
<tr>
<td>Authors: Soomro et al.</td>
<td>Year: 2008</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></td>
<td>SSRIs compared with placebo</td>
</tr>
<tr>
<td><strong>MAIN RESULTS:</strong></td>
<td></td>
</tr>
<tr>
<td>• Yale-Brown Obsessive Compulsive Scale (YBOCS) (WMD -3.21, 95% CI -3.84 to -2.57)</td>
<td></td>
</tr>
<tr>
<td>• Clinical response RR 1.84, 95% CI 1.56 to 2.17</td>
<td></td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td></td>
</tr>
<tr>
<td>• Citalopram vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Overall AEs 71% vs. 58%, RR 1.22 (95% CI 1.02 to 1.45), Nausea 22% vs. 9% RR, 2.47 (95% CI 1.28 to 4.77). Headache 17% vs.167%, RR 1.05 (95% CI 0.63 to 1.76 Insomnia 16% vs. 7%, RR 2.26 (95% CI 1.06 to 4.84) Sexual side effects RR 18.64, (95% CI of 1.15 to 302.80.</td>
<td></td>
</tr>
<tr>
<td>• Fluoxetine vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Nausea, headache, insomnia and anxiety most common, Risk of these side effects for fluoxetine was similar to placebo, with the RR(REmodel) for these three side effects shown to be between 1.11 and 1.42, and 95% confidence intervals crossing 1.</td>
<td></td>
</tr>
<tr>
<td>• Paroxetine vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Overall AEs 81 vs. 72 RR 1.14 (95% CI 0.91 to 1.42) Relative risk for asthenia and headache for paroxetine versus placebo was not statistically significant.</td>
<td></td>
</tr>
<tr>
<td>Insomnia .23% vs. 14% RR1.71 (95% CI 1.15 to 2.53) Somnolence 27% vs. 11% RR 1.85 (95%CI 1.12 to 3.06), Nausea 3.96 (95%CI 1.82 to 8.61) Constipation 4.29 (95% CI 1.26 to 14.56).</td>
<td></td>
</tr>
<tr>
<td>• Sertraline vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Overall AEs 87% vs. 68% RR 1.21 (95% CI 1.08 to 1.37) RR for nausea, dyspepsia, Differences in constipation, sedation, forgetfulness and headache for sertraline compared to placebo were not significant</td>
<td></td>
</tr>
<tr>
<td>Insomnia 31 vs. 13 RR 2.23 (95% CI 1.09 to 4.56) Diarrhea 25 vs 10 RR 2.16 (95% CI 1.11 to 4.23), Sexual side effects 14 vs. 2 RR 5.74 (95% CI 0.68 to 48.31.</td>
<td></td>
</tr>
<tr>
<td><strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong></td>
<td>Yes - CCDANCTR-Studies and CCDANCTR-References</td>
</tr>
<tr>
<td><strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong></td>
<td>Yes</td>
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<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Good</td>
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<tr>
<td>Evidence Table 7</td>
<td>Obsessive-compulsive Disorder</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Stein DJ, et al.131</td>
</tr>
<tr>
<td></td>
<td>Year: 1995</td>
</tr>
<tr>
<td></td>
<td>Country: South Africa and US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: Meta-analysis (SSRI vs. placebo only)</td>
</tr>
<tr>
<td></td>
<td>Number of patients: 516</td>
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<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
<td>Assess and integrate data from multiple clinical trials on drug treatment in OCD</td>
</tr>
<tr>
<td><strong>STUDIES INCLUDED IN META-ANALYSIS</strong></td>
<td>This review addressed placebo-controlled trials, active control, and open label; we focus on SSRI vs. placebo. Perse et al. 1987, Chouinard et al. 1990, Jenike et al. 1990, Montgomery et al. 1993</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
<td>1980-1993</td>
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<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
<td>RCTs; placebo-controlled SSRI trials detected by MedLine &amp; PsychLit search; subjects rated with YBOCS or NIMH obsessive-compulsive global rating scale; trials at least six weeks in length; no specification on sample size</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
<td>Diagnosis of OCD; adults; single medication without concomitant therapy</td>
</tr>
</tbody>
</table>
**Authors:** Stein DJ, et al.  
**Year:** 1995  
**Country:** South Africa, US

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>Fluvoxamine (2 studies), fluoxetine (1 study), sertraline (2 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>• There were no differences in effect sizes between the SSRIs.</td>
</tr>
<tr>
<td></td>
<td>• Effect size was calculated in comparison to placebo:</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine: 0.69 +/- 0.47</td>
</tr>
<tr>
<td></td>
<td>Sertraline: 0.55</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine: 0.51 +/- 0.12</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>N/A</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>Yes</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>No</td>
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<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
<tr>
<td>Evidence Table 7</td>
<td>Obsessive-compulsive Disorder Adults</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Stein et al.¹³c</td>
</tr>
<tr>
<td></td>
<td>Year: 2007</td>
</tr>
<tr>
<td></td>
<td>Country: Multinational (7 countries)</td>
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<tr>
<td><strong>FUNDING:</strong></td>
<td>H. Lundback A/S</td>
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<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
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<tr>
<td></td>
<td>Setting: Multicenter (58)</td>
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<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sample size: 114</td>
</tr>
<tr>
<td></td>
<td>Escitalopram 10</td>
</tr>
<tr>
<td></td>
<td>10 mg/day</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sample size: 113</td>
</tr>
<tr>
<td></td>
<td>Escitalopram 20</td>
</tr>
<tr>
<td></td>
<td>20 mg/day</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sample size: 114</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td></td>
<td>40 mg/day</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sample size: 117</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>18–65 years, with a Y-BOCS of &gt;20 at screening and baseline, an OCD duration &gt; 1 year, and symptoms that were stable for at least 6 months.</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Within 6 months, MDD, panic disorder, GAD, social anxiety disorder, PTSD, eating disorder, body dysmorphic disorder, mental retardation or any pervasive developmental disorder, cognitive disorder (including dementia), schizotypal personality disorder, substance abuse disorder, motor/verbal tic disorder (including Tourette's); a history of bipolar disorder, schizophrenia, or any psychotic disorder, patients with personality disorder that could interfere with the evaluation of the treatment for primary OCD; at risk of suicide (according to the investigator's judgment), or had a score ≥ 5 on item 10 (suicidal thoughts) of the MADRS, or a MADRS total score ≥ 22, ECT, formal psychotherapy, or planned to initiate such therapy; a history of severe drug hypersensitivity, treatment-refractory patients; pregnant, breast-feeding or not using adequate contraception. within 2 weeks prior to screening: monoamine oxidase inhibitors/reversible monoamine oxidase inhibitors, psychoactive herbal remedies, any other antidepressant or drug used for OCD treatment, dopamine antagonists, serotonergic agonists, or oral antipsychotics/mood stabilizers such as lithium; fluoxetine w/in 5 weeks, depot antipsychotics w/in 6 months, or ongoing prophylactic treatment with anticonvulsant or hypnotic drugs (except zolpidem, zopiclone, or zaleplon for insomnia, but not more than 3 days in a row and a maximum of 20 days in total during the study).</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>See above</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 38</td>
</tr>
<tr>
<td></td>
<td>Gender (female %): Placebo 55.3  paroxetine40 53.8 escitalopram10  61.1 escitalopram20 57.9</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: % Caucasian Placebo 94.7  paroxetine40 94.9 escitalopram10 93.8 escitalopram20 97.4</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
</tbody>
</table>
**Authors:** Stein et al.  
**Year:** 2007  
**Country:** Multinational

### OUTCOME ASSESSMENT:

- **Primary Outcome Measures:** mean change in Y-BOCS total score from baseline to week 12
- **Secondary Outcome Measures:** mean change from baseline to week 24 in Y-BOCS total score, mean change from baseline to week 12 and to week 24 in Y-BOCS obsessional and compulsive subscores, change in the National Institute of Mental Health Obsessive–Compulsive Scale (NIMH-OCS)27 and Clinical Global Impressions – Severity (CGI-S) score from baseline to weeks 12 and 24, the CGI-I score, response and remission

#### Timing of assessments:
Baseline weeks 4, 8, 12, 16, 20, 24

### RESULTS:

- Y-BOCS total score at week 12 compared to placebo
  - escitalopram 20 (mean difference of –3.21; 95% CI: –5.19 to –1.23, \( p < 0.01 \))
  - paroxetine (mean difference of –2.47; 95% CI: –4.43 to –0.51, \( p < 0.05 \))
  - escitalopram 10 (mean difference of –1.97; 95% CI: –3.97 to 0.02, \( p = 0.052 \)).

- The standardized effect sizes versus placebo at week 12 were:
  - ESC10 0.26 (95% CI: –0.003 to 0.53)
  - esc20, 0.43 (95% CI: 0.16–0.69)
  - paroxetine 0.33 (95% CI: 0.07–0.66)

- No numbers were reported for 24 weeks, just figures.

### ANALYSIS:

- ITT: Yes
- Post randomization exclusions: 11

### ATTRITION:

- **Loss to follow-up:** Overall 29%  
  - Placebo 32%  
  - paroxetine 32%  
  - escitalopram10 23%  
  - escitalopram20 27%

- **Withdrawals due to adverse events:** NR

- **Withdrawals due to lack of efficacy:** Placebo 18%  
  - paroxetine 8%  
  - escitalopram10 NR  
  - escitalopram20 6%

- **Loss to follow-up differential high:** NO

### ADVERSE EVENTS:

- Placebo vs. ESC 10 mg vs. ESC 20 mg vs. PAR 40 mg
  - Patients with AEs 73 (64.0%) vs. 80 (70.8%) vs. 86 (75.4%) vs. 94 (80.3%)
  - Nausea 14 (12.3%) vs. 22 (19.5%) vs. 31 (27.2%)* vs. 31 (26.5%)*
  - Headache 20 (17.5%) vs. 19 (16.8%) vs. 25 (21.9%) vs. 23 (19.7%)
  - Fatigue 6 (5.3%) vs. 13 (11.5%) vs. 20 (17.5%)* vs. 22 (18.8%)*
  - Somnolence 6 (5.3%) vs. 7 (6.2%) vs. 14 (12.3%) vs. 13 (11.1%)
  - Ejaculation delayed (men) 0 (0.0%) vs. 2 (4.5%) vs. 5 (10.4%)* vs. 5 (9.3%)
  - Libido decreased 1 (0.9%) vs. 3 (2.7%) vs. 8 (7.0%)* vs. 10 (8.5%)*
  - Hyperhidrosis 2 (1.8%) vs. 7 (6.2%) vs. 6 (5.3%) vs. 16 (13.7%)*
  - Influenza 7 (6.1%) vs. 6 (5.3%) vs. 1 (0.9%) vs. 1 (0.9%)*

- \( p < 0.05 \)

### QUALITY RATING:

- Fair
### Evidence Table 8  Panic Disorder

| STUDY: | Authors: Asnis G, et al.  
Year: 2001  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
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</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 188 |
| INTERVENTION: | Drug:  
Dose:  
Duration: |
| | Fluvoxamine  
50-300 mg/d  
8 weeks |
| | Placebo  
N/A  
8 weeks |
| INCLUSION: | DSM-III-R diagnosis; age 18-65; at least 1 panic attack per week for at least 4 weeks prior to study |
| EXCLUSION: | Concurrent systematic illness; other Axis I psychiatric disorder; clinical significant lab abnormalities or ECG; pregnant or lactating women without adequate birth control |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate or lorazepam for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean Age: Fluvoxamine: 34.2, placebo: 36.7  
Gender (% female): fluvoxamine 64.4%, placebo 64.1%  
Ethnicity: Not reported  
Other population characteristics: Number of full panic attacks per week at baseline: fluvoxamine: 2.7, paroxetine: 3.3 |
<table>
<thead>
<tr>
<th>Authors: Asnis G, et al.</th>
<th><strong>Measures:</strong> Primary daily panic attack inventory (DPAI), CAS, SDS, CGI-I, CGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2001</td>
<td><strong>Timing of assessments:</strong> Baseline, weekly intervals thereafter for a maximum of 8 weeks of treatment</td>
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<tr>
<td>Country: US</td>
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<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Significantly more fluvoxamine patients were free from full panic attacks (p = 0.002)</td>
</tr>
<tr>
<td></td>
<td>• Reduction of panic disorder severity was significantly greater in the fluvoxamine group (p = 0.003)</td>
</tr>
<tr>
<td></td>
<td>• Significantly more fluvoxamine patients were CGI-I responders at endpoint (64% vs. 42%; p = 0.002)</td>
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<thead>
<tr>
<th>ANALYSIS:</th>
<th>RESULTS:</th>
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<tr>
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<td><strong>ITT:</strong> Yes</td>
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<td><strong>Post randomization exclusions:</strong> Yes</td>
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<tr>
<th>ATTRITION:</th>
<th>RESULTS:</th>
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<tbody>
<tr>
<td></td>
<td><strong>Loss to follow-up:</strong> fluoxetine 37.6%, placebo 33.6%</td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events:</strong> fluvoxamine: 9.6%; placebo: 5.9%</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> No</td>
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<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Fluvoxamine: nausea: 43%, insomnia: 25%, somnolence: 24%, asthenia: 22%</td>
</tr>
<tr>
<td></td>
<td>• Placebo: nausea: 33%, headache: 22%, anxiety: 16%</td>
</tr>
<tr>
<td></td>
<td>• No significant difference in the number of withdrawals due to adverse events</td>
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</tbody>
</table>

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<thead>
<tr>
<th>QUALITY RATING:</th>
<th>RESULTS:</th>
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<tr>
<td></td>
<td><strong>Fair</strong></td>
</tr>
<tr>
<td>Evidence Table 8</td>
<td>Panic Disorder</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
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</table>
| **STUDY:**       | Authors: Bandelow B, et al.  
Year: 2004  
Country: Germany |
| **FUNDING:**     | Pfizer |
| **DESIGN:**      | Study design: RCT  
Setting: Multi-center  
Sample size: 225 |
| **INTERVENTION:**| Drug: Sertraline  
Dose: 50 – 150 mg/d  
Duration: 12 weeks  
Paroxetine  
Dose: 40 – 60 mg/d  
Duration: 12 weeks |
| **INCLUSION:**   | Male or female outpatients; aged 18-65; primary DSM-IV and ICD-10 disease of PD with or without agoraphobia; minimum of 4 panic attacks during the 4 weeks prior to screening; total score > 18 at baseline on the PAS (clinician-rated) |
| **EXCLUSION:**   | Primary disease other than panic disorder; MADRS rating scale total score > 14; clinically significant and unstable medical illness; current diagnosis of bipolar disorder, schizophrenic disorder, delusional disorder, epilepsy, MDD, OCD, social phobia; history of alcoholism or drug abuse within the past three years; serious risk for suicide; pregnancy or lactation or not using reliable contraceptive methods |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate; zolpidem; zopiclone could be given for severe insomnia on limited basis (< 3 times/wk) |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 38.6  
Gender (% female): sertraline: 60%; paroxetine: 66%  
Ethnicity: Not reported  
Other population characteristics: Patients with agoraphobia subtype: sertraline, 68%; paroxetine, 63%; patients with non-agoraphobia subtype: sertraline, 32%; paroxetine, 66% |
**Authors:** Bandelow B, et al.  
**Year:** 2004  
**Country:** Germany

### OUTCOME ASSESSMENT:
- **Measures:** Safety and efficacy assessments, primary efficacy measure was clinician rated PAS  
- **Timing of assessments:** Weeks 1, 2, 4, 6, 8, 12, 15

### RESULTS:
- Treatment with sertraline and paroxetine resulted in the same level of improvement on the PAS total score ($p = 0.749$)  
- For both groups 35% reduction from baseline PAS total score had been achieved by week 6  
- No significant differences in secondary outcome measures (PAS subscales, CGI-S, HAM-A, Sertraline Quality of Life Scale)  
- Mean improvement on individual PAS subscales was similar at endpoint in both treatment groups stratified by agoraphobia subtype

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** No

### ATTRITION:
- **Loss to follow-up:** sertraline: 28%, paroxetine: 33%  
- **Withdrawals due to adverse events:** sertraline: 12%, paroxetine: 18%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Sexual dysfunctional, diarrhea and sedation occurred at a rate less than 10% (data not reported)  
- Weight gain (> 7% increase in baseline body weight) sertraline: < 1%, paroxetine: 7% ($p < 0.05$)

### QUALITY RATING:
- Fair
### Evidence Table 8

**Panic Disorder**

| STUDY:          | Authors: Black DW, et al.  
|                 | Year: 1993  
|                 | Country: US  |
| FUNDING:        | Reid Rowell Pharma |
| DESIGN:         | Study design: RCT  
|                 | Setting: Multi-center  
|                 | Sample size: 75 |
| INTERVENTION:   | Drug: |
|                 | Dose: |
|                 | Duration: |
|                 | Fluvoxamine |
|                 | Up to 300 mg/d |
|                 | 8 weeks |
|                 | Cognitive therapy |
|                 | Arm 2 |
|                 | 8 weeks |
|                 | Placebo |
|                 | N/A |
|                 | 8 weeks |
| INCLUSION:      | Age 18-65 yrs; DSM III-R criteria for panic disorder; in good physical health |
| EXCLUSION:      | Pregnant, lactating; psychotic; suicidal or demented subjects excluded |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
|                          | Mean Age: 36.5  
|                          | Gender (% female): Not reported  
|                          | Ethnicity: Not reported  
<p>|                          | Other population characteristics: No prior psychiatric treatment: fluvoxamine: 40%, cognitive therapy: 32%, placebo: 20% |</p>
<table>
<thead>
<tr>
<th>Authors: Black DW, et al.</th>
<th>Year: 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
</tr>
</tbody>
</table>

**Outcome Assessment:**

**Measures:** Number of panic attacks and severity as estimated from a patient log, Clinical Anxiety Scale (CAS), CGI-S, CGI-I, Sheehan Disability Scale, MADRS

**Timing of Assessments:** Baseline, during treatment and at endpoint (some were assessed weekly)

**Results:**

- Significantly greater improvement for fluvoxamine on CAS ($p = 0.003$) and CGI ($p = 0.004$), Panic Severity Score ($p = 0.003$) than placebo
- Sheehan Disability Ratings: work ($p = 0.01$) and social/leisure ($p = 0.02$) components were significantly better with fluvoxamine than placebo
- MADRS score was significantly more improved with fluvoxamine than placebo

**Analysis:**

**ITT:** No

**Post randomization exclusions:** Yes

**Attrition:**

**Loss to follow-up:** fluvoxamine: 16%, cognitive therapy: 36%, placebo: 28%

**Withdrawals due to adverse events:** fluvoxamine: 8%, cognitive therapy: 0%, placebo: 0%

**Loss to follow-up differential high:** Yes

**Adverse Events:**

- Fluvoxamine-treated patients reported significantly more adverse events than placebo–treated patients ($p = 0.005$)
- 1 person in the fluvoxamine group attempted suicide

**Quality Rating:** Fair
### Evidence Table 8  
#### Panic Disorder

| STUDY: | Authors: Hoehn-Saric R, et al.  
Year: 1993  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 50 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:** |
| | Fluvoxamine  
50–300 mg/day  
8 weeks |
| | Placebo  
N/A  
8 weeks |
| INCLUSION: | Diagnosis by DMS III-R and the SCID; 1 panic attack per week for at least 4 weeks; severity score of 25 or greater on diary (during run in) to enter randomization phase as well as at least one major panic attack (major panic attack = attack with at least 4 symptoms) one week before randomization |
| EXCLUSION: | No medication that could affect the CNS for past 3 weeks before study; abnormal lab values; ECG and hypertension; history of major mental illness; depression; OCD; substance abuse |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean Age: 38.0  
Gender (% female): 55.6%  
Ethnicity: Not reported  
Other population characteristics: Education 13.7 yr, 78% with mild agoraphobia, age of onset 26.2 years |
**Authors:** Hoehn-Saric R, et al.  
**Year:** 1993  
**Country:** US

**OUTCOME ASSESSMENT:**  
**Measures:** Number of panic attacks per week and severity of attacks, MADRS, Clinical Anxiety Scale (CAS), Sheehan Disability Scale, symptoms from diary  
**Timing of assessments:** Weekly for 8 weeks

**RESULTS:**  
- Fluvoxamine group had significantly fewer major panic attacks than placebo group  
- Significantly more fluvoxamine treated patients were free of panic attacks at endpoint (p < 0.02)  
- Significantly lower scores in the fluvoxamine group on CAS and MADRS (CAS significant at week 6; MADRS significant at week 7)  
- There was no difference between groups in terms of minor panic attacks or Sheehan Disability Scale

**ANALYSIS:**  
**ITT:** No  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up:** 24%; fluvoxamine: 24%, placebo: 24%  
**Withdrawals due to adverse events:** 12%; fluvoxamine: 16%, placebo: 8%  
**Loss to follow-up differential high:** No

**ADVERSE EVENTS:**  
- Fluvoxamine: drowsiness: 28%, dyspepsia: 17%, headache: 11%  
- Fewer side effects at week 8 than week 3

**QUALITY RATING:** Fair
### Evidence Table 8

**Panic Disorder**

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>Authors: Pollack et al. 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2007</td>
<td><strong>Country:</strong> USA (Europe)</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>Wyeth Research</td>
</tr>
<tr>
<td>DESIGN:</td>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td>Setting:</td>
<td><strong>multi-centre</strong></td>
</tr>
<tr>
<td>Sample size:</td>
<td><strong>664</strong></td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td><strong>Venlafaxine ER</strong></td>
</tr>
<tr>
<td>Dose:</td>
<td><strong>75mg/day</strong></td>
</tr>
<tr>
<td>Duration:</td>
<td><strong>(up to) 12 weeks</strong></td>
</tr>
<tr>
<td>Sample size:</td>
<td><strong>166</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Venlafaxine ER</strong></td>
</tr>
<tr>
<td>Dose:</td>
<td><strong>150mg/day</strong></td>
</tr>
<tr>
<td>Duration:</td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td>Sample size:</td>
<td><strong>168</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Paroxetine</strong></td>
</tr>
<tr>
<td>Dose:</td>
<td><strong>40mg/day</strong></td>
</tr>
<tr>
<td>Duration:</td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td>Sample size:</td>
<td><strong>166</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Dose:</td>
<td>n/a</td>
</tr>
<tr>
<td>Duration:</td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td>Sample size:</td>
<td><strong>163</strong></td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Outpatients meeting DSM-IV criteria for panic disorder with or without agoraphobia (confirmed with Mini-International Neuropsychiatric Interview). Score &gt; 4 on CGI-S; at least 8 full panic attacks in 4 weeks before inclusion and 4 attacks in placebo lead-in period</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Patients were excluded if: they had a primary DSM-IV diagnosis of MDD or GAD or elevated depression ratings; any other clinically significant Axis I or II disorder (within 6 months of begin); a history or current diagnosis of any psychotic illness, bipolar affective disorder, or organic brain disease; acutely suicidal, had a history of drug or alcohol dependence or abuse, or who regularly used alcohol, or psychopharmacological drugs, or who had a positive urine toxicology screen; patients who received venlafaxine, paroxetine, or electroconvulsive therapy 6 months before study entry, or CBT within 30 days; clinically significant abnormalities on laboratory tests, electrocardiogram (ECG), vital signs, or physical examination or clinically important medical conditions; women of childbearing potential who were pregnant, breast feeding, or not using a medically acceptable form of contraception</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/ INTERVENTIONS:</td>
<td>None (zaleplon or zolpidem permitted up to 3/week, first 2 weeks)</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: yes</td>
</tr>
<tr>
<td>Mean age: Gender (female %):</td>
<td>427/634 (67.3%) of ITT popl</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td>NR</td>
</tr>
<tr>
<td>Other population characteristics:</td>
<td>NR</td>
</tr>
</tbody>
</table>
**Authors:** Pollack M  
**Year:** 2007  
**Country:** USA (Europe)

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** frequency of full-symptom panic attacks from the Panic and Anticipatory Anxiety Scale-(PAAS). eg: percentage of patients free from full-symptom panic attacks in the last observation carried forward (LOCF) end point analysis.

**Secondary Outcome Measures:**
- changes from baseline in the Panic Disorder Severity Scale (PDSS) total score, panic attack frequency, anticipatory anxiety as measured by the PAAS, phobic fear and avoidance as assessed with the Phobia Scale, HAM-A total score, measures of function and quality of life, as assessed by the Sheehan Disability Scale (SDS) and the Quality-of-Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

**Timing of assessments:** baseline, week 1, 2, 3, 4, 6, 8, 10, 12

### RESULTS:
- All treatment groups better than placebo
- No significant differences in efficacy between active treatment groups (ven 75 vs. ven 150 vs. par 40 vs. placebo)
- Patients panic-free in 2 weeks before endpoint: 54% vs. 60% vs. 61% vs. 35%
- CGI-I responders: 77% vs. 79% vs. 81% vs. 56%
- Remission: 43% vs. 43% vs. 44% vs. 24%

### ANALYSIS:

<table>
<thead>
<tr>
<th>ITT: 634</th>
</tr>
</thead>
</table>

**Post randomization exclusions:** 30

**Loss to follow-up differential high:** No

### ATTRITION:

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
<th>Ven 75</th>
<th>Ven 150</th>
<th>Par 40</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>19.6%</td>
<td>20.1%</td>
<td>18.1%</td>
<td>25.1%</td>
</tr>
<tr>
<td>8.0%</td>
<td>12.0%</td>
<td>10.2%</td>
<td>8.6%</td>
<td></td>
</tr>
<tr>
<td>4.2%</td>
<td>2.4%</td>
<td>3.7%</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:
- at least 1 AE: 74% vs 71% vs 75% vs 67%
- no significant changes in: weight gain or sexual AEs (patient self reporting!)

**Double-blind period (%):**
- Sweating 8 vs. 13% vs. 10% vs. 4%
- Dry mouth 5% vs. 10% vs. 7% vs. 6%
- Anorexia 4% vs. 8% vs. 7% vs. 4%
- Tremor 4% vs. 7% vs. 6% vs. 2%
- Constipation 5% vs. 6% vs. 8% vs. 1%
- Diarrhea 5% vs. 6% vs. 5% vs. 3%
- Somnolence 3% vs. 4% vs. 13% vs. 2%
- Back pain 6% vs. 1% vs. 2% vs. 2%

### QUALITY RATING:
**Fair**
<table>
<thead>
<tr>
<th>Evidence Table 8</th>
<th>Panic Disorder</th>
</tr>
</thead>
</table>
| STUDY:           | Authors: Pollack et al.  
Year: 2007  
Country: USA (middle/south America) |
| FUNDING:         | Wyeth Research |
| DESIGN:          | Study design: RCT  
Setting: multicentre (Argentina, Mexico, Chile, Costa Rica)  
Sample size: 653 |
| INTERVENTION:    | Drug:  
Venlafaxine ER  
Dose: 75mg/day  
Duration: (up to) 12 weeks  
Sample size: 166  
Venlafaxine ER  
Dose: 225mg/day  
Duration: 12 weeks  
Sample size: 168  
Paroxetine  
Dose: 40mg/day  
Duration: 12 weeks  
Sample size: 166  
Placebo  
Dose: n/a  
Duration: 12 weeks  
Sample size: 163 |
| INCLUSION:       | Outpatients, male and female, aged 18 years and over, meeting the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for panic disorder with or without agoraphobia for at least 3 months established using a modified Mini-International Neuropsychiatric Interview (MINI) |
| EXCLUSION:       | Patients were excluded if: they had a primary DSM-IV diagnosis of MDD or GAD or elevated depression ratings; any other clinically significant Axis I or II disorder (within 6 months of begin); a history or current diagnosis of any psychotic illness, bipolar affective disorder, or organic brain disease; acutely suicidal, had a history of drug or alcohol dependence or abuse, or who regularly used alcohol, or psychopharmacological drugs, or who had a positive urine toxicology screen; patients who received venlafaxine, paroxetine, or electroconvulsive therapy 6 months before study entry, or CBT within 30 days; clinically significant abnormalities on laboratory tests, electrocardiogram(ECG), vital signs, or physical examination or clinically important medical conditions; women of childbearing potential who were pregnant, breast feeding, or not using a medically acceptable form of contraception. |
| OTHER MEDICATIONS/INTERVENTIONS: | None (zaleplon or zolpidem permitted up to 3/week, first 2 weeks) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes  
Mean age: between 35.1 (placebo) and 37.5 (paroxetine 40mg)  
Gender (female %): 420/624 (67.3%)  
Ethnicity: middle/south American  
Other population characteristics: NR |
Authors: Pollack M et al.  
Year: 2007  
Country: USA (middle/south America)

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>percentage of patients free from full-symptom panic attacks using LOCF values at end-point.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>changes from baseline in the PDSS total score and panic attack frequency.</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>1,2,3,4,6,8,10 &amp; 12 weeks</td>
</tr>
</tbody>
</table>

### RESULTS:

- All treatments better than placebo
- At endpoint the venlafaxine ER 225mg group had a significantly lowers PDSS score than the paroxetine group (4.78 vs. 6.26 p<0.05) and a greater percentage of patients free of full-symptom panic attacks (70.0 vs. 58.3% p<0.05). (Primary and one secondary outcome)

### ANALYSIS:

| ITT: Yes |
|-------------------|-------------------|-------------------|-------------------|
| Post randomization exclusions: 29 | Loss to follow-up differential high: No |

### ATTRITION:

<table>
<thead>
<tr>
<th>Ven 75</th>
<th>Ven 225</th>
<th>Par 40</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.7%</td>
<td>17.4%</td>
<td>21.7%</td>
<td>26.5%</td>
</tr>
<tr>
<td>1.8%</td>
<td>0.6%</td>
<td>5.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>4.9%</td>
<td>6.0%</td>
<td>7.4%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:

- At least 1 AE: 138 (86%) vs 146 (88%) vs 129 (80%) vs 129 (80%) 
- Data NR

### QUALITY RATING:

- Fair
Evidence Table 8  Panic Disorder

| STUDY: | Authors: Stahl SM, et al.  
Year: 2003  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Forest Laboratories</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 366 |
| INTERVENTION: | Drug:  
Escitalopram  
Dose: 5-20 mg/d  
Duration: 10 weeks  
Citalopram  
Dose: 10-40 mg/d  
Duration: 10 weeks  
Placebo  
Dose: N/A  
Duration: 10 weeks |
| INCLUSION: | DSM-IV criteria for panic disorder with or without agoraphobia; minimum of 4 DSM-IV defined panic attacks during the 4 weeks prior to the screening visit; 3 panic attacks during the 2 week placebo lead in; 18-80 years of age |
| EXCLUSION: | Score > 17 HAM-D; bipolar disorder; schizophrenia; OCD or other psychotic disorders; pregnancy; clinically significant abnormalities |
| OTHER MEDICATIONS/INTERVENTIONS: | Zolpidem as needed for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean Age: Escitalopram: 37.5, citalopram: 37.1, placebo: 38.6  
Gender (% female): Escitalopram: 57.6 %, citalopram: 61.6 %, placebo: 55.3 %  
Ethnicity: Escitalopram: 70.4 % white, citalopram: 75.9 % white, placebo: 71.1 % white  
Other population characteristics: No significant population differences; mean 5 panic attacks per week and estimated 44% of waking hours worrying about future attacks |
**Authors:** Stahl SM, et al.  
**Year:** 2003  
**Country:** US

### OUTCOME ASSESSMENT:

**Measures:** Frequency of panic attacks based on the Modified Sheehan Panic and Anticipatory Anxiety Scale (PAAS), Panic and Agoraphobia Scale, HAM-A, CGI-I, CGI-S, Q-LES-Q, PGE, anticipatory anxiety duration (derived from PAAS)

**Timing of assessments:** Screening, baseline, weeks 1, 2, 4, 6, 8, 10

### RESULTS:

- The frequency of panic attacks was statistically improved in the escitalopram group relative to placebo ($p = 0.04$)
- There was no statistical difference in the frequency of panic attacks in citalopram patients relative to placebo; both escitalopram and citalopram significantly reduced panic disorder symptoms and severity versus placebo at endpoint ($p < 0.05$)
- Escitalopram was not compared to citalopram

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 32%  
**Withdrawals due to adverse events:** 7.4%; escitalopram: 6.3%, citalopram: 8.4%, placebo: 7.6%

**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

No significant differences between study groups

### QUALITY RATING:

Fair
### Evidence Table 9: Post-Traumatic Stress Disorder

**STUDY:**
- **Authors:** Connor K, et al. (1999)
- **Year:** 1999
- **Country:** US

**FUNDING:**
- NIMH

**DESIGN:**
- **Study design:** RCT; 12 week acute with 12 week continuation
- **Setting:** Not reported
- **Sample size:** 54

**INTERVENTION:**
- **Drug:**
  - Fluoxetine
  - Placebo
- **Dose:**
  - Fluoxetine: 10-60 mg/d
  - Placebo: N/A
- **Duration:**
  - Fluoxetine: 12 weeks for acute treatment; 12 weeks for continuation phase
  - Placebo: 12 weeks for acute treatment; 12 weeks for continuation phase

**INCLUSION:**
- Age 18-55; DSM-III-R criteria for PTSD according to the SCI for DSM-III-R and were civilians

**EXCLUSION:**
- Determined by SCID: history of psychosis; bipolar disorder; antisocial personality disorder; current/recurrent/recent risk of suicide; homicide; and drug or alcohol abuse within previous 6 months

**OTHER MEDICATIONS/INTERVENTIONS:**
- Not reported

**POPULATION CHARACTERISTICS:**
- **Groups similar at baseline:** Yes
- **Mean age:** 37; fluoxetine: 36, placebo: 38
- **Gender (% female):** 91%, fluoxetine: 89%, placebo: 93%
- **Ethnicity:** 93% white; fluoxetine: 100%, placebo: 85%
- **Other population characteristics:** 41% married; 93% high school graduates; 43% employed out of home; median age of PTSD onset 25.5; median years of PTSD 6
**Authors:** Connor K, et al.  
**Year:** 1999  
**Country:** US

### OUTCOME ASSESSMENT:

**Measures:** Duke Global Rating for PTSD, SIP (Structured Interview for PTSD), self-rating sales: DTS (Davidson Trauma Scale), SDS (Sheehan Disability Scale), VS (Vulnerability to Effects of Stress Scale)  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12

### RESULTS:

- Using Duke cut off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% vs. 19%; p < 0.005)  
- Using Duke cut off score of 1 (no symptoms) or 2 (minimal symptoms) to define responders, no statistically significant difference could be seen (85% vs. 62%; p < 0.06)  
- The SIP showed significant improvements for fluoxetine: SIP: p < 0.005  
- Fluoxetine subjects responded in significantly less time than placebo treated subjects; Kaplan Meier: p < 0.005  
- Fluoxetine was also associated with significantly greater effects on the disability and stress subscales (SDS, VS, DTS) at 12 weeks (p < 0.05; p < 0.01; p < 0.005)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 31.5%; fluoxetine: 22.2%, placebo: 40.7%  
**Withdrawals due to adverse events:** 0%  
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

Not reported

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 9</th>
<th>Post-Traumatic Stress Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Davidson J et al.\textsuperscript{141}</td>
</tr>
<tr>
<td></td>
<td>Year: 2006</td>
</tr>
<tr>
<td></td>
<td>Country: Multinational</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multicenter</td>
</tr>
<tr>
<td></td>
<td>Sample size: 329</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>V恩flaxine ER</td>
</tr>
<tr>
<td></td>
<td>75-300 mg</td>
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<tr>
<td></td>
<td>24 weeks</td>
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<tr>
<td></td>
<td>Sample size: 161</td>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td>NA</td>
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<tr>
<td></td>
<td>24 weeks</td>
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<tr>
<td></td>
<td>Sample size: 168</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>≥ 18 years of age, could provide legal consent, and were not currently hospitalized; met the <em>DSM-IV</em> criteria for a primary diagnosis of PTSD; had a score of at least 60 on CAPS-SX; and had PTSD symptoms for at least the previous 6 months; a negative serum pregnancy test at screening (for women of childbearing potential); been in generally good health; been willing and able to return for all protocol-defined visits; been fluent in written and spoken forms of English, Spanish, or Portuguese; and been willing and able to provide written informed consent prior to admission.</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Intolerance, hypersensitivity, or nonresponse to a previous adequate trial of venlafaxine; had inability to tolerate or respond to adequate trials of 3 antidepressants; had current primary major depression or panic disorder; had a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder; abused or were dependent on alcohol or other drugs within 6 months or had a positive urine drug screen; showed a high risk of suicide or violence; used any investigational drug, antipsychotic, or monoamine oxidase inhibitor within 30 days; had ECT within 3 months of or likelihood of requiring ECT during the study; used triptans or any other psychoactive drug, including fluoxetine, or herbal preparation within 7 day; had current involvement in criminal proceedings or compensation claims related to trauma; and, for women, were nursing, pregnant, or sexually active without acceptable birth control. Subjects who had initiated or changed psychotherapy of any kind within 3 months</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/ INTERVENTIONS:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: Venlafaxine 42.2  Placebo 40.5</td>
</tr>
<tr>
<td></td>
<td>Gender (female %): Venlafaxine 55.3  Placebo 53.0</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
</tbody>
</table>
**OUTCOME ASSESSMENT:**
- **Primary Outcome Measures:** change in CAPS-SX at 24 weeks
- **Secondary Outcome Measures:** changes from baseline to end point in CAPS-SX17 symptom cluster scores; frequency of remission (CAPS-SX score \( \leq 20 \)); and time to remission; HAMD; CGI-S
- **Timing of assessments:** Baseline, weeks 2, 4, 6, 8, 12, 18, and 24

**RESULTS:**
- CAPs at week 24 Venlafaxine 29.2 (26.00) vs. placebo 38.1 (29.11) \( P = 0.006 \)
- HAMD at week 24 Venlafaxine 6.9 (6.70) vs. placebo 8.3(7.23) \( P = 0.007 \)

**ANALYSIS:**
- ITT: Yes- LOCF
- Post randomization exclusions: none
- Loss to follow-up differential high: no

**ATTRITION:**
- **Venlafaxine ER**
  - Loss to follow-up: 30.4%
  - Withdrawals due to adverse events: 9.3%
  - Withdrawals due to lack of efficacy: 3.1%
- **Placebo**
  - Loss to follow-up: 33.3%
  - Withdrawals due to adverse events: 5.4%
  - Withdrawals due to lack of efficacy: 10.7%

**ADVERSE EVENTS:**
- Venlafaxine vs. placebo n(%)
  - At least 1 AE 125 (78) vs. 114 (69)
  - Headache 46 (28.6) vs. 44 (26.2)
  - Nausea 35 (21.7) vs. 19 (11.3)
  - Dizziness‡ 29 (18) vs. 19 (11.3)
  - Dry mouth 21 (13) vs. 8 (4.8)
  - Constipation 20 (12.4) vs. 5 (3)
  - Fatigue 13 (8.1) vs. 6 (3.6)
  - Insomnia 12 (7.5) vs. 17 (10.1)
  - Decreased libido 8 (5) vs. 6 (3.6)
  - Nasopharyngitis 8 (5) vs. 11 (6.5)
  - Increased sweating 21 (13.0) vs. 6 (3.6)
  - Vomiting 11 (6.8) vs. 4 (2.4)
  - Somnolence 9 (5.6) vs. 9 (5.4)
  - Tremor 10 (6.2) vs. 6 (3.6)

**QUALITY RATING:**
- Fair

---

**Footnotes:**
- ‡: Denotes events reported in a specific category.
## Evidence Table 9: Post-Traumatic Stress Disorder

| STUDY: | Authors: Davidson J et al.142  
Year: 2006  
Country: USA |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 538 |
| INTERVENTION: | Drug:  
Venlafaxine ER  
75-300 mg  
12 weeks  
179  
Sertraline  
50-200 mg  
12 weeks  
173  
Placebo  
NA  
12 weeks  
179 |
| INCLUSION: | Male and female outpatients aged 18 years or older who met DSM-IV criteria for a primary diagnosis of PTSD based on the Structured Clinical Interview for DSM-IV.; a score of at least 40 on the Davidson Trauma Scale; a score of at least 60 on the 17-item CAPS-SX; PTSD symptoms for at least the previous 6 months; a negative serum pregnancy test at screening (for women of childbearing potential); generally good health based on medical history, physical examination, and screening laboratory results; and likelihood of complying with protocol. |
| EXCLUSION: | Decrease of more than 25% on the DTS between screening and baseline; intolerance, hypersensitivity, or nonresponse to a previous adequate trial of venlafaxine or sertraline; inability to tolerate or respond to adequate trials of 3 or more antidepressants; current primary MDD or panic disorder; a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder; alcohol or drug abuse or dependence within 6 months or a positive urine drug screen; and a high risk of suicide or violence; use of any investigational drug, antipsychotic, or MAOIs within 30 days; ECT within 3 months or likelihood of requiring ECT during the study; triptans or any other psychoactive drug (including SSRIs or tricyclic antidepressants) or herbal preparation within 7 days; initiation of or change in psychotherapy within 3 months; current involvement in criminal proceedings or compensation claims related to trauma; and for women, nursing, pregnancy, or sexual activity without acceptable birth control. |
| OTHER MEDICATIONS/INTERVENTIONS: | Zaleplon or zolpidem, 1 dose nightly as needed for insomnia, for up to 6 nights, during the 14 days after the baseline evaluation only. The use of any alternative hypnotics required prior approval of the sponsor. Short-term treatments for allergies, colds, or flu were permitted, provided the medications used had minimal psychotropic effects. |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Can't tell- authors say yes.  
Mean age: NR  
Gender (female %): NR  
Ethnicity: NR |
<table>
<thead>
<tr>
<th>Authors: Davidson</th>
<th>Year: 2006</th>
<th>Country: USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td><strong>Primary Outcome Measures:</strong> Change in CAPS-SX at 12 weeks</td>
<td><strong>Secondary Outcome Measures:</strong> Q-LES-Q, SDS, CGI-S, HAMD17</td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong> Baseline, weeks 2,4,6,8,12</td>
<td><strong>RESULTS:</strong> Change from baseline venlafaxine vs. sertraline vs. placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CAPS-SX -41.51 vs. -39.44 vs. -34.17 Venlafaxine vs. Placebo P = 0.015 Sertraline vs. Placebo P = 0.081 Venlafaxine vs. Sertraline P = 0.494</td>
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<td></td>
<td></td>
<td>• DTS -42.86 vs. -38.92 vs. -34.59 Venlafaxine vs. Placebo P = 0.015 Sertraline vs. Placebo P = 0.203 Venlafaxine vs. Sertraline P = 0.248</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CGI-S -1.60 vs. -1.51 vs. -1.23 Venlafaxine vs. Placebo P = 0.007 Sertraline vs. Placebo P = 0.046 Venlafaxine vs. Sertraline P = 0.492</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HAMD -7.09 vs. -6.42 vs. -5.54 Venlafaxine vs. Placebo P = 0.039 Sertraline vs. Placebo P = 0.244 Venlafaxine vs. Sertraline P = 0.379</td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>ITT:</strong> Yes</td>
<td><strong>Post randomization exclusions:</strong> NR</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> NR</td>
<td></td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Overall</strong> 34%</td>
<td></td>
</tr>
<tr>
<td><strong>Loss to follow-up:</strong></td>
<td><strong>Withdrawals due to adverse events:</strong> 11%</td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawals due to lack of efficacy:</strong></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>Venlafaxine vs. sertraline vs. placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Headache 29 vs. 32 vs. 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nausea 24 vs. 23 vs. 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diarrhea 12 vs. 26 vs. 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dry mouth 18 vs. 15 vs. 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Somnolence 12 vs. 10 vs. 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fatigue 11 vs. 14 vs. 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dizziness 13 vs. 10 vs. 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Insomnia 13 vs. 10 vs. 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Constipation 12 vs. 7 vs. 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Appetite decrease 12 vs. 8 vs. 6</td>
<td></td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 9  
### Post traumatic stress disorder

| STUDY: | Authors: Martenyi F et al.  
Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 411 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
**Sample size:** |
| | Fluoxetine 20  
20 mg  
12 weeks  
163 |
| | Fluoxetine 40  
40 mg  
12 weeks  
160 |
| | Placebo  
NA  
12 weeks  
88 |
| INCLUSION: | Men and women aged 18 to 75 who met DSM-IV criteria for PTSD a score of 50 or more on the CAPS Current Diagnostic Version and a score of 4 or more on the Clinical Global Impression of Severity. |
| EXCLUSION: | Severe (comorbid) depression as defined by MADRS score greater than 20 |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: fluoxetine20 41 fluoxetine40 40 placebo 42  
Gender (female %): fluoxetine20 71.2% fluoxetine40 71.9% placebo 71.6%  
Ethnicity: % white fluoxetine20 76% fluoxetine40 74% placebo 84%  
Other population characteristics: |
OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>TOP-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>The CAPS One Week Symptom Status Version, Davidson Trauma Scale, MADRS, and Hamilton Anxiety Scale</td>
</tr>
</tbody>
</table>

Timing of assessments:

RESULTS:

- Change in CAPS fluoxetine20 -42.9(23.1) fluoxetine40 -42.8(27.9) placebo -36.6(25.7)
- Change in TOP-8 fluoxetine20 -10.59(0.58) fluoxetine40 –10.25(0.60) placebo -10.59(0.81)
- Change in MADRS fluoxetine20 -5.05(0.82) fluoxetine40 -5.04(0.84) placebo -3.45(1.14)

ANALYSIS:

- ITT: Yes
- Post randomization exclusions: NR

ATTRITION:

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
<th>Fluoxetine20</th>
<th>Fluoxetine40</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>4.3%</td>
<td>13.1%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6.7%</td>
<td>NR</td>
<td>6.8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EVENTS:

- Any event fluoxetine20 67.5% fluoxetine40 77.5% placebo 64.8%
- Headache fluoxetine20 16.0% fluoxetine40 18.8% placebo 17.0%
- Nausea fluoxetine20 12.9% fluoxetine40 13.8% placebo 13.2%
- Somnolence fluoxetine20 9.2% fluoxetine40 11.9% placebo 5.2%
- Rhinitis fluoxetine20 7.4% fluoxetine40 11.3% placebo 6.8%

QUALITY RATING: Fair
<table>
<thead>
<tr>
<th>Evidence Table 9</th>
<th>Post-Traumatic Stress Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: McRae A, et al. 144</td>
</tr>
<tr>
<td></td>
<td>Year: 2004</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center (2 medical centers)</td>
</tr>
<tr>
<td></td>
<td>Sample size: 37</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Nefazodone 463 mg/d (mean)</td>
</tr>
<tr>
<td>Drug:</td>
<td>Sertraline 153 mg/d (mean)</td>
</tr>
<tr>
<td>Dose:</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Duration:</td>
<td>18</td>
</tr>
<tr>
<td>Sample size:</td>
<td>19</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Male and female outpatients aged 18-65; met DSM-IV criteria for PTSD; minimum of 3 months duration of PTSD; severity of at least 50 on the CAPS-2</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Any clinically significant medical condition or laboratory abnormality; history of seizure disorder or organic brain disease; pregnancy or breastfeeding; psychotic, eating disorder, or OCD; substance abuse; current diagnosis of major depression; psychotropic medication; drug hypersensitivity; history of non-responsiveness to treatment drugs</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>No other psychotropic medications allowed</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 40</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): 77%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Time since trauma: 22 years</td>
</tr>
<tr>
<td>Authors: McRae A, et al.</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>Year: 2004</td>
<td></td>
</tr>
<tr>
<td>Country: US</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome Measures:</strong> 17 item PTSD scale; Part 2 CAPS-2; CGI-I</td>
</tr>
<tr>
<td><strong>Secondary Outcome Measures:</strong> 17 item Davidson Trauma Scale; MADRS; HAM-A; Pittsburg Sleep Quality Index; Sheehan Disability Scale</td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong> Baseline, weeks 4, 8, and 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No statistically significant differences between the sertraline and the nefazodone treatment groups on any of the outcome measures.</td>
</tr>
<tr>
<td>- Both treatment groups had statistically significant within-group improvements on all outcome measures from baseline to endpoint.</td>
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<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT: Yes</td>
</tr>
<tr>
<td>Post randomization exclusions: Yes</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loss to follow-up:</strong> 38%; nefazodone: not reported; sertraline: not reported</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events:</strong> 11%; nefazodone: 11%; sertraline: 10.5%</td>
</tr>
<tr>
<td><strong>Loss to follow-up differential high:</strong> not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant differences in adverse events reported between treatment groups:</td>
</tr>
<tr>
<td></td>
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<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
</tr>
</tbody>
</table>
**Evidence Table 9**  
**Post-Traumatic Stress Disorder**

| STUDY: | Authors: Saygin MZ et al.  
Year: 2002  
Country: Turkey |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>AÇEV (Mother Child Education Foundation) and Project Hope</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Research center  
Sample size: 60 |
| INTERVENTION: |  
| Drug: | Sertraline  
Dose: 50-100 mg  
Duration: 5 months  
Sample size: 30 |
| | Nefazadone  
Dose: 200-400 mg  
Duration: 5 months  
Sample size: 30 (24 analyzed due to 6 dropouts) |
| INCLUSION: | Patients with PTSD from Marmara earthquake in Izmit, Turkey |
| EXCLUSION: | history of alcohol or drug abuse, neurological disorder, current organic mental disorder and who are under psychiatric medication less than 2 weeks before the study |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No  
Mean age: Sertraline 37.7 Nefazadone 46.1  
Gender (female %): Sertraline 66.6% Nefazadone 87.5%  
Ethnicity: NR  
Other population characteristics: Comorbidity Sertraline 40% Nefazadone 25% TOP-8 scores Sertraline 19.27 Nefazadone 15.75 CGI-S Sertraline 4.73 Nefazadone 4.38 |
| Authors: Saygin  
| Year: 2002  
| Country: Turkey |

**OUTCOME ASSESSMENT:**

| **Primary Outcome Measures:** | Posttraumatic Stress Diagnostic Scale (PDS), the eight-item Treatment-outcome Posttraumatic Stress Disorder Scale (TOP-8), Clinical Global Impression Scale (CGI) ratings. |
| **Secondary Outcome Measures:** | NR |
| **Timing of assessments:** | Baseline and then once a month |

**RESULTS:**

- Endpoint scores
  - Top-8 Sertraline 5.23 (3.24) Nefazadone 4.35 (2.94)
  - CGI-S Sertraline 2.37 (0.93) Nefazadone 2.24 (0.97)

**ANALYSIS:**

- ITT: No
- Post randomization exclusions: 6
- Loss to follow-up differential high: Yes

**ATTRITION:**

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline 0%</td>
</tr>
<tr>
<td>Nefazadone 20%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
</tr>
<tr>
<td>Sertraline NR</td>
</tr>
<tr>
<td>Nefazadone NR</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
</tr>
<tr>
<td>Sertraline NR</td>
</tr>
<tr>
<td>Nefazadone NR</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- CGI side effects score showed a significantly greater amount of side effects in the nefazadone group at endpoint Sertraline 1.33 Nefazadone 1.82

**QUALITY RATING:**

- Poor-completeers analysis
### Evidence Table 9  
#### Post Traumatic Stress Disorder

| STUDY: | Authors: Tucker P et al.  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Forest Pharmaceuticals</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: University hospital outpatient  
Sample size: 59 |
| INTERVENTION: |  
**Drug:**  
Citalopram  
36.2 mg/day  
10 weeks  
Sample size: 25  
Sertraline  
134.1 mg/day  
10 weeks  
Sample size: 23  
Placebo  
N/A  
10 weeks  
Sample size: 10 |
| INCLUSION: | 18-64 years old; PTSD symptoms |
| EXCLUSION: | Medical condition precluded use of an SSRI; previous intolerance or lack of response to an adequate trial of citalopram or sertraline; possible placebo treatment was unsafe; psychotherapy was indicated; current alcohol or substance abuse |
| OTHER MEDICATIONS/INTERVENTIONS: | Diphenhydramine for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: citalopram: 39.2, sertraline: 39.1, placebo: 36.8  
Gender (% female): citalopram: 68%, sertraline: 78.3%, placebo: 80%  
Ethnicity (% white): citalopram: 76%, sertraline: 91.3%, placebo 100%  
Other population characteristics: Not reported |
| Authors: Tucker P et al.  
Year: 2003  
Country: US | **Primary Outcome Measures:** Clinician administered PTSD scale (CAPS) and BDI  
**Timing of assessments:** CAPS: Baseline and weeks 1, 6, and 10; BDI: baseline and weeks 1, 2, 3, 4, 6, 8, and 10  
**RESULTS:**  
- No differences in efficacy between sertraline and citalopram treated patients  
- No differences in efficacy between active treatments and placebo  
**ANALYSIS:**  
- **ITT:** Yes  
- **Post randomization exclusions:** No  
**ATTRITION:**  
- **Loss to follow-up:**  
  - Overall: 14  
  - Citalopram: 5  
  - Sertraline: 6  
  - Placebo: 3  
- **Withdrawals due to adverse events:**  
  - Overall: 2 known  
  - Citalopram: NR  
  - Sertraline: NR  
  - Placebo: NR  
- **Withdrawals due to lack of efficacy:**  
  - Overall: NR  
  - Citalopram: NR  
  - Sertraline: NR  
  - Placebo: NR  
- **Loss to follow-up differential high:**  
  - Overall: No  
  - Citalopram: N/A  
  - Sertraline: N/A  
  - Placebo: N/A  
**ADVERSE EVENTS:**  
- Fatigue: citalopram: 44%, sertraline: 29%, placebo: 30%  
- GI distress: citalopram: 16%, sertraline: 38%, placebo: 30%  
- Insomnia: citalopram: 60%, sertraline: 33%, placebo: 70%  
- Sexual dysfunction: citalopram: 16%, sertraline: 4%, placebo: 20%  
**QUALITY RATING:** Fair
### Evidence Table 9  Post Traumatic Stress Disorder

| STUDY: | Authors: van der Kolk BA et al.\textsuperscript{147}  
Year: 2007  
Country: USA |
| FUNDING: | NIMH |
| DESIGN: | Study design: RCT  
Setting: Research center  
Sample size: 59 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
**Sample size:**  
Fluoxetine  
10-60 mg  
8 weeks  
30  
Placebo  
NA  
8 weeks  
29 |
| INCLUSION: |  
18 to 65 years with PTSD, trauma at least 1 year prior |
| EXCLUSION: |  
Unstable medical condition; contraindication to treatment; inability to discontinue other psychotropic meds; psychotic or bipolar; substance abuse; severe dissociation; prone to suicide; prior exposure to interventions; unstable living conditions. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: |  
Groups similar at baseline: Yes  
Mean age: Fluoxetine 34.1 Placebo 35.7  
Gender (female %): Fluoxetine 86.7 Placebo 86.2  
Ethnicity: % white Fluoxetine 63.3 Placebo 69.0  
Other population characteristics: |
| Authors: van der Kolk | **Primary Outcome Measures**: CAPS  
  **Secondary Outcome Measures**: BID  
  **Timing of assessments**: Baseline and post treatment |
|----------------------|-------------------------------------------------|
| **OUTCOME ASSESSMENT**: | **RESULTS**:  
  - At post treatment drop in total CAPS fluoxetine 46.0% vs. placebo 43.6% |
| **ANALYSIS**: | **ITT**: Yes  
  **Post randomization exclusions**: none  
  **Loss to follow-up differential high**: no |
| **ATTRITION**: | Fluoxetine:  
  - Loss to follow-up: 13%  
  - Withdrawals due to adverse events: NR  
  - Withdrawals due to lack of efficacy: NR  
  - Placebo:  
  - 10% |
<p>| <strong>ADVERSE EVENTS</strong>: | None reported |
| <strong>QUALITY RATING</strong>: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Allgulander C, et al.\(^{148}\)  
                     Year: 2004  
                     Country: Multinational (Sweden, Denmark, Germany, Norway, France, Finland) |
| **FUNDING:**      | Wyeth Research |
| **DESIGN:**       | Study design: RCT  
                     Setting: Multi-center  
                     Sample size: 436 |
| **INTERVENTION:** | Drug: Venlafaxine ER  
                     Dose: 75-225 mg/d  
                     Duration: 12 weeks  
                     Sample size: 129  
                     Paroxetine  
                     Dose: 20-50mg/d  
                     Duration: 12 weeks  
                     Sample size: 128  
                     Placebo  
                     Sample size: N/A |
| **INCLUSION:**    | Over 18 years old with DSM-IV criteria for SAD for at least 6 months prior to study; score of > 4 on CGI-S; 50 on LSAS, with 30% decrease between pre-study and baseline visits; pre-study Raskin depression total score <9, and a 17-item HAM-D score <15 |
| **EXCLUSION:**    | Previous treatment with venlafaxine or venlafaxine ER within 6 months of study day 1; concurrent disorders that confounded the evaluation of treatment: substance disorders, personality disorders (except avoidant personality disorder), depression or other primary anxiety disorders |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: No (differences in gender)  
Mean age: Venlafaxine ER: 38.7; paroxetine: 38.8; placebo: 38.9  
Gender (% female): Venlafaxine ER: 46%; paroxetine: 52%; placebo: 62%  
Ethnicity: Not reported  
Other population characteristics: Baseline LSAS score 86.6 for placebo, 83.2 for venlafaxine ER, 83.9 for paroxetine |
| Authors: Allgulander C, et al. |
| Year: 2004 |
| Country: Multi-country |

**OUTCOME ASSESSMENT:**

| Primary Outcome Measures: | LSAS |
| Secondary Outcome Measures: | CGI-S; CGI-IM; SPIN; SDI |
| Timing of assessments: | Baseline, and days 7, 14, 21, 28, 42, 56, 70 and 84 |

**RESULTS:**

- No significant differences in any outcome measures between venlafaxine ER and paroxetine
- Treatment with venlafaxine ER and paroxetine was associated with significantly greater improvement than treatment with placebo for all primary and secondary efficacy variables (p < 0.05)
- LSAS total scores significantly improved for venlafaxine ER or paroxetine vs. placebo –primary endpoint, the baseline adjusted mean change in LSAS total score was –36.0 (SE 2.35) for venlafaxine, –35.4 (SE 2.46) for paroxetine and –19.1 (SE 2.40) for the placebo group
- SPIN scores significantly improved for venlafaxine ER and paroxetine groups than for placebo group at weeks 3-12 (both p < 0.05 week 3; both p < 0.01 week 4; both p < 0.001 weeks 6-12)

**ANALYSIS:**

- ITT: Yes
- Post randomization exclusions: Yes

**ATTRITION:**

- Loss to follow-up: 16.8%; venlafaxine ER: 16%; paroxetine: 16%; placebo: 18.5%
- Withdrawals due to adverse events: 7.6%, venlafaxine: not reported; paroxetine: not reported
- Loss to follow-up differential high: No

**ADVERSE EVENTS:**

- During the double-blind treatment period, 90% venlafaxine ER, 89% paroxetine, and 82% placebo treated patients reported treatment emergent adverse events; the most common (incidence ≥5%) adverse events among venlafaxine ER treated patients were headache (10%), nausea (7%), dizziness (14%), insomnia (6%), and vertigo (10%); among paroxetine-treated patients were headache (12%), dizziness (13%), and insomnia (6%); among placebo treated patients, no taper/post study emergent adverse event occurred at an incidence of ≥5% and the differences between groups were not statistically significant

**QUALITY RATING:**

- Fair
| STUDY: | Authors: Davidson J, et al.\textsuperscript{149}  
Year: 2004  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>National Institute of Mental Health grant</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: 2 academic medical centers  
Sample size: 117 (295 total in arms including CCBT) |
| INTERVENTION: | Drug:  
Fluoxetine  
Dose: 10-60 mg/day  
Duration: 14 weeks  
Sample size: 57  
Placebo  
Dose: N/A  
Duration: 14 weeks  
Sample size: 60 |
| INCLUSION: | DSM-IV diagnosis of GSP; age between 18 and 65 years; fluency in English; provision of written informed consent |
| EXCLUSION: | Primary comorbid anxiety disorder (defined by which disorder was the more debilitating and clinically salient); lifetime history of schizophrenia, bipolar disorder, or organic brain syndrome; major depression within the last 6 months; substance abuse or dependence within the past year; mental retardation or pervasive developmental disability; unstable medical condition; prior failure of response to fluoxetine at 60 mg/d for at least 4 weeks or to 12 weekly sessions of CCBT for GSP; concurrent psychiatric treatment or other psychoactive medications; positive urine drug screen results; inability to maintain 2 weeks' psychotropic drug-free wash-out; pregnancy or lactation |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: fluoxetine: 36.3, placebo: 36.9  
Gender (female %): fluoxetine: 42.9, placebo: 45.8  
Ethnicity (% white): fluoxetine: 71.4, placebo: 82.8 |
<table>
<thead>
<tr>
<th>Authors: Davidson J, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2004</td>
</tr>
<tr>
<td>Country:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: CGI-I, CGI-S, BSPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures: Social Phobia and Anxiety Inventory</td>
<td></td>
</tr>
<tr>
<td>Timing of assessments: baseline and weeks 4, 8, 14</td>
<td></td>
</tr>
</tbody>
</table>

| RESULTS: |
|---------------------|---------------------------------------------|
| • CGI response rates at week 14 higher for fluoxetine (50.9% vs. 31.7%; p=0.03) |
| • BSPS effect sizes (95% CI): 0.40 (0.02 to 0.77) for fluoxetine vs. placebo |
| • CGI-S scale effect size (95% CI) for fluoxetine vs. placebo: 0.42 (0.04 to 0.80) |
| • CGI-S score at baseline: 4.4 vs. 4.3; at week 14: 2.7 vs. 3.3; fluoxetine treatment superior to placebo (p<0.05) |
| • SPAI score at week 14 69.3 vs. 94.8; fluoxetine superior to placebo (p<0.05) |

| ANALYSIS: |
|---------------------|---------------------------------------------|
| ITT: Yes |
| Post randomization exclusions: yes (9) |

| ATTRITION: |
|---------------------|---------------------------------------------|
| Loss to follow-up: fluoxetine: 32%; placebo: 40% |
| Withdrawals due to adverse events: fluoxetine: 8.8%; placebo: 3.3% |
| Withdrawals due to lack of efficacy: fluoxetine: 1.8%; placebo: 3.3% |
| Loss to follow-up differential high: No |

| ADVERSE EVENTS: |
|---------------------|---------------------------------------------|
| TEAEs (fluoxetine vs. placebo) |
| • Insomnia: 47.9 vs. 42.3; p=0.005 |
| • Headache: 31.2 vs. 38.5; p=0.008 |
| • Nausea: 18.8 vs. 15.4; p<0.04 |
| • Anorgasmia: 32.4 vs. 9.6; p<0.001 |
| • Erectile dysfunction: 10.4 vs. 1.9; p<0.02 |

| QUALITY RATING: |
|---------------------|---------------------------------------------|
| Fair |
### Evidence Table 10: Social Anxiety Disorder

| STUDY: | **Authors:** Hedges D et al.  
**Year:** 2007  
**Country:** Multinational |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Brigham Young University, Department of Psychology</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** Systematic review  
**Number of patients:** 3,361 |
| AIMS OF REVIEW: | To investigate the efficacy of SSRIs in social anxiety disorder |
| TIME PERIOD COVERED: | 1966-2004 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Double-blind, placebo-controlled trials ranging in duration from 10-24 weeks |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Adults with social anxiety disorder (social phobia) |
**Authors:** Hedges D, et al.  
**Year:** 2007

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>• Effect sizes for the Liebowitz Social Anxiety Scale ranged from 0.029 to 1.214</td>
</tr>
<tr>
<td></td>
<td>• Effect sizes for the Sheehan Disability Scale ranged from 0.203 to 0.480 for work, 0.237 to 0.786 for social function, and 0.118 to 0.445 for family function</td>
</tr>
<tr>
<td></td>
<td>• The Θ log-odds ratios for CGI of change scores ranged from 0.644 to 3.267</td>
</tr>
<tr>
<td></td>
<td>• SSRIs appear more effective than placebo for social anxiety disorder, with improvement extending into social and occupational function</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>NR</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>PubMed and PsychINFO were searched as well as the reference lists of pertinent articles.</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>NR</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Evidence Table 10  Social Anxiety Disorder

### STUDY:
- **Authors:** Kasper S, et al.\(^{151}\)
- **Year:** 2005
- **Country:** Multinational

### FUNDING:
- H. Lundbeck A/S

### DESIGN:
- **Study design:** RCT
- **Setting:** Multi-center
- **Sample size:** 358

### INTERVENTION:
- **Drug:**
  - Escitalopram
  - Placebo
- **Dose:**
  - Escitalopram: 10-20
  - Placebo: N/A
- **Duration:**
  - Escitalopram: 12 weeks
  - Placebo: 12 weeks
  - Sample size: 181
  - Sample size: 177

### INCLUSION:
- Outpatients with a primary diagnosis GSAD following DSM-IV criteria; 18-65 years old; a score of at least 70 on the LSAS; evidence of fear or avoidance traits in at least 4 social situations; otherwise healthy

### EXCLUSION:
- Primary diagnosis of other Axis 1 disorders or a history of within the past 6 months; diagnosis of any Axis II cluster; substance abuse within 12 months; if investigator diagnosed a serious risk of suicide; MADRS >19; use of a depot antipsychotic within 6 months or any antipsychotic, anxiolytic or anticonvulsant within 2 weeks before start; known drug allergy or previous lack of therapeutic response to citalopram

### OTHER MEDICATIONS/ INTERVENTIONS:
- Chloral hydrate for sleep

### POPULATION CHARACTERISTICS:
- **Groups similar at baseline:** No – escitalopram group older (39 vs. 36) with greater duration of disease (24 vs. 21 years)
- **Mean age:** 38
- **Gender (% female):** 45%
- **Ethnicity:** NR
- **Baseline LSAS:** placebo: 95.4, escitalopram: 96.3
- **Baseline CGI-S:** placebo: 4.8, escitalopram: 4.8
Authors: Kasper S, et al.
Year: 2005
Country: Multinational

OUTCOME ASSESSMENT:

Primary Outcome Measures: LSAS total score

Secondary Outcome Measures: LSAS subscales; CGI-S; CGI-I; SDS; MADRS

Timing of assessments: Baseline and weeks 1, 2, 3, 4, 6, 8, 12

RESULTS:

- LSAS at 12 weeks: placebo 68.8, escitalopram 62.2 with a treatment difference of 7.3 (p < 0.01)
- Mean reduction in LSAS fear/anxiety subscale: escitalopram -16.9, placebo -12.7 (p < 0.001)
- Mean reduction in LSAS avoidance subscale: escitalopram -17.6, placebo -14.4 (p < 0.05)
- Escitalopram showed significant improvements over placebo in CGI-S (p < 0.01); CGI-I responders 39% for placebo and 54% for escitalopram (p < 0.01)
- Significantly more improvement in SDS work (p < 0.001) and social (p < 0.05) subscales
- MADRS not reported

ANALYSIS:

ITT: Yes

Post randomization exclusions: Yes- 5 had no post-baseline assessment

ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Placebo</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up</td>
<td>19%</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>6.8%</td>
<td>4.5%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy</td>
<td>4.2%</td>
<td>6.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Loss to follow-up differential high</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EVENTS:

- Headache: placebo: 25%, escitalopram: 25%
- Nausea: placebo: 12%, escitalopram: 22%
- Fatigue: placebo: 9%, escitalopram: 14%
- Somnolence: placebo: 5%, escitalopram: 10%
- Diarrhea: placebo: 5%, escitalopram: 9%
- Insomnia: placebo: 6%, escitalopram: 9%

QUALITY RATING: Fair
## Evidence Table 10  Social Anxiety Disorder

| STUDY: | Authors: Kobak KA, et. al.  
Year: 2002  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly &amp; Co.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 60 |
| INTERVENTION: | Drug: Fluoxetine  
Dose: 20-60 mg/d  
Duration: 14 weeks  
Placebo  
N/A  
14 weeks |
| INCLUSION: | DSM-IV criteria for social phobia for at least 6 months; a score of at least 50 on the Liebowitz Social Anxiety Scale (LSAS) before and after the lead-in; score could not decrease by more than 20% |
| EXCLUSION: | Non-response to fluoxetine treatment; pregnancy; previous participation in a fluoxetine study; concurrent use of psychotropic or centrally acting drugs, anticonvulsants, corticosteroids, or tryptophan; serious illness; suicidal; concurrent Axis I disorders in past 12 months; psychotherapy; seizure disorder |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean age: 39.5  
Gender (% female): 58%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
| Authors: | Kobak KA, et. al. |
| Year: | 2002 |
| Country: | US |

| OUTCOME ASSESSMENT: | Measures: Liebowitz Social Anxiety Scale (LSAS) (primary), Social Phobia Subscale of Fear Questionnaire, CGI-S, CGI-I, Patient Global Improvement Scales, HAM-A, Brief Social Phobia Scale, HAM-D (did not report which scale), Global Assessment of Functioning Scale, QOL |
| Timing of assessments: | Weeks 1, 2, 4, 6, 8, 10, 12, 14 |

| RESULTS: | • Fluoxetine was not significantly different from placebo on the LSAS score (p = 0.901)  
• Similar results in secondary outcome measures with no significant difference between fluoxetine and placebo  
• A significant change was found on all outcome measures from baseline to endpoint with both fluoxetine (p < 0.001) and placebo (p < 0.001) |

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: No |

| ATTRITION: | Loss to follow-up: 20%; fluoxetine 16%; placebo 23%  
Withdrawals due to adverse events: 7%; fluoxetine 3%, placebo 10%  
Loss to follow-up differential high: No |

| ADVERSE EVENTS: | • For fluoxetine: headache, insomnia, asthenia, and nervousness  
• For placebo: headache, insomnia, nervousness, and myalgia  
• Significantly more fluoxetine than placebo patients had asthenia (p = 0.02)  
• Significantly more placebo than fluoxetine patients had myalgia (p = 0.04) |

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Lader M, et al.\textsuperscript{153}  
Year: 2004  
Country: Multinational (11 countries) |
| **FUNDING:**      | H. Lundbeck A/S |
| **DESIGN:**       | Study design: RCT  
Setting: Multi-center (47 centers)  
Sample size: 839 |
| **INTERVENTION:** | Drug:  
Dose:  
Duration:  
Sample size:  
Escitalopram 5  
5 mg/d  
24 weeks  
167  
Escitalopram 10  
10 mg/d  
24 weeks  
167  
Escitalopram 20  
20 mg/d  
24 weeks  
170  
Paroxetine 20  
20 mg/d  
24 weeks  
169  
Placebo  
N/A  
24 weeks  
166 |
| **INCLUSION:**    | Healthy female and male outpatients 18-65 years of age; primary diagnosis of generalized SAD according to DSM-IV criteria; score > 70 on the Liebowitz Social Anxiety Scale (LSAS); score > 5 on one or more of the Sheehan Disability Scale (SDS) subscales |
| **EXCLUSION:**    | Another Axis I disorder primary diagnosis within 6 months; MADRS total score > 18; DSM-IV diagnosis of schizophrenia/ other psychotic disorder; Axis II Cluster B diagnosis; learning difficulties or other cognitive disorder; suicidal tendencies; no therapeutic response to SSRIs; drug hypersensitivities; taken a psychoactive drug within 2 weeks of screening; receiving formal psychotherapy |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Escitalopram 5: 36.3; escitalopram 10: 37.2; escitalopram 20: 37; paroxetine 20: 37.4; placebo: 37  
Gender (% female): Escitalopram 5: 50%; escitalopram 10: 57%; escitalopram 20: 53%; paroxetine: 54%; placebo: 49%  
Ethnicity: 99.3% white  
Other population characteristics: Mean duration of disorder (yrs): 19.5 |
**Authors:** Lader M, et al.  
**Year:** 2004  
**Country:** Multinational

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** Mean change from baseline to week 12 in LSAS total score (LOCF)
- **Secondary Outcome Measures:** LSAS subscale scores; CGI-S; CGI-I; change in SDS
- **Timing of assessments:** Baseline and after weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 25, and 26.

### RESULTS:
- No significant difference observed between any escitalopram treatment groups and the paroxetine group in the LOCF analysis of LSAS total score.
- At weeks 16, 20, and 24 (observed case analysis), compared to the paroxetine group (p < 0.05) the 20 mg/d escitalopram group had significantly superior LSAS scores.
- Escitalopram 20mg/d was superior to paroxetine 20mg/d on CGI-S at week 24.
- Escitalopram 20mg/d was superior to paroxetine 20mg/d on some SDS subscales during weeks 16 and 20, but no significant differences were noted at week 24.

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Not reported

### ATTRITION:
- **Loss to follow-up:** 29%; escitalopram 5: 25.1%; escitalopram 10: 33.5%; escitalopram 20: 28.8%; paroxetine: 26.6%; placebo: 30.1%
- **Withdrawals due to adverse events:** 9%; escitalopram 5: 4.8%; escitalopram 10: 9.6%; escitalopram 20: 11.8%; paroxetine: 13.6%; placebo: 6%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Percentage patients experiencing any adverse effect: Escitalopram 5: 68.9%; escitalopram 10: 72.5%; escitalopram 20: 78.2%; paroxetine 20: 79.3%; placebo: 60.8%
- Nausea: Escitalopram 5: 20.4%; escitalopram 10: 19.8%; escitalopram 20: 28.8%; paroxetine 20: 29%; placebo: 10.2%
- Fatigue: 9% placebo; Escitalopram 5: 11.4%; escitalopram 10: 12%; escitalopram 20: 14.1%; paroxetine 20: 17.8%; placebo: 9%
- Increased sweating: Escitalopram 5: 5.4%; escitalopram 10: 10.8%; escitalopram 20: 11.8%; paroxetine 20: 14.2%; placebo: 1.8%

### QUALITY RATING:
- Fair
**Evidence Table 10  Social Anxiety Disorder**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth Research, Collegeville PA</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT Setting: Multi-center (26 centers) Sample size: 440</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine 75-225 mg/d 12 weeks 146</td>
</tr>
<tr>
<td></td>
<td>Paroxetine 20-50 mg/d 12 weeks 147</td>
</tr>
<tr>
<td></td>
<td>Placebo N/A 12 weeks 147</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Outpatients ≥ 18 years who fulfilled DSM-IV criteria for SAD for ≥ 6 months at screening; LSAS ≥ 50 at screening and baseline with ≤ 30% decrease between prestudy and baseline; ≥ 4 on the CGI-S; Covi Anxiety Score total &gt; Raskin Depression Scale total score; HAM-D &lt; 15 with ≤ 2 on depressed mood item.</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Patients with a clinically important Axis I or Axis II disorder other than SAD or avoidant personality disorder; history or current psychotic illness; Suicidal; history of drug or alcohol dependence within 1 year of the study; used anti-depressants (other than fluoxetine), anxiolytics, or herbal products within 14 days of the study; ECT within 6 months of the study; used antipsychotic medications or fluoxetine treatment within 30 days of the study; clinically significant abnormal findings on laboratory tests; pregnant or breastfeeding</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/ INTERVENTIONS:</td>
<td>NR</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes Mean age: venlafaxine: 35.7, paroxetine: 35.8, placebo: 37.3 Gender (% female): venlafaxine: 46.6%, paroxetine: 45.6%, placebo: 47.2% Ethnicity: White: VX: 71.4% PX: 72.8% Placebo: 70.1% African American: VX: 11.3% PX: 8.8% Placebo: 8.3% Hispanic: VX: 15.0% PX: 12.5% Placebo: 13.2% Other population characteristics: Baseline LSAS: VX: 86.2 PX: 87.2 Placebo: 86.1</td>
</tr>
</tbody>
</table>
**Authors:** Liebowitz MR, et al.  
**Year:** 2005  
**Country:** US

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** Reduction in Liebowitz Social Anxiety Scale (LSAS) total score  
- **Secondary Outcome Measures:** CGI-I; CGI-S; Social Phobia Inventory Scores, SDS  
- **Timing of assessments:** Weekly

### RESULTS:
- No significant difference in LSAS improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).  
- No significant difference in CGI-I improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).  
- No significant difference in Social Phobia Inventory improvement was observed between the venlafaxine and paroxetine groups at endpoint; both significantly improved from placebo (p < 0.05).  
- No significant difference in CGI-S improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).  
- No significant differences in SDS domains between venlafaxine and placebo.

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Venlafaxine</th>
<th>Paroxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up</td>
<td>26%</td>
<td>27.0%</td>
<td>28.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>10.4%</td>
<td>14.2%</td>
<td>13.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy</td>
<td>2.3%</td>
<td>0.7%</td>
<td>0.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Loss to follow-up differential high</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>

### ADVERSE EVENTS:

<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine</th>
<th>Paroxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>32.6%</td>
<td>26.1%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27.7%</td>
<td>18.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>27%</td>
<td>26.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.6%</td>
<td>23.9%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17.7%</td>
<td>16.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14.2%</td>
<td>10.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Abnormal ejaculation (men)</td>
<td>10.5%</td>
<td>20.8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### QUALITY RATING:
- **Fair**
### Evidence Table 10  Social Anxiety Disorder

| STUDY: | Authors: Montgomery SA, et al.  
Year: 2005  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Open label followed by randomized, double-blind, parallel group, placebo-controlled, fixed dose relapse prevention comparison  
Setting: 76 private/hospital outpatient clinics & specialized clinical research centers (11 countries)  
Sample size: 517 (open label); 372 (RCT) |
| INTERVENTION: | **Drug:** Escitalopram  
**Dose:** 10 or 20 mg/d  
**Duration:** 24 wks  
**Sample size:** 191 |
| | **Placebo**  
**Dose:** N/A  
**Duration:** 24 wks  
**Sample size:** 181 |
| INCLUSION: | Outpatients between 18 and 80 yrs old; primary DSM-IV diagnosis of generalized social anxiety disorder (GSAD); total Liebowitz Social Anxiety Scale (LSAS) score ≥70 w/ exhibited fear or avoidance traits in ≥ 4 social situations; and score ≥ 5 on 1 or more Sheehan Disability Scale (SDS) subscales; RCT required CGI-I score of 1 or 2 after open-label treatment |
| EXCLUSION: | Other Axis I diagnosis in previous 6 months; MADRS total score ≥ 18; score ≥ 5 on MADRS item 10 (suicidal thoughts); DSM-IV diagnosis of alcohol/drug abuse, eating disorder, major depressive disorder, panic disorder, obsessive-compulsive disorder, body dysmorphic disorder, schizophrenia, other psychotic disorder, mania or hypomania, or any Axis II diagnosis; known lack of response to SSRI; treatment with psychoactive drug in last 2 wks (or 5 wks if fluoxetine); formal psychotherapy in last 2 weeks. |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** Escitalopram: 36, Placebo: 37  
**Gender(% female):** Escitalopram: 46%, placebo: 49%  
**Ethnicity:** 95% white (both groups)  
**Other population characteristics:** Mean BMI = 24.2; Mean age at GSAD onset = 17; Mean duration of GSAD = 19y (escitalopram) and 20y (placebo) |
## Authors: Montgomery, et al.
Year: 2005
Country: Multinational

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** survival analysis estimate of time to relapse in the double-blind period. (Relapse defined as LSAS score increase ≥ 10 or withdrawal of patient due to lack of efficacy.)

**Secondary Outcome Measures:** LSAS total score; LSAS avoidance and fear/anxiety subscale; SDS

**Timing of assessments:** 1,2,4,8,12,16,20, & 24 weeks after randomization; also safety follow-up at 4 weeks after last dose of double-blind treatment

### RESULTS:

- Significant advantage in survival for escitalopram vs. placebo in primary efficacy analysis (log rank test p < 0.001)
- Relapse rates = 22% (escitalopram) vs. 50% (placebo)
- Risk of relapse was 2.8 times higher w/ placebo than escitalopram
- Median time to relapse = 407 days (escitalopram) vs. 144 days (placebo)
- Significant advantage for escitalopram on all secondary measures (LSAS, CGI-S, SDS, and MADRS)
- Improvement on LSAS in escitalopram group (8.3 points), deterioration in placebo group (4.5 points)
- Mean MADRS score change = +0.8 (escitalopram) and +2.6 (placebo)
- Mean CGI-S score change = -0.3 (escitalopram) and +0.3 (placebo)

### ANALYSIS:

**ITT:** Yes, defined as all randomized patients who took at least 1 dose of double-blind medication and had at least 1 valid post baseline assessment of LSAS total score

**Post randomization exclusions:**

### ATTRITION:

- **Loss to follow-up:** Escitalopram: 25 (13%), placebo: 15 (8.3%)
- **Withdrawals due to adverse events:** Escitalopram: 5 (2.6%), placebo: 6 (3.3%)
- **Withdrawals due to lack of efficacy:** N/A
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Assessed via spontaneous report, various clinical exam/lab reports, and 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist at randomization and 1 and 2 wks after.
- Treatment emergent adverse events (TEAEs) with incidence ≥ 5% in either group were: headache, dizziness, increased sweating, nervousness, fatigue, insomnia, nausea, rhinitis, and influenza-like symptoms
- Incidence of TEAEs was lower in escitalopram group (62.6%) vs. placebo group (71.8%)
- Dizziness, increased sweating, and nervousness were significantly higher in placebo group in 1st 2 weeks following discontinuation of escitalopram (p < 0.05). Excluding these TEAEs in 1st 2 weeks post-randomization, adverse events were similar in both treatment groups
- After 1 and 2 weeks of double-blind treatment, mean total DESS score was significantly lower in escitalopram group (week 1: escitalopram =1.17 vs. placebo = 2.61; week 2: escitalopram =1.02 vs. placebo = 1.78) (p < 0.01)

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Muehlbacher M, et al.  
Year: 2005  
Country: Multinational |
| **FUNDING:**     | NR |
| **DESIGN:**      | Study design: Randomized, double-blind, placebo controlled  
Setting: Clinics  
Sample size: 66 |
| **INTERVENTION:** | Drug: Mirtazapine  
Dose: 30 mg/d  
Duration: 10 wks  
Sample size: 33  
Placebo  
Dose: N/A  
Duration: 10 wks  
Sample size: 33 |
| **INCLUSION:**   | Women aged 18 or older with DSM-IV diagnosed social phobia |
| **EXCLUSION:**   | Psychotic symptoms; use of mirtazapine or other psychotropic drug; psychotherapy; currently or planning to be pregnant (or no contraception use); severe somatic illness; currently suicidal; current drug / alcohol abuse; severe major depressive disorder. |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Cannot tell  
Mean age: NR  
Gender: NR  
Ethnicity: NR  
Other population characteristics: Both groups similar in percentage currently living in partnership, and with personality, panic, general anxiety disorders, OCDs |
**Authors:** Muehlbacher M, et al.  
**Year:** 2005  
**Country:** Multinational

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** Change in social anxiety measured w/ social phobia inventory (SPIN) and LSAS  
**Secondary Outcome Measures:** SF-36 Health Survey  
**Timing of assessments:** Weekly for 10 weeks, although intermediate results were not analyzed |
|---------------------|----------------------------------------------------------------------------------------------------------|
| **RESULTS:**        | - Mirtazapine group experienced significantly greater rate of change on both SPIN and LSAS scales  
- Initial SPIN scores = 32.5 +/- 4.7 (mirtazapine) vs. 29.0 +/- 4.6 (placebo)  
- Final SPIN scores = 24.1 +/- 4.3 (mirtazapine) vs. 28.7 +/- 5.1 (placebo)  
- SPIN: Difference in change b/w both groups = -8.1 (95% CI -9.6 to 4.1; p < 0.001)  
- Initial LSAS scores = 71.9 +/- 8.3 (mirtazapine) vs. 72.5 +/- 8.0 (placebo)  
- Final LSAS scores= 46.3 +/- 7.0 (mirtazapine) vs. 67.1 +/- 7.4 (placebo)  
- LSAS: Difference in change b/w both groups = -20.2 (95% CI -27.5 to -4.1; p < 0.001)  
- Mirtazapine group experienced significantly greater rate of change on SF-36 (on general health perceptions, vitality, social functioning, role-emotional, and mental health scales) |
| **ANALYSIS:**       | ITT: No  
**Post randomization exclusions:** Cannot tell |
| **ATTRITION:**      | Loss to follow-up: NR  
**Withdrawals due to adverse events:** NR  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** NR |
<p>| <strong>ADVERSE EVENTS:</strong> | - Most frequently reported adverse events in mirtazapine vs. placebo were: dry mouth (21.2% vs. 12.1%), drowsiness (18.2% vs. 9.1%), sedation (18.2% vs. 6.1%), increased appetite (12.1% vs. 3.0%), and weight gain (21.2% vs. 6.1%) |
| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: van der Linden et. al.\(^{157}\)  
Year: 2000  
Country: South Africa, the Netherlands |
| **FUNDING:** | MRC Research Unit on Anxiety and Stress Disorders; Harry Crossley Trust; Cochrane review collaborators |
| **DESIGN:** | Study design: Meta-analysis  
Number of patients: 1482 |
<p>| <strong>AIMS OF REVIEW:</strong> | To review all available SSRI studies for social anxiety disorder |
| <strong>TIME PERIOD COVERED:</strong> | Not reported (included studies for dates 1994 to 2000) |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | RCTs (placebo controlled); 18 trials; 2 unpublished |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Patients with social anxiety disorder |</p>
<table>
<thead>
<tr>
<th><strong>Authors:</strong></th>
<th>van der Linden, et. al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year:</strong></td>
<td>2000</td>
</tr>
<tr>
<td><strong>Country:</strong></td>
<td></td>
</tr>
</tbody>
</table>

| **CHARACTERISTICS OF INCLUDED INTERVENTIONS:** | RCT data were analyzed for fluvoxamine, paroxetine, and sertraline |
| **MAIN RESULTS:** | Odds ratio of responder status for SSRI vs. placebo varied between 2.1 and 26.2  
The NNT varied from 1.6 to 4.2  
LSAS effect size varied from 0.3 to 2.2  
No difference in efficacy between SSRIs was reported |
| **ADVERSE EVENTS:** | Not reported |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | Not defined in article but described to be consistent with methods of a Cochrane review |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | Not defined in article but described to be consistent with methods of a Cochrane review |
| **QUALITY RATING:** | Fair |
|--------|-------------------------------|------------|---------------|
| FUNDING: | Bristol-Myers Squibb |
| DESIGN: | Study design: RCT |
| Setting: | Outpatient anxiety clinics (4) |
| Sample size: | 105 |
| INTERVENTION: | |
| Drug: | Nefazodone |
| Dose: | 100-600 mg/day |
| Duration: | 14 weeks |
| Sample size: | 52 |
| Placebo | |
| Sample size: | 14 weeks |
| Sample size: | 53 |
| INCLUSION: | Psychiatric outpatients; 18-65 yrs; met DSM-IV criteria for GSP for >1 year; be of at least moderate illness severity based on CGI-S rating; patients with comorbid secondary MDD could participate if MADRS baseline score < 19, no risk of suicidality, and onset of social phobia predated MDD by at least 5 years. |
| EXCLUSION: | Current comorbid Axis I disorders such as panic disorder with agoraphobia, OCD, body dysmorphic disorder, or alcohol/substance abuse; lifetime history of bipolar affective disorder, schizophrenia, psychoses, delirium, dementia, or other cognitive disorders; reporting 2 previous treatment failures for GSP. |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate up to 1000 mg/night for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes |
| Mean age: | nefazodone: 34.6, placebo: 37.0 |
| Gender (female %): | nefazodone: 53.8%, placebo: 50.9% |
| Ethnicity (%white): | nefazodone: 86.5%, placebo: 83.0% |
| Other population characteristics: | |
**Authors:** Van Ameringen M, et al.  
**Year:** 2007  
**Country:** Canada

| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** CGI-I responders at endpoint; mean change in LSAS score  
**Secondary Outcome Measures:** CGI-S, Social Phobia Inventory, SPS, Social Interaction Anxiety Scale, Beck Depression Inventory, Beck Anxiety Scale, Sheehan Disability Scale, RAND 36-Item Health Survey  
**Timing of assessments:** weeks 1, 2, 3, 5, 7, 9, 12, and 16 |
|-------------------------|---------------------------------------------------------------|

| **RESULTS:** | • Higher % of nefazodone patients were CGI-I responders (CGI-I score of 1 or 2) at endpoint: 31.4% vs. 23.5%; p=0.38  
• With the exception of the Social Phobia Scale, no significant differences found in measures of social phobia between treatment groups |
|----------------|---------------------------------------------------------------|

| **ANALYSIS:** | ITT: Yes (N=102)  
**Post randomization exclusions:** |
|----------------|---------------------------------------------------------------|

| **ATTRITION:** | **Loss to follow-up:** 23.8%; nefazodone 30.8%, placebo 17.0%  
**Withdrawals due to adverse events:**  
**Withdrawals due to lack of efficacy:**  
**Loss to follow-up differential high:** No |
|----------------|---------------------------------------------------------------|

| **ADVERSE EVENTS:** | • Headache: 35.3% vs. 29.4%; p=0.53  
• Fatigue: 19.6% vs. 11.8%; p=0.28  
• Dizziness/lightheadedness; p<0.01  
• Nausea/vomiting: 23.5% vs. 7.8%; p=0.03  
• Somnolence/drowsiness: 19.6% vs. 11.8%; p=0.28  
• Dry mouth: 23.5% vs. 2.0%; p<0.01  
• Indigestion: 11.8% vs. 9.8%; p=0.75  
• No significant differences between groups in liver function tests |
|-------------------|---------------------------------------------------------------|

<table>
<thead>
<tr>
<th><strong>QUALITY RATING:</strong></th>
<th>Fair</th>
</tr>
</thead>
</table>
### Evidence Table 11  Premenstrual Dysphoric Disorder

| STUDY: | Authors: Dimmock PW, et al.  
Year: 2000  
Country: |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>No external funding</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 904 |
| AIMS OF REVIEW: | To determine the efficacy of SSRIs in severe premenstrual syndrome |
| TIME PERIOD COVERED: | 1966-1999 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs; 1 head-to-head; all placebo controlled |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Women with PMS |
**Authors:** Dimmock PW, et al.  
**Year:** 2000

| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine |
| **MAIN RESULTS:** | Overall standardized mean difference showed a significant reduction of PMS symptoms in SSRI group compared to placebo  
-1.066 (95% CI -1.381 to -0.750) = OR 6.91 (3.90-12.2)  
SSRIs were effective in physical and behavioral symptoms; there was no significant variation in the overall standardized mean differences (p = 0.386) |
<p>| <strong>ADVERSE EVENTS:</strong> | Insufficient data; some trials did not quote a complete breakdown |
| <strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong> | Yes |
| <strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong> | Yes |
| <strong>QUALITY RATING:</strong> | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Premenstrual Dysphoric Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Freeman EW, et al.160</td>
</tr>
<tr>
<td></td>
<td>Year: 2001</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
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<tr>
<td></td>
<td>Setting: Multi-center</td>
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<tr>
<td></td>
<td>Sample size: 157</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>Dose: Venlafaxine</td>
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<tr>
<td></td>
<td>Duration: 50-200 mg/d</td>
</tr>
<tr>
<td></td>
<td>Four menstrual cycles</td>
</tr>
<tr>
<td></td>
<td>Placebo:</td>
</tr>
<tr>
<td></td>
<td>Duration: N/A</td>
</tr>
<tr>
<td></td>
<td>Four menstrual cycles</td>
</tr>
<tr>
<td></td>
<td>(Dosage increased at the</td>
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<tr>
<td></td>
<td>beginning of each</td>
</tr>
<tr>
<td></td>
<td>menstrual cycle if</td>
</tr>
<tr>
<td></td>
<td>no improvement)</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>18-45 years of age; regular</td>
</tr>
<tr>
<td></td>
<td>menstrual cycles lasting</td>
</tr>
<tr>
<td></td>
<td>22-35 days for the last 6</td>
</tr>
<tr>
<td></td>
<td>months; evidence of ovulation;</td>
</tr>
<tr>
<td></td>
<td>meets DSM-III-R criteria for</td>
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<tr>
<td></td>
<td>PMDD; general good health</td>
</tr>
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<td><strong>EXCLUSION:</strong></td>
<td>Prescription or non-prescription</td>
</tr>
<tr>
<td></td>
<td>medication for PMDD; breastfeeding,</td>
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<tr>
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<td>**OTHER MEDICATIONS/</td>
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<tr>
<td>INTERVENTIONS:**</td>
<td>medications</td>
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<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: No; premenstrual severity lower in placebo group at baseline</td>
</tr>
<tr>
<td></td>
<td>Mean Age: venlafaxine: 35, placebo: 35</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): 100%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Venlafaxine: 89% white, 10% black, 1% Hispanic; placebo: 91% white, 7% black, 3% Hispanic</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Premenstrual daily symptom report was significantly lower at baseline in placebo group (p = 0.032)</td>
</tr>
</tbody>
</table>
**Authors:** Freeman EW, et al.  
**Year:** 2001  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: Premenstrual daily symptom report (maintained by subject), 21 item HAM-D, CGI scale  
| Timing of assessments: Scales administered twice a cycle: once during the premenstrual phase and once during the postmenstrual phase |

| RESULTS: |  
| • Premenstrual Daily Symptom Report scores were significantly more improved in the venlafaxine group than in the placebo group at each time point and at endpoint (p < 0.001)  
| • Venlafaxine showed significantly greater improvement than placebo in four of the factors of the DSR: emotion (p < 0.001), function (p = 0.011), pain (p = 0.016), and physical symptoms (p = 0.003)  
| • The venlafaxine group was significantly more improved on the 21 item HAM-D (p = 0.001)  
| • DSR response (> 50% reduction): venlafaxine 60%, placebo: 35% (p = 0.003) |

| ANALYSIS: | ITT: Yes  
| Post randomization exclusions: Yes |

| ATTRITION: | Loss to follow-up: 36%; venlafaxine: 35%, placebo: 36%  
| Withdrawals due to adverse events: 12.8%; venlafaxine: 9%, placebo: 6.25% |

| ADVERSE EVENTS: |  
| • Nausea 45% vs. 13% (venlafaxine vs. placebo p < 0.001)  
| • Insomnia 34 % vs. 16% (venlafaxine vs. placebo p = 0.05)  
| • Dizziness 32% vs. 5% (venlafaxine vs. placebo p < 0.001)  
| • Decreased libido (venlafaxine vs. placebo p < 0.001)  
| • Fatigue (not significant)  
| • Headache (not significant)  
| • Dry mouth (not significant)  
| • Dysmenorrhea (not significant) |

| QUALITY RATING: | Fair |
## Evidence Table 11: Premenstrual Dysphoric Disorder

| STUDY: | Authors: Landen M, et al.  
Year: 2001  
Country: Sweden |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Swedish Medical Research Council, the Professor Bror Gadelius Foundation, Fredrik and Ingrid Thuring’s Foundation, and Bristol-Myers Squibb</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 69 |
| INTERVENTION: | **Drug:**  
Nefazodone  
100-400 mg/d  
(four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment)  
Buspirone  
10-40mg/d  
(four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment)  
Placebo  
N/A  
(four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment) |
| INCLUSION: | Fulfilled diagnostic criteria A-C of DSM-IV criteria for PMDD (modified to use 2 of 11 criteria); confirmed cyclicity of at least irritability or depressed mood; 18-45 years old; menstrual cycles 22-35 days |
| EXCLUSION: | Psychiatric illness; pregnancy; irregular menstrual cycles; previous antidepressant treatment for menstrual symptoms; ongoing somatic illness; MDD; suicidal; continuous medications; hormonal therapy; other condition that could pose risk; MARDs > 14 |
| OTHER MEDICATIONS/INTERVENTIONS: | No continuous medication or hormonal medication |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean Age: Nefazodone: 37, buspirone: 37, placebo: 33  
Gender (% female): 100%  
Ethnicity: Not reported  
Other population characteristics: No differences reported |
| **Authors:** Landen M, et al.  
**Year:** 2001  
**Country:** Sweden |
|---|

**OUTCOME ASSESSMENT:**  
**Measures:** Daily symptom ratings using a visual analogue scale for the following symptoms: irritability, depressed mood, tension, affect lability, food craving, bloating, breast tenderness. CGI scale after last treatment cycle or after dropout  
**Timing of assessments:** Daily

**RESULTS:**  
- Nefazodone was not significantly different from placebo on the CGI score ($p = 0.22$)  
- Nefazodone did not significantly improve irritability, depressed mood, or tension at any time point  
- After the second cycle of the intermittent phase, nefazodone was significantly better than placebo for affect lability ($p = 0.05$); significance was not maintained after the continuous treatment

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up:** 22%  
**Withdrawals due to adverse events:** 14.5%  
**Loss to follow-up differential high:** No

**ADVERSE EVENTS:**  
Dizziness, blurred vision, insomnia, abnormal dreams, somnolence, and flu-like symptoms were reported more often in nefazodone than placebo ($p < 0.05$)

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Premenstrual Dysphoric Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Wyatt KM, et al.¹⁸²</td>
</tr>
<tr>
<td></td>
<td>Year: 2004</td>
</tr>
<tr>
<td></td>
<td>Country: UK</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Cochrane Collaboration</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: Meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Number of patients: 844</td>
</tr>
<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
<td>To evaluate the effectiveness of SSRIs in reducing symptoms in women diagnosed with severe premenstrual syndrome</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
<td>RCTs; quasi-randomized controlled trials; controlled trials</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
<td>Women of any age who met the diagnostic criteria for premenstrual syndrome, premenstrual dysphoria, PMDD, or LLPDD; diagnosis must have been established by a clinician prior to inclusion in the trial</td>
</tr>
</tbody>
</table>
**CHARACTERISTICS OF INCLUDED INTERVENTIONS:**
SSRIs at any dosage and any dosing regimen for any duration longer than one menstrual cycle versus placebo

**MAIN RESULTS:**
Main outcome measure: reduction in overall symptomatology: SSRIs were found to be highly effective in treating premenstrual symptoms compared to placebo; SMD: -0.75 (95% CI=-0.98 to -0.51); equivalent to: OR 4.51 (95%CI=7.49-2.71)

**ADVERSE EVENTS:**
Withdrawals: higher drop-out rate in SSRI group due to side effects: OR 2.42 (95% CI = 1.59 to 3.67)

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**
Yes

**STANDARD METHOD OF APPRAISAL OF STUDIES:**
Yes

**QUALITY RATING:**
Good
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| STUDY:            | Authors: Acharya N et al.\(^{163}\)  
|                   | Year: 2006  
|                   | Country: |
| DESIGN:           | Study design: Pooled data analysis  
<p>|                   | Number of patients: 2,996 |
| AIMS OF REVIEW:   | To compare the incidence of suicide-related events with duloxetine versus placebo in controlled trials. |
| STUDIES INCLUDED IN REVIEW | 12 placebo-controlled duloxetine trials |
| TIME PERIOD COVERED: | Through February 2, 2004 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Double-blind RCTs comparing duloxetine and placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Adults with MDD |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Duloxetine vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td></td>
</tr>
<tr>
<td>• No significant differences in incidence of suicide-related events</td>
<td></td>
</tr>
<tr>
<td>• MHID for suicide-related behaviors was -0.03% (95% CI: -0.48, 0.42) and MHRD -0.002 (95% CI: -0.02, 0.02)</td>
<td></td>
</tr>
<tr>
<td>• Changes in HAM-D Item-3 suicidality scores showed more improvement with duloxetine (MHID, 9.56%; 95% CI: 4.50, 14.6; p &lt; 0.001) and less worsening of suicidal ideation with duloxetine (MHID, -4.25%; 95% CI: -6.55, -1.95; p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>• Other Item-3 findings showed no consistent pattern</td>
<td></td>
</tr>
<tr>
<td>• Analysis found no evidence of increased risk of suicidal behaviors or ideation during treatment with duloxetine vs. placebo in MDD patients</td>
<td></td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>See Main Results</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>All completed duloxetine trials in MDD with data lock by February 2, 2004 that were sponsored by the manufacturer, Eli Lilly and Company (16 trials) and by Shionogi Company, Ltd, (11 trials) who hold the license for the development of duloxetine in Japan.</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>NR</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Alper K et al.\(^{164}\)  
Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>None</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** Retrospective analysis  
**Setting:** FDA reports  
**Sample size:** 38,684 on second-generation antidepressants |
| INTERVENTION: | Drug: Citalopram  
Fluoxetine  
Venlafaxine  
Bupropion  
Paroxetine  
Nefazodone  
Mirtazapine  
Escitalopram  
Duloxetine  
Sertraline  
Fluvoxamine  
Dose: Various  
Duration: 1985-2004  
Sample size: 38,684 |
| INCLUSION: | All available public domain data in the form of SBA reports which provided information regarding seizure incidence in phase II and phase III clinical trials. The data set included all of the second-generation antidepressants and atypical antipsychotics |
| EXCLUSION: | Any first generation antipsychotics, or first generation antidepressants except for clomipramine, due to the absence of systematic reporting on seizure incidence in clinical trials for psychotropic drugs approved prior to 1985. |
| OTHER MEDICATIONS/ INTERVENTIONS: | NA |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: NR  
Mean age: NR  
Gender (female %): NR  
Ethnicity: NR  
Other population characteristics: NR |
| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** seizures  
**Timing of assessments:** during RCTs |
|---------------------|------------------------------------------|
| RESULTS:            | Incidence of seizure  
- Anti-depressant indication  
  - Bupropion IR 0.6%  
  - Citalopram 0.3%  
  - Fluoxetine 0.2%  
  - Venlafaxine 0.1%  
  - Bupropion 0.1%  
  - Paroxetine 0.07%  
  - Nefazodone 0.04%  
  - Mirtazapine 0.04%  
  - Escitalopram 0%  
  - Duloxetine 0%  
  - Sertraline 0%  
- OCD indication  
  - Fluoxetine 0.1%  
  - Sertraline 0.3%  
  - Fluvoxamine 0.2%  
- Seizure incidence with bupropion IR relative to placebo (SIR = 1.58; 95%CI, 1.03-2.32) |
| ANALYSIS:           | ITT: NA  
**Post randomization exclusions:** NA  
**Loss to follow-up:** NA |
| ATTRITION:          | Withdrawals due to adverse events: NA  
Withdrawals due to lack of efficacy: NA  
Loss to follow-up differential high: NA |
| ADVERSE EVENTS:     | • See results |
| QUALITY RATING:     | Good |
## Evidence Table 12

| STUDY: | Authors: Aursnes I, et al.¹⁸⁵  
| Year: 2005  
| Country: Multinational |
| FUNDING: | NR |
| DESIGN: | Study design: Pooled data analysis  
<p>| Number of patients: 1,466 |
| AIMS OF REVIEW: | To include unpublished data from paroxetine trials for analysis of suicide attempts |
| STUDIES INCLUDED IN REVIEW | 16 studies with unpublished data |
| TIME PERIOD COVERED: | NR |
| CHARACTERISTICS OF INCLUDED STUDIES: | Clinical data on paroxetine as presented to world’s drug regulatory agencies in 1989; all double blind, parallel design studies with adult patients randomized to either paroxetine or placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Adults; patients were excluded from the studies after a suicide-related event |</p>
<table>
<thead>
<tr>
<th>Authors: Aursnes I, et al.</th>
<th>Year: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></td>
<td>Paroxetine (no dosage given) vs. placebo</td>
</tr>
</tbody>
</table>
| **MAIN RESULTS:** | • No suicides in paroxetine or placebo patients  
  • 7 suicide attempts in patients on paroxetine and 1 in patients on placebo  
  • Probability of increased intensity of suicide attempts per year in adults taking paroxetine was 0.90 with a “pessimistic” prior; probability was somewhat less with 2 more neutral priors |
| **ADVERSE EVENTS:** | NR |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | Yes |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | NR |
| **QUALITY RATING:** | Fair |
### Evidence Table 12  Adverse Events

| STUDY: | Authors: Benkert O, et al.  
Year: 2000  
Country: Germany |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Organon, GmBH, Munich, Germany</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (50 centers)  
Sample size: 275 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:**  
- Mirtazapine  
  15-45 mg/d  
  6 weeks  
- Paroxetine  
  20-40 mg/d  
  6 weeks |
| INCLUSION: | 18-70 years of age; DSM-IV criteria for major depression; ≥ 18 on HAM-D-17 |
| EXCLUSION: | Depressive episode longer than 12 months; other psychiatric or psychotic disorder; alcohol or substance abuse; suicidal risk; significant physical illness; non-responders to antidepressants; recent medication with similar drugs; pregnancy |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate for sleep |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** Mirtazapine: 47.2, paroxetine: 47.3  
**Gender (% female):** Mirtazapine: 63%, paroxetine: 65%  
**Ethnicity:** Not reported  
**Other population characteristics:** Not reported |
**Authors:** Benkert O, et al.  
**Year:** 2000  
**Country:** Germany

### OUTCOME ASSESSMENT:
- **Measures:** HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36  
- **Timing of assessments:** Screening, baseline, weeks 1, 2, 3, 4, 6

### RESULTS:
- Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%)  
- Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% (p < 0.002).

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 23%; mirtazapine: 21.6%, paroxetine: 24.2%  
- **Withdrawals due to adverse events:** 8%; mirtazapine: 8.6%, paroxetine: 7.4%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Significantly more mirtazapine patients experienced weight increase (p < 0.05)  
- At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4%  
- Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2%  
- Headache: mirtazapine: 9.6%, paroxetine: 10.4%  
- Nausea: mirtazapine: 4.4%, paroxetine: 11.2%  
- Flu-like symptoms: mirtazapine: 9.6%, paroxetine: 3.7%  
- Differences all p < 0.1

### QUALITY RATING:
- **Fair**
### Evidence Table 12: Adverse Events

| STUDY: Authors: Brambilla P, et al.†
|---|
| Year: 2005
| Country: Multinational

<table>
<thead>
<tr>
<th>FUNDING:</th>
</tr>
</thead>
</table>
| NR

| DESIGN: Study design: Meta-analysis
|---|
| Number of patients: 15,920

<table>
<thead>
<tr>
<th>AIMS OF REVIEW:</th>
</tr>
</thead>
</table>
| To assess the frequency of side-effects in fluoxetine compared to other SSRIs, TCAs and other anti-depressants

<table>
<thead>
<tr>
<th>STUDIES INCLUDED IN META-ANALYSIS</th>
</tr>
</thead>
</table>
| 131 studies

<table>
<thead>
<tr>
<th>TIME PERIOD COVERED:</th>
</tr>
</thead>
</table>
| Not reported

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED STUDIES:</th>
</tr>
</thead>
</table>
| All studies with random assigned patients that received fluoxetine or any other anti-depressant. Cross-over studies and those with patients with concomitant medical illness were excluded.

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED POPULATIONS:</th>
</tr>
</thead>
</table>
| Patients with MDD

---

Second generation antidepressants
<table>
<thead>
<tr>
<th><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></th>
<th>Fluoxetine vs. TCA (65 studies); fluoxetine vs. SSRI (22 studies); fluoxetine vs. another AD (44 studies)</th>
</tr>
</thead>
</table>
| **MAIN RESULTS:**                    | • Fluoxetine 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  
• Fluoxetine less side effects (50.9%) than TCAs (60.3%) RR= 0.84 95% CI 0.76 to 0.94(p = 0.03) but not in comparison to other SSRIs RR 1.00 95% CI 0.95, 1.04  
• Fluoxetine patients had more activating and GI adverse effects and less cholinergic side effects than other ADs |
| **ADVERSE EVENTS:**                  | N/A                                                                                              |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | Yes                                                                                                |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | Yes                                                                                                |
| **QUALITY RATING:**                  | Good                                                                                             |
### Evidence Table 12

<table>
<thead>
<tr>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
</tbody>
</table>
| **Authors:** Bridge JA et al. [16]  
**Year:** 2007  
**Country:** Multinational |
| **FUNDING:** |
| NIMH |
| **DESIGN:** |
| **Study design:** Systematic review and meta-analysis  
**Number of patients:** 5310 |
| **AIMS OF REVIEW:** |
| To assess the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders |
| **STUDIES INCLUDED IN REVIEW** |
| Twenty-seven trials of pediatric MDD (n = 15), OCD (n = 6), and non-OCD anxiety disorders (n = 6) |
| **TIME PERIOD COVERED:** |
| 1988 to July 2006 |
| **CHARACTERISTICS OF INCLUDED STUDIES:** |
| Published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** |
| Participants younger than 19 years with MDD, OCD, or non-OCD anxiety disorders |
| AUTHORS: Bridge JA et al.  
| YEAR: 2007 |  
| CHARACTERISTICS OF INTERVENTIONS: | Second-generation antidepressants (selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine) |  
| MAIN RESULTS: | Responder MDD(11.0%; [95% CI, 7.1% to 14.9%]), NNT = 10 (7 to 15)  
| | OCD(19.8% [95% CI, 13.0% to 26.6%], NNT 6 (4 to 8)  
| | Non-OCD anxiety disorders (37.1% [22.5% to 51.7%]), NNT = 3 (2 to 5), |  
| ADVERSE EVENTS: | Risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs placebo (0.7%; 95%CI, 0.1% to 1.3%) (number needed to harm, 143 [95% CI, 77 to 1000]),  
| | MDD 0.9% (95% CI, −0.1% to 1.9%)  
| | OCD 0.5% (−1.2% to 2.2%)  
| | Non-OCD 0.7% (~0.4% to 1.8%).  
| | Risk difference (95% CI) of Rate of Suicidal Ideation or Suicide Attempt/Preparatory Actions from placebo  
| | MDD  
| | Fluoxetine 2 (~3 to 6)  
| | Paroxetine 2 (~1 to 4)  
| | Escitalopram/citalopram −0 (~3 to 2)  
| | Venlafaxine 4 (1 to 8)  
| | Nefazadone 0 (~1 to 1)  
| | Mirtazapine 1 (~2 to 3)  
| | OCD  
| | Fluoxetine 1 (~4 to 6)  
| | Fluvoxamine 4 (~2 to 9)  
| | Paroxetine 1 (~2 to 4)  
| | Sertraline -1 (~4 to 2)  
| | Non-OCD  
| | Fluoxetine 0 (~5 to 5)  
| | Fluvoxamine 0 (~3 to 3)  
| | Paroxetine 2 (~1 to 4)  
| | Sertraline 0 (~16 to 16)  
| | Venlafaxine 1 (~1 to 2)  
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes- according to the criteria of Detsky et al, with final quality ratings based on consensus (intraclass correlation coefficient between raters, 0.94; 95% confidence interval [CI], 0.92 to 0.95) |  
| QUALITY RATING: | Good |
## Evidence Table 12  Adverse Events

| STUDY: | Authors: Buckley NA, et al.\(^{168}\)  
Year: 2002  
Country: UK |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>None</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Retrospective database analysis  
Setting: General practice  
Sample size: 121,927 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration:  
Sample size: |
| TCAs and related drugs | Serotonergic drugs |
| Varied | Varied |
| N/A | N/A |
| 74,598 | 47,329 |
| INCLUSION: | Used TCAs or SSRIs |
| EXCLUSION: | N/A |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: N/A  
Mean age: NR  
Gender (% female): NR  
Ethnicity: NR  
Other population characteristics: NR |
**Authors:** Buckley NA, et al.  
**Year:** 2002  
**Country:** UK

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures</th>
<th>Death due to acute poisoning by a single drug w/ or w/o co-ingestion of alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td></td>
</tr>
</tbody>
</table>

### RESULTS:

- Among second generation antidepressants, venlafaxine had the highest fatal toxicity index (deaths/million prescriptions):
  - Venlafaxine: 13.2 (9.2-18.5)
  - Fluvoxamine: 3.0 (0.3-10.9)
  - Citalopram: 1.9 (0.6-4.5)
  - Sertraline: 1.2 (0.5-2.4)
  - Fluoxetine: 0.9 (0.5-1.4)
  - Paroxetine: 0.7 (0.4-1.3)
  - Nefazodone: 0 (0-6.4)

### ANALYSIS:

- ITT: N/A
- Post randomization exclusions: N/A

### ATTRITION:

- Loss to follow-up: N/A
- Withdrawals due to adverse events: N/A
- Withdrawals due to lack of efficacy: N/A
- Loss to follow-up differential high: N/A

### ADVERSE EVENTS:

- See above

### QUALITY RATING:

- N/A
### Evidence Table 12: Adverse Events

| STUDY: | Authors: Clayton AH, et al.  
Year: 2002  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Cross sectional survey  
Setting: Multi-center  
Sample size: 6297 |
| INTERVENTION: | Second generation antidepressants  
Drug: Variable  
Dose: Variable  
Duration: |
| INCLUSION: | ≥ 18 years of age; receiving antidepressant monotherapy for depression; sexually active; using one of the newer antidepressants: buproprion IR, buproprion SR, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, venlafaxine XR |
| EXCLUSION: | Taking an antidepressant for an illness other than depression |
| OTHER MEDICATIONS/ INTERVENTIONS: | None |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: N/A  
Mean age: Overall clinical population: 42.7; target population: 32.0 (target population consisted of patients free of other probable causes of sexual dysfunction (e.g., age, comorbid illness)  
Gender (% female): overall clinical population: 28%; target population: 22.8%  
Ethnicity: overall clinical population: white: 93.5%, black: 2.7%, Asian: 0.5%, Hispanic: 2.7%, other: 0.6%; target population: white: 93.1%, black: 2%, Asian: 0.6%, Hispanic: 3.7%, other: 0.5%  
Other population characteristics: Not reported |
**Authors:** Clayton AH, et al.  
**Year:** 2002

| OUTCOME ASSESSMENT: | **Measures:** Changes in sexual functioning questionnaire  
**Timing of assessments:** Completed at one visit |
|---------------------|--------------------------------------------------------|

| RESULTS: | In the overall clinical population:  
- Patients taking buproprion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking fluoxetine, paroxetine, sertraline, or venlafaxine XR  
- Patients taking buproprion IR had a lower prevalence of sexual dysfunction than patients taking paroxetine, sertraline, or venlafaxine XR  
- Patients taking fluoxetine had a lower prevalence of sexual dysfunction than patients taking paroxetine  
In the target population:  
- Patients taking buproprion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking citalopram, paroxetine, sertraline, or venlafaxine XR |

| ANALYSIS: | **ITT:** N/A  
**Post randomization exclusions:** N/A |

| ATTRITION: | **Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Loss to follow-up differential high:** N/A |

| ADVERSE EVENTS: | N/A |

| QUALITY RATING: | N/A |
Evidence Table 12

| STUDY: | Authors: Cipriani A. et al.\textsuperscript{170}  
Year: 2006  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>No external funding- authors associated with Italian, Japanese and English universities</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Systematic review and meta-analysis  
Number of patients: 14391 |
| AIMS OF REVIEW: | To systematically review the efficacy and tolerability of fluoxetine, the most widely studied of newer antidepressants, in comparison with all other antidepressants in the acute treatment of depression in patients aged more than 18 years. |
| STUDIES INCLUDED IN REVIEW | 131 RCTs |
| TIME PERIOD COVERED: | 1966 to 2004 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Published randomized trials, blind or open |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Depressed patients 18 years or older |
| **Authors:** Cipriani et al. |
| **Year:** 2006 |

### CHARACTERISTICS OF INTERVENTIONS:
Fluoxetine in comparison with all other antidepressants in the acute treatment of depression.

### MAIN RESULTS:
- Meta-analysis of Response Fluoxetine vs.
  - Fluvoxamine 0.98 (0.71 to 1.35)
  - Paroxetine 1.18 (0.97 to 1.42)
  - Sertraline 1.18 (1.01 to 1.38)
  - Bupropion 1.11 (0.64 to 1.93)
  - Duloxetine 1.21 (0.67 to 2.20)
  - Mirtazapine 1.28 (0.93 to 1.76)
  - Venlafaxine 1.17 (1.03 to 1.33)

### ADVERSE EVENTS:
- Meta-analysis of tolerability via all withdrawals Fluoxetine vs.
  - Citalopram 0.90 (0.62 to 1.32)
  - Fluvoxamine 0.75 (0.35 to 1.58)
  - Paroxetine 0.96 (0.76 to 1.21)
  - Sertraline 1.18 (0.95 to 1.47)
  - Bupropion 1.28 (0.75 to 2.17)
  - Duloxetine 1.11 (0.52 to 2.35)
  - Mirtazapine 0.92 (0.48 to 1.76)
  - Venlafaxine 0.96 (0.75 to 1.22)

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and the Cochrane Central Register of Controlled Trials up to March 2004; MEDLINE (1966-2004) and EMBASE (1974-2004)

### STANDARD METHOD OF APPRAISAL OF STUDIES:
Yes- Cochrane Collaboration Handbook

### QUALITY RATING:
Good
**Evidence Table 12**

<table>
<thead>
<tr>
<th><strong>STUDY:</strong></th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Clayton A. et al.</td>
<td></td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Country:</strong> USA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>FUNDING:</strong></th>
<th>GlaxoSmithKline</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>DESIGN:</strong></th>
<th>Study design: 2 pooled RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting:</strong> Multicenter</td>
<td></td>
</tr>
<tr>
<td><strong>Sample size:</strong> 785 ITT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INTERVENTION:</strong></th>
<th>Bupropion XL</th>
<th>Escitalopram</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug:</strong></td>
<td>300-450 mg</td>
<td>10-20 mg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>276</td>
<td>281</td>
<td>273</td>
</tr>
<tr>
<td><strong>Sample size:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INCLUSION:</strong></th>
<th>Men and women &gt; 18 years old, MDD; HAMD17 &gt; 19; current episode duration 12 weeks to 2 years; sexually active.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>EXCLUSION:</strong></th>
<th>Other sexual disorders; past or present anorexia nervosa, bulimia, seizure disorder, or brain injury; diagnosis of panic disorder, OCD, PTSD or acute stress disorder within 12 months: bipolar I or II, schizophrenia or other psychotic disorders; attempted suicide within 6 months; any drug that may effect sexual functioning.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></th>
<th>Zolpidem, zaleplon and non-prescription sleep aids were allowed in 1st 10 days only.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>POPULATION CHARACTERISTICS:</strong></th>
<th>Groups similar at baseline: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age:</strong></td>
<td>Bupropion XL 37 Escitalopram 37 Placebo 36</td>
</tr>
<tr>
<td><strong>Gender (female %):</strong></td>
<td>Bupropion XL 58 Escitalopram 57 Placebo 60</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td>White Bupropion XL 70% Escitalopram 68% Placebo 70%</td>
</tr>
<tr>
<td><strong>Black Bupropion XL 20% Escitalopram 19% Placebo 17%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other population characteristics:</strong></td>
<td>NR</td>
</tr>
</tbody>
</table>

Second generation antidepressants
**Authors:** Clayton A et al.  
**Year:** 2006  
**Country:** USA

| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** % patients w/orgasm dysfunction at week 8  
**Secondary Outcome Measures:** CSFQ, HAMD17, CGI-S and CGI-I and HAD  
**Timing of assessments:** Baseline, weeks 1,2,3,4,6 and 8 |
|------------------------|---------------------------------------------------------------|

**RESULTS:**
- % patients w/orgasm dysfunction at week 8  
  - Bupropion XL 15%  
  - Escitalopram 30%  
  - Placebo 9%  
- Change in HAMD17  
  - Bupropion XL -13.2 (0.5)  
  - Escitalopram -13.6 (0.5)  
  - Placebo -12.0 (0.5)  
- HAMD response  
  - Bupropion XL 62%  
  - Escitalopram 65%  
  - Placebo 52%  
- HAMD remission  
  - Bupropion XL 43%  
  - Escitalopram 45%  
  - Placebo 34%  
- Change in CGI-S  
  - Bupropion XL -1.9 (0.1)  
  - Escitalopram -1.9 (0.1)  
  - Placebo -1.6 (0.1)  
- CGI-I response  
  - Bupropion XL 67%  
  - Escitalopram 67%  
  - Placebo 57%

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** 45  
**Loss to follow-up differential high:** No

<table>
<thead>
<tr>
<th><strong>ATTRITION:</strong></th>
<th><strong>Withdrawals due to adverse events:</strong></th>
<th><strong>Withdrawals due to lack of efficacy:</strong></th>
</tr>
</thead>
</table>
| Bupropion XL   | 68 (25%) 6% NR                         | Bupropion XL vs. Escitalopram vs. Placebo %  
| Escitalopram   | 71 (25%) 4% NR                         |  
| Placebo        | 66 (24%) 5% NR                         |  
| NR             | NR                                    |  
| NR             | NR                                    |  |

**ADVERSE EVENTS:**
- Dry mouth 22 vs. 13 vs. 11  
- Fatigue 4 vs. 14 vs. 6  
- Insomnia 14 vs. 10 vs. 8  
- Constipation 9 vs. 3 vs. 6  
- Somnolence 3 vs. 8 vs. 5  
- Decreased appetite 5 vs. 6 vs. 4  
- Nasopharyngitis 5 vs. 5 vs. 3  
- Irritability 5 vs. 1 vs. 4  
- Yawning <1 vs. 5 vs. 1

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Coleman CC, et al.  
Year: 1999  
Country: US |
| **FUNDING:**      | Glaxo Wellcome |
| **DESIGN:**       | Study design: RCT  
Setting: Multi-center (9 centers)  
Sample size: 364 |
| **INTERVENTION:** | Drug: Sertraline: 50-200 mg/d  
Duration: 8 weeks  
Bupropion: 150-400 mg/d  
Duration: 8 weeks  
Placebo N/A  
Duration: 8 weeks |
| **INCLUSION:**    | DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; 18 years of age or older; be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 weeks; currently experiencing recurrent major episode of duration 2-24 months |
| **EXCLUSION:**    | Predisposition to seizure or taking med that lowers seizure threshold; anorexia or bulimia; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or 4 weeks for fluoxetine) |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate for sleep (first 2 weeks only) |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Sertraline: 38.3, buproprion: 38.1, placebo: 38.5  
Gender (% female): Sertraline: 59%, buproprion: 54%, Placebo: 59%  
Ethnicity: Sertraline: white: 92%, black: 8%, other: < 1%; buproprion: white: 87%, black: 11%, other: 2%; Placebo: white: 88%, black: 9%, other: 3%  
Other population characteristics: No significant differences at diagnosis |
Authors: Coleman CC, et al.
Year: 1999
Country: US

OUTCOME ASSESSMENT:
Measures: 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function
Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, 8

RESULTS:
• Mean HAM-D scores in the buproprion but not the sertraline group were statistically better than placebo (by day 28 p < 0.05)
• There was no significant difference between the buproprion and sertraline groups
• CGI-I and CGI-S for buproprion significantly better than placebo but not better than sertraline
• Sertraline not statistically better than placebo
• No differences in HAM-A; significantly fewer buproprion patients had sexual desire disorder than sertraline patients (p < 0.05)
• There was no significant difference between either active treatment group and placebo
• Orgasm dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients (p < 0.05)
• Diagnosed with at least one sexual dysfunction: sertraline: 39%, buproprion: 13%, placebo: 17%

ANALYSIS:
ITT: Yes
Post randomization exclusions: Yes

ATTRITION:
Loss to follow-up: 30%; sertraline: 36%, buproprion sr: 22%, placebo: 32%
Withdrawals due to adverse events: 18.5%; sertraline: 8%, buproprion: 6%, placebo: 2%
Loss to follow-up differential high: No

ADVERSE EVENTS:
• Headache was the most commonly reported event in all treatment groups
• Nausea, diarrhea, dyspepsia occurred more frequently in sertraline patients than buproprion or placebo
• Insomnia and agitation were reported more frequently in buproprion patients than sertraline or placebo

QUALITY RATING: Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td></td>
</tr>
<tr>
<td>Authors: Coleman CC, et al.</td>
<td>Year: 2001</td>
</tr>
<tr>
<td>Country: US</td>
<td></td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Glaxo Wellcome</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td>Setting: Multi-center (15 centers)</td>
<td>Sample size: 456</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>150-400 mg/d</td>
<td>150-400 mg/d</td>
</tr>
<tr>
<td>8 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>8 weeks</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>DSM-IV criteria for major depression; minimum score of 20 on the 21 item HAM-D; ≥18 years of age; have sexual activity at least once every 2 weeks; currently experiencing episode lasting 2-24 months</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal; treatment with bupropion or fluoxetine in the past year; used any psychoactive drug within 1 week of study; non-responders to antidepressant treatment; anorexia or bulimia</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: Fluoxetine: 37.1, bupropion sr: 36.6, placebo: 36.7</td>
</tr>
<tr>
<td></td>
<td>Gender: (% female) Fluoxetine: 66%, bupropion: 63%, placebo: 61%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Fluoxetine: white 82%, black 11%, other 7%; bupropion: white 83%, black 11%, other 5%; placebo: white 82%, black 14%, other 4%</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: At baseline more patients in the fluoxetine and bupropion goups than the placebo group had sexual desire disorder</td>
</tr>
<tr>
<td>Authors: Coleman CC, et al.</td>
<td>Year: 2001</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Country: US</td>
<td></td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Measures:</th>
<th>21item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Baseline, weeks 1, 2, 3, 4, 5, 6, 7, 8</td>
</tr>
</tbody>
</table>

**RESULTS:**

- Mean HAM-D scores were not statistically different between the three groups (in ITT analysis)
- No difference in responders (≥ 50 decrease in HAM-D), remitters (HAMD < 8)
- More buproprion remitters (47%) compared to placebo (32%).
- Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or buproprion patients (p < 0.001)
- At endpoint more fluoxetine treated patients had sexual desire disorder than buproprion-treated patients (p < 0.05).
- More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 (p < 0.05)

**ANALYSIS:**

<table>
<thead>
<tr>
<th>ITT:</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post randomization exclusions:</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**ATTRITION:**

<table>
<thead>
<tr>
<th>Loss to follow-up:</th>
<th>34%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>fluoxetine: 4%, buproprion: 9%, placebo: 3%</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- Headache was the most commonly reported event in all treatment groups
- Headache, diarrhea, and somnolence occurred more frequently in fluoxetine than buproprion or placebo groups
- Dry mouth, nausea, and insomnia were reported more frequently in buproprion than fluoxetine or placebo groups
- Buproprion group had mean increases in DBP and heart rate, authors state these were not clinically significant
- Fluoxetine treated patients had a mean decrease in both DBP and heart rate

**QUALITY RATING:**

| Fair |
### Evidence Table 12 - Adverse Events

| STUDY: | Authors: Coogan PF, et al.\(^{1/1}\)  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>NR</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Case-control  
Setting: 3 centers  
Sample size: 4996 |
| INTERVENTION: | Cases | Controls |
| Drug: | SSRIs | None |
| Dose: | Various | N/A |
| Duration: | N/A | N/A |
| Sample size: | 2138 | 2858 |
| INCLUSION: | Cases: women with a first occurrence of primary invasive breast cancer diagnosed within the last year and no concurrent or previous cancer other than nonmelanoma skin cancer  
Controls: women admitted for nonmalignant diagnoses, unrelated to the use of SSRIs and no history of cancer other than nonmelanoma skin cancer |
| EXCLUSION: | N/A |
| OTHER MEDICATIONS/INTERVENTIONS: | N/A |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Range of age: 24-73  
Gender (% female): 100%  
Ethnicity: NR |
Authors: Coogan PF, et al.  
Year: 2005

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th><strong>Primary Outcome Measures:</strong></th>
<th>Increased risk of breast cancer due to use of SSRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors other than SSRI use that were taken into account include alcohol consumption, religion, family history of breast cancer, center, age and race</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary Outcome Measures:</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Timing of Assessments:</strong></th>
</tr>
</thead>
</table>

### RESULTS:

- Regular use of SSRIs was not associated with breast cancer risk after adjustment for other risk factors OR 1.1 95% 0.8, 1.7

### ANALYSIS:

- **ITT:** N/A
- **Post randomization exclusions:** N/A

### ATTRITION:

- **Loss to follow-up:** N/A
- **Withdrawals due to adverse events:** N/A
- **Withdrawals due to lack of efficacy:** N/A
- **Loss to follow-up differential high:** N/A

### ADVERSE EVENTS:

- **N/A**

### QUALITY RATING:

- **Fair**
### Evidence Table 12  Adverse Events

| STUDY: | Authors: Croft H, et al. 24  
Year: 1999  
Country: US |
| FUNDING: | Glaxo Wellcome |
| DESIGN: | Study design: RCT (active and placebo control)  
Setting: Multi-center (8 centers)  
Sample size: 360 |
| INTERVENTION: | Drug:  
Sertraline  
Dose: 50-200 mg/d  
Duration: 8 weeks  
Bupropion  
Dose: 150-400 mg/d  
Duration: 8 weeks  
Placebo  
Dose: N/A  
Duration: 8 weeks |
| INCLUSION: | DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; > 18 years of age; in a stable relationship; have normal sexual functioning and sexual activity at least once every 2 weeks; current depressive episode of 8 weeks to 24 months |
| EXCLUSION: | Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Sertraline: 36.0, bupropion: 35.9, placebo: 37.4  
Gender (% female): Sertraline: 50%, bupropion: 51%, placebo: 50%  
Ethnicity: Sertraline: white: 87%, black: 8%, other: 4%; bupropion: white: 86%, black: 9%, other: 5%; placebo: white: 88%, black: 8%, other: 3%  
Other population characteristics: Not reported |
**Authors:** Croft H, et al.  
**Year:** 1999  
**Country:** US

### OUTCOME ASSESSMENT:

**Measures:** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview-sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation (men only), overall patient satisfaction with sexual functioning, vital signs  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:

- Mean HAM-D scores in both the buproprion and sertraline group were statistically better than placebo (p < 0.05)
- No significant difference in HAM-D scores between the buproprion and sertraline groups
- CGI-S and CGI-I improvement compared to placebo but no differences between drugs at any week
- No difference in changes of HAM-A scores for any group
- By day 42 significantly fewer buproprion sr-treated patients had sexual desire disorder than sertraline- or placebo-treated patients (p < 0.05)
- At day 56 both buproprion and sertraline groups had higher sexual arousal disorder (p < 0.05) than placebo
- Orgasmic dysfunction occurred significantly more in sertraline group compared with placebo or buproprion groups (p < 0.001)
- At day 56 no difference in overall satisfaction with sexual function between treatment groups

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 32%  
**Withdrawals due to adverse events:** sertraline: 3%, buproprion sr: 3%, placebo: 7%  
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

- Headache was the most commonly reported event in all treatment groups
- Somnolence and insomnia occurred more frequently in sertraline group than buproprion group
- Nausea and diarrhea occurred more frequently with sertraline than buproprion or placebo

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Didham RC, et al.\textsuperscript{1,2}  
                   Year: 2005  
                   Country: New Zealand |
| **FUNDING:**      | The Royal NZ College of General Practitioners Research Unit which receives funding from the NZ government |
| **DESIGN:**       | Study design: Retrospective cohort and nested case control study  
                   Setting: General practice  
                   Sample size: 57,361 |
| **INTERVENTION:** | Drug: SSRIs and other ADS  
                   Dose: Varied  
                   Duration: 120 days  
                   Cases:  
                   Suicides: 26  
                   Self-harms: 330 |
| **INCLUSION:**    | Patients that received a prescription for an anti-depressant from 1996 to 2001 |
| **EXCLUSION:**    | Patients under 10 years old; additional concurrent anti-depressants |
| **OTHER MEDICATIONS/INTerventions:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                   Median age: 46  
                   Gender (\% female): 68.1%  
                   Ethnicity: NR |
Authors: Didham RC, et al.  
Year: 2005

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Suicides or self-harm within 120 days of a prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments: N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• No significant increase in suicides for SSRIs as a group: OR 1.28; 95% CI 0.38-4.35</td>
<td></td>
</tr>
<tr>
<td>• No significant difference in suicides between drugs</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine: 0.80 (0.22-2.89)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine: 2.25 (0.47-10.72)</td>
<td></td>
</tr>
<tr>
<td>• Self-harm SSRIs vs. TCAs incidence rate 2.57 95% CI 2.03-3.28</td>
<td></td>
</tr>
<tr>
<td>• Increased risk of self-harm for SSRIs as a group OR 1.66 95% CI 1.23-2.23</td>
<td></td>
</tr>
<tr>
<td>• No significant differences in self-harm between drugs</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine: 1.30 (0.96-1.75)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine: 1.21 (0.84-1.72)</td>
<td></td>
</tr>
</tbody>
</table>

| ANALYSIS: | ITT: N/A  
Post randomization exclusions: N/A |

| ATTRITION: | Loss to follow-up: N/A  
Withdrawals due to adverse events: N/A  
Withdrawals due to lack of efficacy: N/A  
Loss to follow-up differential high: N/A |

| ADVERSE EVENTS: | N/A |

| QUALITY RATING: | Fair |
### Evidence Table 12  
#### Adverse Events

| STUDY: | Authors: Dunner et al.  
Year: 1998  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome Inc., Research Triangle Park, NC</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational prospective  
Setting: Multi-center (105 sites)  
Sample size: 3100 |
| INTERVENTION: | Drug: Bupropion  
Dose: 100-300 mg/d  
Duration: 8 weeks  
Sample size: 3100 |
| INCLUSION: | Male or female patients at least 18 years of age; met DSM-III-R criteria for MDD, dysthymia, bipolar I or II |
| EXCLUSION: | Previous treatment with bupropion; patients with a history of bulimia or anorexia or with a known predisposition to seizures; pregnant; lactating; suicidal |
| OTHER MEDICATIONS/ INTERVENTIONS: | Benzodiazepines |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: N/A  
Mean age: 42  
Gender (% female): 62.4  
Ethnicity: white: 89.5%, black: 7%, other: 3.5%  
Other population characteristics: NR |
Authors: Dunner et al.  
Year: 1998  
Country: US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Number of seizures; seizure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures: N/A</td>
</tr>
<tr>
<td>Timing of assessments: Biweekly during the study</td>
<td></td>
</tr>
</tbody>
</table>

| RESULTS: | • During the 8 week acute phase of the trial, 2 patients (0.06% -- Upper 1-sided CL of 0.14%) experienced seizures out of 3094 patients. |

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
<th>ITT: N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post randomization exclusions: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: 34%</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse NR</td>
<td></td>
</tr>
<tr>
<td>events: NR</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to lack of NR</td>
<td></td>
</tr>
<tr>
<td>efficacy: N/A</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td></td>
</tr>
</tbody>
</table>

| ADVERSE EVENTS: | • 54 serious adverse events (other than seizure) occurred during the study. Suicide attempt or overdose: 9 patients; accidental injury: 4 patients; myocardial function: 3 patients |

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Ekselius, et al.  
Year: 2001  
Country: Sweden |
| **FUNDING:** | Swedish Medical Research Council and Pfizer AB |
| **DESIGN:** | Study design: Subgroup analysis of RCT  
Setting: Multi-center  
Sample size: 400 |
| **INTERVENTION:** | Drug:  
Dose:  
Duration: |
| Sertraline | Citalopram |
| 50-150 mg/d | 20-60 mg/d |
| 24 weeks | 24 weeks |
| **INCLUSION:** | DSM-III-R criteria for major depression; MADRS score ≥ 21 |
| **EXCLUSION:** | Pregnancy; alcohol or substance abuse; suicidal tendencies; significant physical illness; bipolar disorder; known intolerance or allergic reactions to SSRIs; severe depression or psychotic dimension; previous adequate treatment with citalopram or sertraline; lithium within past month |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Hypnotics for insomnia or daytime anxiolytics |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Gender (% female): Sertraline: 72%, citalopram: 71%  
Ethnicity: Not reported  
Mean age: Sertraline: 47.3, citalopram: 48.1  
Other population characteristics: No significant population differences |
<table>
<thead>
<tr>
<th>Authors: Ekselius, et al.</th>
<th>Year: 2001</th>
</tr>
</thead>
</table>
| **OUTCOME ASSESSMENT:** | Measures: MADRS, CGI-S, CGI-I, sexual function assessed by five items in the Utvalg for Kliniske Undersogelser Side Effect Scale (UKU-SES); increased or decreased sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction  
Timing of assessments: Not reported |
| **RESULTS:** | • No statistically significant differences between sertraline and citalopram in the magnitude or frequency of adverse sexual side effects  
• For both groups sexual desire and mean total score of UKU significantly improved in women; sexual desire improved in men, but not mean score of UKU.  
• In female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported orgasmic dysfunction  
• In male patients reporting no sexual dysfunction at baseline, 16.7% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction |
| **ANALYSIS:** | ITT: Not reported  
Post randomization exclusions: Not reported |
| **ATTRITION:** | Loss to follow-up: 23%; sertraline: not reported, citalopram: not reported  
Withdrawals due to adverse events: 11%; sertraline: not reported, citalopram: not reported  
Loss to follow-up differential high: Not reported |
| **ADVERSE EVENTS:** | Not reported |
| **QUALITY RATING:** | Fair |
## Evidence Table 12: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUNDING: Eli Lilly Research</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DESIGN: Study design: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: Multi-center</td>
</tr>
<tr>
<td>Sample size: 284</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTERVENTION:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug:</strong></td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
</tbody>
</table>

| INCLUSION: |
| < 18 years of age; DSM-V criteria for major depression; DSM-IV for atypical MDD; HAM-D-17 ≥ 16; episode ≥ 1 month |

| EXCLUSION: |
| Pregnancy or lactation, lack of adequate contraception; history of psychotic disorders, bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication; serious comorbid illness not stabilized; anxiolytic or psychotropic within 7 days; MAOI within 2 weeks |

| OTHER MEDICATIONS/INTERVENTIONS: |
| Thyroid medications, chloral hydrate |

<p>| POPULATION CHARACTERISTICS: |
| Groups similar at baseline: Yes |
| Mean age: Fluoxetine: 42.1, sertraline: 44.0, paroxetine: 42.5 |
| Gender (female%): Fluoxetine: 63.0, sertraline: 57.3, paroxetine: 58.3 |
| Ethnicity: Not reported |
| Other population characteristics: Not reported |</p>
<table>
<thead>
<tr>
<th>Authors: Fava M, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title: OUTCOME ASSESSMENT:</td>
</tr>
<tr>
<td>Measures: HAM-D-17, CGI-S, HAM-D sleep disturbance</td>
</tr>
<tr>
<td>Timing of assessments: Not reported</td>
</tr>
<tr>
<td>Year: 2002</td>
</tr>
<tr>
<td>Country: US</td>
</tr>
<tr>
<td>RESULTS:</td>
</tr>
<tr>
<td>No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures</td>
</tr>
<tr>
<td>Response rate: 64.8%, 72.9%, and 68.8% respectively</td>
</tr>
<tr>
<td>Remission rates: 54.4%, 59.4%, and 57.0% respectively</td>
</tr>
<tr>
<td>No statistical differences in sleep disturbance factor scores; no significant differences of treatment groups in patients with high or low insomnia</td>
</tr>
<tr>
<td>Subgroup analysis (Fava 2000): Anxious depression</td>
</tr>
<tr>
<td>No significant differences between treatment groups and changes over time</td>
</tr>
<tr>
<td>Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405</td>
</tr>
<tr>
<td>Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588</td>
</tr>
<tr>
<td>Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score</td>
</tr>
<tr>
<td>ANALYSIS:</td>
</tr>
<tr>
<td>ITT: Yes</td>
</tr>
<tr>
<td>Post randomization exclusions: Not reported</td>
</tr>
<tr>
<td>ATTRITION:</td>
</tr>
<tr>
<td>Loss to follow-up: 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: Fluoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5%</td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
</tr>
<tr>
<td>Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients; the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients</td>
</tr>
<tr>
<td>Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%)</td>
</tr>
<tr>
<td>There was a significant increase in weight for the paroxetine group; fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint</td>
</tr>
<tr>
<td>Subgroup analysis (Fava 1999)</td>
</tr>
<tr>
<td>Adverse events were similar among treatments; only flu-like syndrome was significantly higher in the sertraline treated group overall (p = 0.021)</td>
</tr>
<tr>
<td>QUALITY RATING: Fair</td>
</tr>
<tr>
<td>Evidence Table 12</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
</tbody>
</table>
| STUDY:            | Authors: Fergusson D, et al.  
Year: 2005  
Country: Canada |
| FUNDING:          | Canadian Institutes of Health Research |
| DESIGN:           | Study design: Meta-analysis  
Number of patients: 36,445 |
| AIMS OF REVIEW:   | To establish if an association exists between SSRI use and suicide attempts. |
| STUDIES INCLUDED IN META-ANALYSIS | 345 trials included in analysis |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs comparing an SSRI with either placebo or an active non-SSRI control |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | All patients included in trials comparing SSRIs to either placebo or non-SSRI control; no age, gender, or diagnosis restrictions |
| Authors: Fergusson D, et al. |
| Year: 2005 |

| CHARACTERISTICS OF INTERVENTIONS: | Patients randomized to either an SSRI, placebo, or non-SSRI control |
| MAIN RESULTS: | • A significant increase in the odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving placebo (OR: 2.28; CI: 1.144 to 4.55; p = 0.02)  
• No significant difference found in the odds of suicide attempts between patients receiving SSRIs and patients receiving TCAs (OR: 0.88 (CI: 0.54 to 1.42)) |
| ADVERSE EVENTS: | • No other adverse events reported. |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |
**Evidence Table 12**

| STUDY: | Authors: Gibbons RD et al.  
Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational – retrospective cohort  
Setting: VA hospitals database  
Sample size: 226,866 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration:  
Sample size: |
| No anti-depressant | SSRI monotherapy | Non-SSRI monotherapy |
| NA | Various | Various |
| 6 months | 6 months | 6 months |
| 59,432 | 82,828 | 27,548 |
| (bupropion, mirtazapine, nefazodone, and Venlafaxine) | |
| INCLUSION: | Depressive disorders or unipolar mood disorders in 2003 or 2004, had at least 6 months of follow-up, and had no history of these disorders or antidepressant treatment from 2000 to 2002 |
| EXCLUSION: | NA |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline:  
Mean age: No anti-depressant 57.6 SSRI 60.3 Non-SSRI 55.6  
Gender (female %): No anti-depressant 8.4 SSRI 7.8 Non-SSRI 7.3  
Ethnicity: % black No anti-depressant 8.3 SSRI 5.3 Non-SSRI 6.8 |

**Adverse Events**

---

**Studied Topics**

- Anti-depressant treatment
- Comparative effectiveness
- VA hospitals database
- Retrospective cohort study

**Funding**

- NIMH

**Study Design**

- Observational study
- Retrospective cohort
- VA hospitals database
- Sample size: 226,866

**Intervention**

- No anti-depressant
- SSRI monotherapy
- Non-SSRI monotherapy

- Drug Dose Duration
- Bupropion, mirtazapine, nefazodone, and Venlafaxine

**Inclusion Criteria**

- Depressive disorders or unipolar mood disorders in 2003 or 2004
- At least 6 months of follow-up
- No history of these disorders or antidepressant treatment from 2000 to 2002

**Exclusion Criteria**

- NA

**Population Characteristics**

- Age: No anti-depressant 57.6 SSRI 60.3 Non-SSRI 55.6
- Gender: No anti-depressant 8.4 SSRI 7.8 Non-SSRI 7.3
- Ethnicity: % black No anti-depressant 8.3 SSRI 5.3 Non-SSRI 6.8

---

**Second generation antidepressants**
Authors: Gibbons  
Year: 2007  
Country: USA

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Suicide attempts  
Secondary Outcome Measures:  
Timing of assessments: 6 months |
|---------------------|--------------------------------------------------|

RESULTS: Suicide attempt rates were lower among patients who were treated with antidepressants than among those who were not, with a statistically significant odds ratio for SSRIs and tricyclics. For SSRIs versus no antidepressant, this effect was significant in all adult age groups.

<table>
<thead>
<tr>
<th>Age group</th>
<th>no antidepressant vs SSRI monotherapy</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>0.35 (0.14-0.85)</td>
<td>p = 0.021</td>
<td></td>
</tr>
<tr>
<td>0.44 (0.29-0.65)</td>
<td>p &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-65</td>
<td>0.42 (0.30-0.59)</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.38 (0.16-0.91)</td>
<td>p = 0.036</td>
<td></td>
</tr>
</tbody>
</table>

Age group no anti depressant vs SSRI monotherapy Odds ratio (95% CI) p value
18-25 0.35 (0.14-0.85) p = 0.021
0.44 (0.29-0.65) p < 0.0001
46-65 0.42 (0.30-0.59) p < 0.0001
>65 0.38 (0.16-0.91) p = 0.036

Treatment compared to no treatment, likelihood of suicide attempt
No antidepressant Attempts = 199 Rate per 100,000 =335
SSRI monotherapy Attempts = 102 Rate per 100,000= 123 OR = 0.37 95% CI 0.29–0.47 P <0.0001
Non-SSRI monotherapy Attempts = 76 Rate per 100,000 = 276 OR = 0.83 95% CI 0.64–1.08 P = 0.16

ANALYSIS: ITT: NA  
Post randomization exclusions: NA  
Loss to follow-up: NA

ATTRITION:  
Withdrawals due to adverse events: NA  
Withdrawals due to lack of efficacy: NA  
Loss to follow-up differential high: NA

ADVERSE EVENTS:  
- See results

QUALITY RATING: Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Greist J, et al.¹⁷⁷  
Year: 2004  
Country: US |
| **FUNDING:**      | Eli Lilly |
| **DESIGN:**       | Study design: Pooled analysis  
Number of patients: 2,345 |
| **AIMS OF REVIEW:** | To assess the incidence, severity and onset of nausea among MDD patients treated with duloxetine |
| **STUDIES INCLUDED IN META-ANALYSIS** | Detke et al. 2002; Detke et al. 2002; Goldstein et al 2002; Goldstein et al. 2004; 4 unpublished studies submitted for FDA approval of duloxetine |
| **TIME PERIOD COVERED:** | Not reported |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blinded, placebo or active controlled trials of duloxetine |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult outpatients with MDD |
Authors: Greist J, et al.
Year: 2004
Country: US

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Duloxetine vs. placebo (8 studies); duloxetine vs. paroxetine (4 studies); duloxetine vs. fluoxetine (2 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>• No significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) (14.4% vs. 12%; p = not reported)</td>
</tr>
<tr>
<td></td>
<td>• No significant differences between duloxetine (120mg/d) and fluoxetine (20mg/d) (17.1% vs. 15.7%; p = not reported)</td>
</tr>
<tr>
<td></td>
<td>• Significantly more patients on duloxetine than on placebo reported nausea (19% vs. 6.9%; p &lt; 0.001)</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>N/A</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>No; analysis of published and unpublished trials</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>Not reported</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
<tr>
<td>Evidence Table 12</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
</tr>
</tbody>
</table>
| **STUDY:**        | Authors: Gunnell D, et al.¹⁷⁸  
Year: 2005  
Country: UK |
| **FUNDING:**      | Not Reported |
| **DESIGN:**       | Study design: Meta-analysis  
Number of patients: 40,826 |
| **AIMS OF REVIEW:** | To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults. |
| **STUDIES INCLUDED IN META-ANALYSIS** | Published and unpublished data submitted by pharmaceutical companies to the Medicine and Healthcare Products Regulatory Agency (MHRA) (2004)  
342 placebo controlled trials included in report – citations not given in bibliography |
| **TIME PERIOD COVERED:** | NR |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Randomized, placebo controlled trials of SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) submitted by pharmaceutical companies |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult patients with various indications included in trials comparing SSRIs to placebo. |
## Authors: Gunnell, et al.  
Year: 2005

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Patients randomized to either SSRI or placebo.</th>
</tr>
</thead>
</table>
| MAIN RESULTS:                    | • No significant difference was found between SSRI treatment and placebo treatment in the odds ratios for suicide (OR: 0.85 CI: 0.2 to 3.4), non-fatal self harm (OR: 1.57 CI: 0.99 to 2.55), or suicidal thought (OR: 0.77 CI: 0.37 to 1.55).  
<p>|                                  | • For non-fatal self-harm the NNT to harm is 759 |
| ADVERSE EVENTS:                  | • No other adverse events reported. |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies) |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING:                  | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Hammad TA et al.¹⁷⁹  
Year: 2006  
Country: USA |
| **FUNDING:**      | CDER, FDA |
| **DESIGN:**       | Study design: Meta-analysis  
Number of patients: 4582 |
<p>| <strong>AIMS OF REVIEW:</strong> | The objective of this article is to provide the detailed methods and results of the FDA’s exploration and analysis of the pediatric suicidality adverse event data and suicide item score data. |
| <strong>STUDIES INCLUDED IN REVIEW</strong> | 23 trials and 1 multicenter trial (TADS) |
| <strong>TIME PERIOD COVERED:</strong> | NA - Most of the trials were conducted in the late 1990s, and trial durations ranged from 4 to 16 weeks. |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | 23 placebo-controlled clinical trials conducted in 9 drug development programs of antidepressants in pediatric patients and in a placebo-controlled, multicenter trial funded by the National Institute of Mental Health |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Children and adolescents with MDD (16 trials), obsessive-compulsive disorder (4 trials), generalized anxiety disorder (2 trials), social anxiety disorder (1 trial), and attention-deficit/hyperactivity disorder (1 trial). |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Fluoxetine, sertraline hydrochloride, paroxetine, fluvoxamine maleate, citalopram hydrobromide, bupropion hydrochloride, venlafaxine hydrochloride (extended release), nefazodone hydrochloride, and mirtazapine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>• Overall Suicidal Behavior or Ideation Risk Ratio (95% CI) 1.95 (1.28 - 2.98)</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td></td>
</tr>
<tr>
<td>MDD Trials RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Citalopram 1.37 (0.53-3.50)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine No MDD trials</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 2.15 (0.71-6.52)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine 1.53 (0.74-3.16)</td>
<td></td>
</tr>
<tr>
<td>Sertraline 2.16 (0.48-9.62)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine ER 8.84 (1.12-69.51)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine 1.58 (0.06-38.37)</td>
<td></td>
</tr>
<tr>
<td>Nefazodone No events</td>
<td></td>
</tr>
<tr>
<td>Bupropion No MDD trials</td>
<td></td>
</tr>
<tr>
<td>All trials, all indications RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Citalopram 1.37 (0.53-3.50)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine 5.52 (0.27-112.55)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 2.65 (1.00-7.02)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine 1.52 (0.75-3.09)</td>
<td></td>
</tr>
<tr>
<td>Sertraline 1.48 (0.42-5.24)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine ER 4.97 (1.09-22.72)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine 1.58 (0.06-38.37)</td>
<td></td>
</tr>
<tr>
<td>Nefazodone No events</td>
<td></td>
</tr>
<tr>
<td>Bupropion No events</td>
<td></td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>No- request was from FDA to drug companies</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>NA - Patient level data</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Good</td>
</tr>
<tr>
<td>Evidence Table 12</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
</tr>
</tbody>
</table>
| **STUDY:** | **Authors:** Haffmans, et al.  
**Year:** 1996  
**Country:** The Netherlands |
| **FUNDING:** | Lundbeck |
| **DESIGN:** | **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 217 |
| **INTERVENTION:** |  
**Drug:** Citalopram  
**Dose:** 20-40 mg/d  
**Duration:** 6 weeks  
Fluvoxamine  
**Dose:** 100–200 mg/d  
**Duration:** 6 weeks |
| **INCLUSION:** | Ages 18-70 years; met DSM III-R criteria for major depression (single episode or recurrent) or bipolar disorder; score of > 16 on HAM-D-17; reasonable knowledge of the Dutch language |
| **EXCLUSION:** | MAOI or fluoxetine use within 3 weeks or other psychotropic drugs within 1 week (except for benzos); other primary psychiatric diagnosis (other than MDD); history of epilepsy, alcohol or drug abuse; pregnancy, lactation, or not using contraception; renal, hepatic, cardiovascular, neurological or somatic disorders and/or significant abnormal lab findings |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Selected benzodiazepines; oxazepam, lormetazepam, temazepam, lorazepam, or flurazepam, all non-psychotropic medications were allowed, domperidone for nausea/vomiting allowed |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** No  
**Mean age:** Citalopram: 44.2, fluvoxamine: 40.2  
**Gender (% female):** citalopram: 58%, fluvoxamine: 60%  
**Ethnicity:** Not reported  
**Other population characteristics:** Previous depressive disorder: citalopram: 43%; fluvoxamine: 54%; previous antidepressant therapy (within 3 weeks of starting trial): citalopram: 65%, fluvoxamine: 73% |
| **Authors:** Haffmans, et al.  
**Year:** 1996  
**Country:** The Netherlands |
|---|
| **OUTCOME ASSESSMENT:**  
*Measures:* Primary: HAM-D-17; secondary: CGI, UKU side effect rating scale, Zung self-rating depression scale  
*Timing of assessments:* Baseline, weeks 1, 2, 4, 6 |
| **RESULTS:**  
- No difference in mean HAM-D-17 scores after 6 weeks  
- Complete Response (HAM-D17) ≤ 7: citalopram: 14%, fluvoxamine: 18%; no significant difference  
- Mean % reduction in score at week 6: citalopram: 33%, fluvoxamine: 26%  
- Responders (reduction in score from baseline > 50%): citalopram: 30.5%, fluvoxamine: 28.4% |
| **ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes |
| **ATTRITION:**  
*Loss to follow-up:* 23%; citalopram: 19.4%, fluvoxamine: 26.6%  
*Withdrawals due to adverse events:* Citalopram: 13.9%, fluvoxamine: 21.1%  
*Loss to follow-up differential high:* No |
| **ADVERSE EVENTS:**  
- No differences between groups in laboratory values or vital signs  
- 10 serious adverse events (4 in citalopram and 6 in fluvoxamine) none of which were deemed to be causally related to treatment  
- Similar UKU side effect scale measured impact on functioning between groups  
- Fluvoxamine had the following excess incidence of adverse events as compared to citalopram:  
  - Diarrhea: 13.6% (p = 0.026)  
  - Nausea: 16.0% (p = 0.017)  
  - Vomiting: 9.1% (p = 0.052)  
  - Suicide attempt: 4.6%  
- Citalopram had the following excess incidence of adverse events as compared to fluvoxamine: paraesthesia: 10.4% |
| **QUALITY RATING:** Fair |
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Isacsson G, et al. \(^{181}\)  
Year: 2005  
Country: Sweden |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>The Soderstrom-Konigska Foundation and Karolinska Institute</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Controlled database study  
Setting:  
Sample size: 41,279 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration:  
Sample size: |
| | Cases  
N/A  
9 year period  
14,857  
Controls  
N/A  
9 year period  
26,422 |
| INCLUSION: | Cases: suicide (as a Swedish citizen) investigated by the Department of Forensic Chemistry of the National Board of Forensic Medicine in Sweden where analysis detected therapeutic concentration of antidepressants in femoral blood; includes uncertain cases (overdose that may have been suicide)  
Controls: investigated death during same time period which, after forensic investigation, was judged to be natural or accidental |
| EXCLUSION: | N/A. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes  
Median age: cases: 49, controls: 55  
Gender (female %): cases: 29%, controls: 27%  
Ethnicity: 100% Swedish citizens (no further ethnicity reported) |

---

Second generation antidepressants
**Authors:** Isacsson G, et al.  
**Year:** 2005  
**Country:** Sweden

**OUTCOME ASSESSMENT:**  
**Primary Outcome Measures:** Detection of antidepressants in toxicological screening  
**Secondary Outcome Measures:**  
**Timing of assessments:** N/A

| RESULTS: |  
| --- | --- |
| • 3,411 detections of antidepressants in suicides (cases) vs. 1,538 in controls  
• SSRIs underrepresented compared to other antidepressants (OR=0.83, 99% CI: 0.77-0.90)  
• SSRIs had lower OR (99% CI) than other antidepressants; citalopram: 0.76 (0.69-0.84), fluoxetine: 0.91 (0.60-1.38), fluvoxamine: 3.04 (1.15-8.04), paroxetine: 0.87 (0.60-1.28), sertraline: 1.05 (0.78-1.42)  
• Differences within SSRIs were insignificant with the exception of fluvoxamine  
• Other modern antidepressants (OR, 99%CI): mirtazapine: 1.67 (1.08-2.60), venlafaxine: 1.47 (0.99-2.18)  
• Excluding uncertain suicides from analysis changed ORs only marginally (data NR)  
• 52 suicides in people under 15 yrs of age but no SSRIs detected; venlafaxine detected in 1 case  
• Among the 998 controls under 15 yrs of age, 4 were positive for antidepressants (3 for citalopram); SSRIs vs. non-SSRIs in cases and controls p=0.02 |

| ANALYSIS: | ITT: N/A  
| --- | Post randomization exclusions: N/A |

| ATTRITION: | Loss to follow-up: N/A  
| --- | Withdrawals due to adverse events: N/A  
| --- | Withdrawals due to lack of efficacy: N/A  
| --- | Loss to follow-up differential high: N/A |

**ADVERSE EVENTS:**  
N/A

**QUALITY RATING:**  
Fair
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Jick H, et al.\(^{192}\)  
|        | Year: 2004  
|        | Country: UK |
| FUNDING: | Boston Collaborative Drug Surveillance Program |
| DESIGN: | Study design: Matched case-control; post-hoc database analysis  
|        | Setting: General practices in the UK using VAMP database (General Practice Research Database)  
|        | Sample size: 159,810 (555 cases, 2062 controls) |
| INTERVENTION: | Drug: Dothiepin, amitriptyline, fluoxetine, paroxetine  
|        | Dose: Not reported  
|        | Duration: Not reported |
| INCLUSION: | Received a prescription for at least 1 antidepressant in the VAMP database during the 1993-1999 years; all patients who had a first-time recorded diagnosis of nonfatal suicidal ideation or attempted suicide at age 10-69 years during the 1993-1999 time period; had received at least 1 prescription for a study drug within 90 days before their index date |
| EXCLUSION: | Received prescription for another antidepressant or more than one study drug prior to their index date; history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia, and attention-deficit disorder |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|        | Mean age: not reported  
|        | Gender (% female): 65.4% female (cases only)  
|        | Ethnicity: Not reported  
|        | Other population characteristics: ~85% of cases had attempted suicide while 15% had suicidal ideation |
| Authors: Jick H, et al.  
Year: 2004  
Country: UK |
|--------------------------------------------------|

**OUTCOME ASSESSMENT:**

- **Measures:** Frequency of first-time exposure to amitriptyline, fluoxetine, paroxetine and dothiepin of patients with a recorded diagnosis of first-time nonfatal suicidal behavior or suicide compared with matched patients who did not exhibit suicidal behavior  
- **Timing of assessments:** N/A

**RESULTS:**

- Risk of suicidal behavior was similar among users of amitriptyline (RR: 0.83; 95% CI 0.61 – 1.13), fluoxetine (RR 1.16; 95% CI 0.90 – 1.50), and paroxetine (RR 1.29; 95% CI 0.97 – 1.70) compared to dothiepin  
- Suicide risk was increased in the first month after starting antidepressants, especially during the first 1 – 9 days (RR 4.07; 95% CI 2.89 – 5.74)

**ANALYSIS:**

- **ITT:** N/A  
- **Post randomization exclusions:** N/A

**ATTRITION:**

- **Loss to follow-up:** N/A  
- **Withdrawals due to adverse events:** N/A  
- **Loss to follow-up differential high:** N/A

**ADVERSE EVENTS:**

- Not reported

**QUALITY RATING:**

- N/A
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Jick, et al. 183 |
|        | Year: 1995 |
|        | Country: UK |

| FUNDING: | Various pharmaceutical companies (Berlex, Boots, Burroughs Wellcome, Ciba-Geigy, Hoeschst, Hoffman-LaRoche, RW Johnson, Pfizer, Proctor and Gamble, Sanofi Winthrop |

| DESIGN: | Study design: Cohort study with nested case-control analysis |
|         | Setting: General practices in the UK using VAMP database |
|         | Sample size: 172,598 |

| INTERVENTION: | Drugs studies in this cohort: dothiepin, amitryptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, fluoxetine, doxepin, trazodone, maprotiline, desipramine |
|              | Not reported |
|              | Duration: |

| INCLUSION: | Received a prescription for 1 or more antidepressant in the VAMP database (General Practice Research Database); all patients who committed suicide identified in the cohort evaluation were included as cases |

| EXCLUSION: | Not reported |

| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |

<p>| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported |
|                            | Mean age: Not reported |
|                            | Gender: Not reported |
|                            | Ethnicity: Not reported |
|                            | Other population characteristics: Not reported |</p>
<table>
<thead>
<tr>
<th>Authors: Jick, et al.</th>
<th>Year: 1995</th>
<th>Country: UK</th>
</tr>
</thead>
</table>
| **OUTCOME ASSESSMENT:** | **Measures:** Suicide completion rate, suicides/person time at risk, relative risks of suicide reported with dothiepin as reference group  
**Timing of assessments:** N/A |
| **RESULTS:** | From cohort analysis: Suicide rate/10,000 person years: fluoxetine: 19.0, adjusted RR: 2.1 (95% CI 1.1-4.1) relative to dothiepin  
From case control analysis: Adjusted RR 3.8 (95% CI 1.7- 8.6), analysis restricted to those prescribed antidepressants for the first time and who had no history of suicidal behavior, adjusted RR: 2.1 (95% CI 0.6 - 7.9) |
| **ANALYSIS:** | **ITT:** N/A  
**Post randomization exclusions:** N/A |
| **ATTRITION:** | **Loss to follow-up:** Not reported  
**Withdrawals due to adverse events:** N/A  
**Loss to follow-up differential high:** N/A |
<p>| <strong>ADVERSE EVENTS:</strong> | Not reported |
| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | **Authors:** Johnston et al. 1991  
                    **Year:** 1991  
                    **Country:** US |
| **FUNDING:**      | Burroughs Wellcome Co., RTP, NC |
| **DESIGN:**       | **Study design:** Prospective observational  
                    **Setting:** Multi-center (102 sites)  
                    **Sample size:** 3341 |
| **INTERVENTION:** | **Bupropion**  
                    **Dose:** 225-450 mg/d  
                    **Duration:** 8 weeks with a one year continuation  
                    **Sample size:** 3341 |
| **INCLUSION:**    | Patients 18 years of age or older with a diagnosis of depression for which antidepressant treatment was appropriate |
| **EXCLUSION:**    | Previous use of bupropion; pregnant; lactating; anorexic or bulimic; known predisposition to seizures; received an MAO inhibitor within 14 days of the study or an investigational drug within 30 days of the study |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Other antidepressant medications, neuroleptic drugs, or amphetamine-type drugs were not allowed |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: N/A  
Mean age: 43.5  
Gender (% female): 59.4  
Ethnicity: 96% white; 3% black; 1% other  
Other population characteristics:  
Psychiatric diagnosis:  
Major depression: 73%  
Dysthymic disorder: 10%  
Bipolar depression: 8%  
Atypical depression: 6%  
Atypical bipolar: 2%  
Other: 1% |
<table>
<thead>
<tr>
<th>Authors: Johnston et al.</th>
<th>Year: 1991</th>
<th>Country: US</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Number of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures: N/A</td>
</tr>
<tr>
<td></td>
<td>Timing of assessments: Biweekly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight seizures were reported in the 3277 patients analyzed during the treatment phase. This is a seizure rate of 0.24%. A survival analysis showed a cumulative seizure rate of 0.36% during the 8 week trial.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT: No</td>
</tr>
<tr>
<td>Post randomization exclusions: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: Overall NR 613 (19%)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: NR</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>82 (2.5%) patients experienced major adverse events (life threatening or requiring hospitalization)</td>
</tr>
<tr>
<td>Most common adverse events were nausea (3.6%), agitation (2.4%), anxiety (1.7%), headache (1.5%), insomnia (1.3%), and rash (1.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>N/A</th>
</tr>
</thead>
</table>
**Evidence Table 12**  

<table>
<thead>
<tr>
<th>STUDY:</th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Kennedy SH et al.</td>
<td><strong>Drug:</strong></td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
<td><strong>Dose:</strong></td>
</tr>
<tr>
<td><strong>Country:</strong> Canada</td>
<td><strong>Duration:</strong></td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td><strong>Sample size:</strong></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Bupropion 150-300 mg 8 weeks 69</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td><strong>Sample size:</strong></td>
</tr>
<tr>
<td>Study design: RCT</td>
<td>141 (131 ITT)</td>
</tr>
<tr>
<td>Setting: Multicenter</td>
<td></td>
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<tr>
<td><strong>INTERVENTION:</strong></td>
<td><strong>INCLUSION:</strong></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>Outpatients; age 18 - 65 years; DSM-IV criteria for MDD—current MDE of at &gt; 4 weeks. HAM-D &gt; 18; to be in good physical health, sexual interest and activity within the past month; free of any antidepressant use for 2 weeks (4 weeks for fluoxetine)</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td><strong>EXCLUSION:</strong></td>
</tr>
<tr>
<td><strong>Sample size:</strong></td>
<td>Serious suicide risk; more than 2 failed trials of antidepressant medications at adequate dose and duration during the current episode, drug abuse or dependence within the past 12 months, and a history of bipolar disorder, psychotic disorder, or organic disorder</td>
</tr>
<tr>
<td></td>
<td><strong>OTHER MEDICATIONS/ INTERVENTIONS:</strong></td>
</tr>
<tr>
<td></td>
<td>Hypnotic zopiclone (up to 7.5 mg at night) during the first 2 weeks.</td>
</tr>
<tr>
<td></td>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
</tr>
<tr>
<td></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 37.8</td>
</tr>
<tr>
<td></td>
<td>Gender (female %): 48</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
</tbody>
</table>
| Authors: Kennedy SH et al.  
Year: 2006  
Country: Canada |
|-----------------|
| OUTCOME ASSESSMENT: | Primary Outcome Measures: Sexual function Sex FX, IRSD-F  
Secondary Outcome Measures: HAM-D  
Timing of assessments: Baseline, 2,4,6,8 |
| RESULTS: | • HAMD Bupropion SR (mean 21.8, SD 2.9) vs. paroxetine (mean 22.2, SD 3.6)  
• HAM-D - men (mean 22.1, SD 3.1) responders 62.9% vs. women (mean 21.9, SD 3.5) responders 53.2%  
• Overall more sexual adverse events with paroxetine than with bupropion  
• No difference between drugs for sexual dysfunction in women |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: 10 |
| ATTRITION: | Loss to follow-up: 16% (21) Bupropion 11.6% (8) paroxetine 21% (13)  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | None reported |
| QUALITY RATING: | Fair |
Evidence Table 12  Adverse Events

| STUDY: | Authors: Khan, et al.\textsuperscript{186}  
|        | Year: 2003  
|        | Country: US |
| FUNDING: | Not reported |
| DESIGN: | Study design: Meta-analysis  
|         | Number of patients: 48,277 |
| AIMS OF REVIEW: | Compare suicide rates among depressed patients |
| STUDIES INCLUDED IN META-ANALYSIS | Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs  
<p>| | 2000 publication reports on 1987 to 1997 (same data) |
| TIME PERIOD COVERED: | 1985-2000 |
| CHARACTERISTICS OF INCLUDED STUDIES: | FDA clinical trial data |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Major depression according to DSM-II-R criteria; minimum score of 18 or 20 on HAM-D-17 or HAM-D-21 |</p>
<table>
<thead>
<tr>
<th>Authors: Khan, et al.</th>
<th>Year: 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
</tr>
</tbody>
</table>

**CHARACTERISTICS OF INCLUDED INTERVENTIONS:**
- Fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, nefazodone, mirtazapine, bupropion, venlafaxine, imipramine, amitriptyline, maprotiline, trazadone, mianserin, dothiepin

**MAIN RESULTS:**
- **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 difference
- **Suicide Rate by Patient Exposure Years (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 difference
- 2000 study: looked at suicide attempts and completion and found no difference

**ADVERSE EVENTS:**
- N/A

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**
- No

**STANDARD METHOD OF APPRAISAL OF STUDIES:**
- Not reported

**QUALITY RATING:**
- Fair
## Evidence Table 12

### Adverse Events

| STUDY: | Authors: Kharofa J et al<sup>187</sup>  
Year: 2007  
Country: USA |
| FUNDING: | None |
| DESIGN: | Study design: Case-control study  
Setting: Emergency rooms and hospitals  
Sample size: 916 |
| Sample size: | Cases: patients with intracerebral (ICH) and subarachnoid hemorrhage (SAH) on citalopram, escitalopram, fluoxetine, paroxetine, and sertraline.  
Controls: matched patients on citalopram, escitalopram, fluoxetine, paroxetine, and sertraline.  
916 | 1776 |
| INCLUSION: | Cases of intracerebral (ICH) and subarachnoid hemorrhage (SAH) were identified in the Greater Cincinnati region |
| EXCLUSION: | NR |
| OTHER MEDICATIONS/INTERVENTIONS: | Warfarin Cases 77 (8.4%) Controls 43 (2.4%) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 57.3  
Gender (female %): NR  
Ethnicity: NR  
Other population characteristics: |

---

<sup>363 of 515</sup>
| **Authors:** Kharofa et al.  
**Year:** 2007  
**Country:** USA |
|---|
| **OUTCOME ASSESSMENT:**  
**Primary Outcome Measures:** Hemorrhagic stroke  
**Timing of assessments:** May 1997 to August 2001 and from July 2002 to October 2005 |
| **RESULTS:**  
Of the 916 hemorrhagic stroke patients, 71 (7.8%) were on an SSRI at the time of stroke, and of 1776 demographically matched controls, 158 (8.9%) were on an SSRI. After controlling for multiple risk factors, SSRI use was not independently associated with increased risk for hemorrhagic stroke (OR = 0.8, 95% CI: 0.5 to 1.2; \( P = 0.25 \)). |
| **ANALYSIS:**  
**ITT:** NA  
**Post randomization exclusions:** NA  
**Loss to follow-up:** NA |
| **ATTRITION:**  
Withdrawals due to adverse events: NA  
Withdrawals due to lack of efficacy: NA  
Loss to follow-up differential high: NA |
| **ADVERSE EVENTS:**  
• See results |
| **QUALITY RATING:**  
Fair |
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td><strong>Authors:</strong> Kiev, et al.</td>
</tr>
<tr>
<td></td>
<td><strong>Country:</strong> US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Solvay Pharma, Upjohn</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td></td>
<td><strong>Setting:</strong> Single center</td>
</tr>
<tr>
<td></td>
<td><strong>Sample size:</strong> 60</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td><strong>Drug:</strong> Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td><strong>Dose:</strong> 50-150 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Duration:</strong> 7 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>Paroxetine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dose:</strong> 20-50 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Duration:</strong> 7 weeks</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Age 18-65; meet DMS-III-R criteria for single or recurrent MDD; ≥ 20 on HAM-D-21 (including minimum score of 2 on depressed mood item)</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Non-English speakers; history of medication non-compliance; demonstration of placebo response during run-in, history of substance abuse; severe suicide risk or auto-aggressive behavior; used a drug within 30 days with anticipated major organ toxicity; pregnancy, lactation; hypersensitivity to SSRIs; participation in prior drug 1 studies; other significant organic disease; clinically significant lab abnormalities; other primary psychiatric diagnoses; transportation difficulties</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate, other meds only with permission of study physician</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td><strong>Groups similar at baseline:</strong> Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Mean age:</strong> Fluvoxamine: 42.7, paroxetine: 39</td>
</tr>
<tr>
<td></td>
<td><strong>Gender (female%):</strong> Fluvoxamine: 53%, paroxetine: 53%</td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong> White: fluvoxamine: 87%, paroxetine: 93%</td>
</tr>
<tr>
<td></td>
<td><strong>Other population characteristics:</strong> Not reported</td>
</tr>
</tbody>
</table>
### Authors: Kiev, et al.
**Year:** 1997

| OUTCOME ASSESSMENT: | **Measures:** HAM-D-21, HAM-A, SCL-56, CGI  
Timing of assessments: Baseline, weeks 1, 2, 3, 5, 7 |
|---------------------|--------------------------------------------------|

| RESULTS:          | Mean change in HAM-D score: fluvoxamine: -13.45, paroxetine: -12.86 (p = 0.763)  
No significant differences between groups on HAM-D-21, CGI, HAM-A, or SCL56 |
|-------------------|--------------------------------------------------|

| ANALYSIS:         | **ITT:** Yes  
Post randomization exclusions: Yes |
|-------------------|--------------------------------------------------|

| ATTRITION:        | **Loss to follow-up:** 31%  
Withdrawals due to adverse events: fluvoxamine: 6.8%, paroxetine: 13.8%  
Loss to follow-up differential high: No |
|-------------------|--------------------------------------------------|

| ADVERSE EVENTS:   | Sweating (p = 0.028); fluvoxamine: 10%, paroxetine: 33%  
Headache: fluvoxamine: 40%, paroxetine: 57%  
Nausea: fluvoxamine: 37%, paroxetine: 47%  
No clinically significant labs or vital sign changes in either group |
|-------------------|--------------------------------------------------|

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Fair</th>
</tr>
</thead>
</table>
### Evidence Table 12: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Bristol-Myers Squibb, Sweden</td>
</tr>
<tr>
<td>OBJECTIVE:</td>
<td>To determine: 1) concordance of sexual dysfunction adverse event rates between open-ended questioning and directed questioning; 2) the incidence of sexual side effects of citalopram and paroxetine; 3) the correlation between sexual side effects and illness severity, treatment duration and drug/dose combination</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: Non-randomized trial of adverse event elicitation methods embedded in a RCT (Landen et al 1998 – patients who had not responded to CP or PX were randomized to receive buspirone or placebo) Setting: Multi-center (13 centers) Sample size: 119</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Drug:</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Patients 18 years or older; met criteria for a major depressive episode according to DSM-IV criteria; has not responded to CP or PX for a minimum of 4 weeks prior to start of study</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Pregnancy; epilepsy; severe somatic disease; mental disorder due to a general medical condition; substance abuse; highly suicidal status</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Patients received either buspirone or placebo for 4 week study duration</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes Mean age: 46 Gender (% female): 69% Ethnicity: NR Other population characteristics: NR</td>
</tr>
</tbody>
</table>
**Authors:** Landen M, et al  
**Year:** 2005  
**Country:** Sweden and Norway

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Sexual dysfunction score (0-6); Percent patients reporting any sexual side effect based on open and direct questioning

**Secondary Outcome Measures:** N/A

**Timing of assessments:** Before and after the 4 week trial

### RESULTS:

By objective

1. **Side effect elicitation method**
   - Significantly 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**
   - Open-ended questioning: citalopram 5%, paroxetine 7% ($p = 0.98$)
   - Direct questioning: citalopram 44%, paroxetine 36% ($p = 0.37$)

3. **Correlations with illness severity and treatment parameters**
   - Only weak correlation with duration of current depression episode ($p = 0.043$)

### ANALYSIS:

**ITT:** N/A  
**Post randomization exclusions:** N/A

### ATTRITION:

**Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Withdrawals due to lack of efficacy:** N/A  
**Loss to follow-up differential high:** N/A

### ADVERSE EVENTS:

- Decreased desire reported by 43% of men and 32% of women
- Orgasmic dysfunction reported by 23% women and 32% men

### QUALITY RATING:

Good
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Lopez-Ibor JJ<sup>189</sup>  
**Year:** 1993  
**Country:** Spain |
| **FUNDING:** | NR |
| **DESIGN:** | **Study design:** Retrospective database analysis  
**Setting:** Not reported  
**Sample size:** 4,668 |
| **INTERVENTION:** |  
**Drug:** Paroxetine  
**Dose:** Not reported  
**Duration:** Up to 6 weeks  
**Placebo:** N/A  
**Duration:** Up to 6 weeks  
**Active control:** N/A  
**Duration:** Up to 6 weeks |
| **INCLUSION:** | Depressed patients enrolled in a clinical trial |
| **EXCLUSION:** | Not reported |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Not reported  
**Mean age:** Not reported  
**Gender:** Not reported  
**Ethnicity:** Not reported  
**Other population characteristics:** Not reported |
| **Authors:** Lopez-Ibor, JJ  
**Year:** 1993  
**Country:** Spain |
|---|
| **OUTCOME ASSESSMENT:**  
*Measures:* Suicide item of HAM-D, emergence of suicidal ideation, assessed by the development of HAM-D suicide item score  
*Timing of assessments:* N/A |
| **RESULTS:**  
Paroxetine and active control were significantly better than placebo in reducing suicidal thoughts and behavior from week 1 onwards |
| **ANALYSIS:**  
*ITT:* N/A  
*Post randomization exclusions:* Not reported |
| **ATTRITION:**  
*Loss to follow-up:* N/A  
*Withdrawals due to adverse events:* N/A  
*Loss to follow-up differential high:* N/A |
| **ADVERSE EVENTS:**  
- There were no differences among the groups with regards to suicidality as an adverse event.  
- 0.4% of each group reported suicidality.  
- There were 10 suicides overall and 58 attempts overall. |
| **QUALITY RATING:**  
N/A |
## Evidence Table 12  Adverse Events

| STUDY: | Authors: Mackay, et al.\textsuperscript{190, 191}  
Year: 1997  
Country: UK |
| FUNDING: | Drug Safety Research Unit, UK, various unnamed pharmaceutical companies |
| DESIGN: | Study design: Cohort study (prescription event monitoring)  
Setting: General practice in the UK  
Sample size: Number identified as getting a first prescription: fluvoxamine: 20,504, fluoxetine: 24,738, sertraline: 24,632, paroxetine: 26,194 |
| INTERVENTION: | Drugs compared: fluvoxamine, fluoxetine, sertraline, paroxetine  
Dose: N/A  
Duration: Outcomes assessed after approximately 6 months for all but fluvoxamine (which was 12 months) |
| EXCLUSION: | Not reported |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes; some differences existed between groups as far as indication for prescription  
Mean age: 50  
Gender (% female): 70%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
Authors: Mackay, et al.
Year: 1997
Country: UK

OUTCOME ASSESSMENT:

Measures: GP completion of a simple questionnaire (green form), questions asked: perceived efficacy, reason for stopping, indication for prescribing, duration of therapy, and events during and after treatment. (Event = new diagnosis, reason for referral to a consultant or admission to hospital, unexpected deterioration (or improvement) in a concurrent illness, suspected drug reaction or any complaint which was considered of sufficient importance to enter in patient notes.

Timing of assessments: Mailed 6-12 months after initial prescription written

RESULTS:

- Reasons for discontinuation in 1st month of treatment due to adverse events:

<table>
<thead>
<tr>
<th>Incidence Densities (Events/1000 patient-months)</th>
<th>Fluvoxamine</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>127.2</td>
<td>26.3</td>
<td>34.6</td>
<td>52.9</td>
</tr>
<tr>
<td>Malaise/lassitude</td>
<td>41.5</td>
<td>16.3</td>
<td>12.0</td>
<td>17.8</td>
</tr>
<tr>
<td>Drowsiness/sedation*</td>
<td>22.6</td>
<td>8.2</td>
<td>7.3</td>
<td>20.5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25.5</td>
<td>6.7</td>
<td>8.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Headache/migraine</td>
<td>25.1</td>
<td>13.5</td>
<td>13.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Tremor*</td>
<td>13.2</td>
<td>5.7</td>
<td>6.2</td>
<td>12.4</td>
</tr>
<tr>
<td>* (p &lt; 0.001 for fluoxetine and sertraline vs. fluvoxamine and paroxetine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Adverse Effects Reported:

<table>
<thead>
<tr>
<th>Incidence Densities (Events/1000 patient-months)</th>
<th>Fluvoxamine</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>42.8</td>
<td>9.0</td>
<td>8.6</td>
<td>13.0</td>
</tr>
<tr>
<td>Malaise/lassitude</td>
<td>15.2</td>
<td>5.5</td>
<td>3.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.6</td>
<td>2.7</td>
<td>2.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Headache/migraine</td>
<td>10.1</td>
<td>5.7</td>
<td>5.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Mean</td>
<td>17.6</td>
<td>7.0</td>
<td>6.2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

- No statistical differences in onset of mania or hypomania with any of the SSRIs
- No serious cardiac events with any of the SSRIs
- No deaths attributed to SSRIs. No difference in the number of suicides with each of the four SSRIs (approx 0.2-0.3% in each arm)
### RESULTS:

**SSRIs and nefazodone:**
- Most frequent events for all 5 drugs in the first month of treatment: venlafaxine had the highest rate of occurrence per 1,000 patient months: 71.9, fluoxetine: 26.3, sertraline: 34.6, paroxetine: 52.9, nefazodone: 46.1
- Sertraline and fluoxetine had a significantly lower rate ratio of agitation and anxiety than the remaining drugs
- Drowsiness and sedation were reported most frequently with nefazodone and paroxetine
- Male sexual dysfunction was most frequent with paroxetine and venlafaxine: rate ratios: fluoxetine: 1.0, sertraline: 3.1 (0.9 - 10.9), paroxetine: 11.1 (3.5 - 35.8), venlafaxine: 5.8 (1.9 - 19.3), nefazodone: 2.0 (0.6 - 7.5)
- There were more reports of mania during 90 days with fluoxetine than with the other drugs
- There was no significant difference in deaths between drugs

### ANALYSIS:

**ITT:** N/A  
**Post randomization exclusions:** N/A

### ATTRITION:

**Loss to follow-up:** N/A  
**Completion rates of surveys:** 60%  
**Withdrawals due to adverse events:** N/A  
**Loss to follow-up differential high:** N/A

### ADVERSE EVENTS:

N/A

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Maina G, et al.¹³²  
|                   | Year: 2004  
|                   | Country: Italy |
| **FUNDING:**      | None |
| **DESIGN:**       | Study design: Non-randomized, open-label trial  
|                   | Setting: Single center (Department of Neuroscience, University of Turin)  
|                   | Sample size: 149 started trial |
| **INTERVENTION:** | Drug: Clomipramine  
|                   | Dose: 150-250 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 23 |
|                   | Citalopram  
|                   | Dose: 40-80 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 21 |
|                   | Fluoxetine  
|                   | Dose: 40-80 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 23 |
|                   | Paroxetine  
|                   | Dose: 40-80 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 21 |
|                   | Fluvoxamine  
|                   | Dose: 200-300 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 28 |
|                   | Sertraline  
|                   | Dose: 150-200 mg/d  
|                   | Duration: 2.5 years  
|                   | Sample size: 22 |
| **INCLUSION:**    | Patients 18 years of age or older; Met DSM-IV criteria for OCD based on the Structured Clinical Interview;  
|                   | YBOCS score greater than or equal to 16; completed 6 month acute treatment phase of trial; gave informed consent |
| **EXCLUSION:**    | Pregnant; lactating; current or past diagnosis of eating disorder, schizophrenia, or other psychotic disorders; organic mental disorder; medical illness; met diagnostic criteria for a major depressive episode; had a HAM-D17 score greater than or equal to 15 |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
|                   | Mean age: 34.9 years  
|                   | Gender: 51% female  
|                   | Ethnicity: NR  
|                   | Other population characteristics:  
|                   | • Mean duration of illness: 12.1 years |
Authors: Maina G, et al.  
Year: 2004  
Country: Italy

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Percentage weight gain  
Secondary Outcome Measures: Number of patients with extreme weight gain  
Timing of assessments: Weight recorded at the beginning of treatment and at six months intervals thereafter. |
|---|---|

**RESULTS:**
- An ANOVA analysis showed significant between group differences in weight gain (p = 0.009). Clomipramine had the highest increase in weight and fluoxetine and sertraline had the lowest increase in weight.
- Clomipramine (+2.6 kg; p < 0.001), citalopram (+1.5kg; p = 0.002), paroxetine (+1.7kg; p = 0.001), fluvoxamine (+1.7kg; p < 0.001), and sertraline (+ 1.0kg; p = 0.01) showed significant increases in weight from baseline. No significant increase in weight was observed in the fluoxetine group (+0.5kg; p = NR).
- Patients with significant weight gain (≥ 7%): clomipramine 34.8%; citalopram 14.3%; paroxetine 14.3%; fluvoxamine 14.3%; fluoxetine 10.7%; sertraline 4.5%; fluoxetine 8.7%

**ANALYSIS:**
- ITT: No
- Post randomization exclusions: N/A: above results are reported only for patients who completed the 2 year extension phase of the trial

**ATTRITION:**
- Loss to follow-up: 7%
- Withdrawals due to adverse events: NR
- Loss to follow-up differential high: NR

**ADVERSE EVENTS:**
- NR

**QUALITY RATING:**
- Fair
<table>
<thead>
<tr>
<th><strong>Evidence Table 12</strong></th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Martinez C, et al.\(^{193}\)  
Year: 2005  
Country: UK |
| **FUNDING:** | Medicines and Healthcare products Regulatory Agency |
| **DESIGN:** | Study design: Case control study  
Setting: General Practice Research Database (clinical primary care records in the UK)  
Sample size: 146,095 |
| **INTERVENTION:** | Cases (suicide and non-fatal self-harm)  
Controls  
| Drug: | SSRIs/TCAs  
NR  
| Dose: | NR  
| Duration: | 1995-2001  
2037 (69/1968) |
35,615 |
| **INCLUSION:** | Individuals 90 years or younger with a first prescription for antidepressants between January 1, 1995 and December 31, 2001 entered in the General Practice Research Database; diagnosed with depression |
| **EXCLUSION:** | None |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 31% of patients were in the age cohort 31-45 years old  
Gender: 65% female  
Ethnicity: NR  
Other population characteristics:  
• History of self harm: <1 % patients |
**Authors:** Martinez C, et al.  
**Year:** 2005  
**Country:** UK

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Risk of non-fatal self harm and completed suicide  
**Secondary Outcome Measures:** none  
**Timing of assessments:** N/A

### RESULTS:

- No difference in risk of non-fatal self harm among the different SSRIs (p =0.35). The greatest risk of self harm was found in patients taking paroxetine.
- No difference in the risk of self-harm between SSRIs and TCAs (OR: 0.99 CI: 0.86 to 1.14).
- Significantly higher risk of self-harm among SSRI patients younger than 18 years compared to those on TCAs (OR 1.59; 95% CI 1.01-2.50). Among SSRIs, the greatest risk of self harm was found in patients taking paroxetine.
- No difference in the risk of suicide between SSRIs and TCAs (OR: 0.57 CI: 0.26 to 1.25).

### ANALYSIS:

**ITT:** N/A  
**Post randomization exclusions:** N/A

### ATTRITION:

**Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Loss to follow-up differential high:** N/A

### ADVERSE EVENTS:

N/A

### QUALITY RATING:

Good
## Evidence Table 12  
### Adverse Events

| STUDY: | Authors: Meijer WE, et. al.  
Year: 2002  
Country: The Netherlands |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational study of adverse effects  
Setting: Multi-center (109 psychiatrists)  
Sample size: 1,251 |
| INTERVENTION: | Drug: Observed: Sertraline or fluoxetine, fluvoxamine, or paroxetine  
Dose: Any administered dose  
Duration: 12 month observation period |
| INCLUSION: | All patients with a new sertraline prescription; patients taking fluoxetine, fluvoxamine, or paroxetine were used as controls |
| EXCLUSION: | None reported |
| ALLOWED OTHER MEDICATIONS/INTERVENTIONS: | None reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: N/A  
Mean age: 41  
Gender (% female): 64.1%  
Ethnicity: Not reported  
Other population characteristics: Significantly more sertraline patients had a diagnosis of depressive disorder than patients on other SSRIs (p < 0.001); anxiety disorder was significantly less in sertraline patients than patients with other SSRIs (p < 0.001); MDD: 77.9%, anxiety: 15.5%, multiple diagnoses: 37.8%. |
<table>
<thead>
<tr>
<th>Authors: Meijer WE, et al.</th>
<th>Year: 2002</th>
</tr>
</thead>
</table>

**OUTCOME ASSESSMENT:**

*Measures:* Physicians recorded adverse events at each patient visit, used WHO coding; serious adverse events (SAEs) recorded according to the International Conference on Harmonization of Good Clinical Practice (ICH-CGP)

*Timing of assessments:* Not reported

**RESULTS:**

- 2.2 adverse events per sertraline patient
- 2.1 adverse events per SSRI patient
- 73.4% of sertraline patients and 75.0% of other SSRI patients reported an adverse event
- Diarrhea was reported more frequently by sertraline patients than patients taking other SSRIs (p < 0.05)
- Abdominal pain was reported more frequently by other SSRI users (p < 0.05)
- Nausea: sertraline: 24.3%, SSRI: 27%
- Headache: sertraline: 19.3%, SSRI: 17.1%

**ANALYSIS:**

*ITT:* N/A

*Post randomization exclusions:* N/A

**ATTRITION:**

*Loss to follow-up:* N/A

*Withdrawals due to adverse events:* N/A

*Loss to follow-up differential high:* N/A

**ADVERSE EVENTS:**

N/A

**QUALITY RATING:**

Fair
### Evidence Table 12: Adverse Events

| STUDY: | Authors: Montejo et al.  
Year: 2001  
Country: Spain |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Bristol-Myers Squibb</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational  
Setting: Multi-center  
Sample size: 1022 |
| INTERVENTION: | |
| Drug: | |
| Dose (mean): |  
Sample size: |
| Duration: | fluoxetine  
24.5 mg  
NR  
279  
paroxetine  
23.4 mg  
NR  
208  
fluvoxamine  
115.7 mg  
NR  
77  
sertraline  
90.4 mg  
NR  
159  
citalopram  
28.7 mg  
NR  
66  
venlafaxine  
159.5 mg  
NR  
55  
mirtazapine  
37.7 mg  
NR  
49  
nefazodone  
324.6 mg  
NR  
50 |
| INCLUSION: | Normal sexual functioning prior to taking antidepressants; treatment with an antidepressant alone or in combination with a benzodiazepine; previous regular and satisfactory sexual practices; occurrence of sexual dysfunction within the two months after introduction of an antidepressant |
| EXCLUSION: | Prior sexual dysfunction; combination of antidepressant and neuroleptic treatment; treatment with hormones or any other drug capable of interfering with sexual intercourse; significant intercurrent diseases affecting sexual function; substance abuse |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: NR  
Mean age: Overall: 39.8  
Gender (% female): Overall: 60%  
Ethnicity: NR  
Other population characteristics: MDD: 60.1%; dysthymic disorder: 17.3%; panic disorder: 12.1%; OCD: 5.9%; other disorders: 3.7% |
<table>
<thead>
<tr>
<th>Authors: Montejo et al.</th>
<th>Year: 2001</th>
<th>Country: Spain</th>
</tr>
</thead>
</table>

**OUTCOME ASSESSMENT:**

- **Primary Outcome Measures:** PRSexDQ (Psychotropic-Related Sexual Dysfunction Questionnaire)
- **Secondary Outcome Measures:** None
- **Timing of assessments:** Each clinic visit

**RESULTS:**

- Overall incidence of sexual dysfunction was 59.1% (604/1022) when all antidepressants were considered as a whole
- There were relevant differences when the incidence of any type of sexual dysfunction was compared among different drugs: fluoxetine: 57.7%; sertraline: 62.9%; fluvoxamine: 62.3%; paroxetine: 70.7%; citalopram: 72.7%; venlafaxine: 67.3%; mirtazapine: 24.4%; nefazodone: 8%
- Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity

**ANALYSIS:**

- **ITT:** N/A
- **Post randomization exclusions:** N/A

**ATTRITION:**

- **Loss to follow-up:** N/A
- **Withdrawals due to adverse events:** N/A
- **Withdrawals due to lack of efficacy:** N/A
- **Loss to follow-up differential high:** N/A

**ADVERSE EVENTS:**

- N/A

**QUALITY RATING:**

- Fair
## Evidence Table 12  
### Adverse Events

Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly Inc</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 684 (114 for Clayton subanalysis of CSFQ) |
| INTERVENTION: Drug: Duloxetine  
Dose: 60 mg  
Duration: 8 weeks and 8 months  
Sample size: 273 |  
Escitalopram  
Dose: 10 mg  
Duration: 8 weeks and 8 months  
Sample size: 274 |  
Placebo  
Dose: NA  
Duration: 8 weeks and 8 months  
Sample size: 137 |
| INCLUSION: | 18 years old; diagnosed with MDD; MADRS > 22 and CGI-S > 4; normal or clinically unremarkable exam, lab and ECG |
| EXCLUSION: | Pregnant, lactation; primary Axis 1 disorder other than MDD; previous diagnosis bipolar, schizophrenia or other psychotic disorders or Axis 2 disorder that might interfere; significant risk of suicide; substance dependence; treatment resistant; ECT. |
| OTHER MEDICATIONS/INTERVENTIONS: | Chronic use of certain prescriptions such as ACE inhibitors, alpha and beta blockers, anti-arrhythmics, and calcium channel blockers if on stable dose for at least 3 months |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No  
Mean age: Duloxetine 41.1 escitalopram 43.3 placebo 42.5  
Gender (female %): overall 65.2% duloxetine 63.4% escitalopram 67.9% placebo 63.5%  
Ethnicity: Overall 77.6% Caucasian Duloxetine 75.5% escitalopram 77.4% placebo 82.5%  
Other population characteristics: Mean HAM-D Duloxetine 17.6 escitalopram 17.8 placebo 17.7 |
Authors: Nierenberg, Pigott and Clayton  
Year: 2007  
Country: USA

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Onset of efficacy HAM-D at 8 months and CSFQ  
Secondary Outcome Measures: HAM-D, HAM-A, CGI-S  
Timing of assessments: Baseline, weeks 1,2,3,4,6,8 |
|-------------------|------------------------------------------------|

RESULTS:
- Mean change Duloxetine vs. escitalopram v. placebo 8 weeks and 8 months
- HAM-D -7.61 (0.42) vs. -7.22 (0.40) vs. -5.97 (0.58) P < 0.05 Duloxetine vs. placebo and -10.55 (0.48) vs. -10.91 (0.45) vs. -8.06 (1.13)
- CGI-S -1.44 (0.08) vs. 1.36(0.07) vs. -1.08 (0.11) P < 0.01 Duloxetine vs. placebo and P < 0.05 Escitalopram vs. placebo and -2.17 ((0.09) vs. -2.20 (0.09) vs. -2.11 (0.22)
- HAM-A -5.49 (0.36)) vs. -5.16 (0.34) vs. -4.32 (0.50) and -7.30 (0.44) vs. -7.92 (0.41) vs. -5.73 (1.03)
- Response HAM-D 48.7% vs. 45.3% vs. 36.9%
- Remission HAM-D 37% vs. 32% vs. 70% vs. 75% vs. NR
- 8 week incidence of treatment-emergent sexual dysfunction duloxetine 17/51 (33.3%) escitalopram; 19/39 (48.7%) placebo 4/24 (16.7%) (P = 0.01 escitalopram vs. placebo; P = 0.13 duloxetine vs. placebo) and at 8 months duloxetine 33.3% escitalopram 43.6% placebo 25%

ANALYSIS: ITT: Yes  
Post randomization exclusions:

ATTRITION:  
Loss to follow-up: Duloxetine 85, escitalopram 66, placebo 40  
Withdrawals due to adverse events: Duloxetine 20, escitalopram 14, placebo 8  
Withdrawals due to lack of efficacy: Duloxetine 9, escitalopram 4, placebo 7  
Loss to follow-up differential high: No

ADVERSE EVENTS:  
- Duloxetine vs. escitalopram v. placebo (%) 8 weeks and 8 months  
- Nausea 23.8* ** vs. 12.0 vs. 8.8 and 29.3* vs. 14.2 vs. 10.2  
- Dry mouth 21.6* ** vs. 10.9 vs. 10.9 and 24.2* ** vs. 11.7 vs. 11.7  
- Headache 19.4 vs. 20.1 vs. 14.6 and 25.6* vs. 23.7 vs. 16.1  
- Diarrhea 11.7 vs. 12.0 vs. 8.0 and 13.2 vs. 17.5* vs. 9.5  
- Dizziness 9.5 vs. 7.3 vs. 5.1 and 12.5 vs. 11.7 vs. 7.3  
- Constipation 8.4 vs. 5.8 vs. 11.0 vs. 8.4 vs. 6.6  
- Decreased appetite 8.1* vs. 4.7 vs. 2.2 and 8.1* vs. 5.1 vs. 2.2  
- Insomnia 8.1 vs. 7.7 vs. 6.6  
- Hyperhidrosis* 7.7 vs. 4.0 vs. 0.7 and 9.9* vs. 5.5 vs. 1.5  
- Vomiting 7.3* ** vs. 2.2 vs. 0.7 and 9.2* ** vs. 3.6 vs. 1.5  
- Somnolence 5.9 vs. 6.6 vs. 3.6 and 7.3 vs. 7.3 vs. 4.4  
- Nasopharyngitis 5.5 vs. 6.6 vs. 6.6 and 8.4 vs. 10.9 vs. 8.0  
- Yawning 5.5* ** vs. 2.2 vs. 0 and 5.9* ** vs. 2.2 vs. 0  
- Decreased libido 5.1 vs. 4.0 vs. 2.2 and 6.6 vs. 6.6 vs. 2.9  
- Fatigue 5.1 vs. 6.2 vs. 8.0 and 8.1 vs. 9.9 vs. 8.8  
- Anxiety 4.4 vs. 2.9 vs. 5.8 and 5.3 vs. 3.6 vs. 5.8
<table>
<thead>
<tr>
<th>Condition</th>
<th>Comparison</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>NR and 5.5 vs. 5.5 vs. 3.6</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>NR and 5.9 vs. 4.7 vs. 4.4</td>
<td></td>
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<tr>
<td>Anthralgia</td>
<td>NR and 4.0 vs. 5.1 vs. 3.6</td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>NR and 5.9 vs. 3.3 vs. 2.2</td>
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</tr>
<tr>
<td>Anorgasmia</td>
<td>NR and 4.8* vs. 4.0 vs. 0</td>
<td>* P &lt; 0.05 vs. placebo</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>NR and 3.7 vs. 4.7* vs. 0.7</td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>NR and 2.6 vs. 5.5* vs. 0</td>
<td>** P &lt; 0.05 duloxetine vs. escitalopram</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>NR and 4.8* vs. 1.8 vs. 0.7</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>NR and 4.0* vs. 1.8 vs. 0</td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td>NR and 3.7** vs. 0 vs. 0.7</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>NR and 0.4 vs. 2.9** vs. 0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* P &lt; 0.05 vs. placebo and ** P &lt; 0.05 duloxetine vs. escitalopram</td>
<td></td>
</tr>
</tbody>
</table>

**QUALITY RATING:** Fair
## Evidence Table 12  Adverse Events

| STUDY: | Authors: Nieuwstraten C, et al.  
Year: 2001  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1332 |
| AIMS OF REVIEW: | To assess the benefits and risks of bupropion vs. SSRIs in major depression |
| TIME PERIOD COVERED: | 1966-1999 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs, study durations: 6-16 weeks, median 7 weeks |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8% |
**Authors** Nieuwstraten C, et al.  
**Year:** 2001  
**Country:** Canada

| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Bupropion vs. sertraline (3 trials), bupropion vs. paroxetine (1 trial), bupropion vs. fluoxetine (1 trial) |
| MAIN RESULTS: | Results of HAM-D scores and CGI-I scores could not be pooled due to the unavailability of data; the weighted mean differences of CGI-S and HAM-A scores were not significantly different between bupropion and SSRIs |
| ADVERSE EVENTS: | Nausea, diarrhea, and somnolence occurred significantly less frequently in the bupropion group compared to the 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 significantly less in the SSRI group RR: 1.28 (95%CI: 1.16-1.41) |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Pedersen AG\textsuperscript{156}  
Year: 2005  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>H. Lundbeck A/S</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Retrospective cohort study  
Setting: Clinical trials  
Sample size: 4,091 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration:  
Sample size:  
Placebo  
5-20 mg/day  
8-24 weeks  
2648  
N/A  
8-24 weeks  
1443 |
| INCLUSION: | Adult outpatients with MDD (2277) or anxiety (371) |
| EXCLUSION: | NR |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: NR  
Mean age: NR  
Gender (% female): NR  
Ethnicity: NR  
Other population characteristics: NR |
| Authors: Pederson AG  
Year: 2005  
Country: Multinational | **Primary Outcome Measures:** Rates of suicide and self-harm  
**Secondary Outcome Measures:**  
**Timing of assessments:** N/A |
|---|---|
| **OUTCOME ASSESSMENT:** | **RESULTS:**  
- MADRS item 10 (suicidal thoughts) escitalopram patients had less suicidal thoughts than placebo from weeks 1 (p < 0.05) to 8 (p < 0.001).  
- Suicides in placebo-controlled studies escitalopram n- 0 rate- 0 incidence- 0 Placebo n-1 rate-0.003 incidence- 0.1  
- Non-fatal self harm in placebo-controlled studies: escitalopram n- 5 rate- 0.011 incidence- 0.2 Placebo n-1 rate-0.003 incidence- 0.1 |
| **ANALYSIS:** | **ITT:** N/A  
**Post randomization exclusions:** N/A |
| **ATTRITION:** | **Overall**  
**Loss to follow-up:** NR  
**Withdrawals due to adverse events:** NR  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** Not enough information |
<p>| <strong>ADVERSE EVENTS:</strong> | <strong>N/A</strong> |
| <strong>QUALITY RATING:</strong> | <strong>Fair</strong> |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Schneider LS et al.\(^{197}\) and Nelson JC et al.\(^{198}\)  
                   Year: 2003 and 2007  
                   Country: USA |
| **FUNDING:**      | Pfizer |
| **DESIGN:**       | Study design: RCT  
                   Setting: Multicenter  
                   Sample size: 752 |
| **INTERVENTION:** |               |
| Drug:             | Sertraline  
                   50-100 mg  
                   8 weeks  
                   360 |
| Placebo:          | NA  
                   8 weeks  
                   368 |
| **Sample size:**  |               |
| **INCLUSION:**    | 60 years of age and older with major depression, nonpsychotic, single episode and recurrent, with a duration of at least four weeks and a HAMD score > 18 |
| **EXCLUSION:**    | Depressive disorder with psychotic features, dementia, organic mental disorder, or mental retardation; a score < 24 on the MMSE; any psychotic disorder or bipolar disorder; drug or alcohol abuse or dependence within the previous 6 months (except nicotine); a history of seizure disorder; previous nonresponse, known hypersensitivity, or contraindication to sertraline; participation in an investigational drug trial within 3 months; significant suicide risk, a need for ECT, additional psychotropic drugs, or hospitalization; regular, daily use of benzodiazepines within 3 weeks, antidepressants within 2 weeks, use MAOIs or fluoxetine within 5 weeks; depot antipsychotic drug within 6 months; initiation of individual or group psychotherapy within 3 months; and any clinically significant unstable medical disorder that might affect study participation |
| **OTHER MEDICATIONS/INTERVENTIONS:** | As-needed use of zolpidem, up to 10 mg/day, or temazepam, up to 30 mg/day, for sleep during the first 4 weeks; drugs used as anti-inflammatories or in rheumatic disease and gout (40%), antihypertensive drugs (27%), hormone replacement therapy (41% of women), drugs for hyperlipidemia (14%), thyroid and antithyroid drugs (12%), ulcer-healing drugs (11%), ß-adrenergic antagonists (11%), drugs for diabetes (7%), hypnotics and sedatives (6%), bronchodilators (5%), and corticosteroids (4%). Overall, 87% took concomitant medication. |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Sertraline 70.0 Placebo 69.6  
Gender (female %): Sertraline 54 Placebo 58  
Ethnicity: 93% caucasian  
Other population characteristics: HAMD Sertraline 21.4 Placebo 21.4 |
<table>
<thead>
<tr>
<th>Authors: Schneider et al.; Nelson et al.</th>
<th>Year: 2003; 2007</th>
</tr>
</thead>
</table>

### OUTCOME ASSESSMENT:  
**Primary Outcome Measures:** Clinical response and suicide ideation  
**Secondary Outcome Measures:** Hamilton scale subscales, Patient Global Impression, Quality of Life Enjoyment and Satisfaction Questionnaire, MMSE, and 36-Item Short-Form Health Survey subscales  
**Timing of assessments:** Baseline and weekly

### RESULTS:  
- HAMD response 35% for sertraline and 26% for placebo  
- CGI-S response sertraline 45% vs. placebo 35%  
- Change in HAMD sertraline -7.4 placebo -6.6  
- HAMD Item 3 ratings progressively declined during the trial with significantly lower values for sertraline than placebo (Z=2.41, p < 0.02).  
- In 248 patients with HAMD Item 3 of zero at baseline, the percentage of patients whose Item 3 ratings increased during treatment did not differ in the two groups sertraline 22.4% versus placebo 25.8%

### ANALYSIS:  
**ITT:** Yes  
**Post randomization exclusions:** 19  
**Loss to follow-up differential high:** no

### ATTRITION:  
<table>
<thead>
<tr>
<th>Sertraline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>87 (23%)</td>
<td>65 (17%)</td>
</tr>
<tr>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:  
- Diarrhea 19% vs. 7% P < 0.05  
- Headache 17% vs. 13% P < 0.05  
- Nausea 16% vs. 5% P < 0.05  
- Somnolence 10% vs. 4% P < 0.05  
- Insomnia 9% vs. 6% P < 0.05  
- Dry mouth 8% vs. 6%  
- Dizziness 8% vs. 7%  
- Tremor 6% vs. <1% P < 0.05  
- Fatigue 5% vs. 1% P < 0.05

### QUALITY RATING:  
Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Rapaport ME, et. al.¹⁶  
Year: 1996  
Country: US |
| **FUNDING:** | Solvay Pharmaceuticals, Upjohn |
| **DESIGN:** | Study design: RCT  
Setting: Multi-center (6 sites)  
Sample size: 100 |
| **INTERVENTION:** | Drug:  
Fluvoxamine  
100-150 mg/d  
7 weeks  
Fluoxetine  
20-80 mg/d  
7 weeks |
| **INCLUSION:** | Male and female outpatients; 18-65 years; met DSM-III-R criteria for MDD; minimum HAM-D (21-item) score of 20; minimum score of 2 on the depressed mood item |
| **EXCLUSION:** | Any primary DSM-IV Axis I disorder diagnosis other than MDD; acute suicidality; unstable medical conditions; history of seizure; had been treated with study medications; history of substance abuse or dependence; pregnancy and lack of appropriate birth control for women of child-bearing age |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: fluoxetine: 38.6; fluvoxamine: 40.0  
Gender (% female): fluoxetine: 63; fluvoxamine: 61  
Ethnicity: 95% white; 5% other  
Other population characteristics: NR |
| Authors: Rapaport ME, et al.  |
| Year: 1996  |
| Country: US  |

**OUTCOME ASSESSMENT:**

*Measures:* HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation

*Timing of assessments:* Primary outcome measures weekly; secondary outcome measures at baseline and endpoint

**RESULTS:**

- No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures
- Both drugs significantly improved scores on HAM-D ( <10 for both groups at endpoint)

**ANALYSIS:**

*ITT:* Yes

*Post randomization exclusions:* Yes (7)

**ATTRITION:**

*Loss to follow-up:* 11%

*Withdrawals due to adverse events:* 4%

*Loss to follow-up differential high:* No

**ADVERSE EVENTS:**

- Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR)
- Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03)
- Other frequent adverse events:
  - headache: fluoxetine 53%, fluvoxamine 50% (p not significant)
  - vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant)
  - daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant)

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Raskin et al.\textsuperscript{199}  
Year: 2008  
Country: US |
| **FUNDING:** | |
| **DESIGN:** | Study design: RCT  
Setting: Multicenter  
Sample size: 311 |
| **INTERVENTION:** | | |
| Drug: | Duloxetine | Placebo |
| Dose: | 60 mg/d | N/A |
| Duration: | 8 weeks | 8 weeks |
| Sample size: | 207 | 104 |
| **INCLUSION:** | 65 or older; met DSM-IV criteria for MDD; HAM-D-17 total score ≥ 18 at visits 1 and 2, MMSE score ≥ 20 with or without mild dementia; at least one previous MDD episode |
| **EXCLUSION:** | Current primary axis I diagnosis other than MDD or mild dementia (including dysthymia or psychotic depression); previous diagnosis of psychotic disorder; organic mental disorder, moderate to severe dementia, or mental retardation diagnosis; serious or unstable medical illness |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Acetylsalicyclic acid, levolthyroxine sodium, vitamins, tocopherol, paracetamol were among the most common concomitant medications used by patients in both groups. At least 1 concomitant medication used by 94.2% of duloxetine and 95.2% of placebo patients |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: duloxetine 72.6, placebo 73.3  
Gender (female %): duloxetine 60.4, placebo 57.7  
Ethnicity: duloxetine: 77.8% white, 15.0% Hispanic 6.3% African descent; placebo: 78.8% white, 16.3% Hispanic, 3.8% African descent  
Other population characteristics: |
**Authors:** Raskin et al.  
**Year:** 2008  
**Country:** US

### OUTCOME ASSESSMENT:

- **Primary Outcome Measures:** composite cognitive score based on (1) Verbal Learning and Recall Test, (2) Symbol Digit Substitution Test, (3) 2-Digit Cancellation Test, and (4) Letter-Number Sequencing Test
- **Secondary Outcome Measures:** Geriatric Depression Scale, HAM-D-17, CGI-S
- **Timing of assessments:** Safety measures recorded at each visit

### RESULTS:

- No significant differences in changes in standing and supine BP and pulse
- Statistically significant decrease in change in orthostatic systolic BP for duloxetine vs. placebo (-2.45 vs. 0.93 mm HG; p = 0.017)
- No significant differences in mean changes of QTcB or QTcF between groups
- Significantly greater mean decrease in weight for duloxetine (-0.73 vs. -0.13 kg; p = 0.009)

### ANALYSIS:

- **ITT:** Yes
- **Post randomization exclusions:** No

### ATTRITION:

- **Loss to follow-up:** duloxetine 21.7%, placebo 23.1%; p = 0.775
- **Withdrawals due to adverse events:** duloxetine 9.7%, placebo 8.7%; p = 0.839
- **Withdrawals due to lack of efficacy:** duloxetine 2.9%, placebo 9.6%; p = 0.026
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- **TEAEs (duloxetine vs. placebo)**
  - Any: 70.0% vs. 64.4%, p = 0.367
  - Dry mouth: 14.5% vs. 1.9%, p < 0.001
  - Nausea: 12.6% vs. 3.8%, p = 0.014
  - Constipation: 10.1% vs. 4.8%, p = 0.131
  - Dizziness: 8.2% vs. 2.9%, p = 0.087
  - Diarrhea: 8.2% vs. 1.9%, p = 0.042
  - Fatigue: 6.3% vs. 2.9%, p = 0.279
  - Somnolence: 5.3% vs. 1.0%, p = 0.067

### QUALITY RATING:

- **Fair**
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | *Authors:* Schatzberg et al.73  
*Year:* 2002  
*Country:* US |
| **FUNDING:**      | Organon Pharma |
| **DESIGN:**       | *Study design:* RCT  
*Setting:* Multi-center  
*Sample size:* 255 |
| **INTERVENTION:** | Mirtazapine  
*Dose:* 15-45 mg/d  
*Duration:* 8 weeks  
Paroxetine  
*Dose:* 20-40 mg/d  
*Duration:* 8 weeks  
(There was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study) |
<p>| <strong>INCLUSION:</strong>    | Min. age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score &gt; 25% for age and education; min. score of 18 on HAM-D17 |
| <strong>EXCLUSION:</strong>    | HAMD decrease &gt; 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psych condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazapine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode |
| <strong>OTHER MEDICATIONS/INTERVENTIONS:</strong> | Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit. |
|----------------------------|------------|-------------|
| <strong>POPULATION CHARACTERISTICS:</strong> | | |
| Groups similar at baseline: Yes | Mean age: 72 | |
| Gender (% female): Mirtazapine: 63%, paroxetine: 64% | Ethnicity: Not reported | |
| Other population characteristics: Not reported | | |
| <strong>OUTCOME ASSESSMENT:</strong> | Measures: HAM-D-17, CGI-S, CGI-I | Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, 8 |
| <strong>RESULTS:</strong> | | |
| Mean Ham-D-17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint | Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission) | Time to response: mirtazapine mean 26 days, paroxetine 40 days; p = -0.016 for Kaplan-Meier plot comparing the two |
| No difference in CGI Improvement response | | |
| <strong>ANALYSIS:</strong> | ITT: Yes | Post randomization exclusions: Yes |
| <strong>ATTRITION:</strong> | Loss to follow-up: 26.8% | |
| Withdrawals due to adverse events: 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p &lt; 0.05) | Loss to follow-up differential high: No |
| <strong>ADVERSE EVENTS:</strong> | | |
| Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5% | Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0% |
| <strong>QUALITY RATING:</strong> | | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12 Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING: Glaxo Wellcome Inc</td>
</tr>
<tr>
<td>DESIGN: Study design: RCT Setting: Multi-center Sample size: 248</td>
</tr>
<tr>
<td>INTERVENTION:</td>
</tr>
<tr>
<td>Drug:</td>
</tr>
<tr>
<td>Dose: Sertraline 50-200 mg/d 16 weeks</td>
</tr>
<tr>
<td>Bupropion 100-300 mg/d 16 weeks</td>
</tr>
<tr>
<td>Duration:</td>
</tr>
<tr>
<td>INCLUSION: Received a DSM-IV diagnosis of moderate to severe depression with a minimum duration of 4 weeks and a maximum duration of 24 months; ≥ 18 years of age; in a stable relationship, have normal sexual functioning and sexual activity at least once every 2 weeks</td>
</tr>
<tr>
<td>EXCLUSION: Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS: None reported</td>
</tr>
</tbody>
</table>
### Authors: Segraves et al.
**Year:** 2000  
**Country:** US

### POPULATION CHARACTERISTICS:
- **Groups similar at baseline:** Yes
- **Mean age:** 39
- **Gender** (% female): Sertraline: 48%, bupropion: 48%
- **Ethnicity** (% white): Sertraline: 94%, bupropion: 93%
- **Other population characteristics:** No significant differences in diagnosis

### OUTCOME ASSESSMENT:
- **Measures:** Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation, patient rated overall sexual satisfaction on 6-point Likert scale
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16

### RESULTS:
- Significantly more sertraline patients developed a sexual dysfunction compared to bupropion patients; p < 0.001 for men and women; p < 0.05 for sexual desire disorder
- Overall sexual satisfaction (patient-rated) significantly more improved in bupropion treated patients. Men (p < 0.05) significant difference at day 21, 28, 42, and 56. Women (p < 0.01) beginning at day 56 and continuing to end

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 31.5%; bupropion: 29%, sertraline: 34%
- **Withdrawals due to adverse events:** 1.6%; bupropion 0%, sertraline 1.6%
- **Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:
- Not reported

### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Thase ME&lt;br&gt;Year: 1998&lt;br&gt;Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth-Ayerst Labs; National Institute of Mental Health</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: Meta-analysis&lt;br&gt;Number of patients: 3744</td>
</tr>
<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
<td>To assess the effects of venlafaxine on blood pressure</td>
</tr>
<tr>
<td><strong>STUDIES INCLUDED IN META-ANALYSIS</strong></td>
<td>Original data for the statistical analysis were provided by Wyeth-Ayerst Laboratories.</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
<td>Acute and continuation phase data from randomized controlled trials comparing venlafaxine with placebo and imipramine. (21 outpatient and 6 inpatient trials at 180 different sites)</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
<td>Meet DSM-III-R criteria for a current principal diagnosis of major depression; score at least 20 on the 21-item HAM-D; have no poorly controlled or serious medical illness</td>
</tr>
</tbody>
</table>
**Authors:** Thase  
**Year:** 1998  
**Country:** US

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>Venlafaxine, imipramine, placebo</th>
</tr>
</thead>
</table>

**MAIN RESULTS:**

- **Acute phase results at 6 weeks:**
  - Mean supine DBP: venlafaxine: 78 mmHg, imipramine: 78 mmHg, placebo: 75 mmHg (p < 0.001)
  - Mean increase in supine DBP: venlafaxine 1.02 mmHg.
  - Sustained elevation in supine DBP: venlafaxine: 4.8%, imipramine 4.7%, 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: venlafaxine: 11.5%, imipramine 7.9%, placebo 5.7% (p < 0.001 venlafaxine vs imipramine and venlafaxine vs placebo, p = 0.24 for imipramine vs placebo)

Continuation Phase Results:

- Mean supine DBP: no drug effect p = 0.58 (actual values not reported)
- 4.5% (21 of 467) of subjects with normal supine DBPs developed elevated readings during this phase and it was significantly higher in the venlafaxine group p = 0.058 (actual numbers not reported)
- A significant dose response effect on BP was seen in the venlafaxine group (p < 0.001)

**ADVERSE EVENTS:**

N/A

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**

No

**STANDARD METHOD OF APPRAISAL OF STUDIES:**

No

**QUALITY RATING:**

Fair
## Evidence Table 12  Adverse Events

| STUDY: | Authors: Thase ME, et al.\(^{201}\)  
Year: 2005  
Country: US and Europe |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly and Mental Health Intervention Center grant</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Post hoc analysis  
Setting: Multi-center  
Sample size: 1,568 |
| INTERVENTION: | **Drug:**  
**Dose:**  
**Duration:**  
**Sample size:** |
| | Duloxetine  
40 mg/d-120 mg/d  
8-9 weeks  
1139 |
| | Paroxetine  
20 mg/d  
8-9 weeks  
359 |
| | Fluoxetine  
20 mg/d  
8-9 weeks  
70 |
| INCLUSION: | 18 years of age or older; current primary MDD diagnosis as defined in DSM-IV; HAM-D score >15; CGI-S score >4 |
| EXCLUSION: | Serious or poorly controlled medical illness or condition |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** duloxetine: 42.7; paroxetine: 43.2; fluoxetine: 39.7  
**Gender (% female):** duloxetine: 66.8; paroxetine: 63.8; fluoxetine: 42  
**Ethnicity (%):** duloxetine: white: 89.2; black: 4.8; Hispanic: 4.3; Asian: 0.8; other: 0.8  
paroxetine: white: 89.1; black: 4.7; Hispanic: 5.0; Asian: 0.8; other: 0.3  
fluoxetine: white: 82.9; black: 10; Hispanic: 4.3; Asian: 0; other: 2.9  
**Other population characteristics:**  
**Supine BP systolic (mm Hg):** duloxetine: 121.8; paroxetine: 122.0; fluoxetine: 118.8  
**Supine BP diastolic (mm Hg):** duloxetine: 76.6; paroxetine: 76.4; fluoxetine: 75.1  
**Supine heart rate (bpm):** duloxetine: 73.0; paroxetine: 73.5; fluoxetine: 72.7 |
<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>PRIMARY OUTCOME MEASURES:</th>
<th>SUPINE BLOOD PRESSURE, HEART RATE AND ECG INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIMING OF ASSESSMENTS:</td>
<td>SUPINE BP AND HEART RATE AT EACH STUDY VISIT, ECG AT BASELINE AND LAST VISIT</td>
</tr>
</tbody>
</table>

| RESULTS:          | • GREATER CHANGE IN HEART RATE FOR DULOXETINE VS. FLUOXETINE AND PAROXETINE: MEAN CHANGE OF 2.8 BPM FOR DULOXETINE VS. -1.0 BPM FOR FLUOXETINE (P < 0.01); MEAN CHANGE OF 1.0 BPM FOR DULOXETINE VS. -1.4 BPM FOR PAROXETINE (P < 0.001) |
|                   | • DULOXETINE HAD SLIGHTLY LOWER MEAN CHANGE IN SYSTOLIC BP THAN FLUOXETINE (2.3 MM HG VS. 3.2 MM HG) |
|                   | • NO STATISTICALLY SIGNIFICANT DIFFERENCES IN SYSTOLIC AND DIASTOLIC BP FOR DULOXETINE VS. FLUOXETINE OR PAROXETINE |
|                   | • MEAN CHANGES IN QTcF AND QRS INTERVALS NOT SIGNIFICANTLY DIFFERENT FOR DULOXETINE VS. PAROXETINE |

| ANALYSIS:         | ITT: YES |
| POST RANDOMIZATION EXCLUSIONS: | AT LEAST 7 |

| ATTRITION:        | NR |
| POST RANDOMIZATION EXCLUSIONS: | |

| ADVERSE EVENTS:   | N/A |

| QUALITY RATING:   | N/A |
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Tiihonen et al. 2006  
Year: 2006  
Country: Finland |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>EVO financing (special government subsidies) from Niuvanniemi Hospital.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational cohort  
Setting: Nationwide  
Sample size: 15,390 |
| INTERVENTION: | Drug:  
Dose:  
Duration:  
Sample size: Various  
Various  
Mean follow-up 3.4 years  
15390 |
| INCLUSION: | All individuals in Finland who were hospitalized with a diagnosis of suicide attempt from January 1, 1997, to December 31, 2003 (the first hospital treatment period was considered as the index period), and were at least 10 years old when the index hospitalization began. |
| EXCLUSION: | Psychosis diagnosis |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: NA  
Mean age: 38.8  
Gender (female %): 51.5  
Ethnicity: NR  
Other population characteristics: |
### Authors: Tiihonen  
Year: 2007

#### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** relative risk (RR) of completed suicides, suicide attempts leading to hospitalization, and overall mortality during TCA (amitriptyline or doxepin hydrochloride), SSRI (fluoxetine, citalopram hydrobromide, paroxetine hydrochloride, sertraline, or fluvoxamine maleate), and SNA (mianserin hydrochloride, mirtazapine, or venlafaxine hydrochloride) treatment vs no antidepressant use  

**Secondary Outcome Measures:** NA  

**Timing of assessments:** various

#### RESULTS:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adjusted RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>0.52 (0.30-0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Citalopram hydrobromide</td>
<td>0.80 (0.54-1.19)</td>
<td>0.26</td>
</tr>
<tr>
<td>Paroxetine hydrochloride</td>
<td>0.90 (0.45-1.81)</td>
<td>0.78</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.82 (0.41-1.61)</td>
<td>0.56</td>
</tr>
<tr>
<td>Fluvoxamine maleate</td>
<td>0.95 (0.40-2.26)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.98 (0.68-1.41)</td>
<td>0.91</td>
</tr>
<tr>
<td>Venlafaxine hydrochloride</td>
<td>1.61 (1.01-2.57)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- **Suicide with medication as a time dependent variable**
  - Fluoxetine 1.54 (1.37-1.74) P < 0.001  
  - Citalopram hydrobromide 1.55 (1.38-1.74) P < 0.001  
  - Paroxetine hydrochloride 1.63 (1.33-1.99) P < 0.001  
  - Sertraline 1.41 (1.15-1.72) P = 0.002  
  - Fluvoxamine maleate 1.75 (1.38-2.22) P < 0.001  
  - SNAs 1.57 (1.42-1.73) P < 0.001  
  - Mirtazapine 1.50 (1.32-1.70) P < 0.001  
  - Venlafaxine hydrochloride 1.79 (1.52-2.11) P < 0.001

- **Suicide attempts with medication as a time dependent variable**
  - Fluoxetine 2.44 (1.54-3.86) P < 0.001  
  - Citalopram hydrobromide 2.27 (1.47-3.52) P < 0.001  
  - Paroxetine hydrochloride 2.32 (1.36-3.99) P = 0.002  
  - Sertraline 0.71 (0.29-1.80) P = 0.47  
  - Fluvoxamine maleate 0.82 (0.21-3.23) P = 0.78  
  - Mirtazapine 1.06 (0.56-2.01) P = 0.85  
  - Venlafaxine hydrochloride 2.65 (1.14-6.20) P = 0.02

#### ANÁLYSIS:

**ITT:** NA  
**Post randomization exclusions:** NA

#### ATTRITION:

N/A

#### ADVERSE EVENTS:

- See results

#### QUALITY RATING:

Fair
## Evidence Table 12: Adverse Events

| STUDY: | Authors: Valuck R et al.\(^{203}\)  
|        | Year: 2004  
|        | Country: USA |
| FUNDING: | Unfunded |
| DESIGN: | Study design: Retrospective cohort  
|        | Setting: Health Insurance database  
|        | Sample size: 24119 |
| INTERVENTION: Drug: | SSRIs-citalopram escitalopram fluoxetine fluvoxamine paroxetine, sertraline venlafaxine Various  
| Dose: | Mean 1.36 years  
| Duration: | 4595  
| Sample size: |  |
| INCLUSION: | Adolescents 12–18 years who received either a diagnosis of MDD or an antidepressant medication (or both) between January 1998 and March 2003. A retrospective cohort was created for adolescents with new starts of depression treatment |
| EXCLUSION: | Previous depression claims, antidepressant use or psychotherapy |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: | 12-6.3%, 13-8.7%, 14-11.8%, 15-16.0%, 16-19.8%, 17-20.6%, 18-16.0%  
| Gender (female %): | 63  
| Ethnicity: | NR  
| Other population characteristics: | |

---

Second generation antidepressants
<table>
<thead>
<tr>
<th>Authors: Valuck</th>
<th>Year: 2004</th>
<th>Country: US</th>
</tr>
</thead>
</table>

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>Suicide attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>Various</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Various</td>
</tr>
</tbody>
</table>

### RESULTS:

- Crude rates of Suicide attempt rate per person-month of follow-up (%): SSRI 0.13 Other 0.11 Multiple 0.11 None 0.07 Total 0.09
- Results from cox proportionate model shows that the hazard ratios (95% CI) for SSRI 1.59 (0.89 to 2.82) P = 0.116, Other 1.03 (0.43 to 2.42), Multiple 1.43 (0.70 to 2.89) P = 0.325, None 1.00 referent.
- Other variables of interest include, female 1.97 (1.38 to 2.83) P < 0.001, duration of use >180 days 0.34 (0.21 to 0.55) P < 0.001

### ANALYSIS:

- ITT: NA
- Post randomization exclusions: NA
- Loss to follow-up: NA

### ATTRITION:

- Withdrawals due to adverse events: NA
- Withdrawals due to lack of efficacy: NA
- Loss to follow-up differential high: NA

### ADVERSE EVENTS:

See results

### QUALITY RATING:

Fair
### Evidence Table 12: Adverse Events

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>Authors: Vanderkooy et al.204</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year: 2002</td>
</tr>
<tr>
<td></td>
<td>Country: Canada</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>NR</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: Prospective Observational</td>
</tr>
<tr>
<td></td>
<td>Setting: Tertiary care clinic</td>
</tr>
<tr>
<td></td>
<td>Sample size: 193</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td></td>
</tr>
<tr>
<td>Dose:</td>
<td></td>
</tr>
<tr>
<td>Duration:</td>
<td></td>
</tr>
<tr>
<td>Sample size:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine NR 8 weeks 62</td>
</tr>
<tr>
<td></td>
<td>Paroxetine NR 8 weeks 55</td>
</tr>
<tr>
<td></td>
<td>Sertraline NR 8 weeks 37</td>
</tr>
<tr>
<td></td>
<td>Moclobemide NR 8 weeks 24</td>
</tr>
<tr>
<td></td>
<td>Bupropion NR 8 weeks 15</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Patients that completed 8 weeks of treatment for depression</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>NA</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>NR</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 39.5</td>
</tr>
<tr>
<td></td>
<td>Gender (female %): 62%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
</tbody>
</table>
| OUTCOME ASSESSMENT: | Primary Outcome Measures: Remission and adverse events  
Timing of assessments: Baseline and 6 weeks |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RESULTS:</td>
<td>Remission (HAM-D 17 &lt; 7) bupropion 40%, moclobemide 25%, paroxetine 45%, sertraline 36%, venlafaxine 40%</td>
</tr>
</tbody>
</table>
| ANALYSIS:           | ITT: No  
Post randomization exclusions: NA but 24 or 11% noncompleters |
| ATTRITION:          | Loss to follow-up: bupropion 12%, moclobemide 16%, paroxetine 23%, sertraline 24%, venlafaxine 13%  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |
| ADVERSE EVENTS:     | Adverse events %  
Venlafaxine vs. paroxetine vs. sertraline  
Nervousness 11 vs. 9.1 vs. 16  
Agitation 18 vs. 11 vs. 19  
Tremor 11 vs. 3.6* vs. 16  
Myoclonus 9.7 vs.13 vs.14  
Fatigue 24 vs. 13 vs. 22  
Dizziness 9.7 vs. 11 vs. 14.8  
Postural hypotension 15 vs. 7.3* vs. 22  
Somnolence 27 vs. 29 vs. 32  
Increased sleep 6.5 vs. 7.3 vs. 14  
Decreased sleep 26 vs. 13 vs. 14  
Sweating 27 vs. 27 vs. 32  
Flushing 11 vs. 13 vs. 14  
Edema 1.6 vs. 1.8 vs. 8.1  
Headache 26 vs. 18 vs. 22  
Blurred vision 9.7 vs. 15 vs. 14  
• Differs from results for sertraline, $P < 0.05$ |
<p>| QUALITY RATING:     | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 12</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| STUDY:            | Authors: Whyte et al. 2005  
                  | Year: 2003  
                  | Country: Australia |
| FUNDING:          | NR            |
| DESIGN:           | Study design: Observational-prospective cohort  
                  | Setting: Hospital (Hunter Area Toxicology Service Database, Australia)  
                  | Sample size: 538 (284 venlafaxine and other SSRI records) |
| INTERVENTION:     | Venlafaxine  
                  | Other SSRIs  
                  | overdose           
                  | overdose           
                  | N/A                        
                  | N/A                        
                  | 51                          
                  | 284                         |
| INCLUSION:        | First time admissions for overdose with an SSRI or TCA |
| EXCLUSION:        | Patients who ingested multiple drugs of interest |
| OTHER MEDICATIONS/INTERVENTIONS: | N/A |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No, SSRI group was younger and significantly; took more drug; waited longer to present  
                          | Mean age: VX: 36; SSRI: 29  
                          | Gender: VX: 68.6%; SSRI: 67% female  
                          | Ethnicity: NR  
<pre><code>                      | Other population characteristics: NR |
</code></pre>
<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>PRIMARY OUTCOME MEASURES: Incidence of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SECONDARY OUTCOME MEASURES: Serotonin toxicity; ICU admission; life-threatening arrhythmias; heart rate; blood pressure; coma score; ECG measures; time in hospital</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significantly more patients overdosing on venlafaxine (13.7%) experienced seizures than patients taking other SSRIs (1.3%) $p &lt; 0.001$</td>
</tr>
<tr>
<td>• Significantly more patients overdosing on venlafaxine (29.4%) required ICU admission than patients taking other SSRIs (7.3%) $p &lt; 0.01$</td>
</tr>
<tr>
<td>• No other significant differences were found between venlafaxine overdoses and SSRI overdoses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT: N/A</td>
</tr>
<tr>
<td>Post randomization exclusions: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: Overall N/A</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: N/A</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: N/A</td>
</tr>
<tr>
<td>Loss to follow-up differential high: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
</tr>
</tbody>
</table>
## Evidence Table 13

### Subgroups

| STUDY: | Authors: Andersen et al. 206  
Year: 1994  
Country: Denmark |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Lundbeck Foundation</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: 2 hospitals and 1 outpatient clinic  
Sample size: 66 |
| INTERVENTION: | Drug: Citalopram  
Dose: 10-40 mg/d  
Duration: 6 weeks  
Sample size: 33  
Placebo  
Dose: N/A  
Duration: 6 weeks  
Sample size: 33 |
| INCLUSION: | Adults 25 to 80; minimum HAM-D score of: 13; concomitant condition: post-stroke; diagnosed with post-stroke depression according to DSM-III-R |
| EXCLUSION: | 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 |
| OTHER MEDICATIONS/ INTERVENTIONS: | No differences between groups with respect to concomitant use of other medications (including hypnotics, anxiolytic agents) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: citalopram 68.2, placebo 65.8  
Gender (female %): citalopram 64%, placebo 58%  
Ethnicity: NR  
Other population characteristics:  
Baseline HAM-D: citalopram 19.4 (3.1), placebo 18.9 (2.8) |
<table>
<thead>
<tr>
<th>Authors: Andersen et al.</th>
<th>Year: 1994</th>
<th>Country: Denmark</th>
</tr>
</thead>
</table>

**OUTCOME ASSESSMENT:**
- **Primary Outcome Measures:** HAM-D, MES
- **Secondary Outcome Measures:** ECG
- **Timing of assessments:** baseline and weekly

**RESULTS:**
- Significant improvement in citalopram-treated patients vs. placebo (p < 0.05)
- Decrease in HDS and MES scores from baseline significantly greater in citalopram group than placebo group (p < 0.05)

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** No

**ATTRITION:**
- **Loss to follow-up:** citalopram 21%, placebo 6%
- **Withdrawals due to adverse events:** NR
- **Withdrawals due to lack of efficacy:** NR
- **Loss to follow-up differential high:** Yes

**ADVERSE EVENTS:**
- NR

**QUALITY RATING:** Fair
### Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Book S et al.\(^{207}\)  
Year: 2008  
Country: USA |
| **FUNDING:** | National Institute on Alcohol Abuse and Alcoholism. |
| **DESIGN:** | Study design: RCT  
Setting: Single center  
Sample size: 42 |
| **INTERVENTION:** | Drug:  
Paroxetine  
10-60 mg/day  
16 weeks  
Sample size: 20  
Placebo  
N/A  
16 weeks  
Sample size: 22 |
| **INCLUSION:** | Diagnostic criteria for current social anxiety disorder, generalized type, and current alcohol use disorder (alcohol abuse or dependence); 18–65 years old; have sufficiently severe social anxiety disorder, as defined by a total score of at least 60 on the Liebowitz Social Anxiety Scale; report using alcohol to cope with social anxiety; and consume at least 15 standard drinks in the previous 30-day period |
| **EXCLUSION:** | Current bipolar disorder, schizophrenia, substance abuse or dependence other than alcohol, nicotine, marijuana, or presence of significant suicidality. Medical exclusion factors included: history of prior medical detoxification from alcohol; current use of psychotropic medications; seeking treatment for alcohol problems; urine drug screen positive for illicit drugs other than marijuana; and liver enzymes greater than three times normal levels. History of prior medical detoxification or treatment seeking for alcohol problems was exclusionary for ethical reasons since no explicit alcohol intervention was provided |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: paroxetine 28, placebo 22  
Gender (female %): paroxetine 45, placebo 50  
Ethnicity (% white): paroxetine 100, placebo 82  
Other population characteristics: |
### Authors: Book S et al.  
**Year:** 2008  
**Country:** USA  

**OUTCOME ASSESSMENT:**  
- **Primary Outcome Measures:** Leibowitz Social Anxiety Scale (LSAS)  
- **Secondary Outcome Measures:** CGI-I, Social Phobia Inventory (SPIN)  
- **Timing of assessments:** Baseline and weekly assessments.  

**RESULTS:**  
- LSAS total scores were reduced by an average of 53% (S.E. = 6.6) for the paroxetine group versus 32% (S.E. = 6.2) for the placebo group, a statistically significant difference, $t(40) = 2.34$, $p = .02$.  
- Responders, as defined by a CGI improvement score of 1 or 2, paroxetine 55% versus placebo 27%.  
- SPIN results failed to achieve statistical significance: mean reduction of 46% (S.E. = 7) for paroxetine group vs. 31% (S.E. = 7), $t(40) = 1.49$, $p = 0.15$.  

**ANALYSIS:**  
- **ITT:** Yes  
- **Post randomization exclusions:** No  

**ATTRITION:**  
- **Loss to follow-up:** 10%  
- **Withdrawals due to adverse events:** 5% vs. 0  
- **Withdrawals due to lack of efficacy:** NR  
- **Loss to follow-up differential high:** No  

**ADVERSE EVENTS:**  
- Paroxetine vs. placebo  
  - Tremor: 45% (9) vs. 14% (3), $p = 0.03$  
  - Myoclonus: 35% (7) vs. 5% (1), $p = 0.01$  
  - Anorgasmia/delayed ejaculation: 55% (11) vs. 18% (4), $p = 0.01$  

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| STUDY:           | Authors: Bush D, et al.<sup>208</sup>  
|                  | Year: 2005  
|                  | Country: Multinational |
| FUNDING:         | AHRQ |
| DESIGN:          | Study design: Systematic review  
<p>|                  | Number of patients: NR |
| AIMS OF REVIEW:  | To examine the role of depression post-MI |
| STUDIES INCLUDED IN REVIEW | 86 studies (11 studies addressed SSRI treatment for depression) |
| TIME PERIOD COVERED: | Up to April 2004 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Studies that have examined depression or depressive symptoms in patients after MI and focus on prevalence, clinical significance, treatment, and methods of evaluating condition |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Patients suffering from myocardial infarction and depression |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>SSRIs and therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>In post-MI patients with depression, SSRIs improve depression and some surrogate markers of cardiac risk</td>
</tr>
<tr>
<td></td>
<td>No studies of sufficient power address question of whether treatment improves survival</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>NR</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>MEDLINE®, the Cochrane CENTRAL® Register of Controlled Trials (Issue 1, 2003), the Cochrane Database of Methodology Reviews (CDMR®), the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), the Psychological Abstracts (PsycINFO®), and EMBASE® and handsearches</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>Yes</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
<tr>
<td>Evidence Table 13</td>
<td>Subgroups</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| **STUDY:**        | Authors: Cassano GB, et al.  
Year: 2002  
Country: Italy |
| **FUNDING:**      | SmithKline Beecham, Ravizza Farmaceutici |
| **DESIGN:**       | Study design: RCT  
Setting: Multi-center (38)  
Sample size: 242 |
| **INTERVENTION:** |  
**Drug:** Paroxetine  
Dose: 20-40 mg/day  
Duration: 1 year  
Fluoxetine  
Dose: 20-60 mg/day  
Duration: 1 year |
| **INCLUSION:**    | 65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score |
| **EXCLUSION:**    | History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Paroxetine: 75.6, fluoxetine: 74.9  
Gender (% female): Paroxetine: 61%, fluoxetine: 50%  
Ethnicity: Not reported  
Other population characteristics: Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%; 40% had already been treated for present episode |
**Authors:** Cassano GB, et al.  
**Year:** 2002  
**Country:** Italy

### OUTCOME ASSESSMENT:

**Measures and timing of assessments:** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52  
HAM-D responders = score < 10, anxiety responders = CAS score < 8  
Cognitive tests: Buschke Selective Reminding Test, Blessed Information and Memory Test, Clifton Assessment Schedule, Cancellation Task Test, Wechsler Paired Word Test, Mini-mental State Examination, baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52

### RESULTS:

**Cognitive function:**  
- Both treatment groups showed significant improvement in cognitive performance on all test scales  
- There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests

**Depressive symptoms:**  
- Both treatment groups significantly improved the HAM-D total scores  
- Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: p < 0.05; week 6: p < 0.002), otherwise there were no differences between the treatment groups  
- A Kaplan Meier analysis evaluating the percentage of responders (HAM-D ≥ 10) over time showed a significant difference in favor of paroxetine (p < 0.03)  
- No significant differences on CGI scores

### ANALYSIS:

**ITT:** No  
**Post randomization exclusions:** Not reported

### ATTRITION:

**Loss to follow-up:** 39.3%; paroxetine: 40.6%, fluoxetine: 37.8%  
**Withdrawals due to adverse events:** 15%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- At least 1 adverse event: paroxetine: 27.6%, fluoxetine: 32.8%  
- Fluoxetine had significantly more severe adverse events than paroxetine (22 vs. 9; p < 0.02)

### QUALITY RATING:

Fair
## Evidence Table 13

### Authors:
Clayton AH, et al.

### Year:
2005

### Country:
NR

### FUNDING:
Pfizet, Inc.

### Study design:
Pooled analysis

### Number of patients:
673 (338 women, 335 men)

### AIMS OF REVIEW:
To examine the sex differences in efficacy and safety when panic disorder is treated with sertraline or placebo

### STUDIES INCLUDED IN POOLED-ANALYSIS:
Four double-blinded RCTs (Pohl et al., 1998; Londborg et al, 1998; Pollack and Otto, 1998; and Sheikh et al., 2000)

### TIME PERIOD COVERED:
Not reported

### CHARACTERISTICS OF INCLUDED STUDIES:
Double blinded, placebo controlled trials of sertraline: all used a 2-week single-blind period

### CHARACTERISTICS OF INCLUDED POPULATIONS:
Adult, 18 years or older, outpatients with panic disorder with or without agoraphobia; at baseline males reported an earlier age of onset (28.1 vs. 30.0 years) shorter duration of disease (8.6 vs. 7.3 years), were younger (36 vs. 40 years) and had higher past histories with alcohol/substance abuse/dependence (substance 14% vs. 6% alcohol 20% vs. 9%)
### Authors: Clayton AH, et al.
### Year: 2005

#### CHARACTERISTICS OF INTERVENTIONS:
- 2 fixed dose studies 12 weeks in length, 2 flexible dose studies 10 weeks in length

#### MAIN RESULTS:
- Panic attack frequency- change from baseline males -77% females -82% p = 0.02
- PDSS total score- change from baseline males -5.79 (0.61) females -6.99 (0.47) p = 0.42
- Time spent worrying- change from baseline males -61.4% females -72.1% p = 0.01
- HAM-A total score- change from baseline males -10.74 (0.60) females -10.07 (0.58) p = 0.42
- Q-LES-Q total score- change from baseline males +8.45 (1.84) females +8.89 (1.43) p = 0.85

#### ADVERSE EVENTS:
- Excess over placebo rates of more than 5% in nausea (11% male, 11% female), insomnia (10% male, 5% female), sedation (9% male, 2% female) diarrhea (7% male, 14% female) dry mouth (7% male, 3% female) fatigue (5% male, 6% female)

#### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
No; analysis of published trials

#### STANDARD METHOD OF APPRAISAL OF STUDIES:
Not reported

#### QUALITY RATING:
Fair
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Cornelius JR, et. al.\(^{210-212}\)  
                   Year: 1997, Subgroup analysis, 1998; Follow up study, 2000  
                   Country: US |
| **FUNDING:**      | Not reported |
| **DESIGN:**       | Study design: RCT  
                   Setting: Single-center  
                   Sample size: 51  
                   Subgroup analysis 1998: 17  
                   Follow up study 2000: 31 |
| **INTERVENTION:** | Drug: Fluoxetine  
                   Dose: 20-40 mg/d  
                   Duration: 12 weeks  
                   Placebo  
                   N/A  
                   12 weeks |
| **INCLUSION:**    | 18-65 years old; DSM-III-R criteria for MDD and alcohol dependence  
                   Subgroup analysis 1998: cocaine abuse by DSM-III |
| **EXCLUSION:**    | Serious concomitant medical illness; pregnancy; bipolar; schizoaffective; schizophrenia; non-alcohol substance abuse; antidepressant medication within 1 month |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | None reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: No  
Mean Age: 34.8  
Gender (female%): 49%  
Ethnicity: 47% white, 53% black  
Other population characteristics: The fluoxetine group was significantly more depressed on the BDI scale than the placebo group following washout (p < 0.02) |
| **Authors:** Cornelius JR, et al.  
**Year:** 1997, 1998, 2000  
**Country:** US |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** 24 item HAM-D, BDI, Addiction Severity Index, drinking level  
**Timing of assessments:** Assessments performed weekly |
| **RESULTS:** | • Change in HAM-D score was significantly better for the fluoxetine group than placebo (p < 0.05)  
• Change in BDI score was not significantly different between groups  
• Fluoxetine patients had significantly fewer drinks, number of drinking days, and drinks per day (p < 0.05)  
**Subgroup analysis 1998:**  
• Cocaine abusers showed a significantly worse outcome on HAM-D (p = 0.17) and on BDI (p = 0.001) and multiple measures of alcohol consumption (p = 0.042) compared to non-cocaine abusing alcoholics  
**Follow up study 2000:**  
• HAM-D scores remained significantly lower in the fluoxetine group during the one year follow-up. No additional improvement was reported.  
• Number of days intoxicated decreased in fluoxetine group (p = 0.010) |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** No |
| **ATTRITION:** | **Loss to follow-up:** 10%  
**Withdrawals due to adverse events:** 0  
**Loss to follow-up differential high:** No |
<p>| <strong>ADVERSE EVENTS:</strong> | No side effects observed |
| <strong>QUALITY RATING:</strong> | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Ehde DM et al. 
Year: 2008 
Country: USA |
| **FUNDING:** | National Institute of Disability and Rehabilitation Research, Department of Education, Multiple Sclerosis Rehabilitation Research and Training Center; GSK provided drugs |
| **DESIGN:** | Study design: RCT 
Setting: Single center 
Sample size: 42 |
| **INTERVENTION:** | Drug: Paroxetine 
Dose: 10-40 mg/day 
Duration: 12 weeks 
Sample size: 22 |
|  | Placebo 
Dose: NA 
Duration: 12 weeks 
Sample size: 20 |
| **INCLUSION:** | Age of ≥18 years; a diagnosis of MS as confirmed by a neurologist or an MS-specialized physiatrist; and a diagnosis of MDD and/or dysthymia based on the Structured Clinical Interview for DSM-IV Axis I Disorders |
| **EXCLUSION:** | Had failed treatment with paroxetine in the past; were in psychotherapy; were taking psychotropic medications; were taking >50 mg of amitriptyline or equivalent for pain or sleep; displayed imminent suicidal ideation necessitating immediate psychiatric intervention; pregnant, nursing or not using an effective contraceptive method; had bipolar disorder or evidence of psychosis based on the SCID; diagnosis of alcohol and/or drug dependence based on the SCID; were participating in another FDA drug study; corticosteroids within the 2 weeks prior to study enrollment. |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Yes but not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes 
Mean age: 45.0 
Gender (female %): 52.4 
Ethnicity: 85.7% white, 7.1% Asian 
Other population characteristics: |
Authors: Ehde DM et al.  
Year: 2008  
Country: USA

| OUTCOME ASSESSMENT: | Primary Outcome Measures: HAM-D 17  
Secondary Outcome Measures: SCID, CES-D, MS Quality of Life Inventory  
Timing of assessments: Baseline, weeks 6 and 12 |
|---------------------|--------------------------------------------------------------------------------------------------|
| RESULTS:            | Paroxetine vs. placebo  
50% reduction in HAM-D: 57.1% vs. 40.0%, p = 0.354  
HAM-D < 7: 47.6% vs. 25.0%, p = 0.197  
MFIS: 53.4 vs. 51.8, p = 0.657 |
| ANALYSIS:           | ITT: Yes (LOCF)  
Post randomization exclusions: Yes (3) |
| ATTRITION:          | Loss to follow-up: Paroxetine 23%, Placebo 0%  
Withdrawals due to adverse events: Paroxetine 9%, Placebo 0%  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: Yes |
| ADVERSE EVENTS:     | Paroxetine vs. placebo  
Nausea 57.1% vs. 5%  
Headache 47.6% vs. 10%  
Dry mouth 47.6% vs. 35%  
Sexual dysfunction 23.8% vs. 5% |
<p>| QUALITY RATING:     | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Entsuah AR, et al.  
|                   | Year: 2001  
|                   | Country: Not reported  |
| **FUNDING:**      | Wyeth |
| **DESIGN:**       | Study design: Pooled data analysis  
|                   | Number of patients: 2,045 |
| **AIMS OF REVIEW:** | To detect differences in response and remission rates with respect to age and gender |
| **STUDIES INCLUDED IN META-ANALYSIS:** | No systematic literature search |
| **TIME PERIOD COVERED:** | Not reported |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double-blind, active-controlled, RCTs |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | MDD; ≥ 20 on HAM-D; age 18-85 |
| **Authors:** Entsuah AR, et. al.  
  **Year:** 2001  
  **Country:** Not reported |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</strong></td>
</tr>
<tr>
<td><strong>MAIN RESULTS:</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
</tr>
<tr>
<td><strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong></td>
</tr>
<tr>
<td><strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong></td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
</tr>
</tbody>
</table>
### Evidence Table 13: Subgroups

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>Authors: Glassman AH et al.²¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year: 2002</td>
</tr>
<tr>
<td></td>
<td>Country: Multinational</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multicenter (40 outpatient cardiology centers and psychiatry clinics)</td>
</tr>
<tr>
<td></td>
<td>Sample size: 369</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Dose:</td>
<td>50-200 mg/d</td>
</tr>
<tr>
<td>Duration:</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Sample size:</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>183</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Adults with acute MI or hospitalized for unstable angina in past 30 days; experiencing current MDD episode based on DSM-IV criteria</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Cardiovascular: uncontrolled hypertension; cardiac surgery anticipated during next 6 months; index MI or unstable angina developed less than 3 months after coronary artery bypass graft procedure; resting heart rate &lt; 40/min; MI or unstable angina of nonatherosclerotic etiology (eg, anemia, cocaine use, periprocedural); Killip class III or IV status. Other Medical: persistent clinically significant laboratory abnormalities; significant renal dysfunction, hepatic dysfunction, or other significant noncardiac disease; women of childbearing potential not using adequate contraception. Concomitant Treatment: current use of class I antiarrhythmic medications; use of reserpine, guanethidine, clonidine, or methylidopa; anticonvulsants or neuroleptics; antidepressants; or regular benzodiazepine; initiation of psychotherapy in the 3 months prior to study entry. Psychiatric: alcohol or substance abuse or dependence in past 6 months; psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, dementia (or a MMSE &lt; 23); significant suicide risk.</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Calcium channel blockers, nitrates, digoxin, β-blockers, angiotensin-converting enzyme inhibitors, statins, aspirin, antiplatelet drugs, anticoagulants, diuretics</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: sertraline 56.8, placebo 57.6</td>
</tr>
<tr>
<td></td>
<td>Gender (female %): sertraline 37%, placebo 36%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (% white): sertraline 74%, placebo 79%</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics:</td>
</tr>
<tr>
<td></td>
<td>MI: sertraline 81%, placebo 78%</td>
</tr>
<tr>
<td></td>
<td>Unstable angina: sertraline 19%, placebo 22%</td>
</tr>
</tbody>
</table>
### Authors: Glassman et al.  
**Year:** 2002  
**Country:** Multinational

| OUTCOME ASSESSMENT | Primary Outcome Measures: | Change from baseline in LVEF  
| | Secondary Outcome Measures: | Cardiovascular AEs, HAM-D, CGI-I  
| | Timing of assessments: | 

| RESULTS: | HAM-D mean change from baseline (sertraline vs. placebo)  
| | • All randomized patients: -8.4 (0.41) vs. -7.6 (0.41), p = 0.14  
| | • Any recurrent MDD: -9.8 (0.59) vs. -7.6 (0.61), p = 0.009  
| | • Patients with 2 prior episodes, plus HAM-D score > 18: -12.3 (0.88) vs. -8.9 (0.98), p = 0.01  
| | # CGI responders (sertraline vs. placebo)  
| | • All randomized patients: 125 (67%) vs. 97 (53%), p = 0.01  
| | • Any recurrent MDD: 69 (72%) vs. 46 (51%), p = 0.003  
| | • Patients with 2 prior episodes plus HAM-D score > 18: 39 (78%) vs. 18 (45%), p = 0.001  

| ANALYSIS: | ITT: Yes  
| | Post randomization exclusions: No  

| ATTRITION: | Loss to follow-up: sertraline 28.5%, placebo 25.1%  
| | Withdrawals due to adverse events: sertraline 8.6%, placebo 6.0%  
| | Withdrawals due to lack of efficacy: sertraline 2.7%, placebo 3.3%  
| | Loss to follow-up differential high: No  

| ADVERSE EVENTS: | Emergent adverse events during 24 weeks of treatment (sertraline vs. placebo)  
| | • Cardiovascular, total: 52.7% vs. 59.0%  
| | • Cardiovascular events, severe: 14.5% vs. 22.4%  
| | • Nausea: 19.9% vs. 10.9%  
| | • Diarrhea: 18.8% vs. 7.7%  
| | • Insomnia: 18.8% vs. 18.8%  
| | • Dyspnea: 13.4% vs. 19.7%  
| | • Fatigue: 14.5% vs. 13.7%  
| | • Pain: 10.2% vs. 11.5%  
| | • Headache: 20.4% vs. 16.4%  
| | • Dizziness: 15.6% vs. 12.0%  

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Gual A et al.  
Year: 2003  
Country: Spain |
| **FUNDING:**      | Pfizer |
| **DESIGN:**       | Study design: RCT  
Setting: Hospital alcohol unit  
Sample size: 83 |
| **INTERVENTION:** | Sertraline  
50-150 mg/d  
24 weeks  
44  
Placebo  
N/A  
24 weeks  
39 |
| **INCLUSION:**    | Adult outpatients 18 or older; met DSM IV and ICD-10 criteria for alcohol dependence and for major depression or dysthymia or both; abstinent from alcohol for at least 2 weeks following detoxification; negative drug and alcohol urine test |
| **EXCLUSION:**    | Pregnant; lactating; primary psychiatric disorder apart from alcohol dependence and depressive symptoms; moderate or severe liver disease including active cirrhosis or acute hepatitis; high suicide risk; would require therapy with additional psychotropic drugs, ECT or intensive psychotherapy during the study; history of convulsive disorders, cerebral organic disease or laxative misuse within previous 6 months; depot neuroleptics therapy during prior 6 months; patients requiring therapy with reserpine, methyldopa, guanetidine or clonidine, or who might require general anaesthesia or drugs that interact with sertraline or any serotoninergic drug during the study; severe allergies or multiple adverse reactions to drugs, unstable thyroid disease, severe organic diseases, or patients who had suffered severe infections or major surgery in previous month; prothrombin time out of normal range. |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: sertraline 46.1, placebo 47.3  
Gender (female %): sertraline 48%, placebo 46%  
Ethnicity (% white): NR  
Other population characteristics: |
<table>
<thead>
<tr>
<th>Authors: Gual A et al.</th>
<th>Year: 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Spain</td>
<td></td>
</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome Measures:</strong> MADRS and HAM-D responders</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcome Measures:</strong> overall change in MADRS and HAM-D; SF-36</td>
<td></td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong> Baseline and weeks 2, 4, 8, 12, 18, 24</td>
<td></td>
</tr>
<tr>
<td>RESULTS:</td>
<td></td>
</tr>
<tr>
<td>• Treatment responders (≥ 50% improvement in MADRS score) sertraline 44% vs. placebo 39%</td>
<td></td>
</tr>
<tr>
<td>• Significant improvement in depressive symptoms in both groups according to MADRS and HAM-D scores</td>
<td></td>
</tr>
<tr>
<td>• Marginally better outcome in sertraline group on all depressive measures but differences were not statistically significant</td>
<td></td>
</tr>
<tr>
<td>• No significant difference in SF-36 physical component score</td>
<td></td>
</tr>
<tr>
<td>• Sertraline patients showed greater improvement on mental health item of SF-36 (data NR, p = 0.031)</td>
<td></td>
</tr>
<tr>
<td>• Relapse rates higher in sertraline group (31.8% vs. 23.1%, p = 0.37)</td>
<td></td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td></td>
</tr>
<tr>
<td>ITT: Yes</td>
<td></td>
</tr>
<tr>
<td>Post randomization exclusions: No</td>
<td></td>
</tr>
<tr>
<td>ATTRITION:</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up:</td>
<td></td>
</tr>
<tr>
<td>sertraline 45%, placebo 44%</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events: 7.2%</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: NR</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
<td></td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td></td>
</tr>
<tr>
<td>• Headache: 27.3% vs. 28.2%</td>
<td></td>
</tr>
<tr>
<td>• Flu-like symptoms (13.6% vs. 15.4%</td>
<td></td>
</tr>
<tr>
<td>• Dizziness: 11.4% vs. 12.8%</td>
<td></td>
</tr>
<tr>
<td>• Dyspepsia: 13.6% vs. 5.1%</td>
<td></td>
</tr>
<tr>
<td>• Diarrhea: 9.1% vs. 7.7%</td>
<td></td>
</tr>
<tr>
<td>• Nausea: 9.1% vs. 7.7%</td>
<td></td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 13: Subgroups

| STUDY: | Authors: Hernandez-Avila et al.\textsuperscript{17}  
Year: 2004  
Country: USA (Hartford, CT) |
| FUNDING: | NIH and Bristol-Myers Sqibb |
| DESIGN: | Study design: RCT  
Setting: Outpatient clinic  
Sample size: 41 |
| INTERVENTION: |  
**Drug:** Nefazodone  
**Dose:** 200-600 mg  
**Duration:** 10 weeks  
**Sample size:** 21  
**Placebo**  
**Dose:** N/A  
**Duration:** 10 weeks  
**Sample size:** 20 |
| INCLUSION: | 21 to 65 years of age, able to speak and read English, met DSM-IV criteria for major depression for at least 1 week after discontinuation of heavy drinking and before randomization, scored ≥ 17 on the 17-item HAM-D with a score ≥ 1 on item 1, met criteria for a current DSM-IV diagnosis of alcohol dependence, and drank an average of ≥ 18 drinks per week for men or 14 drinks per week for women, with heavy drinking (≥ 5 drinks for men and ≥ 4 drinks for women) on at least 1 day/week during the month preceding screening. |
| EXCLUSION: | History of major medical or psychiatric problems other than major depression or an anxiety disorder, had clinically significant baseline laboratory abnormalities or a positive pregnancy test, met current DSM-IV criteria for drug dependence other than for alcohol or nicotine, had a positive urine drug screen, were being treated with disulfiram or naltrexone, were deemed to be a serious suicide risk, or were being treated with any psychotropic drug. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** 42.9; nefazodone 43.1, placebo 42.7  
**Gender (female %):** 51; nefazodone 52.4, placebo 50.0  
**Ethnicity:** NR  
Other population characteristics: |
<table>
<thead>
<tr>
<th>Authors: Hernandez-Avila et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2004</td>
</tr>
<tr>
<td>Country: USA</td>
</tr>
</tbody>
</table>

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** HAM-D
- **Secondary Outcome Measures:** alcohol consumption and alcohol-related consequences (with the TLFB and DrInC)
- **Timing of assessments:** Beginning and end at 10 weeks

### RESULTS:
- HAM-D at endpoint: nefazadone 7.05 vs. placebo 7.45 (p = ns)
- Nefazodone-treated subjects (n = 7; 33.3%) vs. placebo-treated subjects (n = 3; 15.0%) were abstinent; the difference did not reach statistical significance (P = 0.17).

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** NR

### ATTRITION:
- **Loss to follow-up:** Nefazadone 38.1% placebo 25%
- **Withdrawals due to adverse events:** NR
- **Withdrawals due to lack of efficacy:** NR
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
In the aggregate, nefazodone-treated subjects reported nonsignificantly more gastrointestinal side effects such as nausea, vomiting, and diarrhea [$F(1,31) = 3.21; p = 0.08$] and neuropsychiatric side effects such as blurred vision, dizziness, and lightheadedness [$F(1,31) = 2.91; p = 0.09$] than did placebo-treated subjects.

### QUALITY RATING:
Fair
### Evidence Table 13

#### Subgroups

| STUDY: | Authors: Honig et al.\(^\text{218}\)  
Year: 2007  
Country: Netherlands |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Netherlands Heart Foundation</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Acute phase  
Setting: 8 hospitals (1 university, 7 general)  
Sample size: 91 |
| INTERVENTION: | Drug:  
Mirtazapine  
30-45 mg/day  
8 weeks acute- 16 wk continuation  
47  
Placebo  
N/A  
8 weeks acute -16 wk continuation  
44 |
| INCLUSION: | 3 to 12 months post acute MI and were free of other life-threatening medical conditions and to fulfill the criteria for DSM-IV major or minor depressive disorder. |
| EXCLUSION: | Suicide risk, current antidepressant treatment |
| OTHER MEDICATIONS/INTERVENTIONS: | Acetylsalicylic acid (92.7%), acenocoumarol (5.4%), nitrate (37%), B-blocking agents (86.6%), calcium-antagonists (22%), digoxin (1.2%), diuretics (12%), ACE-inhibitors (31.7%). All-antagonists (6.1%), and statins (76.1%). The median number of cardiovascular drugs taken was 4 (range 2–7). |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: mirtazapine 56.6, placebo 57.9  
Gender (female %): mirtazapine 12.8, placebo 18.2  
Ethnicity: NR  
Other population characteristics: |


| **Authors:** Honig et al.  
| **Year:** 2007  
| **Country:** Netherlands  

**OUTCOME ASSESSMENT:**

**Primary Outcome Measures:** HAM-D  
**Secondary Outcome Measures:** BDI and the depression scale of the Symptom Check List 90 items (dSCL-90) (21). The CGI was used to evaluate global clinical impression and improvement  
**Timing of assessments:** Baseline, weeks 1,2,4,8,16, 24

**RESULTS:**

- HAM-D score in the acute phase (8 weeks) decreased 7.29 points (SES= 1.30) in the mirtazapine group and 5.31 points (SES = 0.96) in the placebo group  
- HAM-D responders at 8 weeks (mirtazapine vs. placebo): 57.4% vs. 40.1%, p = 0.18  
- Mean HAM-D score: mirtazapine baseline 18.66, 8 weeks 11.37, 24 weeks 10.38; placebo baseline 16.81, 8 weeks 11.50, 24 weeks 11.77  
- Mean CGI score: mirtazapine baseline 4.0, 8-weeks 2.59, 24-weeks 2.50; placebo baseline 3.79, 8-weeks 3.07, 24-weeks 2.91

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up at 8 wks:** mirtazapine 24%, placebo 6.8%  
**Withdrawals due to adverse events:** NR  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** Yes

**ADVERSE EVENTS:**

- Mirtazapine increased the mean weight by 1.7 kg (p < .0001) within the first 8 weeks; in the placebo group, the weight did not change significantly; there was a slight decrease at 16 weeks  
- The ECG variables heart rate, PR duration, QRS duration, and QTc interval did not show any significant changes during the treatment phase.  
- Fatigue: 21% vs. 9%, p = 0.02  
- Appetite changes: 13% vs. 3%, p = 0.02  
- Dizziness: 5% vs. 8%, p = 0.31  
- Headache: 7% vs. 2%, p = 0.61

**QUALITY RATING:** Fair
Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY:</td>
</tr>
<tr>
<td>Authors: Kasper S, et al.</td>
</tr>
<tr>
<td>Year: 2005</td>
</tr>
<tr>
<td>Country: Multinational (11 countries)</td>
</tr>
<tr>
<td>FUNDING:</td>
</tr>
<tr>
<td>H. Lundbeck A/S</td>
</tr>
<tr>
<td>DESIGN:</td>
</tr>
<tr>
<td>Study design: RCT</td>
</tr>
<tr>
<td>Setting: Multicenter (general practice and specialists)</td>
</tr>
<tr>
<td>Sample size: 518</td>
</tr>
<tr>
<td>INTERVENTION:</td>
</tr>
<tr>
<td>Drug: escitalopram, fluoxetine, placebo</td>
</tr>
<tr>
<td>Dose: 10 mg/day, 20 mg/day, NA</td>
</tr>
<tr>
<td>Duration: 8 weeks, 8 weeks, 8 weeks</td>
</tr>
<tr>
<td>Sample size: 174, 164, 180</td>
</tr>
<tr>
<td>INCLUSION:</td>
</tr>
<tr>
<td>≥ 65 years of age; fulfilled DSM-IV criteria for MDD; had a MADRS total score ≥ 22 and ≤ 40 at both screening and baseline; MMSE score of 22 at screening</td>
</tr>
<tr>
<td>EXCLUSION:</td>
</tr>
<tr>
<td>DSM-IV criteria for mania or any bipolar disorder, schizophrenia, or any psychotic disorder, OCD, eating disorders, or mental retardation or any pervasive developmental or cognitive disorder; had a MADRS score ≥ 5 on Item 10 (suicidal thoughts); were receiving treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, AEDs, barbiturates, chloral hydrate, antiparkinsonian drugs, diuretics, 5-HT receptor agonists; ongoing prophylactic treatment with Lithium, sodium valproate, or carbamazepine; ECT; were receiving treatment with behavior therapy or psychotherapy; had received any investigational drug within 30 days of entry; history of schizophrenia, psychotic disorder, or drug abuse; history of severe drug allergy or hypersensitivity (including citalopram); had a lack of response to more than one antidepressant treatment (including citalopram) during the present depressive episode</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
</tr>
<tr>
<td>Oxazepam (max 30 mg/day), temazepam (max 20 mg/day), zopiclone (max 3.75 mg/day), zolpidem (max 5 mg/day)</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
</tr>
<tr>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td>Mean age: 75 (overall and for each treatment group)</td>
</tr>
<tr>
<td>Gender (female %): escitalopram: 75%; fluoxetine: 77%; placebo: 76%</td>
</tr>
<tr>
<td>Ethnicity (% white): escitalopram: 99%; fluoxetine: 100%; placebo: 100%</td>
</tr>
<tr>
<td>Other population characteristics:</td>
</tr>
<tr>
<td>Baseline mean MADRS score: escitalopram: 28.2; fluoxetine: 28.5; placebo: 28.6</td>
</tr>
<tr>
<td>Baseline mean CGI-S score: 4.3 (overall and for each treatment group)</td>
</tr>
</tbody>
</table>
Authors: Kasper S, et al.  
Year: 2005  
Country: Germany

**OUTCOME ASSESSMENT:**  
<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>Change from baseline to endpoint in MADRS total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>CGI-S change/visit, MADRS response and remission at endpoint</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>baseline and weekly</td>
</tr>
</tbody>
</table>

**RESULTS:**  
- No statistically significant difference between escitalopram and placebo in mean change from baseline in MADRS total score; placebo was statistically significantly superior to fluoxetine (p<0.01)  
- MADRS responders at last assessment (LOCF) (escitalopram vs. fluoxetine vs. placebo): 46% vs. 37% vs. 47% (p=NS)  
- MADRS remission: at last assessment (LOCF): 40% vs. 30% vs. 42%; No significant difference between placebo and escitalopram  
- Significantly fewer remitters in fluoxetine vs. placebo (p<0.05)  
- Statistically significant difference between placebo and fluoxetine in adjusted change in mean CGI-S (2.70 vs. 3.02; p<0.05); no significant difference between placebo and escitalopram (2.64); p=NS

**ANALYSIS:**  
- ITT: Yes  
- Post randomization exclusions: yes (4)  
- Loss to follow-up differential high: No

<table>
<thead>
<tr>
<th>Attrition:</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>16.8%</td>
<td>25.6%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>9.8%</td>
<td>12.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>1.7%</td>
<td>1.8%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**  
- TEAEs (escitalopram vs. fluoxetine vs. placebo)  
  - Overall: 50.9% vs. 56.7% vs. 53.3%  
  - Nausea: 6.9%* vs. 7.3%* vs. 1.7% (p<0.01 escitalopram vs. fluoxetine)  
  - Abdominal pain: 6.4% vs. 6.1% vs. 3.9%  
  - Headache: 5.2% vs. 4.3% vs. 8.3%  
  - Hypertension: 2.3% vs. 2.4% vs. 6.1%  
  - Diarrhea: 1.7% vs. 4.9% vs. 5.0%  
  - Back pain: 4.6% vs. 2.4% vs. 3.9%  
  - Anxiety: 2.9% vs. 3.7% vs. 2.8%  
  - Dizziness: 2.9% vs. 3.7% vs. 0.6%  
  - Dyspepsia: 2.3% vs. 4.3% vs. 4.4%  
  - Insomnia: 2.3% vs. 1.8% vs. 2.2%  
  - Somnolence: 2.3% vs. 0% vs. 0.6%  
  - Vertigo: 1.7% vs. 4.3% vs. 1.7%  
  - Anorexia: 1.2% vs. 2.4% vs. 1.1%  
  - Constipation: 1.2% vs. 4.3% vs. 4.4%
<table>
<thead>
<tr>
<th></th>
<th>Depression aggravated: 1.2% vs. 2.4% vs. 0.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dry mouth: 0.6% vs. 2.4% vs. 0.6%</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension: 1.2% vs. 0.6% vs. 0.6%</td>
</tr>
</tbody>
</table>

**QUALITY RATING:** Fair
## Evidence Table 13

### Subgroups

| STUDY:          | Authors: Kennedy SH et al.  
|                 | Year: 2006  
|                 | Country: Canada  
| FUNDING:        | Boehringer Ingelheim  
| DESIGN:         | Study design: RCT  
|                 | Setting: Multicenter  
|                 | Sample size: 141 (131 ITT)  
| INTERVENTION:   |  
| Drug:           | Bupropion  
| Dose:           | 150-300 mg  
| Duration:       | 8 weeks  
| Sample size:    | 69  
|                 | Paroxetine  
|                 | 20-40 mg  
|                 | 8 weeks  
|                 | 62  
| INCLUSION:      | Outpatients; age 18 - 65 years; DSM-IV criteria for MDD—current MDE of at ≥ 4 weeks. HAM-D > 18; to be in good physical health, sexual interest and activity within the past month; free of any antidepressant use for 2 weeks (4 weeks for fluoxetine)  
| EXCLUSION:      | Serious suicide risk; more than 2 failed trials of antidepressant medications at adequate dose and duration during the current episode, drug abuse or dependence within the past 12 months, and a history of bipolar disorder, psychotic disorder, or organic disorder  
| OTHER MEDICATIONS/INTERVENTIONS: | Hypnotic zopiclone (up to 7.5 mg at night) during the first 2 weeks.  
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                 | Mean age: 37.8  
|                 | Gender (female %): 48  
|                 | Ethnicity: NR  
|                 | Other population characteristics:  

---

*Note: Information extracted and formatted for clarity.*
Authors: Kennedy SH et al.  
Year: 2006  
Country: Canada

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Sexual function Sex FX, IRSD-F  
Secondary Outcome Measures: HAM-D  
Timing of assessments: Baseline, 2,4,6,8 |
|---------------------|-------------------------------------------------------------|

| RESULTS:             | • HAMD Bupropion SR (mean 21.8, SD 2.9) vs. paroxetine (mean 22.2, SD 3.6)  
• HAM-D - men (mean 22.1, SD 3.1) responders 62.9% vs. women (mean 21.9, SD 3.5) responders 53.2%  
• Overall more sexual adverse events with paroxetine than with bupropion  
• No difference between drugs for sexual dysfunction in women |

| ANALYSIS:            | ITT: Yes  
Post randomization exclusions: 10 |

| ATTRITION:           | Loss to follow-up: 16% (21) Bupropion 11.6% (8) paroxetine 21% (13)  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |

| ADVERSE EVENTS:      | • None reported |

| QUALITY RATING:      | Fair |
## Evidence Table 13: Subgroups

| STUDY: | Authors: Kranzler et al. \[219\]  
Year: 2006  
Country: USA |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer Pharmaceuticals supported the conduct of this study. Manuscript preparation was supported by NIH grant K24 AA13736</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter (13 sites)  
Sample size: 345 |
| INTERVENTION: | **Group A** HAM-D scores > 17 at randomization.  
Drug: Sertraline  
Dose: 50-200 mg  
Duration: 10 weeks  
Sample size: 89  
Placebo  
N/A  
10 weeks  
100 |
| | **Group B** HAM-D scores < 17 at randomization.  
Drug: Sertraline  
Dose: 50-200 mg  
Duration: 10 weeks  
Sample size: 70  
Placebo  
N/A  
10 weeks  
69 |
| INCLUSION: | Outpatients, 21 to 65 years old, diagnosis of MDD (ie, all met DSM-IV criteria for MDD, except that symptoms could have occurred during a period of heavy alcohol use) and a current DSM-IV diagnosis of AD; a total score of >17 on the HAM-D17. They had to have drunk an average of >18 drinks weekly for men or >14 drinks weekly for women and at least one heavy drinking day per week (ie, >5 drinks on one occasion for men and >4 drinks on one occasion for women) |
| EXCLUSION: | Pregnant or nursing or women of childbearing potential not using an effective method of contraception; clinically significant co-occurring psychiatric or medical diagnoses, including dependence on any psychoactive substance other than alcohol or nicotine during the preceding year or current treatment with disulfiram, naltrexone, or psychotropic medication; serum aminotransferase levels or other measures of hepatic function that were greater than 250% of normal; significant suicidal risk. |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No - group A placebo older, reported more drinks per week during the pretreatment period, and had higher CGI depression scores at baseline. Group B—a significantly greater percentage of patients receiving sertraline had a family history of alcoholism. A trend for sertraline-treated patients to report more drinks per week during the pretreatment period.  
Mean age: 42.7  
Gender (female %): 36.2  
Ethnicity: European American 92.7%.  
Other population characteristics: Mean HAM-D 17.2 |
Authors: Kranzler et al.  
Year: 2006  
Country: USA

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: HAM-D and amount of drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures:</td>
</tr>
<tr>
<td></td>
<td>Timing of assessments: Baseline, weeks 2, 4, 8, 10</td>
</tr>
</tbody>
</table>

| RESULTS:            | Reduction in HAM-D Sertraline -10.8 (6.5) placebo -9.6 (7.8) |
|                     | In Group A, sertraline led to significantly higher response rate (64% vs. 47%, p=0.022)  |
|                     | In Group B, sertraline patients had a significantly lower response rate (58% vs. 77%, p =0.018)  |
|                     | Both depressive symptoms and alcohol consumption decreased substantially over time in both groups. There were no reliable medication group differences on depressive symptoms or drinking behavior in either group A or B patients.  |

| ANALYSIS:           | ITT: Yes  |
|                     | Post randomization exclusions: 17  |

| ATTRITION:          | Loss to follow-up: sertraline 43%, placebo 35%  |
|                     | Withdrawals due to adverse events: sertraline 13%, placebo 6%, p < 0.05  |
|                     | Withdrawals due to lack of efficacy: NR  |
|                     | Loss to follow-up differential high: No  |

| ADVERSE EVENTS:     | Headache: sertraline 31.3%, placebo 25.1%; p = 0.27)  |
|                     | Constipation: sertraline 19.4%, placebo 4.7%  p < 0.001)  |
|                     | Insomnia: sertraline 13.8%, placebo 8.8%; p = 0.21  |

| QUALITY RATING:     | Fair  |
**Evidence Table 13**

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Krishnan KRR, et. al.  
Year: 2001  
Country: US |
| **FUNDING:** | Pfizer |
| **DESIGN:** | Study design: Pooled data of 2 RCTs  
Setting: US  
Sample size: 220 |
| **INTERVENTION:** | Drug: Sertraline  
Dose: 50-150 mg/day  
Duration: 12 weeks |
| **INCLUSION:** | Age 60 or older; DSM-III-R criteria for major depression; ≥ 18 on HAM-D-24; minimal improvement on CGII |
| **EXCLUSION:** | Organic mental disorder; other Axis 1 diagnosis; MMSE less than 23; acute or unstable medical condition; concomitant use of psychotropic drugs; suicidal risk; previous history of non-response to adequate treatment |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Concomitant medications other than psychotropic meds allowed  
Chloral hydrate, temezapam |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
HTN (hypertension); VAS (vascular disease); NOVASC (no hypertension, no vascular comorbidity)  
Mean Age: HTN: 68.6; VASC: 68.9; NOVASC: 67.3  
Gender: (% female) HTN: 69%; VASC: 44%; NOVASC: 62%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
**Authors:** Krishnan KRR, et. al.  
**Year:** 2001  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: HAM-D (change from baseline, > 50% response), HAM-A, CGI-I (1 or 2 = responder), CGI-S  
Timing of assessments: Weeks 1, 2, 3, 4, 6, 8, 10, 12 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RESULTS:</td>
<td>The antidepressant effect of sertraline was not significantly affected by the presence of vascular illness</td>
</tr>
</tbody>
</table>
| ANALYSIS:           | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION:          | Loss to follow-up: Not reported  
Withdrawals due to adverse events: High concomitant medication group: 23.6%; low concomitant medication: 15.7%  
Loss to follow-up differential high: Not reported |
| ADVERSE EVENTS:     | • Vascular comorbidity was not associated with an increase in the reported severity of adverse events, or premature discontinuation for patients on sertraline  
• Sertraline did not have clinically significant effects on blood pressure or heart rate |
| QUALITY RATING:     | FAIR  
(only for subgroup analysis) |
**Evidence Table 13**  

<table>
<thead>
<tr>
<th><strong>Subgroups</strong></th>
<th></th>
</tr>
</thead>
</table>
| **STUDY:**    | **Authors:** Kroenke K, et al.
**Year:** 2001
**Country:**  
**Trial name:** ARTIST (A randomized trial investigating SSRI treatment) |
| **FUNDING:**  | Eli Lilly |
| **DESIGN:**   | **Study design:** RCT (open label)
**Setting:** Multi-center (76 primary care physicians)
**Sample size:** 601 |
| **INTERVENTION:** |  |
| **Drug:**     | Paroxetine
20 mg/day
9 months
| **Dose:**     | Fluoxetine
20 mg/day
9 months
| **Duration:** | Sertraline
50 mg/day
9 months |
| **Mean dose at 9 months:** | Paroxetine: 23.5mg
Fluoxetine: 23.4mg
Sertraline: 72.8mg |
| **INCLUSION:** | 18 years or older; depressive disorder as determined by the primary care physician (PCP); had home telephone |
| **EXCLUSION:** | Cognitive impairment; lack of reading/writing skills; terminal illness; nursing home resident; actively suicidal; SSRI within past 2 months; other antidepressant therapy; bipolar disorder; pregnancy; lactation |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Yes |
| **POPULATION CHARACTERISTICS:** |  |
| **Groups similar at baseline:** | Yes |
| **Mean age:** | Paroxetine: 47.2, fluoxetine: 47.1, sertraline: 44.1 |
| **Gender (% female):** | Paroxetine: 76%, fluoxetine: 86%, sertraline: 75% |
| **Ethnicity:** | (white) Paroxetine: 85%, fluoxetine: 88%, sertraline: 79%; (black) paroxetine: 13%, fluoxetine: 9%, sertraline: 17%; (other) paroxetine: 2%, fluoxetine: 3%, sertraline: 4% |
| **Other population characteristics:** | (MDD) total: 74%, paroxetine: 71%, fluoxetine: 74%, sertraline: 73%; (dysthymia) total: 18%, paroxetine: 22%, fluoxetine: 17%, sertraline: 18%; (minor depression) total: 8%, paroxetine: 7%, fluoxetine: 9%, sertraline: 9% |
**Authors:** Kroenke K, et al.  
**Year:** 2001  
**Country:**  
**Trial name:** ARTIST

### OUTCOME ASSESSMENT:

**Measures:** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS): patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire  
**Timing of assessments:** Months 1, 3, 6, 9

### RESULTS:

- All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function)
- There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures
- Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years
- Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17%

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 24.3%; paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7%  
**Withdrawals due to adverse events:** paroxetine: 30%, fluoxetine: 23%, sertraline: 24%  
**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

No significant differences in adverse events between treatment groups

### QUALITY RATING:

Fair
# Evidence Table 13

## Subgroups

| STUDY: | Authors: Lesperance et al. 2007  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Canadian Institutes of Health Research (CIHR) Clinical Trials Program grant MCT50397, the Fondation du Centre Hospitalier de l’Universite´ de Montré´al, and the Fondation de l’Institut de Cardiologie de Montreal</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter - 9 Canadian academic centers  
Sample size: 284 |
| INTERVENTION: | Drug: Citalopram  
Dose: 20-40 mg/day  
Duration: 12 weeks  
Sample size: 142  
Placebo  
NA  
12 weeks  
142 |
| INCLUSION: | Male and female outpatients of at least 18 years of age who met criteria for MDD as defined by the DSM-IV. established CAD based on hospital chart evidence of a previous acute myocardial infarction or cardiac revascularization or coronary angiography showing 50% blockage or more in at least 1 major coronary artery. Randomization could not occur less than 1 week following discharge for a cardiac hospitalization, and patients had to have stable CAD based on clinical judgment |
| EXCLUSION: | Depression due to a general medical condition, bipolar disorder or major depression with psychotic features, substance abuse or dependency during the previous 12 months, serious suicide risk, current use of antidepressants, lithium, or anticonvulsants for mood disorder, current treatment with any form of psychotherapy, previous absence of response to citalopram or IPT, 2 or more previous unsuccessful treatments, lifetime history of early termination (8 weeks) of citalopram or 2 other SSRIs because of adverse events, Mini-Mental State Examination16 score of less than 24, and clinician judgment that the patient would not adhere to the study regimen; coronary artery bypass graft surgery planned during the next 4 months, those with a Canadian Cardiovascular Society Angina Class of 4 (severe limitations), those participating in other trials, and those unable to speak English or French |
| OTHER MEDICATIONS/ INTERVENTIONS: | Patients took a mean of 7.5 (SD: 3.61) different medications |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 58.2  
Gender (female %): 25  
Ethnicity: NR  
Other population characteristics: |
**Authors:** Lesperance et al.  
**Year:** 2007  
**Country:** USA

| OUTCOME ASSESSMENT: | Primary Outcome Measures: HAM-D$_{24}$  
**Secondary Outcome Measures:** IDS and the BDI-II, the index of function in daily activities (FPI) and the measure of perceived social support (IPRI),  
**Timing of assessments:** baseline, 6 and 12 weeks |
| --- | --- |

| RESULTS: |  
| --- | --- |
| • HAM-D$_{24}$ at endpoint: citalopram 14.9 (9.99) vs. placebo 11.6 (9.99) $p = 0.005$ [between group difference = 3.33 (95% CI: 0.80-5.85)]  
• BDI-II at endpoint: citalopram 14.7 vs. placebo 11.1, $p = 0.005$ [between group difference = 3.64 (95% CI: 0.58-6.64)]  
• Remission $< 8$ HAMD24 citalopram 51 (35.9) vs. placebo 32 (22.5) $p = 0.01$  
• Response $> 50\%$ decline in HAM-D 24 citalopram 75 (52.8) vs. placebo 57 (40.1) $p = 0.03$ |

| ANALYSIS: | ITT: Yes  
**Post randomization exclusions:** Yes |

| ATTRITION: | Loss to follow-up: citalopram 13%, placebo 30%  
**Withdrawals due to adverse events:** Citalopram 7.7%, placebo 4.2%  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** Yes |

| ADVERSE EVENTS: |  
| --- | --- |
| • Citalopram vs. placebo  
• dizziness (48.6% vs. 30.3%; $p = 0.002$)  
• diarrhea (49.3% vs. 23.9%; $p < 0.001$)  
• somnolence (43.7% vs. 25.4%; $p = 0.001$)  
• sweating (39.4% vs. 23.9%; $p = 0.005$)  
• palpitations (25.4% vs. 14.8%; $p = 0.03$)  
• decreased libido or sexual difficulties (21.1% vs. 7.0%; $p = 0.001$) |

<p>| QUALITY RATING: | Fait |</p>
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Lewis-Fernandez et al. and Bailey et al.  
                    Year: 2006  
                    Country: US |
| **FUNDING:**      | Eli Lilly and Co. |
| **DESIGN:**       | Study design: Pooled analysis  
                    Number of patients: 1,452 (Lewis-Fernandez) and 1,423 (Bailey) |
| **AIMS OF REVIEW:** | To evaluate duloxetine for the treatment of MDD in Hispanic, Caucasian and African Americans |
| **STUDIES INCLUDED IN REVIEW** | 7 trials |
| **TIME PERIOD COVERED:** | Feb 1999 to Nov 2002 |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blind RCTs, placebo and active comparator, 7-9 weeks in duration |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | 18 years or more with MDD |
### CHARACTERISTICS OF INTERVENTIONS:
Duloxetine 60 mg/day versus placebo

### MAIN RESULTS:

#### Caucasian and Hispanic
- **HAM-D 17 change from baseline**
  - Duloxetine: Caucasian -7.72 Hispanic -8.67 vs. placebo: Caucasian -5.99 Hispanic -7.53
- **CGI-S change from baseline**
  - Duloxetine: Caucasian -1.31 Hispanic -1.45 vs. placebo: Caucasian -1.03 Hispanic -1.24
- **PGI-I change from baseline**
  - Duloxetine: Caucasian 2.77 Hispanic 2.75 vs. placebo: Caucasian 3.15 Hispanic 3.10
- "No evidence for a differential effect of duloxetine in Hispanic and Caucasian patients was found in efficacy outcomes"

#### Caucasian and African American
- **HAM-D 17 change from baseline**
- **CGI-S change from baseline**
  - Duloxetine: Caucasian -1.31 African-American -1.24 vs. placebo: Caucasian -1.03 African-American -1.04
- **PGI-I change from baseline**
  - Duloxetine: Caucasian 2.77 African-American 2.75 vs. placebo: Caucasian 3.15 African-American 2.77
- "No evidence for a differential effect of duloxetine in African-American and Caucasian patients was found in efficacy outcomes"

### ADVERSE EVENTS:
Discontinuation due to AEs 14.0% for Hispanics and 17.0% for Caucasians, compared with 3.2% and 5.7%, respectively, for placebo-treated patients (p = 0.671)

Discontinuation due to AEs 13.0% for African-American and 17.0% for Caucasians, compared with 3.4% and 5.7%, respectively, for placebo-treated patients

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
No

### STANDARD METHOD OF APPRAISAL OF STUDIES:
No

### QUALITY RATING:
Fair
<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Linden RD, et al. 
Year: 1994 
Country: US |
| **FUNDING:** | Not reported |
| **DESIGN:** | Study design: Retrospective analysis of two RCTs 
Setting: Multi-center 
Sample size: 89 |
| **INTERVENTION:** | Paroxetine: 20-50 mg/d 
12 weeks | Fluoxetine: 20-80 mg/d 
12 weeks | Placebo 
N/A 
12 weeks |
| **INCLUSION:** | 18-70 yrs; DSM-III-R criteria for major depression; ≥17 on HAM-D-17 |
| **EXCLUSION:** | Not reported |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Not reported 
Mean Age: 42 
Gender (female%): 56.6% 
Ethnicity: Not reported 
Other population characteristics: Not reported |
**Authors:** Linden RD, et. al.  
**Year:** 1994

| OUTCOME ASSESSMENT: | **Measures:** HAM-D, Raskin, Covi, CGI, SCL-90  
**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 9, 12 |
|---|---|

| RESULTS: |  
- Subjects with baseline complaints of gastrointestinal symptoms or more severe depression were not more likely to develop gastrointestinal side effects under SSRI treatment |
|---|---|

| ANALYSIS: | **ITT:** No  
**Post randomization exclusions:** Not reported |
|---|---|

| ATTRITION: | **Loss to follow-up:** Not reported  
**Withdrawals due to adverse events:** GI withdrawals: fluoxetine: 5.2%, paroxetine: 0%  
**Loss to follow-up differential high:** No |
|---|---|

| ADVERSE EVENTS: | For this analysis only gastrointestinal side effects were considered  
- Nausea: paroxetine: 28%, fluoxetine: 26%, placebo: 0%  
- Diarrhea: paroxetine: 14%, fluoxetine: 16%, placebo: 7%  
- Weight loss/loss of appetite: paroxetine: 22%, fluoxetine: 8%, placebo: 7% |
|---|---|

| QUALITY RATING: | Fair |
## Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Lyketsos CG et al.  
Year: 2003  
Country: US |
| **FUNDING:** | NIMH Grant 1R01-MH56511 (Depression in Alzheimer's disease study) |
| **DESIGN:** | Study design: RCT  
Setting: University outpatient clinics (3)  
Sample size: 44 |
| **INTERVENTION:** |  
Drug:  
Dose:  
Duration:  
Sample size:  
Sertraline  
12 weeks  
24  
Placebo  
N/A  
12 weeks  
20 |
| **INCLUSION:** | Diagnosis of probable AD by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; MMSE ≥ 10; DSM-IV diagnosis of major depressive episode; current residence in community setting (home or assisted living); caregiver willing to accompany participant to study visits; stable medical history and general health |
| **EXCLUSION:** | Current unstable medical condition; lifetime diagnosis of schizophrenia, bipolar disorder, or pre-AD anxiety disorder; current substance use disorder; acutely suicidal or requiring inpatient psychiatric hospitalization |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: No (more women in sertraline group)  
Mean age: sertraline 75.5, placebo 79.9  
Gender (female %): sertraline 83%, placebo 50%  
Ethnicity (% black): sertraline 33%, placebo 15%  
Other population characteristics: |
Authors: Lyketsos CG et al.
Year: 2003
Country: US

| OUTCOME ASSESSMENT: | Primary Outcome Measures: CSDD and HAM-D response  
Secondary Outcome Measures: Psychogeriatric Dependency Rating Scale, NPI, MMSE  
Timing of assessments: baseline and weeks 3, 6, 9 |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| RESULTS: | • More sertraline patients were full responders (38% vs. 20%) and partial responders (46% vs. 15%); p = 0.006  
• Sertraline was statistically significantly superior to placebo as measured by both the Cornell Scale for Depression in Dementia (P = 0.002) and the Hamilton Depression Rating Scale (P = 0.01)  
• No significant differences between groups on MMSE or total NPI |

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: No |

| ATTRITION: | Loss to follow-up: sertraline 12.5%, placebo 25%  
Withdrawals due to adverse events: sertraline 4.2%, placebo 0  
Withdrawals due to lack of efficacy: sertraline 8.3%, placebo 15%  
Loss to follow-up differential high: No |

| ADVERSE EVENTS: | • No significant differences in frequency of AEs between groups  
• Withdrawals due to AEs twice as high in sertraline group vs. placebo group |

| QUALITY RATING: | Fair |
 Evidence Table 13 | Subgroups
--- | ---
**STUDY:** | Authors: Moak et al. \[226\]
Year: 2003
Country: USA
**FUNDING:** | National Institute on Alcohol Abuse and Alcoholism
**DESIGN:** | Study design: RCT
Setting: Multicenter
Sample size: 82
**INTERVENTION:** | Drug:
Dose: Sertraline 50-200 mg
Duration: 12 weeks
Sample size: 38
Placebo NA
Duration: 12 weeks
Sample size: 44
**INCLUSION:** | Major depressive episode or dysthymic disorder; primary (independent) major depressive episode or dysthymic disorder or a clear family history of affective disorder without comorbid substance abuse in a first degree relative (parent, sibling, or child); at least 17 on the HAM-D-21 both at screening and at the end of 1 week of single-blind placebo; current alcohol dependence or abuse and have drunk a minimum of 40 standard drinks during the month before study entry; mild to moderate alcohol dependence, which was operationally defined as not having more than 1 past inpatient alcohol detoxification. Women of childbearing potential were required to use a reliable form of birth control.
**EXCLUSION:** | Any current psychoactive substance dependence other than nicotine; psychoactive substance abuse in the month before study entry other than marijuana; current panic disorder or PTSD; and lifetime history of bipolar affective or psychotic disorder; treatment-resistant depression; any significant current suicidal ideation or plan, homicidal ideation, unstable medical illness, or history of a seizure disorder were referred for standard clinical treatment; they had to have been off the detoxification medication for at least 48 hours prior; serotonergic medications, including SSRIs, had to be completely off these medications for at least 4 weeks before study entry. Other psychoactive medications, including tricyclic antidepressants, had to be discontinued for at least 2 weeks.
**OTHER MEDICATIONS/ INTERVENTIONS:** | NR
**POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes
Mean age: Sertraline 41, placebo 42
Gender (female %): Sertraline 39, placebo 39
Ethnicity: NR
Other population characteristics:
Years of education: sertraline 15, placebo 15
| Authors: Moak et al.  
| Year: 2003  
| Country: USA |

| OUTCOME ASSESSMENT: | Primary Outcome Measures: HAM-D  
| Secondary Outcome Measures: BDI, OCDS, and TLFB  
| Timing of assessments: Weekly |

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| • HAM-D overall: sertraline 7.8 vs. placebo 8.8  
| • HAM-D men: sertraline 8.3 vs. placebo 8.5 (p = ns)  
| • HAM-D women: sertraline 6.9 vs. placebo 9.3, p < 0.05  
| • Significant difference in BDI scores for women taking sertraline, p=0.005  
| • No difference between groups in time to first heavy drinking day (≥ 5 drinks in 1 day), p = 0.661  
| • Sertraline subjects had less drinks/drinking day vs. placebo subjects, p = 0.027  
| • No difference between groups in percent days abstinent or heavy drinking days/week, p = nr  
| • Less drinking during study was associated with improved depression outcome  
| • Females who received sertraline had less depression than females who received placebo (p = 0.04) |

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
</table>
| ITT: Yes  
| Post randomization exclusions: NR |

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
</table>
| Loss to follow-up: 16% sertraline 33% placebo  
| Withdrawals due to adverse events: NR at least 1  
| Withdrawals due to lack of efficacy: NR  
| Loss to follow-up differential high: Yes |

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 patients experienced serious AEs (3 sertraline, 1 placebo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
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<tbody>
<tr>
<td>Fair</td>
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</tbody>
</table>
### Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
</tbody>
</table>
| Authors: Murray V, et al.  
Year: 2005  
Country: Sweden |
| **FUNDING:** |
| Pfizer AB |
| **DESIGN:** |
| Study design: RCT  
Setting: 4 outpatient stroke centers  
Sample size: 123 |
| **INTERVENTION:** |
| **Drug:** Sertraline  
Dose: 50-100 mg/day  
Duration: 26 weeks  
Sample size: 62 |
| **Placebo:**  
Dose: N/A  
Duration: 26 weeks  
Sample size: 61 |
| **INCLUSION:** |
| ≥ 18 yrs; MDD diagnosis according to DSM-III or IV; stroke (according to WHO criteria); |
| **EXCLUSION:** |
| Adults ≥ 18; MDD diagnosis 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) |
| **OTHER MEDICATIONS/INTERVENTIONS:** |
| Concomitant psychotherapeutic or psychotropic medications; additional mental illnesses or organic mental disorder; significant suicide risk; severe impairment in ability to communicate; current use of opiate analgesics |
| **POPULATION CHARACTERISTICS:** |
| Groups similar at baseline: Yes  
Mean age: 70.7  
Gender (female %): sertraline 48.4%, placebo 55.7%  
Ethnicity: NR  
Other population characteristics: Major depressive episode: sertraline 66.1%, placebo 57.4%  
Minor depressive disorder: sertraline 33.9%, placebo 42.6% |
<table>
<thead>
<tr>
<th>Authors: Murray V, et al.</th>
<th>Year: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Sweden</td>
<td></td>
</tr>
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</table>

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>CGI-S, CGI-I, EDS, HAM-D, SSSS</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Baseline and weeks 2, 4, 6, 8, 12, 18, and 26</td>
</tr>
</tbody>
</table>

**RESULTS:**

- Both groups improved substantially; no differences between treatments either for major depressive episode or minor depressive disorder
- HAM-D responders (% who completed 26 wks of treatment): sertraline 76% vs. placebo 78%
- % remission (defined as MADRS score <10) (percent of those who completed 26 wks of treatment): sertraline 81%, placebo 87%
- Improvement in QoL at wk 26 was significantly better in sertraline treated patients (p<0.05)

**ANALYSIS:**

<table>
<thead>
<tr>
<th>ITT: Yes</th>
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<tbody>
<tr>
<td>Post randomization exclusions:</td>
</tr>
</tbody>
</table>

**ATTRITION:**

<table>
<thead>
<tr>
<th>Loss to follow-up: 44%; sertraline 39%, placebo 49%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events: sertraline 13%, placebo 8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: sertraline 26%, placebo 36%</td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- Dry mouth: 23.6% vs. 7.4%; p<0.05
- Diarrhea: 23.6% vs. 9.3%; p<0.05
- Emotional indifference: 9.1% vs. 0; p<0.05
- Nausea: 21.8% vs. 14.8%
- Tremor: 12.7% vs. 7.4%
- Constipation: 14.5% vs. 9.3%
- Increased dream activity: 14.5% vs. 9.3%
- Weight loss: 17.4% vs. 13.3%
- Postural hypotension: 13.0% vs. 9.3%
- Dyspepsia: 20.0% vs. 16.7%
- Dizziness: 14.5% vs. 13.0%
- Edema: 12.7% vs. 11.3%
- Increased sweating: 16.4% vs. 17.0%
- Weight gain: 15.2% vs. 15.6%
- Headache: 14.5% vs. 16.7%
- Reduced duration of sleep: 9.1% vs. 18.5%

**QUALITY RATING:** Fair
## Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
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</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
</tbody>
</table>
Authors: Newhouse PA, et al.  
Year: 2000  
Country: US |
| **FUNDING:** | Pfizer, Inc. |
| **DESIGN:** | 
Study design: RCT  
Setting: Multi-center  
Sample size: 236 |
| **INTERVENTION:** | 
Drug:  
Dose:  
Duration: |
| Sertraline | 50-100 mg/d  
12 weeks |
| Fluoxetine | 20-40 mg/d  
12 weeks |
| (Doses could be doubled after 4 weeks) |
| **INCLUSION:** | > 60 years of age; DSM-III-R criteria for major depression; ≥ 18 on 24 item HAM-D |
| **EXCLUSION:** | Other psychiatric disorder; significant physical illness; non-responders to antidepressants or ECT therapy |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate, temazepam for sleep |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Sertraline: 68, fluoxetine: 67  
Gender (% female): Sertraline: 63.2%, fluoxetine: 51.3%  
Ethnicity: (white) Sertraline: 95.7%, fluoxetine: 100%; (black) sertraline: 3.4% (other) sertraline: 0.9%  
Other population characteristics: Not reported |
**Authors:** Newhouse PA, et al.  
**Year:** 2000  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: 24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT  
**Timing of assessments:** Baseline, week 1, 2, 3, 4, 6, 8, 10, 12 |
| --- | --- |

| RESULTS: | Sertraline and fluoxetine were effective in the relief of depressive symptoms  
There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI)  
HAM-D Responders: sertraline: 73%, fluoxetine: 71%  
HAMD remitters: sertraline: 45%, fluoxetine: 46%  
Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test) |
| --- | --- |

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| --- | --- |

| ATTRITION: | **Loss to follow-up:** 32.2%; sertraline: 31.6%, fluoxetine: 32.8%  
**Withdrawals due to adverse events:** sertraline: 18.8%, fluoxetine: 24.4%, p = 0.5  
**Loss to follow-up differential high:** No |
| --- | --- |

| ADVERSE EVENTS: | Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018)  
Otherwise no statistically significant differences between groups  
Headache: sertraline: 33.6%, fluoxetine: 31.4%  
Dizziness: sertraline: 7.8%, fluoxetine: 10.2%  
Dry mouth: sertraline: 15.5%, fluoxetine: 7.6%  
Nausea: sertraline: 14.7%, fluoxetine: 18.6%  
Diarrhea: sertraline: 22.4%, fluoxetine: 16.1% |
| --- | --- |

| QUALITY RATING: | Fair |
**Evidence Table 13**

**Subgroups**

| STUDY: | Authors: Nyth AL et al.**28**  
|        | Year: 1992  
|        | Country: Denmark, Norway, Sweden |
| FUNDING: | NR |
| DESIGN: | Study design: RCT  
|        | Setting: Multicenter (7)  
|        | Sample size: 149 |
| INTERVENTION: | Citalopram  
| Drug: | Placebo  
| Dose: | 10-30 mg/d  
| Duration: | 6 weeks  
| Sample size: | 98  
|        | N/A  
|        | 6 weeks  
|        | 51 |
| INCLUSION: | Age ≥ 65; HAM-D score ≥ 14; mild to moderate dementia |
| EXCLUSION: | Patients receiving anti-cancer treatment, had a cerebral infarct or cerebral hemorrhage within last 6 weeks or suffering from other serious somatic illness (heart or lung disease, liver disease, renal disease, hematological disorder or malignant disease involving a risk of considerable changes for the worse over next 2 months); history of schizophrenia, epilepsy, alcoholism or drug dependence; recent treatment with MAOIs; severe depression with severe confusion; suicide risk high enough to warrant ECT; severe dementia; GBS score > 4 on each of the items of orientation in space, orientation in time, personal orientation, recent memory and distant memory |
| OTHER MEDICATIONS/INTERVENTIONS: | Cardiovascularly active drugs, antipsychotics, anxiolytics, hypnotics |
| POPULATION CHARACTERISTICS: | Groups similar at baseline:  
| Mean age: | 76.7  
| Gender (female %): | 69%  
| Ethnicity: NR  
| Other population characteristics: | *Population characteristics at baseline: N=133 |
| Authors: Nyth AL et al.  
Year: 1992  
Country: Denmark, Norway, Sweden |
|---|

**Primary Outcome Measures:** HAM-D, CGI, MADRS, GBS  
**Secondary Outcome Measures:**  
**Timing of assessments:** Baseline and after weeks 2, 4, and 6  

**RESULTS:**  
- HAM-D response rate (≥ 50% score reduction) similar in both groups (data NR)  
- HAM-D differences in mean total score (p < 0.05) and improvement (p < 0.01) significantly favored citalopram after 6 weeks of treatment  
- Differences in MADRS mean total score and improvement significantly favored citalopram after 6 weeks of treatment (p < 0.05)  
- CGI improvement ratings at week 6 showed significantly more citalopram patients were “very much improved” or “much improved” vs. placebo patients (60% vs. 24%, p < 0.001)  
- Higher percentage of MADRS responders (≥ 50% score reduction) in citalopram group than placebo group (53% vs. 28%, p < 0.05)  
- 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 significantly more in the citalopram-treated subgroup of patients with dementia than in the placebo treated subgroup (p < 0.05)  

**ANALYSIS:**  
**ITT:** No  
**Post randomization exclusions:** Yes (16)  

**ATTRITION:**  
**Loss to follow-up:** citalopram 39%, placebo 33%  
**Withdrawals due to adverse events:** NR  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** No  

**ADVERSE EVENTS:**  
- At endpoint, UKU Side Effect Scale indicated no statistically significant difference between groups  
- No side effects recorded during entire trial period: 63% 75%  
- Overall AEs: 37% vs. 25%  
- Decrease in weight: 9.2% vs. 3.9%  
- Constipation: 3.1% vs. 5.9%  
- Dizziness: 7.1% vs. 0  
- Nausea: 5.1% vs. 7.8%  
- Somnolence: 18.4% vs. 5.9%  

**QUALITY RATING:** Poor—completer analysis only
## Evidence Table 13

<table>
<thead>
<tr>
<th>Evidence Table 13</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Oslin DW et al. Volume 228 Year: 2003 Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>National Institute of Mental Health; Department of Veterans Affairs</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT Setting: VA nursing facilities (13) Sample size: 52</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug: Sertraline 25-100 mg/d 10 weeks Sample size: 25 Venlafaxine 18.75-150 mg/d 10 weeks Sample size: 27</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>≥60 yrs of age; DSM-III or DSM-IV diagnosis of MDD; HAM-D ≤ 12; significant dysphoria with score ≥ 10 on GDS and/or rating &gt;2 on depressed mood item of HAM-D; minor depression, dementia with depression, or dysthymia; Blessed Memory Information Concentration test score &lt;21</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Concomitant psychotherapeutic or psychotropic medications (except as needed oxazepam, lorazepam or temazepam); additional mental illnesses or organic mental disorder; illicit drug and alcohol abuse; clinically significant medical disease; investigational drug use within the last 2 wks; suicidal tendencies; communication disorders; weight loss judged to present a danger to patient; unstable medical disorders or terminal conditions likely to lead to death within 6 months</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: No (more African Americans in venlafaxine group) Mean age: sertraline 83.8, venlafaxine 81.2 Gender (female %): sertraline 56%, venlafaxine 33% Ethnicity (% white): sertraline 92%, venlafaxine 63% Other population characteristics: Cardiac disease (moderate to severe) 83%</td>
</tr>
</tbody>
</table>
### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Tolerability, HAM-D  
**Secondary Outcome Measures:** MMSE, CIRS, PSMS, IADL, CGI, GDS  
**Timing of assessments:** baseline and weekly

### RESULTS:

Mean change from baseline to endpoint (sertraline vs. venlafaxine):
- HAM-D: 8.0 vs. 4.6 (F = 3.45, p = 0.69)  
- GDS: 3.5 vs. 0.8 (F = 2.13, p = 0.151)  
- Cornell: 8.5 vs. 4.0 (F = 7.65, p = 0.008)

- Endpoint CGI (sertraline vs. venlafaxine): 2.3 vs. 3.0, p = 0.98
- No differences in categorical responses for ITT sample vs. completers

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:**

### ATTRITION:

**Loss to follow-up:** 44%; sertraline 24%, venlafaxine 63%  
**Withdrawals due to adverse events:** sertraline 16%, venlafaxine 48%  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

- Tolerability estimated by time to termination lower for venlafaxine than sertraline for serious AEs (p = 0.005)  
- No significant differences between groups in effects on blood pressure

### QUALITY RATING:

Poor
### Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
<th></th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Paile-Hyvärinen M, et al.  
Year: 2007  
Country: Finland |
| **FUNDING:** | GlaxoSmithKline |
| **DESIGN:** | Study design: RCT  
Setting: Primary care  
Sample size: 49 |
| **INTERVENTION:** |  |
| Drug: | Paroxetine  
Dose: 20 mg  
Duration: 6 months  
Sample size: 23 |
| Placebo | N/A  
Duration: 6 months  
Sample size: 20 |
| **INCLUSION:** | Mildly depressed; type 2 diabetes; outpatients; 50-70 years of age; diagnosed with type 2 diabetes at least 1 year prior to study entry; on stable hypoglycaemic medication for at least 3 months before study; non-optimal glycaemic control—defined as hemoglobin A₁c (GHbA₁c) > 7.0 % – and mild depression, i.e. not more than six depressive symptoms according DSM-IV criteria. |
| **EXCLUSION:** | .Moderate to severe depression based on DSM-IV criteria; glaucoma; using warfarin; major complications due to diabetes (e.g., major cardiovascular, renal or vascular disease, and blindness); used any kind of antidepressants |
| **OTHER MEDICATIONS/INTERVENTIONS:** |  |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Paroxetine 59.2, placebo 59.5  
Gender (female %): Paroxetine 26.1, placebo 20  
Ethnicity: NR  
Other population characteristics: |
**Authors:** Paile-Hyvärinen M, et al  
**Year:** 2007  
**Country:** Finland

| OUTCOME ASSESSMENT | Primary Outcome Measures: SF-36 quality of life score  
|                    | Secondary Outcome Measures: HADS  
|                    | Timing of assessments: Baseline and months 3 and 6  

**RESULTS:**
- SF-36 scores at 3 months significantly better in paroxetine patients (mean difference = -11.0, p = 0.039)  
- SF-36 scores at 6 months showed no significant difference between groups (mean difference = -8.9, p = 0.135)  
- Both groups showed decrease in anxiety and depressive symptoms according to the HADS with trend for a stronger effect in paroxetine group; however, there were no statistically significant differences between treatment groups at any time point

**ANALYSIS:**  
- **ITT:** Yes  
- **Post randomization exclusions:** Yes (6)

**ATTRITION:**  
- **Loss to follow-up:** 24.5%; paroxetine 4.2%, placebo 44%  
- **Withdrawals due to adverse events:** paroxetine 0%, placebo 8%  
- **Withdrawals due to lack of efficacy:** paroxetine 0%, placebo 8%  
- **Loss to follow-up differential high:** Yes (39.8%)

**ADVERSE EVENTS:**  
- Paroxetine vs. placebo (n)*  
  - Nausea: 4 vs. 0  
  - Headache: 4 vs. 1  
  - Erectile dysfunction: 0 vs. 2  
  *No p-values reported

**QUALITY RATING:** Poor
### Evidence Table 13

**Subgroups**

| STUDY: | Authors: Petrakis I, et. al.231  
Year: 1998  
Country: US |
| FUNDING: | National Institute on Drug Abuse |
| DESIGN: | Study design: RCT  
Setting: Teaching hospital  
Sample size: 44 |
| INTERVENTION: | Fluoxetine  
Dose: 20-60 mg/d  
Duration: 3 months |
| | Placebo  
Dose: N/A  
Duration: 3 months |
| INCLUSION: | Opioid dependent patients; methadone treatment for at least 3 months; DSM-III-R criteria for major depression; ≥ 14 on HAM-D-17; > 8 on BDI |
| EXCLUSION: | MDD independent of drug abuse; history of psychotic disorders; bipolar disorder |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean Age: Fluoxetine: 35.4 years, placebo: 33.3 years  
Gender (% female): Fluoxetine: 39.1%, placebo: 33.3%  
Ethnicity: White: fluoxetine: 91.3% placebo: 85.7%; African American: fluoxetine: 4.3%, placebo: 4.8%; Hispanic: fluoxetine: 4.3%, placebo: 9.5%  
Other population characteristics: MDD: fluoxetine: 47.1%, placebo: 52.9%; dysthymia: fluoxetine: 57.1%, placebo: 42.9% |
| OUTCOME ASSESSMENT: | Measures: BDI, HAM-D (Hamilton Depression Rating Scale), ASI (addiction severity index)  
Timing of assessments: Weekly, weeks 4, 8, 12, urine samples weekly |
|---------------------|--------------------------------------------------------------------------|
| RESULTS:            | • BDI and HADRS scores decreased significantly in both groups (z = 2.37; p = 0.01; z = 5.85, p < 0.01). There were no significant differences between placebo and fluoxetine treated patients.  
• Concomitant heroin use and ASI scores decreased significantly for both groups (z = 2.92, p < 0.01; z = 2.66, p < 0.01) but there was no significant difference between groups |
| ANALYSIS:           | ITT: No  
Post randomization exclusions: Not reported |
| ATTRITION:          | Loss to follow-up: 15.9%; fluoxetine: 13%, placebo: 19%  
Withdrawals due to adverse events: Not reported  
Loss to follow-up differential high: No |
| ADVERSE EVENTS:     | All fluoxetine discontinuations due to possible treatment-related adverse events |
| QUALITY RATING:     | Fair |
### Evidence Table 13: Subgroups

| STUDY: | Authors: Rabkin JG, et al.  
Year: 1999  
Country: US |
| FUNDING: | NIMH, Eli Lilly |
| DESIGN: | Study design: RCT  
Setting: University-affiliated research outpatient clinic  
Sample size: 120 |
| INTERVENTION: | | |
| Drug: | Fluoxetine  
mean dose 37 mg/day  
8 weeks |
| Dose: | Placebo  
N/A  
8 weeks |
| Duration: | (Note responders were followed for an additional 18 weeks to assess effect of drug on immune status) |
| INCLUSION: | Ages 18-70; HIV + for at least 2 months; physically healthy except for HIV; those with an AIDS-defining condition had to be in treatment with a consenting primary care provider; DSM-IV criteria for MDD or dysthymia or both |
| EXCLUSION: | History of psychosis; bipolar disorder within past 6 months of substance use; panic disorder; current risk for suicide; significant cognitive impairment; use of other antidepressant within 2 weeks before study entry; initiation of psychotherapy within past 4 weeks; medical exclusions: HIV wasting syndrome; significant diarrhea; unstable health; onset of opportunistic infections within past 6 weeks |
| OTHER MEDICATIONS/INTERVENTIONS: | Concurrent HIV medications allowed |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean Age: 39  
Gender (% female): 2.5%  
Ethnicity: African American 20%, Latino 15 %, 65% white  
Other population characteristics: 36% receiving disability benefits, 46% college graduates, 88% had some post-high school education |
| **Authors:** Rabkin JG, et al. | **Year:** 1999  |
| **Country:** US |  |

| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D, brief symptom inventory, Beck Hopelessness Scale, Quality of Life Enjoyment and Satisfaction Questionnaire  |
| **Timing of assessments:** Baseline, weeks 4, 8  |

| **RESULTS:** |  |
| • Significantly more responders on HAM-D in the fluoxetine group (fluoxetine: 57%, placebo: 41%; p = 0.03)  |
| • No significant differences in changes of HAM-D scores  |
| • No significant difference in CGI responders  |

| **ANALYSIS:** | **ITT:** Yes  |
| **Post randomization exclusions:** Yes  |

| **ATTRITION:** | **Loss to follow-up:** 27.5%; fluoxetine: 29.6%; placebo: 23.1%  |
| **Withdrawals due to adverse events:** 5%; fluoxetine: 7.4%, placebo: 0  |
| **Loss to follow-up differential high:** No  |

| **ADVERSE EVENTS:** |  |
| • Reporting at least 1 treatment emergent side effect during study: fluoxetine: 50%, placebo 50%  |
| • Mean number of side effects reported: fluoxetine: 1.4 (2.0 sd), placebo: 1.3 (1.8 sd)  |
| • Only headache was reported more significantly more frequently among fluoxetine group as compared to placebo  |

| **QUALITY RATING:** | Fair  |
### Evidence Table 13

**Subgroups**

| STUDY: | Authors: Riggs et al.  
Year: 2007  
Country: USA |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>US National Institute on Drug Abuse, NIH</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: single center  
Sample size: 126 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration:  
Sample size: |
| Fluoxetine & CBT | Placebo & CBT |
| 20 mg | N/A |
| 16 weeks | 16 weeks |
| 63 | 63 |
| INCLUSION: | Age 13 to 19 years; willingness to participate in weekly CBT for SUD; DSM-IV criteria for current MDD; at least 1 nontobacco SUD; lifetime CD |
| EXCLUSION: | Current or past diagnosis of a psychotic disorder or of bipolar disorder (type I or II); serious or unstable medical illness or pregnancy; current use of a psychotropic medication or participation in other concurrent substance or mental health treatment in the past month; considered at high risk for a suicide attempt during the trial in the clinical judgment of the study physician |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 17.2 years  
Gender (female %): 32.6%  
Ethnicity: 48.4% white, 27.0% Hispanic, and 14.3% African American  
Other population characteristics: NR |
Authors: Riggs et al.  
Year: 2007  
Country: USA

**OUTCOME ASSESSMENT:**

- **Primary Outcome Measures:** For depression, Childhood Depression Rating Scale–Revised and Clinical Global Impression Improvement; for SUD, self-reported nontobacco substance use and urine substance use screen results in the past 30 days; and for CD, self-reported symptoms in the past 30 days. Treatment response: CGI-I ≤ 2, Remission of depression: CDRS-R raw score ≤ 28

- **Secondary Outcome Measures:** NR

- **Timing of assessments:** Baseline, monthly (plus weekly urine tests)

**RESULTS:**

- Treatment response (CGI-I): fluoxetine-CBT (76.3%) vs. placebo-CBT (66.7%), LOCF, NS, RR=1.14 (95% CI, 0.91-1.44)
- Decrease in CDRS-R t score (normalized) fluoxetine -22.5 vs. placebo -16.16, difference 5.66 (95%CI 1.45-9.87) at 16 weeks
- Otherwise no differences between groups in SUD or CD or urine drug screen.

**ANALYSIS:**

- **ITT:** Yes- with generalized estimating equation (GEE) or LOCF
- **Post randomization exclusions:** none
- **Loss to follow-up differential high:** no

**ATTRITION:**

<table>
<thead>
<tr>
<th>Loss to follow-up</th>
<th>Fluoxetine &amp; CBT</th>
<th>Placebo &amp; CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events</td>
<td>17.5% NR</td>
<td>14.3% NR</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- No statistically significant differences in AEs

**QUALITY RATING:**

- Fair
**Evidence Table 13**  
**Subgroups**

| STUDY: | Authors: Roscoe JA, et al.  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Department of Defense, SmithKline Beecham provided drug and placebo</td>
</tr>
<tr>
<td>OBJECTIVE:</td>
<td>To evaluate the effect of a serotonin uptake inhibitor on depression and fatigue (both conditions are postulated to share a serotonin link) in a homogeneous sample of breast cancer patients</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: University affiliated hospital and 2 of its affiliated hospitals  
Sample size: 94 |
| INTERVENTION: | Drug:  
Dose:  
Duration:  
Sample size: |
| | Paroxetine  
20 mg/day  
At least 6 weeks  
44 |
| | Placebo  
N/A  
At least 6 weeks  
50 |
| INCLUSION: | Female patients about to begin or currently undergoing chemotherapy treatment for breast cancer, with at least 4 cycles to be completed |
| EXCLUSION: | Concurrent radiation or interferon treatment; history of seizures or mania taking psychotropic medications; treatment cycles of less than 2 weeks apart |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 51.3  
Gender (% female): 100%  
Ethnicity (% white): paroxetine: 93%, placebo 86%  
Other population characteristics:  
Baseline depression (CES-D of 19 or more): paroxetine: 13 (29%), placebo: 13 (26%) |
### Authors: Roscoe JA, et al.
### Year: 2005

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures:</th>
<th>Fatigue using the Fatigue Symptom Checklist (FSCL), Multidimensional Assessment of Fatigue (MAF) and the Fatigue/Inertia subscale of the Monopolar Profile of Mood States (POMS-FI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures:</td>
<td>Depression using the CES-D and the Depression/Dejection subscale of the Monopolar Profile of Mood States (POMS-DD)</td>
</tr>
<tr>
<td></td>
<td>Timing of assessments:</td>
<td>7th day after each of the 4 chemotherapy treatments</td>
</tr>
<tr>
<td>RESULTS:</td>
<td></td>
<td>- Cycle 4 comparisons of paroxetine versus placebo: mean (SE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CES-D: 8.8 (1.11) vs. 12.6 (1.24)  p &lt; 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- POMS-DD: 1.2 (0.30) vs. 2.2 (0.34)  p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MAF (question 1): 4.6 (0.38) vs. 5.9 (0.37)  p = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- POMS-Fi: 6.0 (0.70) vs. 7.1 (0.79)  p = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- FSCL: 44.6 (2.41) vs. 48.0 (2.62)  p = NS</td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td></td>
<td>ITT: No- 122 were randomized, analysis was done on 94 that completed at least 2 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post randomization exclusions: Yes – 28/122 (23%)</td>
</tr>
<tr>
<td>ATTRITION:</td>
<td></td>
<td>Loss to follow-up: 14/94 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawals due to adverse events: NR except in non-completers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawals due to lack of efficacy: NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss to follow-up differential high: No</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td></td>
<td>- 11 patients not in the analysis withdrew because of AEs, primarily headache and nausea (paroxetine: 6, placebo: 5); no other AEs were reported</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td></td>
<td>Poor</td>
</tr>
</tbody>
</table>
### Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
<tr>
<td>Authors: Roy-Byrne PP, et al.(^a)</td>
</tr>
<tr>
<td>Year: 2005</td>
</tr>
<tr>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
</tr>
<tr>
<td>NIMH</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
</tr>
<tr>
<td>Study design: Pooled analysis</td>
</tr>
<tr>
<td>Number of patients: 14,875</td>
</tr>
<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
</tr>
<tr>
<td>To explore differences in minorities response and tolerability to paroxetine</td>
</tr>
<tr>
<td><strong>STUDIES INCLUDED IN ANALYSIS</strong></td>
</tr>
<tr>
<td>104 placebo controlled paroxetine trials</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
</tr>
<tr>
<td>Double blinded, placebo controlled trials of paroxetine at least 6 weeks in length.</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
</tr>
<tr>
<td>Adult outpatients with: MDD (7603), anxiety disorders GAD, SAD, OCD, PTSD (6156) and PMDD (1116); 63% were women, 89% white, 4% black, 3% Hispanic, 0.9% Asian, 3% unknown or other, mean age 42.3 years</td>
</tr>
</tbody>
</table>
| **Authors:** Roy-Byrne PP, et al.  
**Year:** 2005 |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></td>
</tr>
</tbody>
</table>
| **MAIN RESULTS:** | - Significant treatment by ethno-racial groups for response (p = 0.014) and full response (p = 0.012)  
- Response rates white- OR 2.1 95% CI 2.0 to 2.3 (p < 0.001), black- OR 2.1 95% CI 1.5 to 3.0 (p < 0.001),  
  Hispanic- OR 1.1 95% CI 0.5 to 2.4 (p = 0.554), Asian- 1.1 95% CI 0.5 to 2.4 (p = 0.743)  
- Hispanics and Asians had a substantially lower response rate than white and black  
- Full response rates white- OR 2.0 95% CI 1.8 to 2.2 (p < 0.001), black- OR 1.6 95% CI 1.1 to 2.4 (p = 0.016),  
  Hispanic- OR 0.9 95% CI 0.6 to 1.5 (p = 0.554), Asian- 2.7 95% CI 1.0 to 2.0 (p = 0.061)  
- Asians had the highest rate of “full response” and Hispanics had the lowest |
| **ADVERSE EVENTS:** | Insomnia was the only event to show a significance difference due to a higher rate shown in Asians |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | No; analysis of published and unpublished trials in GSK database |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | Not reported |
| **QUALITY RATING:** | Fair |
### Evidence Table 13

#### Subgroups

| STUDY: | Authors: Schatzberg et al.  
Year: 2002  
Country: US |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Organon Pharma</td>
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</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 255 |
| INTERVENTION: | Drug: Mirtazapine  
Dose: 15-45 mg/d  
Duration: 8 weeks  
Paroxetine  
Dose: 20-40 mg/d  
Duration: 8 weeks  
(There was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study) |
| INCLUSION: | Min. age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score > 25% for age and education; min. score of 18 on HAM-D17 |
| EXCLUSION: | HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; H/o seizures; recent drug or alcohol abuse or any principal psych condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazapine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 72  
Gender (% female): Martazapine: 63%, paroxetine: 64%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
### Authors: Schatzberg et al.
**Year:** 2002  
**Country:** US

### OUTCOME ASSESSMENT:
- **Measures:** HAM-D 17, CGI-S, CGI-I  
  **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:
- Mean Ham-D17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint
- Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission)
- Time to response: mirtazapine mean 26 days, paroxetine 40 days (p = -.016 for Kaplan-Meier plot comparing the two)
- No difference in CGI Improvement response

### ANALYSIS:
- **ITT:** Yes
  - **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 26.8%; mirtazapine 22.7%, paroxetine 31.0%
  - **Withdrawals due to adverse events:** 20.4%; mirtazapine 14.8, paroxetine 26.2% (p < 0.05)
  - **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5%
- Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0%

### QUALITY RATING:
- Fair
### Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Schatzberg A and Roose S<sup>38</sup>  
Year: 2006  
Country: USA |
| **FUNDING:** | Wyeth Research |
| **DESIGN:** | Study design: RCT  
Setting: Multicenter (21 university-affiliated and private research clinics)  
Sample size: 300 |
| **INTERVENTION:** |  
**Drug:**  
Venlafaxine IR  
37.5 titrated to 225 mg/day  
8 weeks  
104  
Fluoxetine  
20 titrated to 60 mg/day  
8 weeks  
100  
Placebo  
N/A  
8 weeks  
96 |
| **INCLUSION:** | Male or female subjects; 65 years or older and not living in a residential setting; met DSM-IV criteria for unipolar depression (single or recurrent, nonpsychotic), with a current episode of at least four weeks in duration; HAM-D-21 score> 20 at visit; had no more than a 20% decrease in score after a single-blind, placebo lead-in week |
| **EXCLUSION:** | Bipolar disorder; a psychotic disorder not related to depression; current substance abuse or substance dependence within the past year (other than nicotine); current suicidal intent; MSME <18; had received treatment with fluoxetine or venlafaxine in the past six months; ECT within the prior three months, or any investigational drug or antipsychotic medication within the prior 30 days; used astemizole, cisapride, sumatriptan, terfenadine, paroxetine, sertraline, or any monoamine oxidase inhibitor within 14 days; used any other antidepressant, anxiolytic, or sedative-hypnotic drug (except chloral hydrate), or any other psychotropic drug or substance within seven days of the start of the double-blind treatment period; known hypersensitivity to venlafaxine or fluoxetine; clinically significant hepatic or renal disease, seizure disorder, or myocardial infarction within the prior 6 months; severe, acute, or unstable medical illness |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate (up to 1,000 mg) or zolpidem (up to 10 mg) as needed for sleep; nonpsychopharmacologic drugs with psychotropic effects if patient was on stable dose for at least one month (3 months for thyroid or hormonal medications) before start of study |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: venlafaxine: 71, fluoxetine: 71, placebo: 71  
Gender (female %): venlafaxine: 56, fluoxetine: 45, placebo: 46  
Ethnicity (% white): venlafaxine: 93, fluoxetine: 93, placebo: 93  
Other population characteristics: Using concomitant medications (%): venlafaxine: 91, fluoxetine: 95, placebo: 95 |
**Authors:** Schatzberg and Roose  
**Year:** 2006  
**Country:** USA

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** HAM-D-21, MADRS, CGI-S, CGI-I  
- **Secondary Outcome Measures:** Response and remission rates  
- **Timing of assessments:** Weeks 1, 2, 3, 4, 6 and 8

### RESULTS:
- No overall difference between groups in HAM-D response or remission rates based on LOCF analysis of HAM-D-21 scores  
- No significant differences between groups in MADRS, CGI-S, or HAM-D depressed mood scores  
- No significant difference in HAM-D-17 response at endpoint (p=0.7220)  
- No significant difference in MADRS response at endpoint (p=0.732)  
- At 8 weeks, remission rates for venlafaxine, fluoxetine and placebo were 27% vs. 20% vs. 24% (p=0.549)

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes  
- **Loss to follow-up differential high:** No

### ATTRITION:
- **Loss to follow-up:**  
  - Venlafaxine: 37 (36%)  
  - Fluoxetine: 30 (30%)  
  - Placebo: 23 (24%)  
- **Withdrawals due to adverse events:**  
  - Venlafaxine: 27%  
  - Fluoxetine: 19%  
  - Placebo: 2%  
- **Withdrawals due to lack of efficacy:**  
  - Venlafaxine: 2%  
  - Fluoxetine: 6%  
  - Placebo: 8%

### ADVERSE EVENTS:
- Overall: 92% vs. 94% vs. 86%  
- Nausea: 45% vs. 23% vs. 14%; p<0.001 (venlafaxine vs. fluoxetine p<0.01)  
- Headache: 26% vs. 18% vs. 22%; p=0.349  
- Dry mouth: 23% vs. 6% vs. 15%; p=0.004 (venlafaxine vs. fluoxetine p<0.01)  
- Constipation: 22% vs. 10% vs. 4%; p<0.001 (venlafaxine vs. fluoxetine p<0.01)  
- Dizziness: 17% vs. 8% vs. 5%; p=0.019  
- Diarrhea: 12% vs. 13% vs. 14%; p=0.928  
- Fatigue: 12% vs. 10% vs. 5%; p=0.254  
- Dyspepsia: 11% vs. 17% vs. 8%; p=0.157  
- Appetite decreased: 11% vs. 11% vs. 4%; p=0.157  
- Sweating: 11% vs. 4% vs. 1%; p=0.007  
- Insomnia: 10% vs. 11% vs. 4%; p=0.185  
- Oversedation: 10% vs. 5% vs. 2%; p=0.060  
- Libido decreased: 9% vs. 8% vs. 1%; p=0.043  
- Vomiting: 9% vs. 2% vs. 2%; p=0.025  
- Vision blurred: 8% vs. 3% vs. 5%; p=0.311  
- Drowsiness: 8% vs. 2% vs. 3%; 0.098  
- Loose stools: 7% vs. 3% vs. 2%; p=0.189
- Limb tremor: 6% vs. 6% vs. 0%; p=0.051
- Eructation: 6% vs. 5% vs. 5%; p=0.959
- Lightheaded: 6% vs. 5% vs. 1%; p=0.186
- Urinary frequency: 6% vs. 3% vs. 3%; p=0.501
- Lethargy: 5% vs. 6% vs. 1%; p=0.181
- Blood pressure increased: 5% vs. 4% vs. 5%; p=0.917
- Upper respiratory infection: 3% vs. 6% vs. 4%; p=0.564
- Shakiness: 3% vs. 5% vs. 0%; p=0.094
- Back pain: 3% vs. 0% vs. 6%; p=0.038
- Anxiety: 2% vs. 10% vs. 4%; p=0.033 (venlafaxine vs. fluoxetine p<0.05)
- Coughing: 2% vs. 8% vs. 4%
- Agitation: 2% vs. 6% vs. 0%; p=0.029
- Nervousness: 2% vs. 5% vs. 2%; p=0.365
- Irritability: 2% vs. 5% vs. 0%; p=0.066
- Flu syndrome: 2% vs. 5% vs. 0%; p=0.066
- Weight decrease: 1% vs. 6% vs. 0%; p=0.011
- Nasal congestion: 0% vs. 5% vs. 3%; p=0.085
- Pruritus: 0% vs. 2% vs. 5%; p=0.052
- Rate of discontinuation due to AEs significantly greater in venlafaxine group compared with placebo (p=0.0017); no significant differences in fluoxetine vs. placebo (p=0.0666) or fluoxetine vs. venlafaxine (p=0.1838)

**QUALITY RATING:** Fair
## Evidence Table 13

### Subgroups

<table>
<thead>
<tr>
<th>STUDY: Authors: Schmitz JM et al.</th>
<th>Year: 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: US</td>
<td></td>
</tr>
<tr>
<td>FUNDING: National Institute on Drug Abuse and Department of Psychiatry and Behavioral Sciences, University of Texas-Houston</td>
<td></td>
</tr>
<tr>
<td>DESIGN: Study design: RCT</td>
<td>Setting: University hospital</td>
</tr>
<tr>
<td>Sample size: 68</td>
<td></td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
</tr>
<tr>
<td>Drug:</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Dose: 40 mg/d</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration: 12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Sample size: 34</td>
<td>34</td>
</tr>
<tr>
<td>INCLUSION: Adults 18 to 50; diagnosed with MDD according to DSM-III or IV; diagnosed dually with MDD and cocaine dependence; BDI score &gt; 10; English speaking; free of serious legal and medical problems</td>
<td></td>
</tr>
<tr>
<td>EXCLUSION: Current dependence on alcohol or any other psychoactive substance (except nicotine or cannabis); met criteria for current primary Axis I disorders other than depression</td>
<td></td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS: NR</td>
<td></td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td></td>
</tr>
<tr>
<td>Groups similar at baseline: Yes</td>
<td></td>
</tr>
<tr>
<td>Mean age: fluoxetine 37.2, placebo 37.4</td>
<td></td>
</tr>
<tr>
<td>Gender (female %): fluoxetine 41, placebo 44%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% white): fluoxetine 38%, placebo 56%</td>
<td></td>
</tr>
<tr>
<td>Other population characteristics:</td>
<td></td>
</tr>
</tbody>
</table>
Authors: Schmitz JM et al.
Year: 2001
Country: US

OUTCOME ASSESSMENT:

| Primary Outcome Measures: | Retention, BDI, HAM-D, compliance, tolerability |
|___________________________|______________________________________________|
| Secondary Outcome Measures: | cocaine use and depression |
| Timing of assessments:     | baseline and weekly |

RESULTS:

- No significant difference in response among depressed cocaine abusers
- More fluoxetine patients 'completed' treatment (defined as attending at least 50% or 12 of the 24 sessions) than placebo patients (52.9% vs. 41%, p = ns)
- The number of subjects who attended all 24 therapy sessions was the same in both groups
- Analysis of BDI scores showed a significant decrease in depressive symptoms during treatment, $F(11, 318)=2.52$, $p = 0.004$, but no medication effect. Similarly, there was a significant effect for time in HRSD scores from intake ($M=28.9$, $S.D.=8.1$) to posttreatment ($M=19.2$, $SD=11.4$), $F(2, 66)=13.8$, $p = 0.00001$, but no medication effect
- Mean percentage of urine samples positive for riboflavin was 78% for the fluoxetine and 79% for the placebo group (ns)

ANALYSIS:

- ITT: NR
- Post randomization exclusions: NR

ATTRITION:

- Loss to follow-up: fluoxetine 47%, placebo 59%
- Withdrawals due to adverse events: 0
- Withdrawals due to lack of efficacy: NR
- Loss to follow-up differential high: No

ADVERSE EVENTS:

- Weekly side effect scores were tested for group, time, and interaction effects using the REML mixed model ANCOVA with baseline scores as the covariate. There was an overall reduction during treatment, $F(10, 309)=4.8$, $p = 0.0001$, but no differences between the medication groups on reported side effects.
- The mean number of weekly side effects reported was 6.1 (S.D.=4.4) for the placebo group and 6.2 (S.D.=3.7) for the fluoxetine group.
- No participant in either group discontinued treatment prematurely because of AEs

QUALITY RATING:

- Poor
### Evidence Table 13

| **STUDY:** | Authors: Schöne W, et al.  
Year: 1993  
Country: Austria and Germany |
| **FUNDING:** | SmithKline, Beecham |
| **DESIGN:** | Study design: Randomized, double-blind trial  
Setting: Geriatric outpatients at 6 centers in Austria and Germany  
Sample size: 108 |
| **INTERVENTION:** | **Drug:** Paroxetine  
Dose: 20-40 mg/d  
Duration: 6 weeks  
Fluoxetine  
Dose: 20-60 mg/d  
Duration: 6 weeks |
| **INCLUSION:** | Age 65 or more; met DSM-IIR for MDD; HAM-D21 score > 18 at baseline |
| **EXCLUSION:** | Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Prohibited psychotropic meds except temazapam for sleep; other allowed nonpsychotropic medications not specifically reported |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
Mean age: 74, paroxetine: 74.3, fluoxetine: 73.7  
Gender (% female): 87%, paroxetine: 83%, fluoxetine: 90%  
Ethnicity: Not reported  
Other population characteristics: History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27% |
| Authors: Schöne W, et al.  
Year: 1993  
Country: Germany |
| --- |
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D 21, MADRS, CGI  
**Timing of assessments:** Days 7, 21, 42 |
| **RESULTS:** | • No significant difference in mean changes on HAM-D score  
• HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D 21): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03)  
• MADRS: no significant difference in mean change scores between groups  
• MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5% (p = 0.04) |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** Not reported  
**Withdrawals due to adverse events:** 12%; paroxetine: 11.1%, fluoxetine: 13.5%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event |
| **QUALITY RATING:** | Fair |
## Evidence Table 13

<table>
<thead>
<tr>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
<tr>
<td>Authors: Stewart DE et al.</td>
</tr>
<tr>
<td>Year: 2006</td>
</tr>
<tr>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
</tr>
<tr>
<td>Eli Lilly</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
</tr>
<tr>
<td>Study design: Pooled analysis</td>
</tr>
<tr>
<td>Number of patients: 1,622</td>
</tr>
<tr>
<td><strong>AIMS OF REVIEW:</strong></td>
</tr>
<tr>
<td>To assess the safety and tolerability of duloxetine in the treatment of MDD in male and female patients.</td>
</tr>
<tr>
<td><strong>STUDIES INCLUDED IN REVIEW</strong></td>
</tr>
<tr>
<td>Seven (5 published and 2 unpublished) placebo-controlled duloxetine trials</td>
</tr>
<tr>
<td><strong>TIME PERIOD COVERED:</strong></td>
</tr>
<tr>
<td>NR</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong></td>
</tr>
<tr>
<td>Double-blind, placebo controlled trials of duloxetine 7-9 weeks in length</td>
</tr>
<tr>
<td><strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong></td>
</tr>
<tr>
<td>Adult (≥ 18); DSM-IV diagnosis of MDD; HAM-D-17 total score ≥15; CGI-S score ≥4</td>
</tr>
</tbody>
</table>
**Authors:** Stewart DE et al.  
**Year:** 2006

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Duloxetine 40-120 mg/d vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAIN RESULTS:</strong></td>
<td></td>
</tr>
<tr>
<td>• No evidence of clinically meaningful sex differences in safety and tolerability of duloxetine</td>
<td></td>
</tr>
<tr>
<td>• Overall withdrawals males: 44% vs. 37.6%, p = 0.486</td>
<td></td>
</tr>
<tr>
<td>• Overall withdrawals females: 43.9% vs. 34.5%, p = 0.032</td>
<td></td>
</tr>
<tr>
<td>• Withdrawals due to AEs males: 18.6% vs. 5.4%, p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• Withdrawals due to AEs females: 13.5% vs. 5.0%, p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• Nausea rate among placebo-treated patients almost three times greater in females than in males (10.7% vs. 3.7%, p &lt; 0.008)</td>
<td></td>
</tr>
<tr>
<td>• Treatment-by-sex interactions for mean changes in BP not statistically significant</td>
<td></td>
</tr>
</tbody>
</table>

| **ADVERSE EVENTS:**              | See Main Results                   |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | No; authors state that these 7 studies represent all currently available data from acute-phase studies of duloxetine in depressed patients that were carried out in the US |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | NR                                 |
| **QUALITY RATING:**              | Fair                               |
### Evidence Table 13

#### Subgroups

| STUDY:          | Authors: Strik J et al.
|                 | Year: 2006
|                 | Country: The Netherlands
| FUNDING:        | Eli Lilly; Dutch Prevention Fund; Maastricht University Hospital Research Fund
| DESIGN:         | Study design: RCT
|                 | Setting: Hospitals (2)
|                 | Sample size: 54
| INTERVENTION:   | Drug: Fluoxetine
|                 | Dose: 20-60 mg
|                 | Duration: 9 wk acute; 16 wk continuation
|                 | Sample size: 27
|                 | Placebo
|                 | N/A
|                 | 9 wk acute; 16 wk continuation
|                 | Sample size: 27
| INCLUSION:      | 18 and 75 years, clinical picture typical of MI, ECG changes specific for MI and a maximum plasma concentration of aspartate aminotransferase (ASAT) twice the upper normal range (80 U/liter); met DSM-III-R criteria for a major depressive episode within the first 12 months post-MI; HAM-D17 score > 17
| EXCLUSION:      | Psychotic symptomatology; a second psychiatric diagnosis; history of mania; pregnancy or lactation; life-threatening noncardiac physical illness; concurrent use of psychotropic drugs; hypersensitivity to fluoxetine; liver or severe kidney dysfunction; ATVI < 20 cm; right ventricular filling pressure > 30 mm HG
| OTHER MEDICATIONS/INTERVENTIONS: | Aspirin, lipophilic β-blockers, benzodiazepines, isosorbide nitrate, cholesterol-lowering medication, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, anticoagulation agents (other than PAI) and hydrophilic β-blockers
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes
|                 | Mean age: Fluoxetine 54.1 placebo 58.7
|                 | Gender (female %): Overall 30; fluoxetine 22, placebo 37
|                 | Ethnicity: NR
|                 | Other population characteristics: HAM-D fluoxetine 22.0, placebo 21.2
Authors: Strik et al.  
Year: 2006  
Country: The Netherlands

### OUTCOME ASSESSMENT:
**Primary Outcome Measures:** HAM-D<sub>17</sub> response and remission; SCL-90 Hostility Scale  
**Secondary Outcome Measures:** Cognitive performance  
**Timing of assessments:** Baseline and 9 weeks (for HAMD)

### RESULTS:
#### Fluoxetine vs. placebo 9 week results:
- HAM-D<sub>17</sub> score decrease: -8.34 vs. -5.84 (difference = 2.50); \(p = 0.06\)
- HAM-D responders (n): 9 vs. 8; \(p = 0.39\)
- HAM-D remitters (n): 3 vs. 1; \(p = 0.15\)
- Mean decrease in SCL-90 hostility score: -2.61 vs. -1.18 (difference = 1.44); \(p = 0.08\)
- No significant differences between groups in cognitive test scores

#### Fluoxetine vs. placebo 25 week results:
- HAM-D<sub>17</sub> score decrease: -9.65 vs. -6.92; \(p = 0.06\)
- HAM-D responders: 48% vs. 26%; \(p = 0.05\)
- HAM-D remitters: 26% vs. 14.8%; \(p = 0.06\)
- Mean decrease in SCL-90 hostility score: -2.44 vs. -0.07; \(p = 0.02\)

### ANALYSIS:
**ITT:** Yes  
**Post randomization exclusions:**  
**Loss to follow-up differential high:** No

### ATTRITION:

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loss to follow-up:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 weeks</td>
<td>2 (7.4%)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>25 weeks</td>
<td>18.5%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 weeks</td>
<td>0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>25 weeks</td>
<td>7.4%</td>
<td>11.1%</td>
</tr>
<tr>
<td><strong>Withdrawals due to lack of efficacy:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:
- Fluoxetine vs. placebo (n)  
  - Chest pain: 5 vs. 4; \(p = 1.0\)  
  - GI complaints: 8 vs. 6; \(p = 0.54\)  
  - Agitation: 6 vs. 3; \(p = 0.47\)  
  - Rehospitalization for a cardiac event: 1 vs. 6; \(p = 0.13\)  
  - Decrease in ATVI: 8 vs. 0; \(p = 0.02\)

### QUALITY RATING:
**Good**
## Evidence Table 13

### Subgroups

| STUDY: | Authors: Thase et al.  
Year: 2005  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Pooled data from 8 randomized, double-blind, placebo controlled trials  
Setting: Various  
Sample size: 2045 |
| INTERVENTION: |  
Drug:  
Dose: 75 - 375mg/d  
Duration: 6-12 wks  
Sample size: 851  
SSRIs (fluoxetine, paroxetine, fluvoxamine)  
Dose: varying  
Duration: 6-12 wks  
Sample size: 748  
Placebo  
Dose: N/A  
Duration: 6-12 weeks  
Sample size: 446 |
| INCLUSION: | 18 years or older with DSM-IV diagnosed MDD; HAM-D > 20 |
| EXCLUSION: | Malignancies; history of significant or unstable cardiovascular, renal, endocrine or hepatic diseases, seizure disorders; alcohol or substance abuse; pregnant or nursing; any investigational or anti-psychotic drugs. |
| OTHER MEDICATIONS/INTERVENTIONS: | As required |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes, except within the older group men receiving placebo were younger than those taking anti-depressants and within younger male placebo group CGIS were significantly lower.  
Mean age: 42  
Gender: 64% female  
Ethnicity: NR |
Authors: Thase et al.  
Year: 2005  
Country: Multinational

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Remission (HAM-D ≤ 7)  
Timing of assessments: Study days 7,14,21,28,42,56 |
|---------------------|--------------------------------------------------|
| RESULTS:            | Remission rates on venlafaxine therapy were not affected by age or sex.  
Poorer SSRI response in the older age group (Wald chi-square = 4.21, df = 1, \(p = 0.04\))  
With SSRIs, older women age > 50 had a 28% chance of remission compared to younger women, 36% |
| ANALYSIS:           | ITT: N/A  
Post randomization exclusions: Cannot tell |
| ATTRITION:          | Overall | Mirtazapine | Placebo |
| Loss to follow-up:  | NR      | NR          | NR      |
| Withdrawals due to adverse events: | NR | NR | NR |
| Withdrawals due to lack of efficacy: | NR | NR | NR |
| Loss to follow-up differential high: | NR | NR | NR |
| ADVERSE EVENTS:     | NR      |
| QUALITY RATING:     | Fair    |
# Evidence Table 13

## Subgroups

| STUDY: | Authors: Ushiroyama T, et al.<sup>12</sup>  
Year: 2004  
Country: Japan |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
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</table>
| DESIGN: | Study design: RCT  
Setting: University hospital clinic  
Sample size: 105 |
| INTERVENTION: | Fluvoxamine  
Dose: 50 mg/day  
Duration: 3 months  
Sample size: 53  
Paroxetine  
Dose: 20 mg/day  
Duration: 3 months  
Sample size: 52 |
| INCLUSION: | Perimenopausal women; met DSM-IV criteria for major depression; HAM-D ≥ 13 |
| EXCLUSION: | Serious organic or neurological disorder; current psychoactive drug use; alcoholism |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: yes  
Mean age: fluvoxamine: 51.1; paroxetine: 51.4  
Gender (female %): 100  
Ethnicity: 100% Japanese  
Other population characteristics: Age at menopause: fluvoxamine: 50.4; paroxetine: 49.9 |
| Authors: Ushiroyama et al.  
Year: 2004  
Country: Japan |
|---|
| OUTCOME ASSESSMENT: | Primary Outcome Measures:  
Secondary Outcome Measures:  
Timing of assessments: |
| RESULTS: | • Significant reduction in HAM-D and HAM-A scores in both groups; no significant differences between groups  
• HAM-D at endpoint (fluvoxamine vs. paroxetine): 9.3 vs. 10.1; p=0.45  
• HAM-A at endpoint (fluvoxamine vs. paroxetine): 6.5 vs. 7.0; p=0.53  
• Reduction of VAS score at endpoint (fluvoxamine vs. paroxetine): 33.1 vs. 42.8; p=0.0338  
• A significant difference observed in % change for hot flashes (fluvoxamine vs. paroxetine): -81.1 vs. -66.8; p<0.01 |
| ANALYSIS: | ITT: yes  
Post randomization exclusions: NR |
| ATTRITION: | Loss to follow-up: fluvoxamine: 18.9%; paroxetine: 30.8%  
Withdrawals due to adverse events: fluvoxamine: 9.4%; paroxetine: 5.8%  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | • NR |
| QUALITY RATING: | Fair |
**Evidence Table 13**

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<tr>
<th>Subgroups</th>
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</table>
| STUDY:    | Authors: Wagner GJ, et. al.\(^{241}\)  
Year: 1998  
Country: US |
| FUNDING:  | National Institute for Mental Health |
| DESIGN:   | Study design: RCT  
Setting: Not reported  
Sample size: 118 |
| INTERVENTION: |  
**Drug:**  
Fluoxetine  
Placebo  
20-80 mg/d  
N/A  
8 weeks  
8 weeks |
| INCLUSION: | HIV pos; DSM-IV diagnosis of major depression; under care of HIV physician |
| EXCLUSION: | History of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; unstable medical condition; severe cognitive impairment |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean Age: 39  
Gender (% female): 2%  
Ethnicity: White: 67%, black: 19%, Latino: 14%  
Other population characteristics: All HIV + |
**Outcomes Assessment:**

**Measures:** HAM-D, CGI, BSI (Brief Symptom Inventory)

**Timing of assessments:** Not reported

**Results:**

- Responders in the fluoxetine group among patients who completed study: white: 84%, black: 50%, Latino: 67%
- Dosages did not differ significantly comparing whites/blacks (p < 0.05)
- Responders among patients who completed the placebo group: white: 43%, black: 36%, Latino: 80%
- In a direct linear regression model ethnicity was not a significant predictor of study completion (p = 0.08)
- Attrition rate was significantly higher among Latinos (p < 0.05), white: 28%, black: 14%, Latino: 52%
- When adjusting for covariates HAM-D score was only predictor of attrition

**Analysis:**

**ITT:** No

**Post randomization exclusions:** Not reported

**Attrition:**

**Loss to follow-up:** white: 38%, black: 14%, Latino: 52% (p < 0.05)

**Withdrawals due to adverse events:** Not reported

**Loss to follow-up differential high:** Yes

**Adverse Events:**

There was no significant difference in the frequency of adverse events, white: 53%, black: 50%, Latino: 35%

**Quality Rating:** Poor
## Evidence Table 13

### Subgroups

| STUDY: | Authors: Weihs KL, et al., Doraiswamy PM, et al.\textsuperscript{85, 86}  
Year: 2000, 2001  
Country: US |
<table>
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<tr>
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<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome</td>
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</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 100 |
| INTERVENTION: | **Drug:** Bupropion SR  
Dose: 100-300 mg/d  
(Mean daily dose: 197 mg/d)  
Duration: 6 weeks  
Paroxetine  
Dose: 10-40 mg/d  
(Mean daily dose: 22 mg/d)  
Duration: 6 weeks |
| INCLUSION: | 60 yrs or older; DSM-IV criteria for major depression; recurrent episode of non-psychotic depression; ≥ 18 on HAM-D-21; duration at least 8 weeks not more than 24 months |
| EXCLUSION: | History of seizures; dementia; alcohol or substance abuse; existing suicidal risk; clinically relevant; unstable medical disorder; psychoactive drugs within 1 week or investigational drugs within 4 weeks; taking other drugs known to lower seizure threshold; anorexia or bulimia; previous treatment with buproprion or paroxetine |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: Bupropion sr: 69.2, paroxetine: 71.0  
Gender (% female): Bupropion sr: 54, paroxetine: 60  
Ethnicity: (white%) Bupropion sr: 98, paroxetine: 90  
Other population characteristics: Prior antidepressant use for current episode: buproprion sr: 17%, paroxetine: 12% |
**Authors:** Weihs KL, et al., Doraiswamy PM et al.  
**Year:** 2000, 2001  
**Country:** US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures and timing of assessments: HAM-D, CGI-S, CGI-I, HAM-A weekly for 6 weeks, Short Form 36 Health Survey (SF-36), Quality of Life Depression Scale (QLDS) at baseline and week 6</th>
</tr>
</thead>
</table>

| RESULTS: | • No significant differences in any outcome measures between the treatment groups (LOCF and observed)  
• Response rates (≥ 50% reduction in HAM-D) were similar in both groups: bupropion sr: 71%, paroxetine: 77%  
• CGIS, CGI, and HAMA were all similar at each week of the study  
• No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at endpoint  
• Overall significant improvement in QLDS and QOL at day 42 (p < 0.0001) |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| ATTRITION: | Loss to follow-up: 16%; bupropion sr: 16.6%, paroxetine: 15.4%  
Withdrawals due to adverse events: Bupropion sr: 8.3%, paroxetine: 5.8%  
Loss to follow-up differential high: No |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| ADVERSE EVENTS: | • Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; p < 0.05), diarrhea (21% vs. 6%; p < 0.05), and constipation (15% vs. 4%; p < 0.05)  
• More than 10% in either group reported headache, insomnia, dry mouth, nausea, dizziness, and agitation  
• Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Fair</th>
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<tbody>
<tr>
<td>Evidence Table 13</td>
<td>Subgroups</td>
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</tr>
</tbody>
</table>
| STUDY:            | **Authors:** Whittington CJ, et. al.\textsuperscript{115}  
                   **Year:** 2004  
                   **Country:** UK |
| FUNDING:          | NICE (National Institute for Clinical Excellence) |
| DESIGN:           | **Study design:** Systematic review, SSRI versus placebo  
                   **Number of patients:** 2145 |
| AIMS OF REVIEW:   | To evaluate risk versus benefit of SSRI’s when used to treat childhood depression |
| STUDIES INCLUDED IN META-ANALYSIS | Emslie GJ et. al., 1997, Emslie GJ et. al., 2002, Keller MB et. al., 2001, Wagner, KD et. al., 2003. Also unpublished results included in a report by the Committee on Safety of Medicines (UK) |
| TIME PERIOD COVERED: | All studies up to 2003 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Patients randomized to either an SSRI or placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Included trials had patients aged 5-18 years old; no other population information given |
| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Fluoxetine vs. placebo (2 trials); paroxetine vs. placebo (3 trials); sertraline vs. placebo (2 trials); citalopram vs. placebo (1 trial); venlafaxine vs. placebo (3 trials) |
| MAIN RESULTS: | • Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile  
• Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response  
• Unpublished data on sertraline in children indicate it is not as effective as reported in published trials  
• One unpublished study of citalopram a negative risk-benefit profile  
• Combined published and unpublished data of venlafaxine suggested a negative risk-benefit profile |
| ADVERSE EVENTS: | Paroxetine, sertraline, citalopram, and venlafaxine all indicated an increased risk of adverse events |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Fair |
### Evidence Table 13

#### Subgroups

| STUDY: | Authors: Wise TN et al.282, 283  
Year: 2007  
Country: US |
<table>
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<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly and Boehringer-Ingelheim GmbH</td>
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</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multicenter  
Sample size: 233 (subpopulation with any of 3 comorbidities of interest) |
| INTERVENTION: | Drug: Duloxetine  
Dose: 60 mg/day  
Duration: 8 weeks  
Sample size: 155  
Placebo  
Dose: N/A  
Duration: 8 weeks  
Sample size: 78 |
| INCLUSION: | ≥ 65 years; met DSM-IV criteria for MDD; HAM-D17 ≥ 18 at visits 1 and 2, MMSE score ≥ 20 with or without mild dementia and at least one previous episode of major depression |
| EXCLUSION: | Current primary axis I diagnosis other than MDD or mild dementia (including dysthymia or psychotic depression); previous diagnosis of psychotic disorder; organic mental disorder, moderate-to-severe dementia or mental retardation diagnosis; serious or unstable medical illness; psychological condition or clinically significant lab abnormality that would compromise participation in study or be likely to lead to hospitalization during study; ALT, AST, or GGT > 1.5 times upper limit of normal |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: No  
Mean age: 73.4  
Gender (female %): 64.4  
Ethnicity (% white): 78.5  
Other population characteristics:  
Vascular disease: duloxetine: 44%, placebo: 56%  
Diabetes: duloxetine: 23%, placebo: 14%  
Arthritis: duloxetine: 75%, placebo: 71% |
**Authors:** Wise TN et al.  
**Year:** 2007  
**Country:** US

| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** VLRT, SDST, 2DCT, LNST  
**Secondary Outcome Measures:** GDS, HAM-D_{17}, VAS for pain, CGI-S, SF-36  
**Timing of assessments:** |
|--------------------------|---------------------------------------------------------------|

| **RESULTS:** |  
• No statistically significant treatment-by-comorbidity interactions for any comorbidity (p=0.266)  
• No statistically significant treatment-by-comorbidity interactions for GDS or HAM-D_{17} total scores  
• No statistically significant treatment-by-comorbidity interactions for either response or remission rate  
• No statistically significant treatment-by-comorbidity interactions for SF-36 physical component summary |

| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** NR |

| **ATTRITION:** | **Loss to follow-up:** NR for subpopulations (21.7% vs. 23.1% for overall study population)  
**Withdrawals due to adverse events:** NR for subpopulations (9.7% vs. 8.7% for total study population)  
**Withdrawals due to lack of efficacy:** NR for subpopulations (2.9% vs. 9.6% for total study population)  
**Loss to follow-up differential high:** No |

| **ADVERSE EVENTS:** |  
• No significant treatment-by-comorbidity interactions for incidences of discontinuation because of an AE  
• There was a statistically significant treatment-by-comorbidity interaction in TEAEs (data NR; p=0.030)  
• There was no statistically significant treatment-by-comorbidity interaction for the incidence of any of the common TEAEs |

| **QUALITY RATING:** | **Fair** |
References


127. Montgomery SA, Kasper S, Stein DJ, Bang Hedegaard K, Lemming OM. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol 2001;16(2):75-86.
130. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database of Systematic Reviews 2008(1).


