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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** | **Assessments** | **Study Appraisals and Quality Rating** |
| Author:  Aursnes et al., 2005174  Country and setting:  NR  Funding:  None | Study design:  Pooled analysis  Number of Patients:  1,466  Studies Included:  16 studies with unpublished data | Included Studies:  Clinical data on PAR as presented to world's drug regulatory agencies in 1989  Included Populations  NR  Interventions:  PAR vs. PBO, no other info provided | Study Results:  7 suicide attempts in patients on drug and 1 in a patient on PBO. Probability of increased intensity of suicide attempts per yr in adults taking PAR was 0.90 with a "pessimistic" prior, and somewhat less with 2 more neutral priors | NR | Publication Bias:  No  Heterogeneity:  No | Standard Method of Study Appraisals:  NR  Quality Rating:  Fair |

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| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
| Author, Year:  Barbui et al., 2009175  Country and setting:  US  Funding:  Fondazione Cariverona  Aims of Review:  To quantify the risk of completed or attempted suicide among people in different age groups with depression after exposure to SSRIs.  Quality Rating:  Good | Study design:  Systematic Review  Number of Patients:  NR  Studies Included:  Gibbons et al., 2007  Olfson et al., 2006.  Olfson and Marcus, 2008  Rahme et al., 2008  Sondergard et al., 2007  Sondergard et al., 2006  Tiihonen et al., 2006  Valuck et al., 2004 | Characteristics of Included Studies:  Observational cohort and case–control studies in any language that reported data on completed or attempted suicide among people exposed to SSRIs and among those who were not exposed to antidepressants; studies that reported relative risk [RR] estimates suitable for re-analysis; studies that used International Classification of Disease (ICD,ninth or tenth revision) definitions of completed or attempted suicide  Characteristics of Included Populations  Either sex and any age with a diagnosis of major depression.  Characteristics of Interventions:  Observational cohort (6)and case– control studies (2) | Study Results:  The risk was decreased among adults (OR 0.57,95% CI, 0.47–0.70). Among people aged 65 or more years, exposure to SSRIs had a protective effect (OR 0.46, 95% CI, 0.27–0.79). Sensitivity analyses did not change these findings. In particular, for studies that used completed suicide as an outcome, decreased risk among adults (OR 0.66, 95% CI, 0.52–0.83) and older people (OR 0.53, 95% CI, 0.26–1.06). Among adults, no individual antidepressant was significantly associated with completed or attempted suicide.  Random-effect meta-analysis of the risk of suicide attempt and completion associated with the use of individual antidepressants compared with no exposure to any antidepressants.  Citalopram OR 0.87 (0.58–1.29)  Fluoxetine OR (95% CI) 0.83 (0.32–2.14)  Fluvoxamine OR (95% CI) 1.39 (0.66–2.92)  Paroxetine OR (95% CI) 0.91 (0.52–1.58)  Sertraline OR (95% CI) 0.46 (0.09–2.23)  Venlafaxine OR (95% CI) 1.32 (0.74–2.35) | Adverse Events:  N/A |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author:**  Brambilla et al., 2005176  **Country and** **setting**:  NR  **Funding:**  Multinational  **Research objective:**  To assess frequency of side-effects in FLUOX compared to other SSRIs, TCAs and other anti-depressants | **Study design:**  Meta-analysis  **Number of Patients:**  15,920  **Studies Included:**  131 studies | **Included Studies:**   * All studies with random assigned patients that received FLUOX or any other anti-depressant * Cross-over studies and those with patients with concomitant medical illness were excluded   **Included Populations**  Patients with MDD  **Interventions:**   * FLUOX vs. tricyclic antidepressant (65 studies) * FLUOX vs. SSRI (22 studies) * FLUOX vs. another AD (44 studies) | **Study Results:**   * 59.4% of patients treated with FLUOX and 59.3% of patients treated with other SSRIs experienced AEs.RR, 1.00 95% CI, 0.95, 1.04 * FLUOX 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 * FLUOX had less side effects (50.9%) than TCAs (60.3%) RR, = 0.84 95% CI, 0.76 to 0.94(*P* = 0.03) * FLUOX patients had more activating and GI adverse effects and less cholinergic side effects than other ADs | NR | **Publication Bias:**  Yes  **Heterogeneity**:  Yes | **Standard Method of Study Appraisals:**  Yes  **Comprehensive Search Strategy:**  Yes  **Quality Rating:**  Good |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| Author:  Bush et al., 2005229  Country and setting:  Multinational  Funding:  AHRQ  Research objective:  To examine role of depression post-MI | Study design:  Systematic review  Number of Patients:  NR  Studies Included:  Studies (86) have examined depression or depressive symptoms in patients after MI and focuses on prevalence, clinical significance, treatment, and methods of evaluating condition | Included Studies:  See above  Included Populations  Patients suffering from myocardial infarction and depression  Interventions:  SSRIs and therapy | Study Results:  In post-MI patients with depression, selective serotonin reuptake inhibitors improve depression and some surrogate markers of cardiac risk, but no studies of sufficient power address question of whether treatment improves survival | Adverse Events:  NR | Publication Bias:  Yes  Heterogeneity:  Yes | Standard Method of Study Appraisals:  Yes  Comprehensive Search Strategy:  MEDLINE®, Cochrane CENTRAL Register of Controlled Trials (Issue 1, 2003), Cochrane Database of Methodology Reviews (CDMR®), Cumulative Index of Nursing and Allied Health Literature (CINAHL®), Psychological Abstracts (PsycINFO®), and EMBASE  Quality Rating:  Fair |

| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
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| Author, Year:  Cipriani et al., 2010178  Country and setting:  Multinational  Funding:  Cochrane  Aims of Review:  1) the efficacy of sertraline in comparison with other  antidepressive agents in alleviating the acute symptoms of MDD  2) the acceptability of treatment with sertraline in  comparison with other antidepressive agents  3)e the adverse effects of sertrali  Quality Rating:  Good | Study design:  Systematic Review and Meta-analysis  Number of Patients:  See adverse events  Studies Included: | Characteristics of Included Studies:  Mostly RCTs that compared sertraline to another drug  Characteristics of Included Populations  Patients aged 18 or older, of both sexes with a primary diagnosis  of major depression  Characteristics of Interventions:  Sertraline (as monotherapy).  Comparator interventions  All other antidepressive agents in the treatment of acute depression,  including:  1) conventional tricyclic ADs (TCAs)  2) heterocyclic ADs (e.g. maprotiline)  3) SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram)  4) newer antidepressants (SNRIs such as venlafaxine, duloxetine,  milnacipran; MAOIs or newer agents such as mirtazapine, bupropion,  reboxetine; and non-conventional ADs, such as herbal products  - e.g. hypericum). | Study Results:  See Aes | Adverse Events:  Constipation - sertraline vs paroxetine (OR 0.31, 95% CI, 0.16 to 0.58, P = 0.0002; 2 trials, 545 participants)  diarrhoea - sertraline vs. escitalopram (OR 2.10, 95% CI, 1.22 to 3.61, P = 0.007; 2 trials, 489 participants) or paroxetine (OR 2.51, 95% CI, 1.66 to 3.80, P<0.0001; 2 trials, 545 participants)  Urinary problems - sertraline vs. paroxetine (OR0.09, 95%CI 0.01 to 0.68, P = 0.02; 1 trial, 353 participants)  paroxetine, sertraline vs paroxetine anorgasmia (OR 0.19, 95% CI, .04 to 0.89, p = 0.03; 1 trial, 353 participants) ejaculation disorder (OR 0.29, 95% CI, 0.14 to 0.60, p = 0.0009; 2 trials, 545 participants) or tremor (OR 0.55, 95% CI, 0.32 to 0.94, p = 0.03, 2 trials, 545 participants  Constipation - Sertraline vs. venlafaxine (OR 0.05, 95% CI, 0.00 to 0.85, P = 0.04; 1 trial, 89 participants)  Diarrhoea - sertraline vs. bupropion (OR 3.88, 95%CI 1.50 to 10.07, P = 0.005; 3 trials, 727 participants), or mirtazapine (OR 2.74, 95% CI, 1.52 to 4.97, P = 0.0009; 2 trials, 596 participants) d) Dry mouth - sertraline vs. venlafaxine (OR 0.02, 95% CI, 0.00 to 0.33, P = 0.006; 1 trial, 89 participants)  Insomnia - sertraline vs. mirtazapine (OR 2.72, 95% CI, 1.15 to 6.43, P = 0.02; 2 trials, 596 participants)  Nausea - sertraline vs. bupropion (OR 2.14, 95% CI, 1.12 to 4.08, P = 0.02; 3 trials, 727 participants), or mirtazapine (OR 3.68, 95% CI, 2.10 to 6.45,  P<0.00001; 2 trials, 596 participants)  Sleepiness/drowsiness - sertraline vs. bupropion (OR 5.10, 95% CI, 2.53 to 10.31, P<0.00001; 3 trials, 727 participants); vs. mirtazapine (OR 0.33, 95% CI, 0.20 to 0.54, P<0.00001; 2 trials, 596 participants)  mirtazapine vs sertraline appetite increase (OR 0.20, 95% CI, 0.09 to 0.46, p = 0.0002; 2 trials, 596 participants,fatigue (OR 0.44, 95% CI, 0.25 to 0.77, p = 0.004; 2 trials, 596 participants (see Analysis 31.4) and weight gain (OR 0.18, 95% CI, 0.09 to 0.37, p<0.00001; 2 trials, 596 participants, and gastrointestinal symptoms or dyspepsia (OR 3.54, 95% CI, 1.52 to 8.23, p = 0.003; 1 trial,  250 participants, headache (OR 1.53, 95% CI, 1.01 to 2.30, p = 0.04; 2 trials, 596 participants, libido decrease (OR 5.44, 95% CI, 1.17 to 25.19, p = 0.03; 1 trial, 346 participants, sweating increase (OR  4.86, 95% CI, 1.04 to 22.85, p = 0.05; 1 trial, 346 participants  nefazodone vs. sertraline dizziness (OR 0.17, 95%CI 0.06 to 0.44, p = 0.0003; 1 trial |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| Author:  CSM Expert Working Group, 2004183  Country and setting:  UK  Funding:  Not reported  Research objective:  Evaluating safety of SSRI antidepressants (CIT, ESC, FLUOX, FLUV, MIR, PAR, SER, VEN) | Study design:  Systematic review  Number of Patients:  NR  Studies Included:  All published and unpublished trials including output from GPRD- 477 studies  Intervention:  D1: VEN  D2: Other SSRIs | **Characteristics of Included Studies:**   * Studies that included safety information on suicide, withdrawal, and dose response   **Characteristics of Included Populations**   * Individuals taking SSRIs   **Characteristics of Interventions:**  SSRIs | Study Results:  Suicide  No diffs in risk among second-generation antidepressants  Withdrawal  Based on observational studies, spontaneous reporting data, and clinical trials data, experts concluded that discontinuation syndromes occur most commonly with PAR and VEN and least commonly with FLUOX | N/A | **Publication Bias:**  No- however review was designed to eliminate publication bias  **Heterogeneity**:  Yes | **Standard Method of Study Appraisals:**  Yes  **Comprehensive Search Strategy:**  Clinical trial data from pharmaceutical companies, spontaneous reporting data, GPRD, expert evidence, regular searches of published literature  Quality Rating:  Good |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author:**  Fergusson et al., 2005190  **Country and setting:**  Canada  **Funding:**  Canadian Institutes of Health Research  **Research objective:**  To establish if an association exists between SSRI use and suicide attempts | **Study design**:  Systematic review  **Number of Patients:**  36,445  **Studies Included**:  345 RCTs | **Included Studies:**  RCTs comparing an SSRI with either PBO or an active non-SSRI  **Included Populations**   * All patients included in trials comparing SSRIs to either PBO or non-SSRI control * No age, gender, or diagnosis restrictions   **Interventions:**  Patients randomized to either an SSRI, PBO, or non-SSRI control for any clinical condition | **Study Results:**  A sig increase in odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving PBO  (OR, 2.28 (95% CI, 1.144 - 4.55) *P =* 0.02)  No diffs in actual suicides between SSRIs and PBO were found  (OR, 0.95; 95%CI, 0.24-3.78)  No sig diff found in odds of suicide attempts between patients receiving SSRIs and patients receiving tricyclic antidepressants (OR, 0.88 (95% CI, 0.54 - 1.42) | NR | **Publication Bias:**  NR  **Heterogeneity:**  Yes | **Standard Method of Study Appraisals:**  Yes--independent review of all citations by 3 authors  **Comprehensive Search Strategy:**  Yes  Systematic literature search to identify all RCTs of SSRIs indexed on Medline between 1967 and 2003; search of Cochrane Collaboration's register of controlled trials for trials produced by Cochrane depression, anxiety, and neurosis group; reviewed biliographies of 3 systematic reviews to identify relevant trials and reports  **Quality Rating:**  Good |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author**:  Greist et al., 2004193  **Country and setting:**  US (6 studies); Europse (2 studies)  **Funding:**  Eli Lilly  **Research objective:**  To assess incidence, severity and onset of nausea among MDD patients treated with DUL | **Study design:**  Pooled analysis  **Number of Patients:**  2,345  **Studies Included:**   * Detke et al., 2002162 * Detke et al., 2002163 * Goldstein et al., 200244 * Goldstein et al., 2004265 * 4 unpublished studies submitted for FDA approval of DUL | **Included Studies:**  Double-blind, randomized, PBO or active-controlled trials of DUL  **Included Populations**  Adult outpatients with MDD  **Interventions:**   * Duloxetine (40-120 mg/d) vs. Placebo (8 studies) * Duloxetine (40-120 mg/d) vs. Paroxetine (20 mg/d) (4 studies) * Duloxetine (120 mg/d) vs. Fluoxetine (20 mg/d) (2 studies) | **Study Results:**  No sig diffs in nausea between DUL (40-120 mg/d), PAR (20 mg/d) (14.4% vs. 12%, *P* -NR), and FLUOX (20mg) (17.1% vs. 15.7%, *P* -NR)  No sig diffs between DUL (120 mg/d) and FLUOX (20 mg/d) (17.1% vs. 15.7%, *P* -NR)  Sig more DUL- than PBO-treated patients reported nausea (19% vs. 6.9%, *P*< 0.001)  Incidence of treatment-emergent nausea dudring 6-mo continuation of DUL (80 mg/d or 120 mg/d) was similar to PBO (2.1% vs. 1.3% vs. 1.6%)  Following abrupt discontinuation after 8 mos of treatment, nausea was reported by 1.6% of DUL (120 mg/d) patients vs. 0% for those receiving DUL (80 mg/d) and 0% for PBO | NR | **Publication Bias**:  No  **Heterogeneity**:  No | **Standard Method of Study Appraisals:**  NR  **Comprehensive Search Strategy:**  No; analysis of all published and unpublished trials  **Quality Rating:**  Fair |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author:**  Gunnell et al., 2005194  **Country and setting:**  Multinational  **Funding:**  NR  **Research objective**:  To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults | **Study design:**  Meta-analysis  **Number of Patients:**  40,826  **Studies Included:**   * Published and unpublished data submitted by pharmaceutical companies to MHRA (2004) * 342 PBO controlled trials included in report – citations not given in bibliography | **Included Studies:**  Randomized, PBO controlled trials of SSRIs (CIT, ESC, FLUOX, FLUV, PAR, and SER) submitted by pharmaceutical companies  **Included Populations**  Adult patients with various indications included in trials comparing SSRIs to PBO  **Interventions:**  Patients randomized to either SSRI or PBO | **Study Results:**  No sig diff was found between SSRI treatment and PBO treatment in odds ratios for suicide (OR, 0.85 CI, 0.2 to 3.4), or suicidal thought (OR, 0.77 CI, 0.37 to 1.55)  Non-fatal self harm (OR, 1.57 CI, 0.99 to 2.55) was more common in SSRI-treated than in PBO treated patients but did not reach statistical significance. For non-fatal self-harm NNH is 759 | NR | **Publication Bias:**  Yes  **Heterogeneity:**  Yes, vaguely | **Standard Method of Study Appraisals:**  Yes  **Comprehensive Search Strategy:**  No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies)  **Quality Rating:**  Good |

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| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
| Author, Year:  Kasper et al., 2009200  Country and setting:  NR  Funding:  H. Lundbeck A/S  Aims of Review:  To analyze pooled data from two previous studies comparing escitalopram to paroxetine for the long-term treatment of MDD.  Quality Rating:  Fair | Study design:  Post-hoc pooled analysis of data from two 6-month RCTs in patients with MDD.  Number of Patients:  777  Studies Included:  Baldwin, D.S., Cooper, J.A., Huusom, A.K., Hindmarch, I., 2006. A  double-blind, randomized, parallel-group, flexible-dose study to  evaluate the tolerability, efficacy and effects of treatment  discontinuation with escitalopram and paroxetine in patients with  major depressive disorder. Int. Clin. Psychopharmacol. 21, 159–169.  Boulenger, J.P., Huusom, A.K., Florea, I., Baekdal, T., Sarchiapone, M., 2006. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely  depressed patients. Curr. Med. Res. Opin. 22, 1331–1341. | Characteristics of Included Studies:  -RCTs  -24-week and 27-week trials  -Compared escitalopram to paroxetine  Characteristics of Included Populations  -Treatment groups had a mean age of 44.6 + or - 13.2 yrs  -Baseline MADRS total score of 32.8 + or - 4.7  -Women comprised approx 70% of each group  -No significant or clinically relevant differences at baseline between patients treated with escitalopram or paroxetine  Characteristics of Interventions:  Escitalopram 10-20 mg/d  Paroxetine 20-30 mg/d | Study Results:  see adverse events (KQ4 only) | Adverse Events:  -No differences in weight gain between treatmetn groups  -There were no statistically significant differences between treatment groups  -Headache and nausea were the most frequent AEs (~20%)  -The most common AEs (>10 patients in total) reported during the taper period were:  -dizziness (escitalopram 12, paroxetine 15)  -headache (escitalopram6, paroxetine 11)  -nausea (escitalopram 4, paroxetine 7)  -depression (escitalopram 7, paroxetine 4) |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events (%)** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author:**  Khan et al., 2003202  **Country and setting:**  US  **Funding:**  NR  **Research objective:** Compare suicide rates among depressed patients | **Study design:**  Meta-analysis  **Number of Patients:**  48,277  **Studies Included:**   * Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs * 2000 publication reports on 1987 to 1997 (same data) | **Included Studies:**  FDA clinical trial data  **Included Populations**   * Major depression according to  DSM-III-R criteria * Minimum score of 18 or 20 on HAM-D-17 or HAM-D-21   **Interventions:**  FLUOX  SER  PAR  CIT  FLUV  NEF  MIR  BUP  VEN  Imipramine  Amitrptyline  Maprotiline  TRA  Mianserin  Dothiepin | **Study Results:**  No statistically sig diff in suicide rates between SSRIs, other antidepressants, and PBO (*P* > 0.05)  Absolute Suicide Rate   * SSRI: 0.15% (0.10-0.20% 95% CI) * “Other”: 0.20% (0.09-0.27% 95% CI) * PBO: 0.10% (0.01-0.19% 95% CI) * *P* > 0.05 for diff   Suicide Rate by Patient Exposure Yrs (PEY)   * SSRI: 0.59%/PEY (0.31-0.87 95% CI) * “Other”: 0.76%/PEY (0.49-1.03 95% CI) * PBO: 0.45%/PEY (0.01-0.89 95% CI) * *P* > 0.05 for diff | NR | **Publication Bias:**  NR  **Heterogeneity**:  No | **Standard Method of Study Appraisals:**  NR  **Comprehensive Search Strategy:**  No  **Quality Rating:**  Fair |

| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
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| Author, Year:  Krebs et al., 2008168  Country and setting:  Conducted in USA, studies involved are multinational  Funding:  Agency for Healthcare Research and Quality  Aims of Review:  The effect of newer antidepressants on  pain in patients with depression.  Quality Rating:  Good | Study design:  Systematic Review and Meta-analysis  Number of Patients:  2,352  Studies Included:  seven published trials21–27 and one unpublished  trial (Eli Lilly and Co.: Clinical Study Summary:  Study F1J-MC-HMAT, Study Group A: Eli Lilly and Co.,  2004; 21. Brannan SK, Mallinckrodt CH, Brown EB, et al: Duloxetine 60  mg once daily in the treatment of painful physical symptoms in  patients with major depressive disorder. J Psychiatr Res 2005;  39:43–53  22. Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine, 60 mg once daily,  for major depressive disorder: a randomized, double-blind, placebo-  controlled trial. J Clin Psychiatry 2002; 63:308–315  23. Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine 60 mg once-daily  dosing versus placebo in the acute treatment of major depression.  J Psychiatr Res 2002; 36:383–390  24. Detke MJ, Wiltse CG, Mallinckrodt CH, et al: Duloxetine in the  acute and long-term treatment of major depressive disorder: a placebo-  and paroxetine-controlled trial. Eur Neuropsychopharmacol  2004; 14:457–470  25. Dickens C, Jayson M, Sutton C, et al: The relationship between  pain and depression in a trial using paroxetine in sufferers of  chronic low back pain. Psychosomatics 2000; 41:490–499  26. Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine in the treatment  of depression: a double-blind, placebo-controlled comparison with  paroxetine. J Clin Psychopharmacol 2004; 24:389–399  27. Perahia DGS, Wang F, Mallinckrodt CH, et al: Duloxetine in the  treatment of major depressive disorder: a placebo- and paroxetinecontrolled  trial. Eur Psychiatry 2006; 21:367–378 | Characteristics of Included Studies:  Trials of second-  generation antidepressants that enrolled depression patients and reported pain outcomes  Characteristics of Included Populations  Adolts with depression  Characteristics of Interventions:  second-generation antidepressants, duloxetine and paroxetine | Study Results:  duloxetine versus paroxetine  (WMD:-0.8 mm; 95% confidence interval [CI]:-3.8 to  2.3; negative values favor paroxetine).WMD for duloxetine versus placebo: 5.2 mm; 95% CI: 2.7–7.7; WMD for paroxetine versus placebo: 5.8 mm;95% CI: 2.2–9.4). | Adverse Events:  N/A |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** | **Assessments** | **Study Appraisals and Quality Rating** |
| Author:  Nieuwstraten and Dolovich, 2001212  Country and setting:  Canada  Funding:  NR | Study design:  Meta-analysis  Number of Patients:  1,332  Studies Included:   * Kavoussi RJ et al. 1997 * Segraves RT, et al. 2000 * Weihs KL, et al. 2000 * Croft H, et al. 1999 * ColemanCC, et al. 1999 * Feighner JP, et al. 1991 | Included Studies:   * RCTs * Study durations: 6 to 16 wks * Median 7 wks   Included Populations   * Age: 36 to 70 yrs * Proportion of females: 48.0% to 61.8%   Interventions:  BUP vs. SER (3 trials)  BUP vs. PAR (1 trial)  BUP vs. FLUOX (1 trial) | Study Results:  Results of HAM-D scores and CGI-I scores could not be pooled due to unavailability of data; weighted mean diffs of CGI-S and HAM-A scores not sig different between BUP and SSRIs | Adverse Events:  Nausea, diarrhea, and somnolence occurred sig less frequently in BUP group compared to SSRI group RR, nausea: 0.6 (95%CI, 0.41-0.89), diarrhea: 0.31 (95%CI, 0.16-0.57), somnolence: 0.27 (95% CI, 0.15-0.48). Satisfaction with sexual function was sig less in SSRI group RR, 1.28  (95% CI, 1.16-1.41) | Publication Bias:  No  Heterogeneity:  Yes- indirectly | Standard Method of Study Appraisals:  Yes  Quality Rating:  Good  Comprehensive Search Strategy:  Yes |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** | **Assessments** | **Study Appraisals and Quality Rating** |
| Author:  Pedersen, 2005214  Country and setting:  Denmark  Funding:  Drug Development, H. Lundbeck A/S | Study design:  Retrospective cohort study  Number of Patients:  4091  Studies Included:  12 PBO-controlled studies and 2 relapse prevention studies | Included Studies:  Studies are from adult clinical database at H. Lund  Included Populations  Adult outpatients with MDD (2,277) or anxiety (371)  Interventions:  ESC and PBO | Study Results:  MADRS item 10 (suicidal thoughts): ESC patients had fewer suicidal thoughts than PBO from wks 1 (*P* < 0.05) to 8 (*P* < 0.001)  Suicides in PBO-controlled studies:  ESC n = 0 Rate = 0 Incidence = 0  PBO n = 1 Rate = 0.003 Incidence = 0.1  Non-fatal self harm in PBO controlled studies:  ESC n = 5 Rate = 0.011 Incidence = 0.2  PBO n = 1 Rate = 0.003 Incidence = 0.1 | NR | Publication Bias:  No  Heterogeneity:  No | Standard Method of Study Appraisals:  Yes  Quality Rating:  Fair  Comprehensive Search Strategy:  No |

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| **Study Characteristics** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** | **Assessments** | **Study Appraisals and Quality Rating** |
| **Author:**  Perahia et al., 2005215  **Country and setting:**  NR  **Funding:**  Eli Lilly and Company  **Research objective:**  To characterize DEAEs of DUL hydrochloride | **Study design:**  Pooled analysis (9 trials: 6 short-term treatment trials, 2 extension trials and 1 open trial)  **Number of Patients:**  3,624  **Studies Included:**  9 multicenter clinical trials assessing efficacy and safety of DUL in treatment of major depressive disorder | **Characteristics of Included Studies:**   * Conducted in US, Europe, and Latin America * 8 studies randomized, double blind, PBO controlled trials, examining 8-9 wks of acute treatment (2 had 26-wk PBO-controlled extension phase and grouped as long-term treatment) * 1 study was a 52-wk open-label trial   **Characteristics of Included Populations**   * Depression defined by DSM-IV * Baseline total HAMD-17≥15 * Baseline CGI-S >+4   **Characteristics of Interventions:**   * DUL (40-120 mg/d) * DUL discontinued, followed by lead-out phase of 1 or 2 wks * PBO-controlled trials, PBO given during lead-out phase | **Study Results:**  In 6-study pooled analysis, significanlty more DUL patients (44.3%) had > 1 DEAE than PBO (22.9%) (*P* = NR). Dizziness most common symptom in all groups analyzed. Mild, moderate, and severe DEAEs were 39.8%, 50.6%, and 9.6% for DUL vs. 46%, 48.9%, and 5.0% for PBO. Withdrawal due to DEAEs occured in 3.1% of DUL patients and 0% of PBO. A higher, but nonlinear, incidence of DEAEs was seen with 120 mg/d compared to lower doses  In 2 long-term studies, significanlty more DUL patients (9.1%) had > = 1 DEAE than PBO-treated (2.0%) (*P* = NR). Mild, moderate, and severe DEAEs were 70.6%, 26.5%, and 2.9% for DUL group. No difference in DEAEs between 80 and 120 mg/d groups. 47.5% of DEAEs resolved prior to final contact with study patients.  In open label study 50.8% reported ≥1 DEAE | **Adverse Events:**  Events registered as DEAEs if they occured for first time or worsened following discontinuation of treatment. Observation period for DEAEs was 2 wks | **Publication Bias:**  No  **Heterogeneity:**  No | **Standard Method of Study Appraisals:**  Not described  **Comprehensive Search Strategy:**  Not described  **Quality Rating:**  Fair |

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| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
| Author, Year:  Vanderburg et al., 2009223  Country and setting:  Multinational  Funding:  Pfizer Inc.  Aims of Review:  To identify possibly suicide-related adverse events in Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline in adult patients and evaluate the risk of suicidality with sertraline versus placebo.  Quality Rating:  Fair | Study design:  Pooled analysis  Number of Patients:  19,923  MDD only 3857  Studies Included:  126 studies conducted between the mid-1980s and the mid-2000s, Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline - MDD only 19 studies | Characteristics of Included Studies:  Placebo controlled RCTs  Characteristics of Included Populations  Any patients that were included in studies  Characteristics of Interventions:  Sertraline or placebo | Study Results:  Four cases of completed suicides among 10,917 sertraline-treated subjects yielded an incidence of 0.04% (95% CI, 0.01-0.09) and 3 cases among 9,006 placebo treated subjects yielded an incidence of 0.03% (95% CI,  0.01-0.10). No statistically significant differences between sertraline and placebo in any of the individual categories or combined suicidality risk category across all performed analyses. | Adverse Events:  Suicidality:   * All conditions: Sertraline 19 (0.29%) 95% CI, 0.17-0.45 vs. placebo 29 (0.53%) (95% CI, 0.35-0.76); RR, 0.55 (95% CI, 0.31-0.97) * MDD only: Sertraline 5 (0.23%) (95% CI, 0.07-0.54) vs. placebo 8 (0.47%) (95% CI, 0.21-0.93); RR, 0.46 (95% CI, 0.16 to 1.48) |

| **Study Characteristics** | **Research Objective, Intervention, Duration, etc** | **Inclusion/Exclusion** | **Population Characteristics** | **Health Outcome Results** | **Adverse Events** |
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| Author, Year  Vestergaard et al. 2008224  Country and Setting  Denmark  National Hospital Discharge Registry  Funding  Danish Medical Research Council  Quality rating:  Good | Research objective  Risk of fractures in users of antidepressants  Drugs, Doses, and Range  D1: Cases 124, 655  D2: Controls 373, 962  age and gender matched  Fixed dose  N/A  Dosages equivalent  N/A  Study design  Case control observational  Duration  January 1, 2000 to December 31, 2000  Type of depression   * MDD | Inclusion criteria:   * Cases: All subjects who had sustained a fracture between January 1, 2000, and December 31, 2000 (n = 124,655). * Controls: randomly selected 3 for each case matched by yr of birth; selected using incidence-density sampling technique; i.e., controls had to be alive and at risk for fracture diagnosis at time corresponding case was diagnosed. | Groups similar at baseline n =  D1: 124,655  D2: 373,962  Mean age, yrs  D1: 43.44  D2: 43.44  Sex, % female  D1: 51.8  D2: 51.8  Race, % white  NR  Baseline HAM-A  NR  Insomnia, %  NR  Concomitant anergia, %  NR  Experienced prior depressive episodes, %  NR  Comments:  NR | Risk of fractures by length of drug use  CIT   * 6 mos or less: 1.58 (1.45-1.71)\* * 6 mos to a yr: 1.67 (1.53-1.83)\* * 1.1 to 2.5 yrs: 1.22 (1.15-1.29)\* * More than 2.5 yrs 1.15 (1.10-1.19)\*   FLUOX   * 6 mos or less: 1.31 (1.05-1.65)\* * 6 mos to a yr: 1.29 (1.00-1.66)\* * 1.1 to 2.5 yrs: 1.14 (1.00-1.30)\* * More than 2.5 yrs: 1.08 (1.02-1.14)\*   FLUV   * 6 mos or less: 0.73 (0.22-2.43) * 6 mos to a yr: 0.43 (0.12-1.56) * 1.1 to 2.5 yrs: 1.17 (0.67-2.05) * More than 2.5 yrs: 1.12 (0.87-1.45)   PAR   * 6 mos or less: 1.24 (1.02-1.50)\* * 6 mos to a yr: 1.19 (0.96-1.46) * 1.1 to 2.5 yrs: 1.24 (1.11-1.39)\* * More than 2.5 yrs: 1.04 (0.96-1.12)   SER   * 6 mos or less: 1.09 (0.95-1.25) * 6 mos to a yr: 1.35 (1.17-1.56)\* * 1.1 to 2.5 yrs: 1.08 (1.00-1.18)   More than 2.5 yrs: 1.10 (1.03-1.17)\*  \* 2*P* < 0.05 | Attrition  N/A  Conditional OR of fracture depending on dose:  CIT   * DDD < 0.251: OR, 1.11 (95% CI, 1.06-1.16)\* * DDD 0.251- 0.5: OR, 1.31 (95% CI, 1.21-1.41)\* * DDD >0.5 OR, 1.38 (95% CI, 1.33-1.44)\*   FLUOX   * DDD < 0.251: OR, 1.06 (95% CI, 1.00-1.13)\* * DDD 0.251-0.5: OR, 1.16 (95% CI, 1.01-1.33)\* * DDD > 0.5 OR, 1.20 (95% CI, 1.09-1.32)\*   FLUV   * DDD < 0.251: OR, 1.04 (95% CI, 0.78-1.40) * DDD 0.251-0.5: OR, 1.46 (95% CI, 0.84-2.56) * DDD > 0.5: OR, 0.95 (95% CI, 0.61-1.49)   PAR   * DDD < 0.251: OR, 1.08 (95% CI, 0.99-1.17) * DDD 0.251-0.5: OR, 1.12 (95% CI, 0.94-1.33) * DDD > 0.5: OR, 1.21 (955 CI 1.10-1.33)\*   SER   * DDD < 0.251: OR, 1.04 (95% CI, 0.97-1.11) * DDD 0.251-0.5: OR, 1.08 (95% CI, 0.95-1.23) * DDD > 0.5: OR, 1.25 * (95% CI, 1.16-1.34)\*   DDD = defined daily dose  \* = 2*P* < 0.05 |

| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics** | **Results** | **Adverse Events** |
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| Author, Year:  Wise et al., 2006 226  Country and setting:  Conducted in USA, studies involved are multinational  Funding:  Eli Lilly and Co.  Aims of Review:  To assess the effect of duloxetine on body weight of patients with major depressive disorder (MDD)  Quality Rating:  Quality rating for the reporting of adverse events: Fair Overall quality rating: Fair | Study design:  Meta-analysis  Number of Patients:  Acute studies = 2,878  Long-term studies = 2,316  Studies Included:  all 10 phase II and III registration studies of duloxetine in the treatment of MDD performed by Eli Lilly and Company, study durations: 8 - 52 weeks | Characteristics of Included Studies:  Except for study 10 and the acute phase of study 9 (a relapse-prevention study), all studies were randomized, double-blind, controlled (with placebo, fluoxetine, and/or paroxetine used as comparators).  Characteristics of Included Populations  1. Acute Studies: Gender, F (%)- placebo = 68.2; Duloxetine = 66.8; Fluoxetine 20 mg qd = 60.0; Paroxetine 20 mg qd = 63.8; and Acute Uncontrolled Duloxetine 60 mg qd = 71.9; Age, mean (SD)- placebo = 42.2 (12.9); Duloxetine = 42.7 (12.2); Fluoxetine 20 mg qd = 39.7 (11.6); Paroxetine 20 mg qd = 43.2 (12.0); Acute Uncontrolled Duloxetine 60 mg qd = 43.4 (12.7); Ethnicity, white (%)- placebo = 86.7; Duloxetine = 89.2; Fluoxetine 20 mg qd = 82.9; Paroxetine 20 mg qd = 89.1; and Acute Uncontrolled Duloxetine 60 mg qd = 89.9; weight, mean (SD) kg - placebo = 78.3 (20.0); Duloxetine = 79.7 (20.7); Fluoxetine 20 mg qd = 82.3 (20.8); Paroxetine 20 mg qd = 77.8 (22.4); and Acute Uncontrolled Duloxetine 60 mg qd = 82.1 (22.3)  2. Long-term studies: Gender, F (%)- (Study 5 and 6) placebo = 69.8%; Duloxetine 40 mg bid = 70.2; Duloxetine 60 mg bid = 75.0; and Paroxetine 20 mg qd = 69.4; (Study 9) placebo = 77.5 and Duloxetine 60 mg qd = 67.6; (Study 10) Duloxetine 40-60 mg bid = 72.6; Age, mean (SD)- (Study 5 and 6) placebo = 44.2 (11.1); Duloxetine 40 mg bid = 44.8 (12.0); Duloxetine 60 mg bid = 44.3 (10.7); and Paroxetine 20 mg qd = 44.0 (10.8); (Study 9) placebo = 44.8 (11.9) and Duloxetine 60 mg qd = 45.7 (12.7); (Study 10) Duloxetine 40-60 mg bid = 44.4 (13.2); Ethnicity, white (%)- (Study 5 and 6) placebo = 100; Duloxetine 40 mg bid = 100; Duloxetine 60 mg bid = 99.5; and Paroxetine 20 mg qd = 100; (Study 9) placebo = 93.0 and Duloxetine 60 mg qd = 94.1; (Study 10) Duloxetine 40-60 mg bid = 42.2; weight, mean (SD) kg -(Study 5 and 6) placebo = 69.3 (14.4); Duloxetine 40 mg bid = 70.9 (14.4); Duloxetine 60 mg bid = 72.4 (17.4); and Paroxetine 20 mg qd = 69.7 (14.1); (Study 9) placebo = 80.9 (22.2) and Duloxetine 60 mg qd = 83.3 (22.1); (Study 10) Duloxetine 40-60 mg bid = 70.3 (17.4)  Characteristics of Interventions:  Study 1 and 2 [acute, 8 wks]: duloxetine 20-60 mg bid vs. fluoxetine 20 mg qd. vs. placebo; Study 3 and 4 [acute, 8 wks]: duloxetine 20 mg bid vs. duloxetine 40 mg bid vs. paroxetine 20 mg qd vs. placebo; study 5 and 6 [acute, 8 wks + long-term continuation, 26 wks]: duloxetine 40 mg bid vs. duloxetine 60 mg bid vs. paroxetine 20 mg qd vs. placebo; study 7 and 8 [acute, 9 wks]: duloxetine 60 mg qd vs. placebo; study 9 [acute, 12 wks]: duloxetine 60 mg qd; study 9 [long-term continuation, 26 wks]: duloxetine 60 mg qd vs. placebo; and study 10 [long-term, 52 wks]: duloxetine 40-60 mg bid | Study Results:  Acute Placebo-Controlled Dataset: Duloxetine-treated patients (pooled doses) versus placebo (-0.5 kg vs. 0.2 kg, P < .001). Repeated analysis revealed no consistent relationship between duloxetine dose and weight change. The incidence of PCS (potentially clinically significant) weight loss (more or equal to 7%) from baseline to endpoint or any time were significantly greater for duloxetine-treated than for placebo-treated patients P = 0.035 and 0.010 resprectively).  Acute fluoxetine-controlled and paroxetine-controlled datasets: The mean change in weight from baseline to endpoint for duloxetine-treated compared with fluoxetine-treated patients(-0.7 kg vs. -0.6 kg). In studies that compared duloxetine with paroxetine, ts (-0.3 kg vs. -0.2 kg).  Long-term treatment datasets: Pooling the arms of studies 5 and 6, the mean changes in weight from baseline to the end of the acute phase ranged across the 4 treatment groups from -0.17 to 0.18 kg for all randomnly assigned patients and from -0.06 to 0.19 kg for the patients who entered the continuation phase. The least squares mean weight change from baseline to endpoint for patients freated with duloxetine at a dose of 40mg bid vs. placebo-treated patients (0.7 kg vs. 0.1 kg). Weight changes in duloxetine 60mg bid-treated patients (0.9kg) and paroxetine 20mg qd-treated patients (1.0) kg versus placebo-treated patients (0.1kg, P <= 0.05 for each). The treatment groups did not differ significantly in the rates of PCS weight loss at endpoint or any time, whereas the rates of PCS weight gain at endpoint versus placebo (dulox 40mg bid vs. placebo P <= 0.05, dulox 60mg bid and parox 20 mg qd vs. placebo P <= 0.001, respectively). | Adverse Events:  Treatment-emergent weight-related adverse events were report in acute placebo-controlled studies (studies 1-8). Duloxetine-treated patients reported the treatment emergent weight-related adverse events of appetite decreased (P < .001) and anorexia (p = .001) significantly more often than did placebo-treated patients. A lower percentage of duloxetine-treated patiens (1.1%) compared with placebo-treated patients (1.4%) reported appetite increased (n.s.). The incidences of weight-related events were similar across duloxetine doses. Anorexia was the only weight-related event reported as a reason for treatment discontinuation (duloxetine, 0.1%; placebo, 0.0%). [Appetite decreased was reported in 1.9 % (n = 15) of placebo patients, compared to 5.9 % (n = 67) in duloxetine patients (p < .001). Appetite increased in 1.4% (n = 11) of placebo patients and 1.1 % (n = 12) of duloxetine patients (p = .637. Anorexia was reported in 0.1 % (n = 1) of placebo patients and 1.7 % (n = 19) of duloxetine patients (p = .001)]  Among long-term studies, no significant differences between treatment groups were seen in the incidence of treatment-emergent weight-related adverse events. No patients discontinued from the studies due to appetite decreased, appetite increase, or anorexia. In the long-term uncontrolled dataset (study 10), anorexia (0.1%) was the only treatment-emergent weight related adverse event reported as a reason for treatment discontinuation. [studies 5 and 6: appetite decreased was reported in 0 of placebo patients, 1.6% (n=3) of duloxetine 40mg bid patients, 1.5% (n=3) of duloxetine 60mg bid patients, 0 in paroxetine 20mg qd patients; appetite increased was reported in 0 of placebo patients, 0.5% (n=1) of duloxetine 40mg bid patients, 0 of duloxetine 60mg bid patients, 0.5% (n=1) in paroxetine 20mg qd patients; anorexia was reported in 1.0% (n=2) of placebo patients, 1.6% (n=3) of duloxetine 40mg bid patients, 0.5% (n=1) of duloxetine 60mg bid patients, 1.1% (n=2) in paroxetine 20mg qd patients; study 10: appetite decreased was reported in 8.1% (n=104), appetite increased was reported in 3.9% (n=50) and anorexia was reported in 8.1% (n=104)] |