



Comparative benefits and harms of second-generation anti-depressants and cognitive behavioral therapies in the initial treatment of major depressive disorder: systematic review and meta-analysis

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4 **behavioral therapies in the initial treatment of major depressive disorder: systematic**
5 **review and meta-analysis**
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Abstract

Objective To conduct a systematic review and meta-analysis of the benefits and harms of second-generation antidepressants (SGAs) and cognitive behavioral therapies (CBTs) in the initial treatment of adults with major depressive disorder (MDD)

Design Systematic review including qualitative assessment and meta-analyses using random- and fixed-effects models to yield risk ratios (RRs) and weighted mean differences (WMDs)

Data sources MEDLINE, EMBASE, the Cochrane Library, AMED, PsycINFO, and CINAHL from January 1990 through January 2015

Eligibility criteria for selecting studies Studies that compared an SGA with CBT for the initial outpatient treatment of adults with MDD. We required studies to report response, remission, speed of response, speed of remission, relapse, quality of life, functional capacity, reduction of suicidal ideas or behaviors, reduction of hospitalization, and/or a range of adverse effects. We included randomized controlled trials (RCTs), systematic reviews, and meta-analyses.

Results Eleven RCTs compared an SGA with CBT. Ten trials compared SGA monotherapy with CBT alone; three compared SGA monotherapy with SGA plus CBT. Meta-analyses found no statistically significant difference in effectiveness between SGAs and CBT for response (RR, 0.91; 95% CI, 0.77 to 1.07), remission (RR, 0.98; 95% CI, 0.73 to 1.32), or change in HAM-D-17 score (WMD, -0.38; 95% CI, -2.87 to 2.10). Similarly, we found no significant differences in rates of overall study discontinuation (RR, 0.90; 95% CI, 0.49 to 1.65) or discontinuation attributable to lack of efficacy (RR, 0.40; 95% CI, 0.05 to 2.91). Although more patients treated with an SGA withdrew from studies due to adverse events than receiving CBT, the difference was not statistically significant (RR, 3.29; 95% CI, 0.42 to 25.72). We were unable to draw conclusions about other outcomes because of lack of evidence.

Conclusions Available evidence suggests similar beneficial treatment effects of SGAs and CBT, either alone or in combination. When deciding how to treat MDD patients, clinicians and patients should consider not only the efficacy and potential harms of SGAs and CBT but also patient preferences, costs and availability of each treatment, and expectancy of treatment effects.

INTRODUCTION

Major depressive disorder (MDD) is the most prevalent and disabling form of depression, affecting more than 32 million Americans.¹ In any given year, nearly 7 percent of the U.S. adult population experiences an episode of MDD, but only about half of these individuals seek care.¹ For patients who do obtain care, only 20 percent receive adequate treatment.¹ Based on available evidence-based guidelines, this would include either pharmacotherapy (at least 2 months of an appropriate medication for MDD plus more than four visits to any type of physician) or psychotherapy (at least eight visits with any health care professional lasting an average of at least 30 minutes).²⁻⁴

Treatment for MDD is often initiated in a primary care setting,⁵ and patients are generally prescribed medication as the standard treatment.⁶ Of the available antidepressants, second-generation antidepressants (SGAs) are the most commonly prescribed agents.⁶ These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that target specific neurotransmitters. Although these drugs have different mechanisms of action, evidence indicates that no substantial differences in benefits exist among them as a class.⁷

Although medication is the treatment most frequently offered to depressed primary care patients, data from studies of antidepressant medications show that approximately 20 percent of patients do not fill their prescriptions. Moreover, even if they start a course of treatment, they may discontinue early before receiving an adequate course.⁸ One reason for lack of adherence to SGAs is frequency and severity of side effects. More than 60 percent of patients experience at least one adverse effect during treatment with an SGA. Although most adverse effects are minor, such as constipation, diarrhea, and dizziness, they frequently lead to discontinuation of treatment.⁹

Patient preference for initiating or switching treatment may also play a key role in acceptance and continuation of treatment for MDD. Some research suggests that patients might prefer treatment with psychotherapy over medication.¹⁰⁻¹⁴ Reasons for preferring psychotherapy over medication include concerns about side effects and perceived “addictiveness” of drugs.^{12 15-18} In addition, women and ethnic minorities may be more likely to prefer psychotherapies over medications.^{12 13 19 20} Regardless of which treatment patients prefer, some evidence suggests that patients who receive their treatment of choice fare better than patients whose treatment is incongruous with their preferences.^{11 21}

In general, psychotherapeutic interventions aim to help patients identify how past and present factors may contribute to their depression and to teach them how to deal effectively with them.²²⁻²⁵ Cognitive behavioral therapy (CBT) is based on a combination of basic behavioral and cognitive principles. Briefly, CBT helps patients understand and examine how their thoughts, moods, and behaviors interact in a way that can result in or worsen depression. Patients are taught how to replace dysfunctional thoughts and behaviors with more adaptive ones, which can reduce distress and improve mood.

Given the range of available treatments for MDD patients, each with its own evidence base of benefits and harms, primary care physicians require high quality evidence of the comparative effectiveness of the available treatments to select and manage the best options for their patients. This paper focuses on the comparative benefits of SGAs and CBTs as an initial treatment for adult patients with MDD. Our results come from a larger comparative effectiveness review of benefits and harms of SGAs, psychotherapies, complementary and alternative medicine

treatments, and exercise interventions for MDD funded by the U.S. Agency for Healthcare Research and Quality.²⁶

METHODS

Detailed methods are available in the full report.²⁶ The full search strategy is available in Appendix A. In brief, we searched MEDLINE via PubMed, EMBASE, the Cochrane Library, AMED (Allied and Complementary Medicine Database), PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) for randomized and nonrandomized controlled trials published from January 1990 through January 2015. For pharmaceuticals, we searched for individual generic drug names and broader SGA-related terms; for CBT studies we used the terms “psychotherapy,” “cognitive therapy,” and “cognitive behavioral therapy” in titles or abstracts. To detect unpublished studies, we searched ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform, Drugs@FDA, the European Medicines Agency, the National Institute of Mental Health website, the American Psychological Association website, Scopus, the Conference Proceedings Citation Index, and reference lists of pertinent reviews and included trials.

Table 1 contains the eligibility criteria we applied to search results. Briefly, we included studies that compared an SGA with CBT for the initial outpatient treatment of adults with MDD. CBT is considered the umbrella “class” to which we compare SGAs. However, we recognize the challenge in organizing and categorizing psychological interventions in systematic reviews. In an effort to enhance consistency of categorization of psychotherapies in this review and our ability to compare our findings to those of other large reviews, we have used the Cochrane Collaborative Depression, Anxiety and Neurosis (CCDAN) Group’s framework for categorizing psychological interventions.²⁷ In addition to the umbrella term CBT, the CCDAN Group’s CBT category includes the following: problem solving therapy, rational emotive therapy, reality therapy, restructuring, role play, schemas, self-control, and stress management. If the authors of an included trial specified the particular form of the behavioral intervention, we mention it; if they do not, we use the term CBT.

Table 1. Inclusion criteria for studies comparing an SGA with CBT

Population	Adult (18 years or older) outpatients with major depressive disorder during an initial treatment attempt
Interventions	Second-generation antidepressants approved for treatment of major depressive disorder by the U.S. Food and Drug Administration: Bupropion, citalopram, desvenlafaxine, duloxetine, fluoxetine, escitalopram, fluvoxamine, levomilnacipran, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine, vilazodone, vortioxetine Cognitive behavioral therapies as classified by the CCDAN Group’s framework. ²⁷

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4	Outcomes
5	Benefits:
6	Response, remission, speed of response, speed of remission, relapse, quality of
7	life, functional capacity, suicidal ideas or behaviors, hospitalization
8	Harms:
9	Overall adverse events, withdrawals because of adverse events, serious adverse
10	events, specific adverse events (including hyponatremia, seizures, suicidal ideas
11	or behaviors, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual
12	side effects), withdrawals because of specific adverse events
13	Study designs
14	Benefits:
15	Randomized controlled trials, systematic reviews, and meta-analyses
16	In addition for harms:
17	Nonrandomized controlled trials, prospective controlled cohort studies,
18	retrospective controlled cohort studies, case-control studies, all with a minimum
19	sample size of 500 participants
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Two trained team members independently reviewed all abstracts and full-text articles against predefined inclusion/exclusion criteria. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer. We designed, pilot-tested, and used a structured data abstraction form to ensure consistency of data abstraction. Trained reviewers initially abstracted data from each study; a senior reviewer evaluated the completeness and accuracy of the data abstraction.

We rated the risk of bias for each relevant outcome of a study as low, moderate, or high. To determine risk of bias in a standardized way, we used the Cochrane Risk of Bias tool to appraise RCTs.²⁸ Two independent reviewers assigned risk-of-bias ratings. They resolved any disagreements by discussion and consensus or by consulting a third member of the team. We included all eligible studies regardless of risk of bias in this review, but studies rated high risk of bias were used only in sensitivity analyses.

We graded the strength of evidence (SOE) based on guidance established by the U.S. Agency for Healthcare Research and Quality for the Evidence-based Practice Center program.²⁹ This approach incorporates five domains: study limitations, consistency, directness, precision, and reporting bias. Grades (high, moderate, low, insufficient) reflect confidence we had about the evidence for a specific outcome on the comparative benefits and harms of the interventions.

Evidence indicates that no substantial differences in benefits exist among the different types of SGAs;⁷ therefore, in all meta-analyses we compared SGAs as a class with CBTs. When we conducted meta-analyses, we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and Cochran's q . We used the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity) to estimate the magnitude of heterogeneity. We examined potential sources of heterogeneity using sensitivity and subgroup analyses.

For all analyses, we used random- and fixed-effects models to estimate comparative effects. We used DerSimonian & Laird models for random effects analyses. For studies with attrition, we used a "worst-case" assumption that non-completers failed to respond or remit. We assessed publication bias using funnel plots, but given the small number of studies in our meta-analyses, these tests have low sensitivity to detect publication bias. All meta-analyses were conducted using Comprehensive Meta-analysis, version 3.2 (Biostat; Englewood, New Jersey, U.S.A.).

RESULTS

Literature Searches and Evidence Base

Our searches for the full report identified 7,813 citations, of which we included 11 primary RCTs (reported in 14 articles) that compared an SGA with CBT and provided data relevant to this paper (Figure 1).³⁰⁻⁴³ Those studies provided information on 1,511 patients with MDD.

Two trials^{38 39} were conducted in primary care settings; the remainder took place in outpatient mental health care locations. Four trials^{30 35 37 38} took place solely in the United States; other countries included Canada,^{33 36 42} England,³⁹ Germany,⁴⁰ Iran,⁴³ and Romania,³²

Generally, patients were between 18 and 65 years of age; most trials reported a mean age between 35 and 45 years. In all trials, the majority of patients were female. One trial enrolled only women.³⁸ In the few trials that reported race or ethnicity, one-quarter of trial patients were nonwhite. All trials reported mean baseline depressive severity of at least a moderate degree; most trials reported mean baseline scores on the Hamilton Depression Rating Scale (17 items) (HAM-D-17) between 16 (moderate depression) and 23 (severe). The total daily dose of each SGA medication was within the usual ranges prescribed for adults.

Table 2 describes the 11 included trials (13 publications) of an SGA compared with CBT. SGAs used in the trials were fluoxetine,³² fluvoxamine,³⁹ paroxetine,^{35-37 39} sertraline,^{36 40} venlafaxine,^{33 36} citalopram,⁴³ and escitalopram,^{30 42}. Because of the inherent heterogeneity in delivery of psychotherapy, even those under the umbrella of CBT, we used the individual studies' definitions of the cognitive therapies provided. Six trials employed CBT,^{30 33 36 38 40 42} four used the specific cognitive therapy (CT) modality,^{32 35 37 43} and one each used PST³⁹ and REBT³² modalities. Trial counts exceed 11 because one trial had both CT and REBT arms.³² All but one trial compared SGA monotherapy with CBT alone; Lam and colleagues compared SGA monotherapy with SGA plus CBT.⁴² Two trials included an additional comparison of SGA monotherapy with a combination of SGA and CBT.^{39 43} Treatment duration ranged from 8 weeks to 1 year; some trials also reported followup results once patients were no longer receiving active treatments.

Table 2. Second-generation antidepressants versus cognitive behavioral therapy: Trial characteristics, main outcomes, and risk of bias ratings

First author, year	N ^a Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Subtype: Number of Sessions	Response ^b (%) and Significance Level	Remission ^b (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
David et al., 2008 ³²	170	HAM-D-17: 22.5	Fluoxetine: 40 to 80	At 14 weeks: vs. CT: 58 vs. 63 p>0.05	At 14 weeks: vs. CT: 47 vs. 50 p>0.05	At 14 weeks: vs. CT: -12.6 vs. -14.3 p>0.05	Medium
Sava et al., 2009 ³¹	14 treatment; 36 followup		CT: 20 REBT: 20	vs. REBT: 58 vs. 65 p>0.05	vs. REBT: 47 vs. 44 p>0.05	vs. REBT: -12.6 vs. -14.3 p>0.05	

First author, year	N ^a Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Subtype: Number of Sessions	Response ^b (%) and Significance Level	Remission ^b (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
DeRubeis et al., 2005 ³⁷ Leykin et al., 2007 ³⁴ Landenberger, 2002 ⁴¹	180 8 ^c	HAM-D-17: 23.4	Paroxetine: 10 to 50 CT: 20 to 28	50 vs. 43 p=0.40	NR	Effect size estimate: 0.16 (favors SGA) p=0.46	Medium for response and remission; high for change in HAM-D ^d
Dimidjian, 2006 ³⁵	145 16	HAM-D-17: 20.7	Paroxetine: 10 to 50 CT: 24	43 versus 58 p=NR	27 versus 42 p=NR	NR ^c	Medium
Hegerl, 2010 ⁴⁰	48 10	HAM-D-17: 16.1	Sertraline: 50 to 200 CBT: 14	38 vs. 50 p=NR	NR	-6.5 vs. -8.8 p=NR	Medium for response and remission; high for change in HAM-D
Kennedy et al., 2007 ³³	31 16	HAM-D-17: 20.5	Venlafaxine: 75 to 225 CBT: 16	64 vs. 41 p=NR	57 vs. 29 p=NR	-12.9 vs. -10.8 p=NR	High ^f
Lam et al., 2013 ⁴²	105 12	MADRS: 27.6	Escitalopram: 10 to 20 CBT (via telephone): 8 + escitalopram: 10 to 20	61 vs. 63 p=0.86	53 vs. 56 ^g p=0.74	MADRS: -14.3 vs. -15.7 p=0.60	Low
McGrath et al., 2013 ³⁰	82 12	HAM-D-17: 18.8	Escitalopram: 10 to 20 CBT: 16	60 vs. 57 p=NR	28 vs. 29 p=NR	NR	High ^h

First author, year	N ^a Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Subtype: Number of Sessions	Response ^b (%) and Significance Level	Remission ^b (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Mynors-Wallis et al., 2000 ³⁹	151 52	HAM-D-17: 20.3	Fluvoxamine: 100 to 150 or Paroxetine: 10 to 40 PST (provided by GP): 6 PST (provided by nurse): 6 PST (provided by nurse): 6 + fluvoxamine: 100 to 150 or paroxetine: 10 to 40	At 12 weeks: 78 vs. 64 vs. 69 vs. 74 p=NR	At 12 weeks: 67 vs. 51 vs. 54 vs. 6 p=NR	-14.0 vs. -12.0 vs. -11.8 vs. -12.3 p>0.05	Medium
Segal et al., 2006 ³⁶	301 24 96 followup	HAM-D-17: 19.5	Sertraline: 50 to 200 or paroxetine: 20 to 50 or venlafaxine: 75 to 225 CBT: 20	At 24 weeks: 80 vs. 72 p=NR	At 24 weeks ^f : 71 vs. 61 p=NR	NR	High ^l
Shamsaei et al., 2008 ⁴³	120 8	BDI: 42.8	Citalopram: 20 CT: 8 Citalopram 20 + CT: 8	NR	NR	NR	High ^k
WECare, 2003 ³⁸	178 4 ^l	HAM-D (version NR): 16.9	Paroxetine: 10 to 50 CBT: 8	NR	NR	-5.0 vs. -2.1 p=0.17	Medium

^a Total number of randomized participants in relevant arms of trial.

^b Response (≥ 50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured using the HAM-D unless indicated otherwise.

^c Nonresponders were switched to and/or augmented with another pharmacotherapy at 8 weeks.

^d For dropouts, only the data gathered prior to attrition were used in continuous outcome models.

^e Continuous data were only provided stratified by depression severity.

^f High attrition, completers analysis, difference in baseline age between groups.

^g Response was defined as ≥ 50 percent decrease in MADRS; remission was defined as MADRS ≤ 12 .

^h High attrition, completers analysis, no baseline data for part of the population.

ⁱ Definition of response was not reported.

^j Very high attrition, completers analysis, unclear randomization method.

^k Several important aspects of study design and analysis not reported.

^l Although patients received SGA for 8 weeks, only the 4-week time point was reported.

Abbreviations: BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CT = cognitive therapy; GP = general practitioner; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; mg = milligram; N = number; NR = not reported; PST = problem solving therapy; REBT = rational emotive behavior therapy; SGA = second-generation antidepressant; vs. = versus.

We present our findings first by treatment comparison (monotherapy comparisons followed by combination therapy comparisons). Within each comparison, we present the benefits followed by the harms. Table 3 summarizes the findings and respective strength of evidence ratings for all comparisons and outcomes.

Table 3. Strength of evidence and summary of findings

Comparison and Outcome of Interest	Strength of Evidence ^a	Findings
SGA versus CBT monotherapy comparisons		
Remission	Low	Results from direct comparisons in 3 trials indicate that no differences in remission exist between SGAs and CBT monotherapy.
Response	Moderate	Results from direct comparisons in 5 trials indicate that no substantial differences in response exist between SGAs and CBT monotherapy.
Functional capacity	Low	Results from 1 trial indicate that no substantial differences in functional capacity exist between SGAs and CBT monotherapy.
Overall risk of adverse events	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
Overall discontinuation of treatment	Moderate	Results from direct comparisons in 4 trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with CBT.
Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 3 trials indicate that patients treated with SGAs experience a numerically but not statistically significant higher rate of discontinuation because of adverse events than those treated with CBT.
SGA versus combination of SGA and CBT		
Remission	Low	Results from direct comparisons in 2 trials indicate that no substantial differences in remission exist between SGAs and SGAs combined with CBT.
Response	Low	Results from direct comparisons in 2 trials indicate that no substantial differences in response exist between SGAs and SGAs combined with CBT.
Functional capacity	Low	Results from 1 trial indicate that the combination of SGA with CBT results in statistically significantly greater improvement on 3 of 4 work functioning measures than SGA alone.
Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with CBT.
Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in discontinuation because of adverse events between patients treated with SGAs and those treated with CBT.

^aSOE grades (high, moderate, low, or insufficient) are based on methods guidance for the AHRQ EPC program.⁴⁴

Abbreviations: CBT, cognitive behavioral therapy; SGA, second-generation antidepressant

Second-Generation Antidepressant Versus Cognitive Behavioral Therapy: Monotherapy Comparisons

We conducted random-effects meta-analyses of trials rated low or medium risk of bias for remission,^{32 35 39} response, and change in HAM-D-17 score. We also performed sensitivity analyses for those outcomes including additional trials rated high risk of bias.^{30 33 36}

For remission, we included three trials (four comparisons)^{32 35 39} with a total of 432 patients. We analyzed results measured between 12 and 16 weeks. The three trials defined remission based on a HAM-D-17 score of either less than 7³² or less than or equal to 7.^{35 39} One trial³⁵ also required a score less than or equal to 10 on the Beck Depression Inventory for remission. Patients treated with SGAs had numerically lower but not significantly different remission rates than patients receiving CBT (40.7 percent versus 47.9 percent; risk ratio [RR], 0.98; 95% CI, 0.73 to 1.32; Figure 2; low SOE). Our sensitivity analysis including three high risk of bias^{30 33 36} trials yielded a similar, nonsignificant difference (RR, 1.08; 95% CI, 0.90 to 1.29).

For response, we included results from 660 patients studied in five trials (six comparisons).^{32 35 37 39 40} We analyzed results measured between 8 and 16 weeks. The five trials defined response as a 50 percent or greater reduction in HAM-D-17 score from baseline. Treatment effects were similar for SGAs and CBTs (44.2 percent versus 45.5 percent; RR, 0.91; 95% CI, 0.77 to 1.07; Figure 3; moderate SOE). The sensitivity analysis including three high risk of bias studies^{30 33 36} yielded a similarly nonstatistically significant difference in response between SGAs and CBTs (RR, 1.02; 95% CI, 0.83 to 1.25).

Our weighted mean difference (WMD) analysis of the two trials (three comparisons; 249 patients)^{32 39} that reported change in HAM-D-17 scores at 8 weeks or longer found no statistically significant difference between SGAs and CBTs (WMD, -0.38; 95% CI, -2.87 to 2.10; Figure 4). Adding the high risk of bias trials^{33 40} to the model yielded no difference in comparative effectiveness (RR, -0.27; 95% CI, -2.44 to 1.90).

Two trials, both rated medium risk of bias, reported response, remission, or change in HAM-D-17 score at time points beyond 16 weeks. In one,³² patients receiving either REBT or CT reported higher rates of remission and response at 6 months than patients taking an SGA, although neither difference was statistically significant. At 6 months, patients receiving REBT or CT reported significantly lower HAM-D-17 scores than the patients taking the SGA. In the trial that compared SGAs with PST,³⁹ rate of remission at 1 year was higher in the PST arms, although rate of response at 1 year was higher in the SGA arm. In that trial, patients' HAM-D-17 scores continued to decline, with 1-year scores being lower in the PST arms than the SGA arm. Again, these differences failed to reach statistical significance.

With respect to other health outcomes, three trials reported relapse rates during off-treatment followup.^{32 35 36 45} Two trials defined relapse as symptom levels meeting criteria for MDD; the third³⁵ defined relapse as either a HAM-D-17 score of 14 or greater or a psychiatric status rating of 5 or greater during the first year of followup. During the followup period of that trial,³⁵ patients who had initially received CT did not receive any treatment, and patients who had received SGA were randomized to continue SGA or switched to pill placebo.

In one medium risk of bias trial,³² 10.6 percent of patients treated with SGA relapsed within 6 months, compared with 2.1 percent and 6.1 percent of patients treated with REBT and CT, respectively (statistical significance not reported). In the other medium risk of bias trial,^{35 45} the rates of relapse within the first year of followup were 39 percent for prior CT, 53 percent for patients who were on SGA and continued to receive it during followup, and 59 percent for patients who received SGAs during acute phase but were switched to placebo during followup.

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Prior CT was significantly different from prior switch to placebo ($p = 0.02$). In the trial rated high risk of bias,³⁶ 47 percent of patients treated with an SGA who achieved remission and 39 percent of those treated with CBTs who achieved remission relapsed within 18 months ($p = 0.40$).

Finally, one medium risk of bias trial³⁵ reported recurrence during the second year of followup, defined as either a HAM-D-17 score of 14 or greater or a psychiatric status rating of 5 or greater among those who did not relapse during year 1 of followup. The rates of recurrence during year 2 were 24 percent for prior CT and 52 percent for patients who were on SGAs during the acute phase ($p = 0.06$). Owing largely to small numbers of patients in each group (17 in each group), the difference was not statistically significant. The single trial (also medium risk of bias) that reported measures of functional capacity used the Social Adjustment Scale;³⁹ SGA and PST did not differ at end of treatment or at 40-week off-treatment followup ($p > 0.05$ at both times).

With regard to adverse events, reporting was generally poor, particularly for serious adverse events and specific adverse events. As a result, we analyzed rates of discontinuation as proxies for adverse events. Overall discontinuation from the six medium risk of bias studies^{32 35 37-40} did not differ significantly between SGAs and CBTs (RR, 0.90; 95% CI, 0.49 to 1.65; moderate SOE). Adding 3 high risk of bias studies^{30 33 36} did not change the result (RR, 0.94; 95% CI, 0.59 to 1.51), and heterogeneity was high ($I^2 > 80\%$) in both cases. More patients treated with an SGA withdrew from studies due to adverse events than patients receiving CBT (RR, 3.29; 95% CI, 0.42 to 25.72; 5 studies^{35 37-40}), but the difference was not statistically significant (low SOE). Again, heterogeneity exceeded 80%, and including a high risk of bias trial³⁶ did not affect results (RR, 1.96; 95% CI, 0.67 to 5.72). Finally, SGAs and CBTs did not differ significantly in terms of dropouts attributed to lack of efficacy in either the main analysis (RR, 0.40; 95% CI, 0.05 to 2.91; 3 studies;^{35 37 39} $I^2 = 62\%$) or the sensitivity analysis including a high risk of bias trial³⁶ (RR, 0.66; 95% CI, 0.15 to 2.89).

Second-Generation Antidepressant Versus Cognitive Behavioral Therapy: Combination Comparisons

The three trials that compared SGA monotherapy with a combination of SGA and CBT reported no statistically significant between-group differences in rates of either remission or response (low SOE).^{39 42 43} All reported change in depression scale score between baseline and endpoint; one⁴³ reported a significant between-group difference—namely, a smaller decrease in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) for patients on SGA alone than for patients treated with SGA plus CT. That trial, however, was rated high risk of bias, whereas the other two were rated low⁴² and medium³⁹ risk of bias.

The trial that compared SGA alone with SGA plus telephone CBT measured several work-related outcomes.⁴² Patients receiving the combination of SGA and telephone CBT reported greater improvement on three of four work functioning measures. The authors found no between-group differences in reduction of hours of work missed, although both groups reported a decrease at the end of treatment. In the trial that compared SGA alone with the combination of SGA and PST, groups did not differ in the Social Adjustment Scale at end of treatment or at 40-week off-treatment followup.³⁹

Two of the three trials reported adverse events.^{39 42} In the trial rated low risk of bias, more patients withdrew for any reason from the combination arm than from the SGA alone arm (23 percent vs. 13 percent; significance not reported).⁴² However, slightly more patients withdrew from the SGA alone arm due to adverse events (6 percent) compared with the combination arm (4 percent). In the other trial, rated medium risk of bias, discontinuation rates were similar

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2
3 between SGA alone and combination arms (17 percent in each arm).³⁹ Eleven percent and 6
4 percent of patients in the combination and SGA arms, respectively, withdrew because of adverse
5 events. No patients in either arm withdrew because of lack of treatment efficacy. The few events
6 in each of these outcomes results in a low strength of evidence rating.
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9 DISCUSSION

10 For SGAs compared with CBTs, the available evidence based on 11 RCTs with 1,511
11 patients suggests similar beneficial treatment effects of SGAs and CBTs, either alone or in
12 combination. Our findings are relatively consistent with two similar meta-analyses that compared
13 SGAs with CBT.^{25 46} In addition to containing several more recent studies, our analyses have
14 some key methodologic differences. Cuijpers and colleagues⁴⁶ conducted meta-analyses of SGAs
15 compared with any psychotherapy and for CBT compared with any medication, but they did not
16 report results from a specific comparison between SGA and CBT for adults with MDD. They
17 found that only SSRIs, rather than SGAs as a class, were more effective than any type of
18 psychotherapy in treating patients with MDD; however, the effect was small and potentially
19 clinically insignificant.
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22 Spielmans and colleagues²⁵ found that bona fide CBT (based on their included studies'
23 descriptions of therapist training, therapist-client relationship, and therapy components) resulted
24 in better outcomes compared with SGA, but the effect sizes were small and heterogeneity was
25 high. Though we considered treatment fidelity in our risk of bias assessment, we did not attempt
26 to determine whether the CBT offered in the included trials was "bona fide." Because primary
27 care clinicians are unlikely to have the information necessary to determine whether the CBT to
28 which they refer patients is bona fide, our results may be more relevant to primary care
29 providers.
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32 Our results are also consistent with the recommendations of both the American Psychiatric
33 Association³ and the U.S. Department of Veterans Affairs/Department of Defense.⁴⁷ Those
34 groups consider both medication and psychotherapy to be appropriate individual initial
35 treatments for patients with mild to moderate MDD. Furthermore, they state that
36 pharmacotherapy plus psychotherapy may be a useful initial treatment for patients with moderate
37 to severe MDD and for those with MDD and coexisting conditions.
38

39 This review, and the evidence that informed it, does have limitations. The scope of this
40 review was limited to trials that enrolled adult patients with MDD and compared an SGA with
41 CBT (alone or in combination with an SGA). We did not attempt to review literature on
42 interventions for MDD in children or for patients with subthreshold depression, dysthymia, or
43 perinatal depression. The included trials enrolled mostly patients with moderate to severe MDD;
44 therefore, results may not be applicable to patients with milder MDD. Most trials excluded
45 patients with medical comorbidities or suicidal ideation; few trials included elderly patients. We
46 found insufficient evidence to confirm or refute whether treatments are more or less efficacious
47 for various subgroups: patients characterized by sex, race, or ethnicity or individuals with
48 coexisting psychiatric conditions.
49

50 Many of the included trials, even those rated medium risk of bias, had methodological
51 shortcomings that may limit confidence in some of our findings. Several studies reported very
52 high attrition, although rates were usually similar between treatment groups. Our "worst-case"
53 assumption of withdrawals as failures to respond or remit should alleviate some of that concern.
54 Most of the included trials provided data only for acute-phase treatment; information to help
55 providers help manage ongoing depression or prevent relapse and recurrence is lacking.
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Although studies of psychotherapy contain some inherent heterogeneity of the content and delivery, the included trials followed manualized protocols. Type, training, and experience of the clinicians who render these various interventions were also quite diverse. Unlike the case with SGAs that are broadly equivalent and have standardized dosing, the cumulative effect of the various sources of heterogeneity within and across psychological interventions may limit the applicability of our findings. Clinician type, training, experience, and degree of treatment fidelity are likely to be even less consistent in routine clinical practice than in the trials in this review. Along with psychotherapist availability, these are important factors for clinicians to consider when recommending psychological treatment and interventions. Finally, comparative effectiveness at a group level did not detect a difference between SGAs and CBTs, but how best to tailor this information to an individual patient is still not clear. Analyses of individual patient data are best suited to address that issue and should be performed in the future. Although we searched for unpublished literature, publication bias and selective outcome reporting may still be potential limiting factors.

In clinical decisionmaking, providers should consider not only the efficacy of SGAs and CBT interventions but also patient preferences about potential adverse events, costs and availability of each treatment, and expected treatment effects. Currently, the biggest barrier to offering psychotherapy either alone or in combination with medication may be how well patients can gain access to such mental health care clinicians. Given that the benefits of SGAs CBT do not differ significantly in treating MDD and that primary care patients may have personal preferences for one first-line treatment over the other, both treatments should be made accessible, either alone or in combination, to primary care patients with MDD.⁸

Having access to psychotherapeutic interventions in the primary care setting might improve treatment outcomes for patients with MDD. It has the potential to improve use of psychiatric consultation and therapy and enhance coordination of care between primary care clinicians and mental health professionals. It may also have additional downstream effects of reducing the stigma associated with mental illness in general, empowering patients to address the symptoms and issues associated with not only depression but also other mental health-related concerns, and encouraging them to seek and maintain treatment more quickly at an earlier stage of their illness.

CONTRIBUTORSHIP

HRA reviewed studies for inclusion and exclusion, entered, cleaned and analysed the data, conducted statistical analyses, and drafted and revised the paper. GG oversaw the design and conduct of the full report from which this manuscript was devised, reviewed included studies, analysed data, and revised the draft paper. BNG, CF, GNA, LCM, EC-S, EB, LJJ, SG, CB, and CBP participated fully in the report from which this manuscript was devised, reviewed included studies, entered and cleaned data, and revised the draft paper. BNG, LCM, and CB also preformed data analyses. KNL contributed to the full report from which this project was based and revised the draft paper.

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COMPETING INTERESTS

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2
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14 Health and Human Services.
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26 Contribution.
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Figure 1: PRISMA diagram for second-generation antidepressants vs. cognitive behavioral therapy in the treatment of major depressive disorders

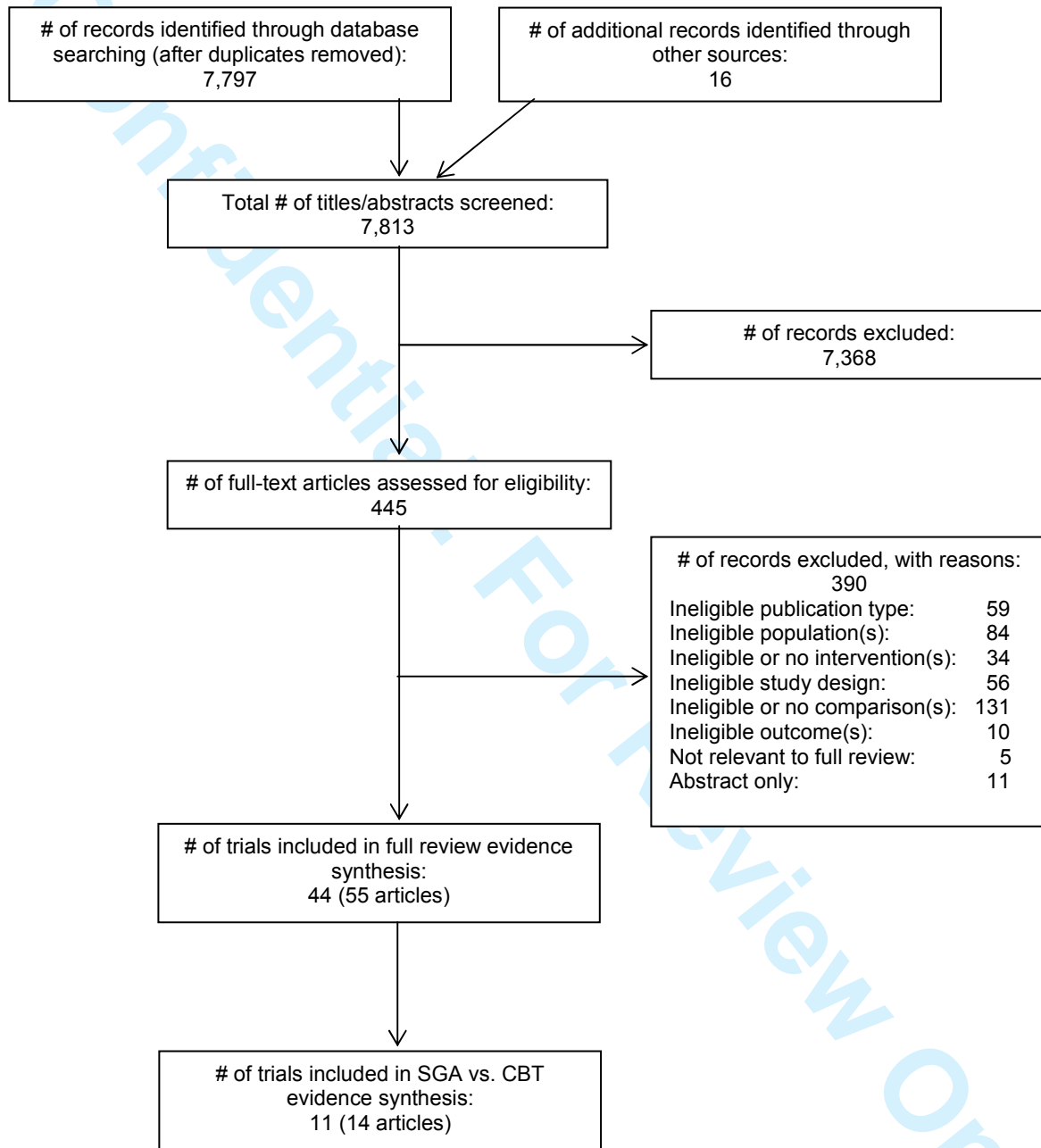
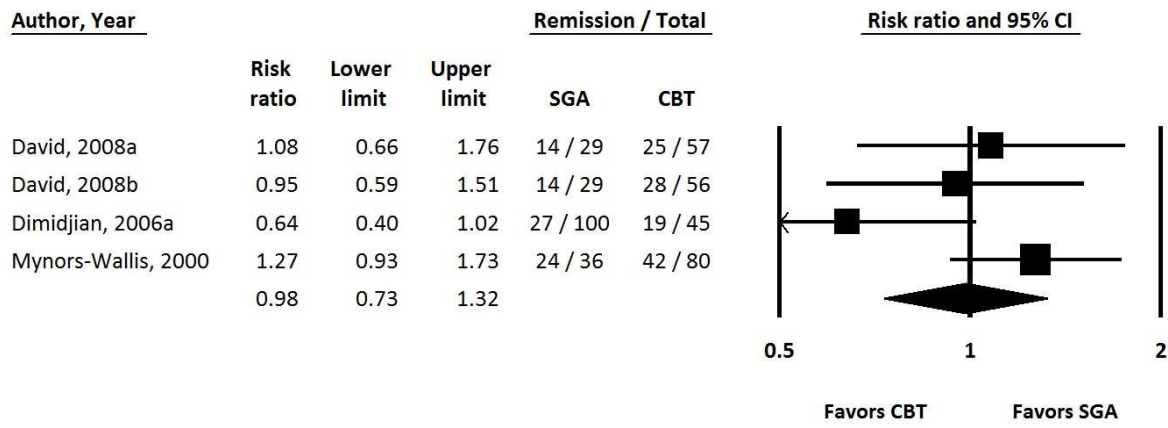


Figure 2. Second-generation antidepressants versus cognitive behavioral therapy: remission

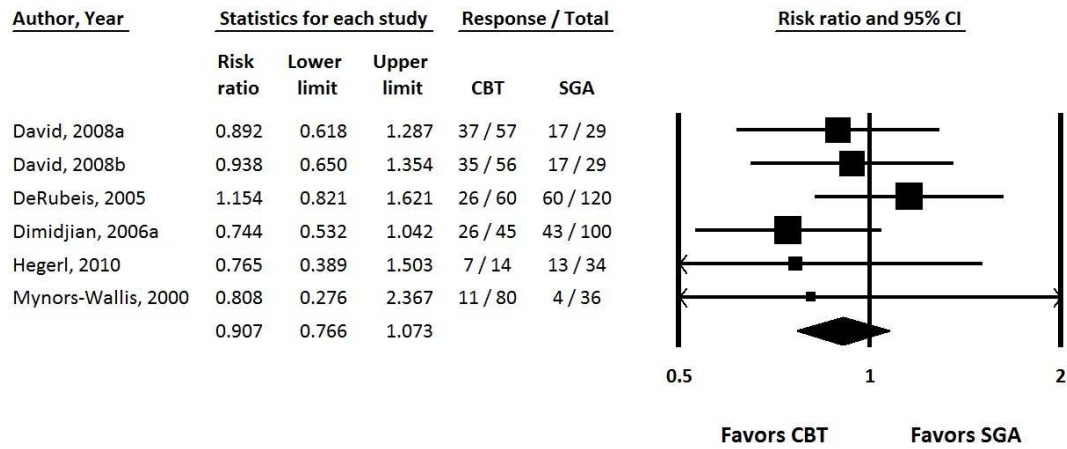


Random effects meta-analysis; I-squared 49%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; SGA = second-generation antidepressant;

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Figure 3. Second-generation antidepressants versus cognitive behavioral therapy: response

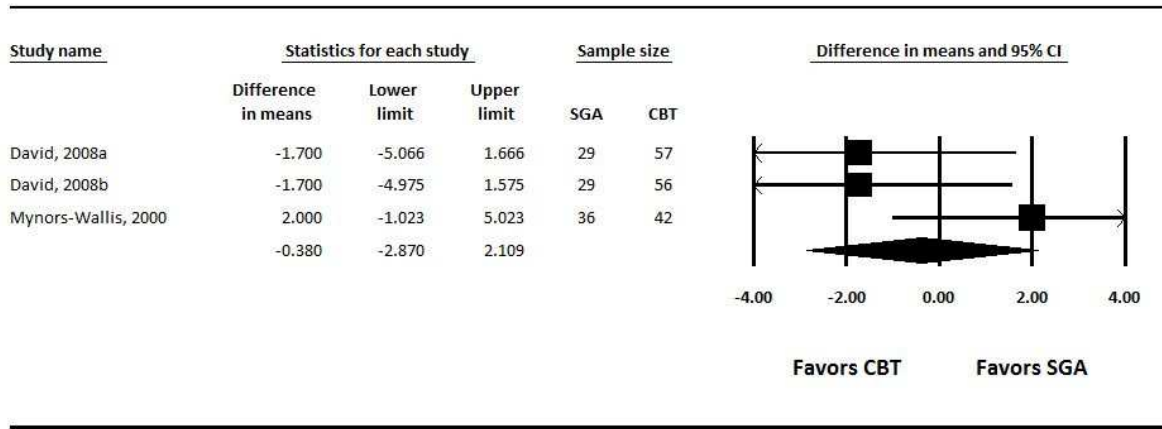


Random effects meta-analysis; I-squared 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; SGA = second-generation antidepressant.

For Review Only

Figure 4. Second-generation antidepressants versus cognitive behavioral therapy: Change in HAM-D-17



Random effects meta-analysis; I-squared 44%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D-17 = Hamilton Depression Rating Scale (17 items); SGA = second-generation antidepressant.

Comparative benefits and harms of second-generation anti-depressants and cognitive behavioral therapies in the initial treatment of major depressive disorder: systematic review and meta-analysis

ONLINE SUPPLEMENT: SEARCH STRATEGY

Searches were performed as part of a full comparative effectiveness review of benefits and harms of second-generation antidepressants, psychotherapies, complementary and alternative medicine treatments, and exercise interventions for patients with major depressive disorders.²⁶ Therefore, the table below has search terms for interventions that are irrelevant for this specific paper.

MEDLINE via PubMed: 02/05/2014

Search	Query	Items found
#1	Search ("Bupropion"[Mesh] OR "Bupropion"[tiab] OR 34911-55-2[rn])	3570
#2	Search ("Citalopram"[Mesh] OR "Citalopram"[tiab] OR 59729-33-8[rn])	5061
#3	Search ("Escitalopram"[tiab] OR 128196-01-0[rn])	4031
#4	Search ("O-desmethylvenlafaxine" [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn])	234
#5	Search ("Fluoxetine"[Mesh] OR "Fluoxetine"[tiab] OR 54910-89-3[rn])	10911
#6	Search ("Fluvoxamine"[Mesh] OR "Fluvoxamine"[tiab] OR 54739-18-3[rn])	2551
#7	Search (("milnacipran"[Supplementary Concept] OR "Levomilnacipran"[tiab] OR 96847-54-0[rn]))	346
#8	Search ("mirtazapine"[Supplementary Concept] OR "mirtazapine"[tiab] OR 85650-52-8[rn])	1574
#9	Search ("nefazodone"[Supplementary Concept] OR "nefazodone"[tiab] OR 82752-99-6[rn])	706
#10	Search ("Paroxetine"[Mesh] OR "Paroxetine"[tiab] OR 61869-08-7[rn])	5220
#11	Search ("Sertraline"[Mesh] OR "Sertraline"[tiab] OR 79617-96-2[rn])	3732
#12	Search ("Trazodone"[Mesh] OR "Trazodone"[tiab] OR 19794-93-5[rn])	1685
#13	Search ("venlafaxine"[Supplementary Concept] OR "venlafaxine"[tiab] OR 93413-69-5[rn])	3124
#14	Search ("vilazodone"[Supplementary Concept] OR "vilazodone"[tiab] OR 163521-12-8[rn])	65
#15	Search ("vortioxetine"[Supplementary Concept] OR "vortioxetine"[tiab] OR 508233-74-7[rn])	50
#16	Search ("Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Second-Generation"[Pharmacological Action])	57579
#17	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	67046
#18	Search ("Psychotherapy"[Mesh] OR psychotherap*[tiab])	156412
#19	Search (Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab])	8028
#20	Search (#18 OR #19)	158665
#21	Search ("Hypericum"[Mesh] OR "Hypericum"[tiab] OR "St. Johns Wort"[tiab] OR "Saint Johns Wort"[tiab] OR "St. John's Wort"[tiab] OR "Saint John's Wort"[tiab] OR L1160[tiab] OR L1160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab])	2591
#22	Search ("s adenosyl l methionine"[tiab] OR "s adenosylmethionine"[tiab] OR "S-Adenosylmethionine"[Mesh])	8814
#23	Search ("Fatty Acids, Omega-3"[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening	27732

Search	Query	Items found
	primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab]	
#24	Search "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab]	20337
#25	Search "Yoga"[Mesh] OR yoga[tiab]	2387
#26	Search "Meditation"[Mesh] OR meditation[tiab] OR mindfulness[tiab]	4174
#27	Search ("Exercise"[Mesh] OR physical activit*[tiab] OR "physical exercise"[tiab])	159734
#28	Search (#22 OR #23 OR #24 OR #25 OR #26 OR #27)	221143
#29	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35489
#30	Search (#29 AND (#28 OR #20 OR #17))	7950
#31	Search (systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab]))	241160
#32	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	542163
#33	Search (("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab]))	349594
#34	Search ("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab])	319105
#35	Search (#30 AND (#31 OR #32 OR #33 OR #34))	3642
#36	Search ("Animals"[Mesh] NOT "Humans"[Mesh])	3882887
#37	Search (#35 NOT #36)	3635
#38	Search ("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]	1490657
#39	Search (#37 NOT #38)	3398
#40	Search #39 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la])	3231

Addendum duloxetine 07/05/2014

Search	Query	Items found
#1	Search ("duloxetine" [Supplementary Concept] OR duloxetine[tiab])	1677
#2	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35518
#3	Search (#1 AND #2)	430
#4	Search ((systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab]))	241577
#5	Search (("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	542686
#6	Search (((("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab])))	349872
#7	Search (("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab]))	319351

Search	Query	Items found
#8	Search (#3 AND (#7 OR #6 OR #5 OR #4))	234
#9	Search (("Animals"[Mesh] NOT "Humans"[Mesh]))	3884483
#10	Search (#8 NOT #9)	234
#11	Search (("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])	1491426
#12	Search (#10 NOT #11)	234
#13	Search (#12 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la]))	229

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Cochrane Library 02/05/2014

ID	Search	Hits
#1	[mh Bupropion] or "Bupropion":ti,ab	934
#2	[mh Citalopram] or "Citalopram":ti,ab	1196
#3	Escitalopram:ti,ab	588
#4	Desvenlafaxine:ti,ab	71
#5	[mh Fluoxetine] or "Fluoxetine":ti,ab	2364
#6	[mh Fluvoxamine] or "Fluvoxamine":ti,ab	687
#7	Levomilnacipran:ti,ab	12
#8	mirtazapine:ti,ab	439
#9	nefazodone:ti,ab	194
#10	[mh Paroxetine] or "Paroxetine":ti,ab	1770
#11	[mh Sertraline] or "Sertraline":ti,ab	1350
#12	[mh Trazodone] or "Trazodone":ti,ab	335
#13	venlafaxine:ti,ab	989
#14	vilazodone:ti,ab	19
#15	vortioxetine:ti,ab	13
#16	[mh "Antidepressive Agents, Second-Generation"]	1230
#17	^{1-#16}	9063
#18	[mh Psychotherapy] or psychotherap*:ti,ab	17066
#19	(Acceptance near/2 Commitment next Therap*):ti,ab or (Cognitive near/2 Therap*):ti,ab or ((interpersonal or psychodynamic or behavioral) next therap*):ti,ab	5015
#20	#18 or #19	19087
#21	[mh yoga] or yoga:ti,ab	688
#22	[mh meditation] or (meditation or mindfulness):ti,ab	1064
#23	[mh Acupuncture] or [mh "Acupuncture Therapy"] or (Acupuncture or Electroacupuncture):ti,ab	7130
#24	[mh Hypericum] or "Hypericum":ti,ab or (john* next wort):ti,ab or (LI160 or WS5572 or WS5573 or LoHyp-57):ti,ab	295
#25	("s adenosyl l methionine" or "s adenosylmethionine"):ti,ab or [mh S-Adenosylmethionine]	191
#26	[mh "fatty Acids, Omega-3"] or (omega-3 and fatty next acid*):ti,ab or ("fish oil" or "flax seed" or "borage seed" or Borago or "evening primrose" or Oenothera or "eicosapentaenoic acid" or PUFA):ti,ab	3661
#27	[mh Exercise] or (physical next (activit* or exercise)):ti,ab	18551
#28	{or #21-#27}	31146
#29	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#30	#29 and (#17 or #20 or #28)	3544
#31	#30 Publication Date from 1990 to 2014	3460
#32	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#33	#31 not #32	2867
#34	#31 and (adult or adults):ti,ab	393
#35	#33 or #34	2945
#36	[mh animals] not [mh humans]	5655
#37	#35 not #36 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2940
#38	(review:pt and systematic:ti,ab) or "systematic review"	37971
#39	meta-analysis:pt or (meta next analy*):ti,ab or metaanaly*:ti,ab or [mh Meta-Analysis] or [mh "Meta-Analysis as Topic"]	20924
#40	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#41	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149716
#42	([mh "cohort studies"] or (cohort next stud*):ti,ab or [mh "case-control studies"] or (case-control next stud*):ti,ab or (observational next stud*):ti,ab or "observational study":pt or ((observational or longitudinal or retrospective) near/2 (study or trial)):ti,ab) and ("comparative study":pt or [mh "Comparative Study"] or comparison:ti,ab or comparative:ti,ab)	51743

ID	Search	Hits
#43	{or #38-#42}	458686
#44	#37 and #43 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2000

Addendum duloxetine 07/05/2014

No.	Query	Results
#30	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#31	#30 and "duloxetine":ti,ab	163
#32	#31 Publication Date from 1990 to 2014	163
#33	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#34	#32 not #33	143
#35	#32 and (adult or adults):ti,ab	29
#36	#34 or #35	149
#37	[mh animals] not [mh humans]	5655
#38	#36 not #37 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	149
#39	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#40	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149722
#41	#38 and (#39 or #40) in Trials	87
#42	#38 in Other Reviews	8
#43	#42 or #41	95

EMBASE 06/05/2014

No.	Query	Results
#1.1	'amfebutamone'/exp OR bupropion:tn,ab,ti OR '34911 55 2':rn	
#1.2	'citalopram'/exp OR citalopram:tn,ab,ti OR '59729 33 8':rn OR 'escitalopram'/exp OR escitalopram:tn,ab,ti OR '128196 01 0':rn	
#1.3	'desvenlafaxine'/exp OR desvenlafaxine:tn,ab,ti OR '93413 62 8':rn	
#1.4	'fluoxetine'/exp OR fluoxetine:tn,ab,ti OR '54910 89 3':rn	
#1.5	'fluvoxamine'/exp OR fluvoxamine:tn,ab,ti OR '54739 18 3':rn	
#1.6	'milnacipran'/exp OR levomilnacipran:tn,ab,ti OR '96847 54 0':rn	
#1.7	'mirtazapine'/exp OR mirtazapine:tn,ab,ti OR '85650 52 8':rn	
#1.8	'nefazodone'/exp OR nefazodone:tn,ab,ti OR '82752 99 6':rn	
#1.9	'paroxetine'/exp OR paroxetine:tn,ab,ti OR '61869 08 7':rn	
#1.10	'sertraline'/exp OR sertraline:tn,ab,ti OR '79617 96 2':rn	
#1.11	'trazodone'/exp OR trazodone:tn,ab,ti OR '19794 93 5':rn	
#1.12	'venlafaxine'/exp OR venlafaxine:tn,ab,ti OR '93413 69 5':rn	
#1.13	'vilazodone'/exp OR vilazodone:tn,ab,ti OR '163521 12 8':rn	
#1.14	'vortioxetine'/exp OR vortioxetine:tn,ab,ti OR '508233 74 7':rn	
#1.15	'antidepressant agent'/exp AND 'second generation':ab,ti	
#1.16	#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15	87062
#1.17	'psychotherapy'/exp	187201
#1.18	((acceptance OR cognitive OR interpersonal OR psychodynamic OR behavioral) NEXT/3 (therapy OR therapies OR psychotherapy)):ab,ti	20374
#1.19	#1.17 OR #1.18 AND 'treatment outcome'/exp	25169
#1.20	'hypericum'/exp OR hypericum:ab,ti OR (john* NEXT/1 wort):ab,ti OR li160:ab,ti OR ws5572:ab,ti OR ws5573:ab,ti OR 'lohyp 57':ab,ti	4193
#1.21	's adenosylmethionine'/exp OR 's adenosylmethionine' OR 's adenosyl methionine':ab,ti OR 's adenosylmethionine':ab,ti	10557
#1.22	'omega 3 fatty acid'/exp OR ('omega 3':ab,ti AND acid*:ab,ti) OR 'fish oil':ab,ti OR 'flax	34034

No.	Query	Results
	seed':ab,ti OR 'borage seed':ab,ti OR borago:ab,ti OR 'evening primrose':ab,ti OR oenothera:ab,ti OR 'eicosapentaenoic acid':ab,ti OR pufa:ab,ti	
#1.23	'acupuncture'/exp OR acupuncture:ab,ti OR electroacupuncture:ab,ti	33369
#1.24	'yoga'/exp OR yoga:ab,ti	4138
#1.25	'meditation'/exp OR meditation:ab,ti OR mindfulness:ab,ti	6584
#1.26	'exercise'/exp	209232
#1.27	#1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25 OR #1.26 AND 'treatment outcome'/exp	19807
#1.28	'major depression'/exp OR 'major depressive disorder':ab,ti OR (major NEXT/2 depress*):ab,ti	52013
#1.29	#1.28 AND (#1.27 OR #1.19 OR #1.16)	13000
#1.30	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti)) OR (review:it AND review:ab,ti AND (rationale:ab,ti OR evidence:ab,ti))	287380
#1.31	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#1.32	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#1.33	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#1.34	#1.29 AND (#1.30 OR #1.31 OR #1.32 OR #1.33)	
#1.35	'human'/exp	14753345
#1.36	#1.34 AND #1.35	4575
#1.37	'adult'/exp	5294678
#1.38	#1.36 AND #1.37	2399
#1.39	#1.38 AND [1990-2014]/py	2374
#1.40	#1.39 AND [english]/lim	2316
#1.41	#1.39 AND (german:la OR italian:la)	17
#1.42	#1.40 OR #1.41	2333
#1		2333
#2	#1 AND [embase]/lim	2232

Addendum duloxetine 07.05.2014

No.	Query	Results
#6	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#7	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#8	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#9	#5 OR #6 OR #7 OR #8	1017694
#10	#4 AND #9	582
#11	#10 AND 'human'/exp AND 'adult'/exp	210
#12	#11 AND [1990-2014]/py AND [embase]/lim	205
#13	#12 AND ([english]/lim OR german:la OR italian:la)	205

CINAHL (via Ebsco) 02.05.2014

#	Query	Results
S1	(MH "Bupropion") OR "Bupropion"	1,072
S2	(MH "Citalopram") OR "Citalopram"	644
S3	"Escitalopram"	202
S4	(MH "Desvenlafaxine Succinate") OR TX Desvenlafaxine	49
S5	(MH "Fluoxetine+") OR "Fluoxetine"	1,144
S6	(MH "Fluvoxamine Maleate") OR "Fluvoxamine"	145
S7	"Levomilnacipran"	5
S8	(MH "Mirtazapine") OR "mirtazapine"	255
S9	(MH "Nefazodone") OR "nefazodone"	68
S10	(MH "Paroxetine") OR "Paroxetine"	732
S11	(MH "Sertraline Hydrochloride") OR "Sertraline"	643
S12	(MH "Trazodone") OR "Trazodone"	168
S13	(MH "Venlafaxine+") OR "venlafaxine"	605
S14	"vilazodone"	11
S15	"vortioxetine"	5
S16	(MH "Antidepressive Agents, Second Generation+")	2,806
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	4,599
S18	(MH "Psychotherapy+") OR (TI psychotherap*) OR (AB psychotherap*)	86,97
S19	TI (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*) OR AB (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*)	4,172
S20	S18 OR S19	87,95
S21	(MH "Yoga+") OR (TI yoga) OR (AB yoga)	2,268
S22	(MH "Meditation") OR (TI (meditation OR mindfulness)) OR (AB (meditation OR mindfulness))	2,652
S23	(MH "St. John's Wort") OR "hypericum" OR (TI john* N2 wort) OR (AB john* N2 wort) OR (TI (LI160 OR WS5572 OR WS5573 OR LoHyp-57)) OR (AB (LI160 OR WS5572 OR WS5573 OR LoHyp-57))	932
S24	(MH "Fatty Acids, Omega-3+") OR (TI "omega 3" N1 fatty acid*) OR (AB "omega 3" N1 fatty acid*) OR (TI ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR "evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)) OR (AB ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR "evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA))	4,996
S25	(MH "S-Adenosylmethionine") OR (TI ("s adenosyl I methionine" OR "s adenosylmethionine")) OR (AB ("s adenosyl I methionine" OR "s adenosylmethionine"))	204
S26	(MH "Acupuncture+") OR (TI (acupuncture OR electroacupuncture)) OR (AB (acupuncture OR electroacupuncture))	8,556
S27	(MH "Exercise+") OR TI (physical N1 (activit* OR exercise)) OR AB (physical N1 (activit* OR exercise))	65,646
S28	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	83,353
S29	(MH "Depression+") AND (TX major N2 depress*)	3,393
S30	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	3,998
S31	S29 OR S30	4,08
S32	S31 AND (S17 OR S20 OR S28)	1,115
S33	(MH "Animals") NOT (MH "Human")	24,505
S34	S32 NOT S33	1,114
S35	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,397
S36	S34 NOT S35	1,012
S37	S36 AND (PY 1990-2014) AND (LA (english OR german Or italian))	1,003
S38	S37 NOT (PT (editorial OR letter OR commentary))	867

Addendum duloxetine 07.05.2014

#	Query	Results
S1	(MH "Duloxetine Hydrochloride") OR (TX Duloxetine)	378
S2	(MH "Depression+") AND (TX major N2 depress*)	3,397
S3	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	4
S4	S2 OR S3	4,082
S5	S4 AND S1	51
S6	(MH "Animals") NOT (MH "Human")	24,582
S7	S5 NOT S6	51
S8	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,684
S9	S7 NOT S8	51
S10	S9 AND (PY 1990-2014) AND (LA (english OR german Or italian))	51
S11	S10 NOT (PT (editorial OR letter OR commentary))	50

AMED (via Ovid) 02.05.2014

#	Suchen	Ergebnisse
1	exp antidepressive agents/	272
2	Bupropion.mp.	15
3	Citalopram.mp.	9
4	Escitalopram.mp.	3
5	(Desvenlafaxine or O-desmethylvenlafaxine).mp.	0
6	Fluoxetine.mp.	50
7	Levomilnacipran.mp.	0
8	mirtazapine.mp.	6
9	(nefazodone or Paroxetine or Sertraline or Trazodone or venlafaxine or vilazodone or vortioxetine).mp.	69
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	363
11	exp psychotherapy/	8542
12	((acceptance or cognitive or interpersonal or psychodynamic or behavioral) adj3 (therap\$ or psychotherap\$)).mp.	1395
13	11 or 12	8895
14	exp fatty acids/ or exp fish oils/ or (omega 3 and acid*).mp. or (flax seed or borage seed or Borago or evening primrose or Oenothera or eicosapentaenoic acid or PUFA).mp.	640
15	exp hypericum/ or (hypericum or (john\$ adj1 wort)).mp. or (LI160 or WS5572 or WS5573 or LoHyp-57).mp.	415
16	(S-Adenosylmethionine or s adenosyl l methionine).mp.	21
17	exp acupuncture/ or exp electroacupuncture/ or (acupuncture or electroacupuncture).mp.	9182
18	exp meditation/ or (meditation or mindfulness).mp.	658
19	exp Yoga/ or yoga.mp.	501
20	(physical adj1 (activit* or exercise)).mp. or exp Exercise/	9857
21	14 or 15 or 16 or 17 or 18 or 19 or 20	20984
22	exp depressive disorder/	890
23	((major adj2 depress\$) or major depressive disorder).mp.	352
24	22 or 23	1126
25	10 or 13 or 21	29843
26	24 and 25	283
27	26	283
28	limit 27 to yr="1990 -Current"	282
29	(exp infant/ or exp child/ or exp adolescent/) not exp adult/	15352
30	28 not 29	269
31	28 and (adult or adults).ti,ab.	39
32	30 or 31	271

Addendum duloxetine 07.05.2014

#	Suchen	Ergebnisse
1	duloxetine.mp.	22
2	exp depressive disorder/	894
3	((major adj2 depress\$) or major depressive disorder).mp.	353
4	2 or 3	1131
5	1 and 4	5

PsycInfo (via Ebsco) 02.05.2014

#	Query	Results
S1	TX (Bupropion OR Citalopram OR Escitalopram OR O-desmethylvenlafaxine OR Desvenlafaxine OR Fluoxetine OR Fluvoxamine OR Levomilnacipran OR mirtazapine OR nefazodone OR Paroxetine OR Sertraline OR Trazodone OR venlafaxine OR vilazodone OR vortioxetine)	15,857
S2	DE "antidepressant drugs" AND TX (second generation)	144
S3	S1 OR S2	15,958
S4	(DE "acceptance and commitment therapy") or ((DE "cognitive therapy") or (DE "behavior therapy")) OR (DE psychotherapy)	64,196
S5	TI ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*)) OR AB ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*))	24,311
S6	S4 OR S5	78,648
S7	(DE acupuncture) OR (TX (acupuncture OR electroacupuncture))	1,717
S8	(DE meditation) OR (TX (meditation OR mindfulness))	8,986
S9	(DE hypericum perforatum) OR (TX (hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57))	392
S10	(DE yoga) OR (TX yoga)	1,907
S11	TX ((omega-3 N1 fatty acid*) OR "fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)	982
S12	TX ("s adenosyl I methionine" OR "s adenosylmethionine")	205
S13	DE exercise OR TI physical activit* OR AB physical activit*	30,086
S14	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	43,124
S15	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,026
S16	S15 AND (S3 OR S6 OR S14)	13,953
S17	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S18	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S19	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S20	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR (TI "research integration") OR (AB "research integration")) OR (TI "research synthesis") Or (AB "research synthesis")) OR (TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S21	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731
S22	(S17 OR S18 OR S19 OR S20 OR S21) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S23	S16 AND S22	3,595
S24	((ZP "animal")) not ((ZP "human"))	279,088

#	Query	Results
S25	S23 NOT S24	3,586
S26	((((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)") or ((ZG "adolescence (13-17 yrs)")))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S27	S25 NOT S26	3,4
S28	LA (english OR german OR italian)	3,441,047
S29	PY 1990-2014	2,451,294
S30	S27 AND S28 AND S29	3,172

Addendum duloxetine 07.05.2014

#	Query	Results
S1	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,027
S2	S1 AND (TX duloxetine)	375
S3	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S4	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S5	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S6	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S7	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731
S8	(S3 OR S4 OR S5 OR S6 OR S7) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S9	S2 AND S8	161
S10	((ZP "animal")) not ((ZP "human"))	279,088
S11	S9 NOT S10	161
S12	((((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)") or ((ZG "adolescence (13-17 yrs)")))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S13	S11 NOT S12	161
S14	LA (english OR german OR italian)	3,441,047
S15	PY 1990-2014	2,451,294
S16	S13 AND S14 AND S15	154

Update Searches

MEDLINE via PubMed 12 January 2015

Search	Query	Items found
#1	Search "Bupropion"[Mesh] OR "Bupropion"[tiab] OR 34911-55-2[rn]	3714
#2	Search "Citalopram"[Mesh] OR "Citalopram"[tiab] OR 59729-33-8[rn]	5305
#3	Search Escitalopram[tw] OR 128196-01-0[rn]	4250
#4	Search "O-desmethylvenlafaxine" [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn]	255
#5	Search "Fluoxetine"[Mesh] OR "Fluoxetine"[tiab] OR 54910-89-3[rn]	11275
#6	Search "Fluvoxamine"[Mesh] OR "Fluvoxamine"[tiab] OR 54739-18-3[rn]	2609
#7	Search "milnacipran"[Supplementary Concept] OR "Levomilnacipran"[tiab] OR 96847-54-0[rn]	372
#8	Search "mirtazapine"[Supplementary Concept] OR "mirtazapine"[tiab] OR 85650-52-8[rn]	1650
#9	Search "nefazodone"[Supplementary Concept] OR "nefazodone"[tiab] OR 82752-99-6[rn]	715
#10	Search "Paroxetine"[Mesh] OR "Paroxetine"[tiab] OR 61869-08-7[rn]	5379
#11	Search "Sertraline"[Mesh] OR "Sertraline"[tiab] OR 79617-96-2[rn]	3875
#12	Search "Trazodone"[Mesh] OR "Trazodone"[tiab] OR 19794-93-5[rn]	1716
#13	Search "venlafaxine"[Supplementary Concept] OR "venlafaxine"[tiab] OR 93413-69-5[rn]	3290
#14	Search "vilazodone"[Supplementary Concept] OR "vilazodone"[tiab] OR 163521-12-8[rn]	83
#15	Search "vortioxetine"[Supplementary Concept] OR "vortioxetine"[tiab] OR 508233-74-7[rn]	75
#16	Search "duloxetine" [Supplementary Concept] OR duloxetine[tiab]	1778
#17	Search "Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Second-Generation"[Pharmacological Action]	58607
#18	Search #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	69934
#19	Search "Psychotherapy"[Mesh] OR psychotherap*[tiab]	160809
#20	Search Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab]	8733
#21	Search (#19 OR #20)	163324
#22	Search "Hypericum"[Mesh] OR Hypericum[tiab] OR St. Johns Wort[tiab] OR Saint Johns Wort[tiab] OR St. John's Wort[tiab] OR Saint John's Wort[tiab] OR LI160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab]	2688
#23	Search "s adenosyl l methionine"[tiab] OR "s adenosylmethionine"[tiab] OR "S-Adenosylmethionine"[Mesh]	9025
#24	Search "Fatty Acids, Omega-3"[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab]	29253
#25	Search "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab]	21423
#26	Search "Yoga"[Mesh] OR yoga[tiab]	2633
#27	Search "Meditation"[Mesh] OR meditation[tiab] OR mindfulness[tiab]	4674
#28	Search "Exercise"[Mesh] OR physical activit*[tiab] OR "physical exercise"[tiab]	169750
#29	Search #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	237070
#30	Search "Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab]	37436
#31	Search (#30 AND #18)	5363
#32	Search (#30 AND #21)	3258
#33	Search (#30 AND #29)	808
#34	Search (#31 OR #32 OR #33)	8749
#35	Search (systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab])	265837

Search	Query	Items found
	OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab])	
#36	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	565406
#37	Search (("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab]))	363532
#38	Search ("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab])	334900
#39	Search (#34 AND (#35 OR #36 OR #37 OR #38))	4018
#40	Search "Animals"[Mesh] NOT "Humans"[Mesh]	3963556
#41	Search (#39 NOT #40)	4011
#42	Search ("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]	1523966
#43	Search (#41 NOT #42)	3767
#44	Search #43 AND 2014:2015[dp] AND (english[la] OR german[la] OR italian[la])	202

Cochrane Library 12 January 2015

ID	Search	Hits
#1	[mh Bupropion] or Bupropion:ti,ab	990
#2	[mh Citalopram] or Citalopram:ti,ab	1238
#3	Escitalopram:ti,ab	655
#4	Desvenlafaxine:ti,ab	83
#5	[mh Fluoxetine] or Fluoxetine:ti,ab	2423
#6	[mh Fluvoxamine] or Fluvoxamine:ti,ab	693
#7	Levomilnacipran:ti,ab	15
#8	mirtazapine:ti,ab	457
#9	nefazodone:ti,ab	194
#10	[mh Paroxetine] or Paroxetine:ti,ab	1814
#11	[mh Sertraline] or sertraline:ti,ab	1415
#12	[mh Trazodone] or Trazodone:ti,ab	342
#13	venlafaxine:ti,ab	1030
#14	vilazodone:ti,ab	26
#15	vortioxetine:ti,ab	18
#16	duloxetine:ti,ab	541
#17	[mh "Antidepressive Agents, Second-Generation"]	1236
#18	^{1-#17}	9842
#19	[mh Psychotherapy] or psychotherap*:ti,ab	17633
#20	(Acceptance near/2 Commitment next Therap*):ti,ab or (Cognitive near/2 Therap*):ti,ab or ((interpersonal or psychodynamic or behavioral) next therap*):ti,ab	5514
#21	#19 or #20	20047
#22	[mh yoga] or yoga:ti,ab	856
#23	[mh meditation] or (meditation or mindfulness):ti,ab	1296
#24	[mh Acupuncture] or [mh "Acupuncture Therapy"] or (Acupuncture or Electroacupuncture):ti,ab	7617
#25	[mh Hypericum] or "Hypericum":ti,ab or (john* next wort):ti,ab or (LI160 or WS5572 or WS5573 or LoHyp-57):ti,ab	302
#26	("s adenosyl l methionine" or "s adenosylmethionine"):ti,ab or [mh S-Adenosylmethionine]	202
#27	[mh "fatty Acids, Omega-3"] or (omega-3 and fatty next acid*):ti,ab or ("fish oil" or "flax	3983

ID	Search	Hits
	seed" or "borage seed" or Borago or "evening primrose" or Oenothera or "eicosapentaenoic acid" or PUFA):ti,ab	
#28	[mh Exercise] or (physical next (activit* or exercise)):ti,ab	19836
#29	{or #22-#28}	33596
#30	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6816
#31	#30 and (#18 or #21 or #29)	3847
#32	#31 Publication Year from 2014	119
#33	[mh animals] not [mh humans]	5683
#34	#32 not #33	119
#35	(([mh infant] or [mh child] or [mh adolescent]) not [mh adult])	88719
#36	#34 not #35	119

Embase (embase.com) 13 January 2015

No.	Query	Results
#1	'amfebutamone'/exp OR bupropion:tn,ab,ti OR '34911 55 2':rn	14498
#2	'citalopram'/exp OR citalopram:tn,ab,ti OR '59729 33 8':rn	18173
#3	'escitalopram'/exp OR escitalopram:tn,ab,ti OR '128196 01 0':rn	7453
#4	'desvenlafaxine'/exp OR desvenlafaxine:tn,ab,ti OR '93413 62 8':rn	926
#5	'fluoxetine'/exp OR fluoxetine:tn,ab,ti OR '54910 89 3':rn	38642
#6	'fluvoxamine'/exp OR fluvoxamine:tn,ab,ti OR '54739 18 3':rn	11640
#7	'milnacipran'/exp OR levomilnacipran:tn,ab,ti OR '96847 54 0':rn	2006
#8	'mirtazapine'/exp OR mirtazapine:tn,ab,ti OR '85650 52 8':rn	9260
#9	'nefazodone'/exp OR nefazodone:tn,ab,ti OR '82752 99 6':rn	4885
#10	'paroxetine'/exp OR paroxetine:tn,ab,ti OR '61869 08 7':rn	23598
#11	'sertraline'/exp OR sertraline:tn,ab,ti OR '79617 96 2':rn	20413
#12	'trazodone'/exp OR trazodone:tn,ab,ti OR '19794 93 5':rn	10064
#13	'venlafaxine'/exp OR venlafaxine:tn,ab,ti OR '93413 69 5':rn	16550
#14	'vilazodone'/exp OR vilazodone:tn,ab,ti OR '163521 12 8':rn	264
#15	'vortioxetine'/exp OR vortioxetine:tn,ab,ti OR '508233 74 7':rn	231
#16	'duloxetine'/exp OR '116539 59 4':rn OR duloxetine:tn,ab,ti	7135
#17	'antidepressant agent'/exp AND 'second generation':ab,ti OR (antidepressant NEAR/2 'second generation'):ab,ti	1393
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	93111
#19	'psychotherapy'/exp	193315
#20	((acceptance OR cognitive OR interpersonal OR psychodynamic OR behavioral) NEXT/3 (therapy OR therapies OR psychotherapy)):ab,ti	21899
#21	#19 OR #20	195814
#22	'hypericum'/exp OR hypericum:ab,ti OR (john* NEXT/1 wort):ab,ti OR li160:ab,ti OR ws5572:ab,ti OR ws5573:ab,ti OR 'lohyp 57':ab,ti	4330
#23	's adenosylmethionine'/exp OR 's adenosylmethionine' OR 's adenosyl I methionine':ab,ti OR 's adenosylmethionine':ab,ti	10883
#24	'omega 3 fatty acid'/exp OR ('omega 3':ab,ti AND acid*:ab,ti) OR 'fish oil':ab,ti OR 'flax seed':ab,ti OR 'borage seed':ab,ti OR borago:ab,ti OR 'evening primrose':ab,ti OR oenothera:ab,ti OR 'eicosapentaenoic acid':ab,ti OR pufa:ab,ti	35965
#25	'acupuncture'/exp OR acupuncture:ab,ti OR electroacupuncture:ab,ti	34890
#26	'yoga'/exp OR yoga:ab,ti	4566
#27	'meditation'/exp OR meditation:ab,ti OR mindfulness:ab,ti	7307
#28	'exercise'/exp OR (physical NEXT/2 (activit* OR exercis*)):ab,ti	284231
#29	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	374358
#30	'major depression'/exp OR 'major depressive disorder':ab,ti OR (major NEXT/2 depress*):ab,ti	55229
#31	#18 AND #30	12883
#32	#21 AND #30	5686

No.	Query	Results
#33	#29 AND #30	1555
#34	#31 OR #32 OR #33	17290
#35	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti)) OR (review:it AND review:ab,ti AND (rationale:ab,ti OR evidence:ab,ti))	312865
#36	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	460334
#37	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	160923
#38	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	618207
#39	#35 OR #36 OR #37 OR #38	1077437
#40	#34 AND #39	5782
#41	'animal'/exp NOT 'human'/exp	4405184
#42	#40 NOT #41	5779
#43	'groups by age'/exp NOT 'adult'/exp	5494792
#44	#42 NOT #43	2942
#45	#44 AND [2014-2015]/py	205
#46	#45 AND [english]/lim	204
#47	#45 AND (german:la OR italian:la)	0
#48	#46 OR #47	204
#49	#48 AND [embase]/lim	198

CINAHL Plus (Ebsco) 13 January 2015

#	Query	Results
S1	(MH "Bupropion") OR "Bupropion"	1,448
S2	(MH "Citalopram") OR "Citalopram"	1,094
S3	Escitalopram	397
S4	(MH "Desvenlafaxine Succinate") OR Desvenlafaxine	97
S5	(MH "Fluoxetine+") OR "Fluoxetine"	1,534
S6	(MH "Fluvoxamine Maleate") OR "Fluvoxamine"	207
S7	"Levomilnacipran"	11
S8	(MH "Mirtazapine") OR "mirtazapine"	363
S9	(MH "Nefazodone") OR "nefazodone"	82
S10	(MH "Paroxetine") OR "Paroxetine"	1,03
S11	(MH "Sertraline Hydrochloride") OR "Sertraline"	927
S12	(MH "Trazodone") OR "Trazodone"	234
S13	(MH "Venlafaxine+") OR "venlafaxine"	876
S14	"vilazodone"	25
S15	"vortioxetine"	17
S16	(MH "Duloxetine Hydrochloride") OR (TX Duloxetine)	1,305
S17	(MH "Antidepressive Agents, Second Generation+")	3,975
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	7,776
S19	(MH "Psychotherapy+") OR (TI psychotherap*) OR (AB psychotherap*)	117,68
S20	TI (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*) OR AB (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*)	6,208
S21	S19 OR S20	119,031
S22	(MH "Yoga+") OR (TI yoga) OR (AB yoga)	4,665

#	Query	Results
S23	(MH "Meditation") OR (TI (meditation OR mindfulness)) OR (AB (meditation OR mindfulness))	4,231
S24	(MH "St. John's Wort") OR "hypericum" OR (TI john* N2 wort) OR (AB john* N2 wort) OR (TI (LI160 OR WS5572 OR WS5573 OR LoHyp-57)) OR (AB (LI160 OR WS5572 OR WS5573 OR LoHyp-57))	1,145
S25	(MH "Fatty Acids, Omega-3+") OR (TI "omega 3" N1 fatty acid*) OR (AB "omega 3" N1 fatty acid*) OR (TI ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR "evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)) OR (AB ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR "evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA))	7,684
S26	(MH "S-Adenosylmethionine") OR (TI ("s adenosyl I methionine" OR "s adenosylmethionine")) OR (AB ("s adenosyl I methionine" OR "s adenosylmethionine"))	291
S27	(MH "Acupuncture+") OR (TI (acupuncture OR electroacupuncture)) OR (AB (acupuncture OR electroacupuncture))	11,43
S28	(MH "Exercise+") OR TI (physical N1 (activit* OR exercise)) OR AB (physical N1 (activit* OR exercise))	85,935
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	112,416
S30	(MH "Depression") AND (TX major N2 depress*)	8,569
S31	TI (major N2 depress* OR "major depressive disorder") OR AB (major N2 depress* OR "major depressive disorder")	6,57
S32	S30 OR S31	9,83
S33	S18 AND S32	1,091
S34	S21 AND S32	1,482
S35	S29 AND S32	462
S36	S33 OR S34 OR S35	2,742
S37	(MH "Animals") NOT (MH "Human")	51,653
S38	S36 NOT S37	2,737
S39	(((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+"))	315,299
S40	S38 NOT S39	2,525
S41	S40 AND (LA (english OR german OR italian))	2,513
S42	S41 AND (PY 2014-2015)	136
S43	S42 NOT (PT (editorial OR letter OR commentary OR "case study"))	131

AMED (Ovid) 13 January 2015

#	Suchen	Ergebnisse
1	exp antidepressive agents/	281
2	Bupropion.mp.	15
3	Citalopram.mp.	9
4	Escitalopram.mp.	3
5	(Desvenlafaxine or O-desmethylvenlafaxine).mp.	0
6	(Fluoxetine or Fluvoxamine).mp.	56
7	Levomilnacipran.mp.	0
8	mirtazapine.mp.	6
9	(nefazodone or Paroxetine or Sertraline or Trazodone or venlafaxine or vilazodone or vortioxetine or duloxetine).mp.	91
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	393
11	exp psychotherapy/	8680
12	((acceptance or cognitive or interpersonal or psychodynamic or behavioral) adj3 (therap\$ or psychotherap\$)).mp.	1443
13	11 or 12	9045
14	exp fatty acids/ or exp fish oils/ or (omega 3 and acid*).mp. or (flax seed or borage seed or Borago or evening primrose or Oenothera or eicosapentaenoic acid or PUFA).mp.	666
15	exp hypericum/ or (hypericum or (john\$ adj1 wort)).mp. or (LI160 or WS5572 or WS5573 or LoHyp-57).mp.	420
16	(S-Adenosylmethionine or s adenosyl I methionine).mp.	21
17	exp acupuncture/ or exp electroacupuncture/ or (acupuncture or	9406

#	Suchen	Ergebnisse
	electroacupuncture).mp.	
18	exp meditation/ or (meditation or mindfulness).mp.	678
19	exp Yoga/ or yoga.mp.	521
20	(physical adj1 (activit* or exercise)).mp. or exp Exercise/	10153
21	14 or 15 or 16 or 17 or 18 or 19 or 20	21568
22	exp depressive disorder/	997
23	((major adj2 depress\$) or major depressive disorder).mp.	360
24	22 or 23	1235
25	10 or 13 or 21	30590
26	24 and 25	306
27	exp animals/ not exp humans/	7987
28	26 not 27	287
29	(exp infant/ or exp child/ or exp adolescent/) not exp adult/	15990
30	28 not 29	272
31	limit 30 to yr="2014 -Current"	10

PsycINFO (Ebsco) 13 January 2015

#	Query	Results
S1	DE "Bupropion" OR TI Bupropion OR AB Bupropion	1,739
S2	DE "Citalopram" OR TI Citalopram OR AB Citalopram	2,213
S3	TX Escitalopram	1
S4	TX Desvenlafaxine	94
S5	DE "Fluoxetine" OR TI Fluoxetine OR AB Fluoxetine	5,746
S6	DE "Fluvoxamine" OR TI Fluvoxamine OR AB Fluvoxamine	1,479
S7	TX Levomilnacipran	11
S8	TX mirtazapine	995
S9	DE "Nefazodone" OR TI nefazodone OR AB nefazodone	457
S10	DE "Paroxetine" OR TI Paroxetine OR AB Paroxetine	2,924
S11	DE "Sertraline" OR TI Sertraline OR AB Sertraline	2,316
S12	DE "Trazodone" OR TI Trazodone OR AB Trazodone	784
S13	DE "Venlafaxine" OR TI venlafaxine OR AB venlafaxine	1,957
S14	TX vilazodone	23
S15	TX vortioxetine	24
S16	TX duloxetine	768
S17	DE "antidepressant drugs" AND TX (second generation)	155
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	16,934
S19	(DE "acceptance and commitment therapy") or ((DE "cognitive therapy") or (DE "behavior therapy")) OR (DE psychotherapy)	66,057
S20	TI ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*)) OR AB ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*))	25,883
S21	S19 OR S20	81,679
S22	(DE acupuncture) OR TI ((acupuncture OR electroacupuncture)) OR AB ((acupuncture OR electroacupuncture))	1,682
S23	(DE meditation) OR TI ((meditation OR mindfulness)) OR AB ((meditation OR mindfulness))	9,174
S24	(DE hypericum perforatum) OR TI ((hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57)) OR AB ((hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57))	399
S25	DE yoga) OR TI yoga OR AB yoga	1,72
S26	TX ((omega-3 N1 fatty acid*) OR "fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)	1,06
S27	TX ("s adenosyl l methionine" OR "s adenosylmethionine")	218

#	Query	Results
S28	DE exercise OR TI (physical W1 (activit* OR exercis*)) OR AB (physical W1 (activit* OR exercis*))	31,426
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	44,488
S30	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	99,261
S31	S18 AND S30	7,216
S32	S21 AND S30	6,383
S33	S29 AND S30	2,047
S34	S31 OR S32 OR S33	14,918
S35	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	39,02
S36	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	43,179
S37	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	45,025
S38	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR (TI "research integration") OR (AB "research integration")) OR (TI "research synthesis") Or (AB "research synthesis")) OR (TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	35,443
S39	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	11,52
S40	S35 OR S36 OR S37 OR S38 OR S39	127,772
S41	S34 AND S40	4,196
S42	((ZZ "comment/reply") or (ZZ "editorial") or (ZZ "letter"))	150,398
S43	S41 NOT S42	3,957
S44	((ZP "animal")) not ((ZP "human"))	289,185
S45	S43 NOT S44	3,947
S46	((((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)")))) not ((ZG "adulthood (18 yrs & older)"))	411,03
S47	S45 NOT S46	3,746
S48	LA (english OR german OR italian)	3,603,958
S49	S47 AND S48	3,619
S50	PY 2014-2015	155,082
S51	S49 AND S50	257

Grey Literature Search

ClinicalTrials.gov 04.06.2014

41 studies found for:

("major depressive disorder" OR "major depression") AND Bupropion Adult, Senior Phase 2, 3, 4

170 studies found for:

("major depressive disorder" OR "major depression") AND Citalopram Adult, Senior Phase 2, 3, 4

170 studies found for:

("major depressive disorder" OR "major depression") AND Escitalopram Adult, Senior Phase 2, 3, 4

35 studies found for:

("major depressive disorder" OR "major depression") AND Desvenlafaxine Adult, Senior Phase 2, 3, 4

45 studies found for:

("major depressive disorder" OR "major depression") AND Fluoxetine Adult, Senior Phase 2, 3, 4

6 studies found for:

("major depressive disorder" OR "major depression") AND Fluvoxamine Adult, Senior Phase 2, 3, 4

7 studies found for:

("major depressive disorder" OR "major depression") AND Levomilnacipran Adult, Senior Phase 2, 3, 4

21 studies found for:

("major depressive disorder" OR "major depression") AND mirtazapine Adult, Senior Phase 2, 3, 4

Found no studies with search of: ("major depressive disorder" OR "major depression") AND nefazodone Adult, Senior Phase 2, 3, 4

61 studies found for:

("major depressive disorder" OR "major depression") AND Paroxetine Adult, Senior Phase 2, 3, 4

66 studies found for:

("major depressive disorder" OR "major depression") AND Sertraline Adult, Senior Phase 2, 3, 4

4 studies found for:

("major depressive disorder" OR "major depression") AND Trazodone Adult, Senior Phase 2, 3, 4

66 studies found for:

("major depressive disorder" OR "major depression") AND venlafaxine Adult, Senior Phase 2, 3, 4

13 studies found for:

("major depressive disorder" OR "major depression") AND vilazodone Adult, Senior Phase 2, 3, 4

24 studies found for:

("major depressive disorder" OR "major depression") AND vortioxetine Adult, Senior Phase 2, 3, 4

74 studies found for:

("major depressive disorder" OR "major depression") AND duloxetine Adult, Senior Phase 2, 3, 4

ICTRP 04.06.2014

342 records for 243 trials found for: major depress* AND antidepress*

Drugs@FDA 02.06.2014**Levomilnacipran:**

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&AppNo=204168&DrugName=FETZIMA&ActiveIngred=LEVOMILNACIPRAN%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails

Vilazodone:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&AppNo=022567&DrugName=VIBRYD&ActiveIngred=VILAZODONE%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails

Vortioxetine:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&AppNo=204447&DrugName=BRINTELLIX&ActiveIngred=VORTIOXETINE%20HYDROBROMIDE&SponsorApplicant=TAKEDA%20PHARMS%20USA&ProductMktStatus=1&goto=Search.DrugDetails

European Medicines Agency 02.06.2014

Levomilnacipran: 0

Vilazodone: 0

Vortioxetine:

http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/medicines/human/medicines/002717/human_med_001714.jsp&mid=WC0b01ac058001d124

National Institute of Mental Health website 11.06.2014

Search Terms: "major depression", "major depressive disorder"

American Psychological Association 11.06.2014

Search terms, "major depressive disorder", major depression"

Scopus 16.06.2014

(TITLE-ABS-KEY({major depressive disorder} OR {major depression}) OR KEY({disorder, major depressive})) AND (TITLE-ABS-KEY((bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine) OR ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy") OR (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort") OR ("s adenosyl I methionine" OR "S-Adenosylmethionine") OR ("omega 3") OR (acupuncture OR electroacupuncture) OR (yoga OR meditation OR mindfulness) OR ("physical activity" OR "physical exercise")) OR KEY(psychotherapy)) AND (TITLE-ABS-KEY(adult*)) AND (DOCTYPE(cp))

162 document results

Web of Science Conference Proceedings Citation Index- Science 16.06 2014

Set	Results	Search
		Indexes=CPCI-S Timespan=All years
# 1	3,944	TOPIC: ("major depressive disorder" OR "major depression")
		Indexes=CPCI-S Timespan=All years
# 2	4,014	TOPIC: (bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine)
		Indexes=CPCI-S Timespan=1990-2014
# 3	628	TOPIC: ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy")
		Indexes=CPCI-S Timespan=1990-2014
# 4	404	TOPIC: (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort")
		Indexes=CPCI-S Timespan=1990-2014
# 5	456	TOPIC: ("s adenosyl I methionine" OR "S-Adenosylmethionine")
		Indexes=CPCI-S Timespan=1990-2014
# 6	1,749	TOPIC: ("omega 3")
		Indexes=CPCI-S Timespan=1990-2014
# 7	1,068	TOPIC: (acupuncture OR electroacupuncture)
		Indexes=CPCI-S Timespan=1990-2014
# 8	517	TOPIC: (yoga OR meditation OR mindfulness)
		Indexes=CPCI-S Timespan=1990-2014
# 9	6,836	TOPIC: ("physical activity" OR "physical exercise")
		Indexes=CPCI-S Timespan=1990-2014
# 10	15,492	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
		Indexes=CPCI-S Timespan=1990-2014
# 11	874	#10 AND #1

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		Indexes=CPCI-S Timespan=1990-2014
		Refined by: TOPIC: (adult*)
# 12	55	#10 AND #1

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