Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

Jonathan Henssler, MD[a,b,‡]; Mona Kurschus[a,‡]; Jeremy Franklin, Dr. rer. medic[c]; Tom Bschor, MD[d,e]; and Christopher Baethge, MD[a,*]

ABSTRACT

Objective: In clinical practice, acute antidepressant treatment is often applied for several months until remission is achieved. However, data on treatment outcomes beyond 8 weeks are sparse and no systematic review exists to date. This study aims at assessing efficacy and tolerability of antidepressants compared to placebo in acute treatment at and beyond 8 weeks.

Data Sources: MEDLINE, Embase, PsycINFO, and CENTRAL databases were systematically searched through March 2014 using generic terms for depressive and affective disorders combined with generic terms for individual drugs and placebo.

Study Selection: Double-blind, randomized, placebo-controlled studies of 8 weeks or more comparing antidepressant monotherapy to placebo in adult patients with acute depressive disorder.

Data Extraction: Data extraction and synthesis followed guidelines of the Cochrane Collaboration. All data were extracted independently by 2 reviewers. Primary outcome was standardized mean difference (SMD) between antidepressant and placebo; secondary outcomes were response, remission, and dropouts.

Results: Of 6,043 articles screened, we selected 104 studies that met criteria and included 35,052 patients. Active treatment was statistically significantly superior to placebo, with consistent effect sizes (SMD [95% CL]) after 8, 12, 16, 20, and 24 weeks: 0.27 (0.24, 0.30), 0.34 (0.25, 0.43), 0.24 (0.09, 0.40), 0.31 (0.12, 0.51), and 0.34 (0.18, 0.50), respectively. Results remained stable across secondary outcomes and subgroup and sensitivity analyses.

Conclusions: Effect sizes of antidepressant monotherapy compared to placebo seem to be stable over 6 months. These results challenge the assumption that long-term antidepressant effects are due to the natural course of the disorder rather than to a pharmacologic effect.

J Clin Psychiatry 2018;79(1):15r10545
https://doi.org/10.4088/JCP.15r10545

[a]Department of Psychiatry and Psychotherapy, University of Cologne Medical School, Cologne, Germany
[b]Charité University Medicine, St Hedwig-Krankenhaus, Clinic for Psychiatry and Psychotherapy, Berlin, Germany
[c]Institute of Medical Statistics, Informatics, and Epidemiology, University of Cologne Medical School, Cologne, Germany
[d]Department of Psychiatry, Schlosspark-Hospital, Berlin, Germany
[e]Department of Psychiatry, Technical University of Dresden Medical School, Dresden, Germany
‡Equal contributors to this work.
**Corresponding author:* Christopher Baethge, MD, Klinik für Psychiatrie und Psychotherapie, Universität zu Köln; Kerpener Straße 62, 50937 Köln, Germany (cbaethge@uni-koeln.de).

With an increase of illness burden of 37% over the past 2 decades[1] and 12-month prevalence of depressive episodes ranging from 1% to 10%,[2] major depressive disorder (MDD) is one of the major medical challenges. The length of a depressive episode has been reported to average 12 weeks in population-based settings[3,4] and 20 weeks in tertiary care centers.[5] Untreated episodes are thought to last for 3 to 12 months, with a remission rate of 32% within 6 months.[6]

Duration of acute antidepressant treatment is subject to debate. The *German National Clinical Practice Guideline*[7] recommends reconsideration of hitherto ineffective treatment after 3–4 weeks (6 weeks in older patients). The American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*,[8] however, suggests continuation of antidepressant treatment for up to 12 weeks to observe full improvement, especially in "real-world" patients.

The efficacy of antidepressants compared to placebo has been summarized in various meta-analyses.[9,10] These studies, however, did not separately analyze antidepressant efficacy depending on trial duration but instead combined data of trials spanning 6–12 weeks. As a result, it is unknown whether efficacy is similar at different time points during the first months of treatment, eg, between 8 and 12 weeks or between 3 and 6 months. Also, it is often unclear in practice whether late remissions under antidepressants reflect the natural course of the disorder or a pharmacologic effect. Data regarding time course of antidepressant efficacy are therefore of scientific and clinical interest.

Accordingly, we conducted a systematic review and meta-analysis of randomized controlled trials of 8 to 24 weeks duration comparing antidepressant monotherapy to placebo in adult patients with acute depression. Specifically, we analyzed efficacy at different time points to test whether effect size between antidepressant and placebo treatment changes over time.

METHODS

This systematic literature review, meta-analysis, and meta-regression was registered on PROSPERO International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42014010105).

Literature Search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) without language and date restrictions until March 20, 2014. CENTRAL comprises, among other sources, articles indexed in MEDLINE, PsycINFO, and Embase databases as screened by the Cochrane Depression, Anxiety, and Neurosis (CCDAN) group. It is often used in systematic reviews.[11,12] Additionally, we searched MEDLINE, PsycINFO, and Embase from January 1, 2013, to March 20, 2014, because CENTRAL has not been updated by CCDAN since January 1, 2013. We used trial filters for placebo-controlled studies and generic terms for depressive disorders as well as affective disorders combined with generic terms for individual drugs. In brief, the search terms included the following: (*depress** OR *dysthymi** OR *adjustment disorder** OR *mood disorder** OR *affective disorder* OR *affective symptoms*) AND (individual drug names, combined with OR) AND (*placebo** OR *dummy**). (For explicit search entry, see Supplementary eFigure 1 at PSYCHIATRIST.COM.) We also searched reference lists of all articles included and of relevant review articles.

Eligibility Criteria

Trials had to meet the following inclusion criteria: participants aged ≥18 years; acute episode of a depressive disorder diagnosed according to standard operationalized criteria, such as Research Diagnostic Criteria, *DSM-III* to *DSM-IV-TR*, Chinese Classification of Mental Disorders, and *ICD-10*; the existence of a placebo-control group (for the whole duration of the trial); and severity of depression assessed via standardized and established rating scales (eg, Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], Clinical Global Impressions scale). Concurrent psychiatric disorders or medical comorbidities were not exclusion criteria, as long as they were not the primary condition of interest. Studies specifically focusing on bipolar depression or dysthymia were excluded as were trials on continuation or maintenance therapy. The latter are based on different patient populations (ie, responders/remitters to previous treatment only), while the purpose of our study was the investigation of the course of symptom changes in all patients receiving antidepressants.

We included all interventions using a monotherapy of antidepressants. Trials on first-step treatment or among patients with resistance to previous antidepressant treatment(s) were both considered relevant. Minimum duration of antidepressant therapy prior to final assessment needed to be 8 weeks for the current episode.

Data Collection

Screening of studies retrieved by the literature search, reading of full texts, retrieval of data from included studies, and risk of bias assessment were all independently carried out by 2 reviewers (J.H. and M.K.) and followed the Cochrane Collaboration Handbook and Cochrane's risk of bias tool.[13] Unclear cases were solved by discussion or with the senior author (C.B.).

Clinical Points

- Antidepressant use is established in acute-phase treatment, but evidence on its efficacy in the long term is sparse.
- Antidepressants are superior to placebo for up to 6 months. Efficacy is not declining over time.
- Even if patients who spontaneously remit are accounted for, those receiving ongoing antidepressant treatment will be more likely to have a better outcome after half a year than patients taking placebo.

Outcome Criteria

Primary outcome. The prespecified primary outcome criterion was the standardized mean difference (SMD) (Hedges *g*) between antidepressant and placebo. As efficacy assessment varies among studies, we combined different measurements. For example, differences in means or odds ratios (ORs) were transformed into SMDs and standard errors (SEs). For each study, we selected the primary outcome criterion as defined by the authors. If no primary outcome was designated, parameters were selected according to the following hierarchy:

1. Rating scale scores: if more than 1 rating scale was used, we selected HDRS (then MADRS, then other).
2. Remission: defined as scores below thresholds on a depression scale. We adopted trial authors' definitions.
3. Response: defined as a decrease on depression rating scales (eg, at least 50% on the HDRS or the MADRS). We adopted trial authors' definitions.

Primary outcome analysis of highest evidential priority was analysis of those studies reporting outcomes on any time point from 8 to 24 weeks. Second-line analyses were conducted based on all available data at each time point.

Secondary outcomes. Prespecified secondary outcomes were remission rates, response rates, difference in depression ratings, and tolerability defined as dropouts due to any reason and dropouts due to adverse effects.

We calculated number needed to treat based on response rates from our primary outcome main analysis.

Subgroup and Sensitivity Analyses

Prespecified subgroup and sensitivity analyses were conducted regarding classes of antidepressants (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA]), low risk of bias studies, studies explicitly excluding bipolar patients, and age of study population.

Additional Moderator Analyses

Additional moderator analyses investigated the role of possible confounders. In random-effects meta-regression,

we analyzed associations of SMD with baseline severity of depression and with both the difference and ratio of imipramine-equivalent doses. Imipramine-equivalent doses were calculated by multiplying the imipramine-equivalent potency ratio of the particular antidepressant (as provided in Baldessarini[14]) with the target dose documented in the given trial. If no target dose was stated, we used the mean antidepressant dose of the trial. If more than 1 dose was tested, we used the mean weighted by the number of patients assigned to each dose.

Post Hoc Analyses

Before data extraction started, we decided to analyze the prevalence of treatment-emergent suicidal ideation and behavior (attempts and completion). The association of SMD with date of study publication was analyzed and emerged as a potential confounder for the comparison of different antidepressants. We adjusted effect sizes for time of publication using the corresponding regression coefficients estimated from meta-regression.

Data Analysis

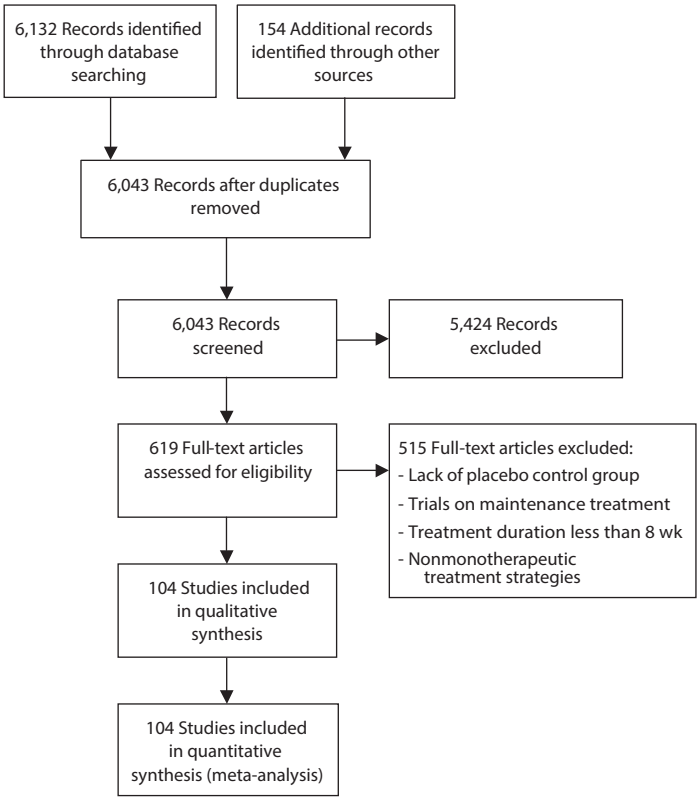
Analyses are based on intention-to-treat (ITT) populations or, if only such data were available, based on ITT populations including all patients receiving at least 1 dose of treatment. The method used to handle missing data was extracted from every trial (eg, last observation carried forward [LOCF], mixed-effects model repeated measures [MMRM]). If more than 1 method was used, we selected LOCF as the most widely used approach. If standard deviation (SD) was not stated, we extracted other measures of dispersion, such as confidence limit (CL) or SE, or extracted *P* values and calculated SDs. In 1 case only, we imputed SD by linear regression, using SDs of 9 studies matched for rating scale.

Even in the absence of statistically significant heterogeneity, effect estimates were calculated using random-effects models because the studies selected differed regarding several methodological aspects, such as diagnostic criteria and measurement scales used. Heterogeneity among studies was assessed by both I^2 and τ^2 statistics, as the former is known to become inflated with increasing sample size.[15]

The main meta-analysis was conducted for 5 predefined time points or intervals (8–9, 10–12, 16, 20, 24 weeks). We determined the intervals as soon as it was clear how many studies would be included for each time point but without knowing any efficacy results. If a trial provided more than 1 value within an interval, the latest value was included.

If studies presented more than 1 comparison (eg, more than 1 monotherapy group), we combined intervention groups to avoid counting patients twice.[13] Outcome data of multiple groups were pooled and corresponding SDs were calculated.

Figure 1. Flow Chart of Trials Considered, Eliminated, and Included in Study (adapted from PRISMA)



Publication bias with regard to the primary outcome was assessed by a funnel plot. Also, Egger test, a trim-and-fill procedure, and a fail-safe N calculation (Orwin) were carried out.

To avoid undue reliance on single studies, analyses of the primary outcome were repeated by removing all studies one by one from the analysis.

Statistical significance was set at an α of .05 for the primary outcome. For all secondary outcomes and all other analyses, *P* values are presented in a nonconfirmatory sense.

Analyses were conducted according to the Cochrane Collaboration Handbook[13] and using Review Manager (RevMan 5.2.5), Comprehensive Meta-Analysis (Version 2) (Biostat), and Microsoft Excel (Version 12.3.6) (Microsoft Corp). If data were presented only in figures, values were extracted using Plot Digitizer 2.6.4 MacOSX (Slashdot Media).

RESULTS

Our literature search retrieved 6,043 different articles. After screening titles and abstracts, the full texts of 619 articles were read, out of which 104 (Supplementary eTable 1) published between 1971 and 2014 met the inclusion criteria (Figure 1).

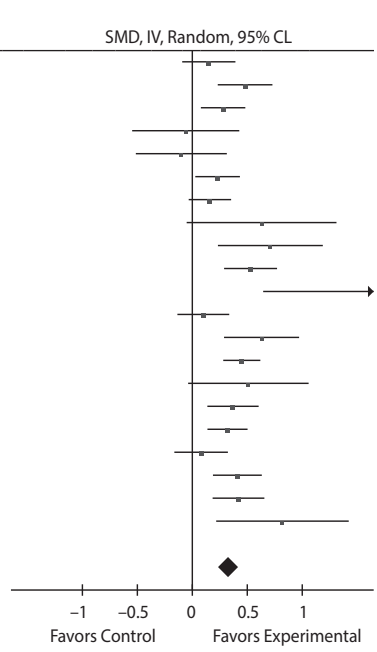
The 104 trials included 35,052 patients, 22,809 receiving antidepressant monotherapy and 12,243 receiving placebo. Articles were published in English and 1 in Spanish. All studies were randomized and double blind. Two studies were conducted among patients with resistance to previous antidepressant treatment.

Table 1. Results of Primary Outcome Analysis[a]

Time Point	All Studies, SMD (95% CL)	TCA, SMD (95% CL)	SNRI, SMD (95% CL)	SSRI, SMD (95% CL)
8 wk	0.27 (0.24, 0.30) N = 32,322 (91 studies) I^2 = 37%	0.50 (0.37, 0.63) N = 1,761 (10 comparisons) I^2 = 41%	0.30 (0.26, 0.34) N = 13,132 (35 comparisons) I^2 = 21%	0.22 (0.17, 0.27) N = 11,040 (44 comparisons) I^2 = 29%
12 wk	0.34 (0.25, 0.43) N = 5,737 (21 studies) I^2 = 54%	0.66 (0.37, 0.95) N = 254 (4 comparisons) I^2 = 0%	0.38 (0.25, 0.51) N = 2,143 (6 comparisons) I^2 = 49%	0.27 (0.15, 0.39) N = 2,903 (11 comparisons) I^2 = 49%
16 wk	0.24 (0.09, 0.40) N = 905 (4 studies) I^2 = 17%	(Numbers were too low for analyses beyond 12 wk of treatment.)		
20 wk	0.31 (0.12, 0.51) N = 708 (3 studies) I^2 = 18%			
24 wk	0.34 (0.18, 0.50) N = 686 (2 studies) I^2 = 0%			

[a]Primary outcome was SMD > 0 in favor of antidepressant.
Abbreviations: CL = confidence limit, SMD = standardized mean difference, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 2. Primary Outcome Second-Line Analysis: Treatment Effect (standardized mean difference [SMD]) After 12 Weeks of Antidepressant Monotherapy Versus Placebo in Randomized Double-Blind Trials[a]



[a]Weighted according to random-effects analysis.
Abbreviations: CL = confidence limit, SE = standard error.

Efficacy

Primary outcome: main analysis. Two studies (Malt et al,[16] Stahl[17]) including 688 patients reported outcomes on every time point from 8 to 24 weeks. Effect sizes (as SMD [95% CL]) were consistent over time: 0.28 (0.11, 0.45), 0.26 (−0.05, 0.57), 0.25 (0.07, 0.43), 0.30 (0.09, 0.50), and 0.34 (0.18, 0.50) after 8, 12, 16, 20, and 24 weeks, respectively.

The corresponding numbers needed to treat, as calculated from response rates at every time point, were 8, 8, 7, 7, and 7 after 8, 12, 16, 20, and 24 weeks of treatment, respectively.

Primary outcome: second-line analyses. Week 8. The analysis sample regarding our primary outcome criterion after 8 weeks consisted of 91 studies with 32,322 patients. Antidepressant monotherapy had an effect size (SMD) of 0.27 (95% CL = 0.24, 0.30) compared to placebo (P < .001) (Table 1). When each study was removed one by one, summary effect sizes varied between 0.26 and 0.27.

Week 12. The analysis sample after 12 weeks of trial duration consisted of 21 studies with 5,737 patients. Antidepressant monotherapy had an effect size (SMD) of 0.34 (95% CL = 0.25, 0.43) compared to placebo (P < .001) (Figure 2). Effect sizes varied between 0.32 and 0.35 after removing of each study one by one from the analysis.

Week 16. The analysis sample after 16 weeks of trial duration consisted of 4 studies with 905 patients. The SMD was 0.24 (95% CL = 0.09, 0.40) (P = .002), varying between

0.19 (after elimination of Stahl[17]) and 0.28 (after removal of Malt et al[16] or Blumenthal et al[37]).

Week 20. After 20 weeks, there were 3 studies with 708 patients. The SMD was 0.31 (95% CL = 0.12, 0.51) in favor of antidepressants ($P = .001$).

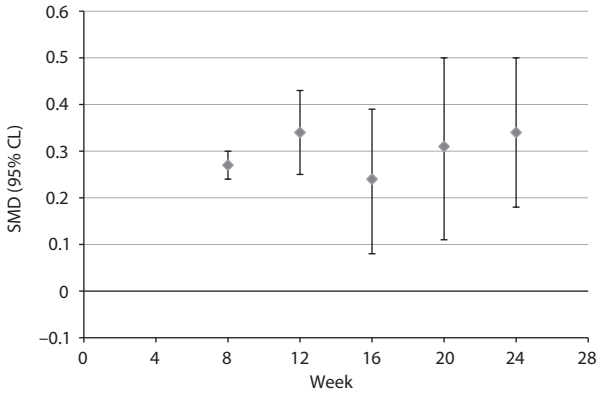
Week 24. Two studies with 686 patients assessed efficacy after 24 weeks. The SMD was 0.34 (95% CL = 0.18, 0.50) in favor of antidepressants ($P < .001$) (Table 1 and Figure 3).

Sensitivity Analyses

Antidepressant efficacy was similar across sensitivity analyses with respect to trials with only low risk of bias (SMD [95% CL]: 0.26 [0.22, 0.30] and 0.34 [0.18, 0.50] after 8 and 24 weeks, respectively) and with respect to trials explicitly excluding bipolar depressed patients (SMD [95% CL]: 0.26 [0.22, 0.29] and 0.34 [0.18, 0.50] after 8 and 24 weeks, respectively) (complete data available on request).

Secondary outcomes. All secondary outcome analyses (depression score differences, response and remission rates) supported the primary outcome analysis (Table 2).

Figure 3. Primary Outcome Second-Line Analysis: Standardized Mean Differences (SMDs) Over Time in Randomized Double-Blind Trials of Antidepressant Monotherapy Versus Placebo



Abbreviation: CL = confidence limit.

Suicidality

During treatment, antidepressant and placebo groups did not differ substantially with regard to suicidal ideation (1.57 per 100 patients [95% CL = 1.29, 1.89] vs 1.72 [95% CL = 1.32, 2.21], respectively) and suicidal behavior (0.36 [95% CL = 0.24, 0.52] vs 0.22 [95% CL = 0.09, 0.43], respectively). Among studies in patients ≤ 65 years, proportions for antidepressant versus placebo remained similar: 0.44 (95% CL = 0.19, 0.86) vs 0.91 (95% CL = 0.34, 1.98) for suicidal ideation and 0.44 (95% CL = 0.26, 0.68) vs 0.29 (95% CL = 0.11, 0.62) for suicidal behavior. There were not enough data on elderly populations for analysis.

Tolerability

In active intervention arms, patients were more likely to drop out for any reason during the first 8 weeks of treatment (OR = 1.09 [95% CL = 1.01, 1.19]), but less likely at 12, 16, and 24 weeks (0.81 [0.68, 0.97], 0.56 [0.31, 1.02], and 0.53 [0.37, 0.75], respectively; no data available for 20 weeks). During the first 8 and 12 weeks of treatment, there were more dropouts due to adverse events in intervention arms (OR = 2.03 [95% CL = 1.73, 2.39] and 1.56 [1.18, 2.07], respectively), with sparse and inconsistent data after 16, 20, and 24 weeks (Table 2).

Table 2. Results of Outcomes Across Predefined Secondary Analyses

		Secondary Outcome[a]					
Time Point[b]	Primary Outcome, SMD (95% CL)[c]	Change, SMD (95% CL)[d]	Score, SMD (95% CL)[e]	Remission, OR (95% CL)	Response, OR (95% CL)	Dropouts, OR (95% CL)	Dropouts Due to Adverse Effects, OR (95% CL)
8 wk (91 studies)	0.27 (0.24, 0.30) N = 32,322, I^2 = 37%	0.27 (0.23, 0.30) N = 24,535 I^2 = 40%	−0.27 (−0.34, −0.20) N = 6,307 I^2 = 33%	1.52 (1.40, 1.66) N = 20,469 I^2 = 36%	1.63 (1.53, 1.74) N = 27,465 I^2 = 29%	1.09 (1.01, 1.19) N = 27,433 I^2 = 40%	2.03 (1.73, 2.39) N = 27,606 I^2 = 38%
12 wk (21 studies)	0.34 (0.25, 0.43) N = 5,737 I^2 = 54%	0.28 (0.19, 0.36) N = 3,934 I^2 = 32%	−0.44 (−0.63, −0.25) N = 1,500 I^2 = 58%	1.63 (1.34, 1.98) N = 4,094 I^2 = 42%	1.90 (1.59, 2.26) N = 5,107 I^2 = 49%	0.81 (0.68, 0.97) N = 4,771 I^2 = 34%	1.56 (1.18, 2.07) N = 4,606 I^2 = 14%
16 wk (4 studies)	0.24 (0.09, 0.40) N = 905 I^2 = 17%	0.21 (−0.11, 0.53) N = 414 I^2 = 51%	−0.43 (−0.80, −0.07) N = 119 I^2 = NA[f]	2.35 (1.32, 4.19) N = 217 I^2 = 0%	1.76 (1.02, 3.04) N = 688 I^2 = 65%	0.56 (0.31, 1.02) N = 217 I^2 = 0%	0.32 (0.03, 3.18) N = 98 I^2 = NA[f]
20 wk (3 studies)	0.31 (0.12, 0.51) N = 708 I^2 = 18%	0.40 (0.17, 0.64) N = 316 I^2 = NA[f]	−0.75 (−1.67, 0.16) N = 20 I^2 = NA[f]	No data available	1.76 (1.12, 2.79) N = 688 I^2 = 51%	No data available	No data available
24 wk (2 studies)	0.34 (0.18, 0.50) N = 686 I^2 = 0%	0.34 (0.18, 0.50) N = 686 I^2 = 0%	No data available	1.76 (1.06, 2.91) N = 316 I^2 = NA[f]	1.82 (1.28, 2.59) N = 688 I^2 = 18%	0.53 (0.37, 0.75) N = 695 I^2 = 0%	2.89 (1.17, 7.13) N = 372 I^2 = NA[f]

[a]Secondary outcomes: OR > 1 designates superiority of antidepressant.
[b]Study number in the first column refers to the number of studies in a subgroup: for example, there are 21 studies reporting 12-week data. Of note, depending on design specifics, studies from column 1 may not be included in all outcome analyses (eg, only 15 of those 21 studies reported data on the number of dropouts due to adverse effects).
[c]Primary outcome: SMD > 0 in favor of antidepressant.
[d]Change: SMD > 0 designates superiority of antidepressant.
[e]Score: SMD < 0 designates superiority of antidepressant.
[f]One study only.
Abbreviations: CL = confidence limit, NA = not applicable, OR = odds ratio, SMD = standardized mean difference.

Heterogeneity

There was no indication of high between-study heterogeneity in the primary outcome meta-analyses (τ^2, I^2): week 8 ($\tau^2 = 0.01$, $I^2 = 37\%$), week 12 ($\tau^2 = 0.02$, $I^2 = 54\%$), week 16 ($\tau^2 = 0.00$, $I^2 = 17\%$), week 20 ($\tau^2 = 0.01$, $I^2 = 18\%$), and week 24 ($\tau^2 = 0.00$, $I^2 = 0\%$). Among secondary outcomes and subgroup and sensitivity analyses, I^2 values exceeded 60% in 1 analysis and exceeded 50% in 4 analyses (ie, 11% of analyses) (Table 2).

Importantly, beyond the parameters analyzed in subgroup and sensitivity analyses, studies were homogeneous regarding their inclusion criteria and thus their samples are similar. In particular, we did not find substantial differences in inclusion criteria among the samples of studies representing different durations of treatment (ie, 8- and 12-week trials versus 16, 20, and 24 weeks).

Publication Bias

Publication bias could not be ruled out in the funnel plot regarding the primary outcome at 8 weeks (Supplementary eFigure 2), and the Egger test was positive ($P = .007$, $df = 89$). A trim-and-fill procedure (Duval and Tweedie) with 18 studies trimmed to the left of the mean reduced the effect size to 0.23 (95% CL = 0.19–0.26). An additional 148 studies with an effect size of 0.0 were necessary to result in a total effect size of 0.1 (Orwin fail-safe N).

At 12 weeks of treatment, the funnel plot did not indicate publication bias (Supplementary eFigure 3); the Egger test was negative ($P = .15$, $df = 19$), and a trim-and-fill procedure (Duval and Tweedie) with 3 studies trimmed to the left of the mean resulted in a similar effect: 0.31 (95% CL = 0.21, 0.40). Orwin fail-safe N for a total SMD of 0.1 would require an additional 48 studies with an effect size of 0.0.

Meta-Regressions and Moderator Analyses

Mean imipramine-equivalent dose was 166.26 mg/d (SD = 152.42) in active intervention arms. In meta-regression, there was no association of dose and SMD (95% CL) (slope: 0.66×10^{-4} [-1.15×10^{-4}, 2.47×10^{-4}], $P = .47$). A similar result emerged when 8 high-dosage trials were excluded from the analysis (slope: 3.84×10^{-4} [-3.39×10^{-4}, 0.11×10^{-4}], $P = .30$).

We found no association of baseline severity of depression (percentage of rating scale score and Z value) and SMD (95% CL) (slope: -0.07×10^{-2} [-0.67×10^{-2}, 0.52×10^{-2}], $P = .81$; and -0.47×10^{-2} [-1.35×10^{-2}, 0.41×10^{-2}], $P = .30$, respectively).

Year of study publication was associated with SMD (95% CL) for 8-week data (slope: -0.82×10^{-2} [-1.27×10^{-2}, -0.37×10^{-2}], $P = .0004$), with higher effect sizes reported in older publications. Adjustment for outliers (Heller et al,[25] Thomson et al[36]) resulted in a reduced but still substantial association (slope: -0.64×10^{-2} [-1.10×10^{-2}, -0.17×10^{-2}], $P = .007$). The association was of similar magnitude (but nonsignificant) for 12-week data (slope: -0.57×10^{-2} [-1.50×10^{-2}, 0.43×10^{-2}], $P = .26$).

Moderator analyses of dichotomized variables did not reveal statistically significant confounders: studies with low risk of bias versus studies without low risk of bias ($P = .87$) and trials excluding bipolar patients versus those that did not ($P = .97$). Active treatment was numerically less effective in studies that included patients aged > 60 years compared to studies that excluded patients aged > 65 years (SMD [95% CL]: 0.22 [0.08, 0.36] versus 0.29 [0.25, 0.32]; $P = .33$).

Moderator analyses regarding effectiveness of different classes of antidepressant agents showed higher values for TCAs relative to SNRIs and SSRIs after 8 and 12 weeks, while after 8 weeks only, SNRIs were superior to SSRI, with SMD (95% CL) values of 0.50 (0.37, 0.63), 0.30 (0.26, 0.34), and 0.22 (0.17, 0.27) at 8 weeks and 0.66 (0.37, 0.95), 0.38 (0.25, 0.51), and 0.27 (0.15, 0.39) at 12 weeks for TCAs, SNRIs, and SSRIs, respectively (Table 1).

After adjustment for time of publication, differences between classes of antidepressant agents decreased to 0.32 [95% CL = 0.22, 0.43], 0.25 [95% CL = 0.22, 0.28], and 0.12 [95% CL = 0.08, 0.17] after 8 weeks and to 0.57 [95% CL = 0.31, 0.83], 0.34 [95% CL = 0.23, 0.44], and 0.20 [95% CL = 0.07, 0.32] after 12 weeks for TCA, SNRI, and SSRI, respectively.

DISCUSSION

According to our data, antidepressant treatment is consistently clinically and statistically significantly superior to placebo over 8 to 24 weeks. While results are consistent over time, data on treatment periods exceeding 16 weeks are particularly sparse. Only 2 studies[16,17] reported outcomes on every time point from 8 to 24 weeks and thus met inclusion criteria of our analysis of highest evidential priority. Still, and importantly, low heterogeneity among trials and the results of several subgroup and sensitivity analyses indicate that our finding is robust.

Although there is extensive evidence on the efficacy of antidepressants after 6 weeks of treatment (evidence on superiority after 12 weeks is less extensive), with estimates at about 0.3 SMDs compared to placebo,[38,39] additional evidence on consistency of this effect over time is not trivial and is of clinical importance. Existing studies[9,10] that averaged end points of trials after 6–12 weeks did not focus on different time points and did not include older antidepressant agents.[40]

Our findings are relevant for discussions on the natural course of a depressive episode. They indicate that even after 6 months, antidepressant treatment is superior to placebo treatment, which, in turn, may be superior to the natural course of the disease. Confirming earlier investigations, however, our analysis indicates that the effect size of antidepressants was moderate.[38,41]

Placebo response rates have increased over the last decades,[42–44] and our meta-regression confirmed the association of publication year with effect size, even when adjusted for outliers. Trials of TCAs have been conducted earlier than studies on second-generation antidepressants. Adjustment for publication time, however, did not entirely flatten the differences among drug classes. Of note, the findings have to be viewed with extreme caution because they resulted from post hoc analyses and, most of all, are not

based on a literature search for direct comparisons among classes of antidepressants. In the 3 studies[29,45,46] (included in our analyses) directly comparing TCAs and SSRIs, however, the former were more effective, and a meta-analysis[47] of 102 randomized studies directly comparing SSRI with TCA reported evidence of superior efficacy of TCA (for amitriptyline and for TCA as a group when restricted to inpatients).

Our tolerability analyses confirm common assumptions: dropouts due to adverse events are lower with placebo, but overall dropout rates are higher, particularly with ongoing treatment duration. We believe inconsistencies in our analyses after 16 to 24 weeks are due to low sample sizes.

Our findings are relevant for clinical decision making. According to the published data, the effect size of antidepressant treatment versus placebo did not diminish over half a year. Clinically, therefore, there seems to be no reason to discontinue hitherto effective antidepressant treatment—not for the first 12 weeks and possibly not for as long as half a year. However, it would be important to know at what time point it is unlikely to expect added benefit and when to change hitherto ineffective treatment. Further studies should identify the best time point to reconsider treatment options and alternatives.

Limitations

First, it is possible that we missed relevant studies. With MEDLINE, Embase, PsycINFO, and CENTRAL, however, 4 different large international databases were used, and we employed ample and sensitive search entries as recommended by the Cochrane Collaboration. The search resulted in more than 6,000 articles screened independently by 2 reviewers. Publication bias, however, has been reported in trials of antidepressant monotherapies.[38] Reassuringly, adjusting for publication bias resulted in merely slightly weakened effects, and fail-safe N was high.

Second, interpretation of meta-analyses can be complicated by heterogeneity of included studies. While I^2 statistics indicated moderate heterogeneity of effects in some of our analyses, I^2 values are known to increase with accumulating size of patient samples.[15] Reassuringly, there was no indication of substantial heterogeneity among included trials in additional τ^2 statistics. In addition, various sensitivity and subgroup analyses of more homogeneous study samples were conducted, random-effects models were used, and the robustness of results was tested after each study was left out. Finally, 3 meta-regressions and 4 additional moderator analyses addressed the role of possible confounders.

Third, the findings of some meta-analyses are inflated. While Pereira and Ioannidis[48] showed that most meta-analyses represent true effects, effect inflation may be of particular importance when data are sparse. With a sample size of 35,052 and 5,678 patients for our primary outcome (after 8 and 12 weeks, respectively), however, results of our meta-analysis are probably stable.[49] While outcome analyses after 16, 20, and 24 weeks included few studies only and results may therefore be less reliable, patient samples of 905, 708, and 686, respectively, still represent considerable numbers. Moreover, these studies were mainly of high methodological quality and consistently considered to carry a low risk of bias. Still, only 2 studies[16,17] addressed treatment over half a year—a not uncommon duration of acute antidepressant treatment in clinical practice. More studies covering this time span are warranted.

Fourth, increasing attrition rates due to overall dropouts over time are a potentially crucial source of bias in trials of long follow-up periods. While application of last-observation-carried-forward or MMRM methods may account partly for these biases, results of our analyses may be inflated by the particularly higher overall dropout rates in placebo arms over time. As dropouts for any reason are known to be a consequence, among others, of subject dissatisfaction through nonresponse to treatment, this high dropout rate may have downsized effect sizes and superiority of antidepressant treatment over placebo at 12, 16, and 24 weeks. For example, at week 8, the dropout rate in active treatment arms was 25% compared to 23% in placebo arms. At week 24, however, the dropout rate was 34% compared to 40% with active treatment and placebo, respectively (nonweighted data analysis).

Finally, to some extent, meta-analyses will inherit limitations of included trials. We have, however, taken into account the risk of bias. Still, due to incomplete reporting, some possible sources of bias may remain unknown. For example, the use of active placebos[39] and the assessment of the quality of reporting of blinding measures have been shown to be insufficient in psychiatric research.[50]

The strengths of the present study include its focus on treatment effect *and* on treatment tolerability and its analysis of a large number of studies. To our knowledge, this is the first meta-analysis on the duration of treatment of all commonly used classes of antidepressants. Outcome parameters were prespecified, and heterogeneity of trials as well as possible confounders were taken into account using sensitivity and subgroup analyses, meta-regression, and network meta analyses.

CONCLUSIONS

Superiority of antidepressant monotherapy compared to placebo seems to be stable over a time period of up to 6 months. The results challenge the assumption that long-term antidepressant effects reflect the natural course of the disorder rather than pharmacologic effects, ie, the assumption heard in clinical practice of the long-term antidepressant effects being rather a shift of the spontaneous course of remittance. Results thus emphasize utility of pharmacologic agents in treatment of depression, as even after 6 months antidepressant treatment is superior to the natural course of major depression—as long as one considers placebo arms a proxy for natural course. Future research should focus on changes of response rates and of psychopathology over time in order to identify time points when treatment should be reconsidered in incomplete responders.

Submitted: November 20, 2015; accepted June 1, 2016.

Online first: January 3, 2017.

Drug name: imipramine (Tofranil and others).

Author contributions: Dr Baethge had the idea for the study and its design. Dr Bschor contributed to the design and gave important input on the scientific background. Ms Kurschus and Dr Henssler conducted the literature search and screened the articles (with the help of Dr Baethge). Drs Baethge and Henssler and Ms Kurschus reviewed all full texts for inclusion. Ms Kurschus and Dr Henssler collected the data independently. All authors analyzed the data, Dr Henssler drafted the paper, and all authors revised the paper and approved the final version.

Potential conflicts of interest: **Drs Henssler**, **Franklin**, **Bschor**, and **Baethge** and **Ms Kurschus** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: Ms Kurschus was supported by the Koeln Fortune Program/Faculty of Medicine, University of Cologne, Germany.

Role of the sponsor: The funding agency had no influence on the idea, the design, the execution, data analysis, and the publication of this work.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–2223.
2. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(9):655–679.
3. Spijker J, de Graaf R, Bijl RV, et al. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Br J Psychiatry*. 2002;181:208–213.
4. Eaton WW, Shao H, Nestadt G, et al. Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry*. 2008;65(5):513–520.
5. Solomon DA, Keller MB, Leon AC, et al. Recovery from major depression: a 10-year prospective follow-up across multiple episodes. *Arch Gen Psychiatry*. 1997;54(11):1001–1006.
6. Whiteford HA, Harris MG, McKeon G, et al. Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychol Med*. 2013;43(8):1569–1585.
7. Härter M, Klesse C, Bermejo I, et al. Unipolar depression: diagnostic and therapeutic recommendations from the current S3/National Clinical Practice Guideline. *Dtsch Arztebl Int*. 2010;107(40):700–708.
8. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
9. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746–758.
10. Purgato M, Papola D, Gastaldon C, et al. Paroxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev*. 2014;4(4):CD006531.
11. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
12. Cipriani A, Hawton K, Stockton S, et al. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013;346:f3646.
13. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. http://handbook.cochrane.org. Updated March 2011.
14. Baldessarini RJ. *Chemotherapy in Psychiatry. Pharmacologic Basis of Treatments for Major Mental Illness*. New York, NY: Springer; 2013:183.
15. Rücker G, Schwarzer G, Carpenter JR, et al. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.
16. Malt UF, Robak OH, Madsbu HP, et al. The Norwegian naturalistic treatment study of depression in general practice (NORDEP)-I: randomised double blind study. *BMJ*. 1999;318(7192):1180–1184.
17. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry*. 2000;48(9):894–901.
18. Bose A, Li D, Gandhi C. Escitalopram in the acute treatment of depressed patients aged 60 years or older. *Am J Geriatr Psychiatry*. 2008;16(1):14–20.
19. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. *Ann Clin Psychiatry*. 1997;9(3):157–164.
20. Dunlop BW, Reddy S, Yang L, et al. Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo. *J Clin Psychopharmacol*. 2011;31(5):569–576.
21. Fava M, Amsterdam JD, Deltito JA, et al. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. *Ann Clin Psychiatry*. 1998;10(4):145–150.
22. Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *J Clin Psychopharmacol*. 2005;25(5):441–447.
23. GlaxoSmithKline. A multicenter, randomized, double-blind, placebo-controlled comparison of paroxetine and fluoxetine in the treatment of major depressive disorder, 1991. GSK - Clinical Study Register Web site. http://www.gsk-clinicalstudyregister.com/study/29060/115?search=study&#csr.
24. GlaxoSmithKline. A Multi-Centre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible Dose Study to Evaluate the Efficacy, Safety and Tolerability of Extended-release Bupropion Hydrochloride (150mg–300mg once daily) in Elderly Subjects with Major Depressive Disorder. 2005 GSK - Clinical Study Register Web site. http://www.gsk-clinicalstudyregister.com/study/AK130940?search=compound&compound=bupropion#rs.
25. Heller A, Zahourek R, Whittington HG. Effectiveness of antidepressant drugs: a triple-blind study comparing imipramine, desipramine, and placebo. *Am J Psychiatry*. 1971;127(8):1092–1095.
26. Jarrett RB, Schaffer M, McIntire D, et al. Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1999;56(5):431–437.
27. Khan A, Upton GV, Rudolph RL, et al; Venlafaxine Investigator Study Group. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. *J Clin Psychopharmacol*. 1998;18(1):19–25.
28. Lopez Rodriguez J, Lopez Butron MA, Vargas Terrez BE, et al. Double blind study with antidepressant, brief psychotherapy and placebo in patients with mild to moderate depression. *Salud Ment*. 2004;27(5):55–61.
29. McGrath PJ, Stewart JW, Janal MN, et al. A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. *Am J Psychiatry*. 2000;157(3):344–350.
30. Montgomery SA, Mansuy L, Ruth A, et al. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry*. 2013;74(4):363–369.
31. Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, et al. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *BMJ*. 1995;310(6977):441–445.
32. Rapaport MH, Schneider LS, Dunner DL, et al. Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry*. 2003;64(9):1065–1074.
33. Rapaport MH, Lydiard RB, Pitts CD, et al. Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(1):46–57.
34. Robinson M, Oakes TM, Raskin J, et al. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. *Am J Geriatr Psychiatry*. 2014;22(1):34–45.
35. Silverstone PH, Ravindran A; Venlafaxine XR 360 Study Group. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. *J Clin Psychiatry*. 1999;60(1):22–28.
36. Thomson J, Rankin H, Ashcroft G. The treatment of depression in general practice: a comparison of L-tryptophan and amitriptyline with placebo. *Psychol Med*. 1982;12(4):741–751.
37. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587–596.
38. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252–260.
39. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. *Cochrane Database Syst Rev*. 2004;(1):CD003012.
40. Taylor MJ, Freemantle N, Geddes JR, et al. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63(11):1217–1223.
41. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008;5(2):e45.
42. Stolk P, Ten Berg MJ, Hemels ME, et al. Meta-analysis of placebo rates in major depressive disorder trials. *Ann Pharmacother*.

2003;37(12):1891–1899.
43. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
44. Schalkwijk S, Undurraga J, Tondo L, et al. Declining efficacy in controlled trials of antidepressants: effects of placebo dropout. *Int J Neuropsychopharmacol*. 2014;17(8):1343–1352.
45. Lydiard RB, Stahl SM, Hertzman M, et al. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *J Clin Psychiatry*. 1997;58(11):484–491.
46. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry*. 1990;51(suppl B):18–27.
47. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord*. 2000;58(1):19–36.
48. Pereira TV, Ioannidis JP. Statistically significant meta-analyses of clinical trials have modest credibility and inflated effects. *J Clin Epidemiol*. 2011;64(10):1060–1069.
49. Trikalinos TA, Churchill R, Ferri M, et al; EU-PSI project. Effect sizes in cumulative meta-analyses of mental health randomized trials evolved over time. *J Clin Epidemiol*. 2004;57(11):1124–1130.
50. Baethge C, Assall OP, Baldessarini RJ. Systematic review of blinding assessment in randomized controlled trials in schizophrenia and affective disorders 2000–2010. *Psychother Psychosom*. 2013;82(3):152–160.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

Authors: Jonathan Henssler, MD; Mona Kurschus; Jeremy Franklin, Dr. rer. medic; Tom Bschor, MD; and Christopher Baethge, MD

DOI Number: 10.4088/JCP.15r10545

List of Supplementary Material for the article

1. eFigure 1 Database search entry
2. eTable 1 Characteristics of trials
3. eFigure 2 Funnel Plot: Primary Outcome Analysis 8 weeks
4. eFigure 3 Funnel Plot: Primary Outcome Analysis 12 weeks
5. References References for trials

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Online Supplement

Supplementary eFigure 1: ***Database search entry***

Search term for the systematic literature search as used in CENTRAL, Embase, PsycINFO and Pubmed:

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or venlafaxin* or viloxazin*)

AND

(placebo* or dummy*)

Supplementary eTable 1: ***Characteristics of trials***

Author	Year	N (ITT)	Diagnosis	Age +65	Exclusion Bipolar Patients	Follow-up (weeks)	Med1: N (ITT)	MED2	MED3	MED4	PLC: N(ITT)	baseline score severity (+SD/SE)	risk of bias
Amsterdam(1)	2003	289	MDD (DSM IV)	n	y	8	Selegiline transdermal, N=145,				N=144	hamd-17, S: 22.72 + 2.92, PLC: 22.99 + 3.04;	unknown/ high

Andreoli(2)	2002	381	MDD (DSM III-R)	n	n.s.	8	Reboxetine, N=126,	Fluoxetine, N=127,		N=128	hamd, R:26.8 + 3.4, F:26.9 + 3.6, PLC:27.4 + 3.6	unknown/ high
Asnis(3)	2013	704	MDD (DSM IV-TR)	n	y	8	Levomilnacipran, N=176,	Levomilnacipran, N=177,	Levomilnacipran, N=176,	N=175	MADRS, L1:36.0 + 4.1, L2: 36.1 + 3.9, L3:36.0 + 3.9, PLC:35.6 + 4.5	low
Bakish(4)	2014	557	MDD (DSM IV-TR)	y	y	8	Levomilnacipran, N=185,	Levomilnacipran, N=187,		N=185	MADRS, L1:30.8, L2:31.2, PLC:31.0,	low
Baldwin(5)	2012	755	MDD (DSM IV-TR)	y	y	8	Vortioxetine, N=155,	Vortioxetine, N=155,	Vortioxetine, N=151,	Duloxetine, N=149,	N=145	MADRS, V1:31.6 + 4.0, V2:32.7 + 4.8, V3:31.8 + 3.9, D:31.4 + 4.2, PLC:31.7 + 4.3	unknown/ high
Barber(6)	2012	105	MDD (DSM IV)	y	y	8	Sertraline, N=55,				N=50	hamd, S:19.0, PLC:19.3,	unknown/ high
Blumenthal(7)	2007	49	MDD (DSM IV)	n	y	16	Sertraline, N=49,				N=49	hamd, S: 16+4, PLC: 17+4	low
Bose(8)	2008	263	MDD (DSM IV)	60 + only	y	12	Escitalopram, N=129,				N=134	MADRS, E: 29.4 + 4.1, 28.4 + 3.6	unknown/ high
Boyer(9)	2008	483	MDD (DSM IV)	n	y	8	Desvenlafaxine, N=164,	Desvenlafaxine, N=158,			N=161	hamd, D1:24, D2:24, PLC:24,	low
Burke(10)	2002	485	MDD (DSM IV)	n	y	8	Escitalopram, N=118,	Escitalopram, N=123,	Citalopram, N=125,		N=119	MADRS, E1: 28.0 + 4.9, E2: 28.9 + 4.6, C:29.2 + 4.5, PLC:29.5 + 5.0,	unknown/ high
Clayton(11)	2003	378	MDD (DSM IV)	n	y	8	Reboxetine, N=128,	Fluoxetine, N=130,			N=120	hamd, R:25.6, F:26.0, PLC:25.5,	unknown/ high
Clayton(12)	2013	432	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=216(217),				N=216 (217)	hamd, MED1: 22,4±3,5; PLC: 22,8±3,3	unknown/ high
Cohn(13)	1996	119	MDD (DSM III-R)	n	n.s.	8	Nefazodone, N=39,	Imipramine, N=38,			N=42	hamd, N:22.8, I:23.6, PLC:23.4,	low
Coleman(14)	1999	344	MDD (DSM IV)	y	n.s.	8	Bupropion SR, N=118,	Sertraline, N=109,			N=117	hamd, B:34.5, S:34.8, PLC:34.0,	unknown/ high

Coleman(15)	2001	427	MDD (DSM IV)	y	n.s.	8	Bupropion SR, N=136,	Fluoxetine, N=146,			N=145	hamd, B:24.6, F:24.5, PLC:24.4,	low
Cook(16)	1999	24	MDD (DSM IV)	n	y	8	Fluoxetine, N=13,				N=11	hamd, MED1: 22,85±4,49; PLC: 20,82±3,71	unknown/ high
Corrigan(17)	2000	174	MDD (DSM III-R)	n	y	8	Fluoxetine, N=35,				N=35	hamd, F:22, PLC:20.8,	unknown/ high
Croft(18)	1999	348	MDD (DSM IV)	y	n.s.	8	Bupropion SR, N=116,	Sertraline, N=116,			N=116	hamd, MED1: 33,27; MED2: 32,69; PLC: 32,40	unknown/ high
Cunningham(19)	1997	278	MDD (DSM III-R)	y	y	12	Venlafaxine XR, N=92,	Venlafaxine IR, N=87			N=99	hamd, V1: 24.5, V2: 24.0, PLC: 24.9	low
DeMartinis (20)	2007	461	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=114,	Desvenlafaxine, N=116,	Desvenlafaxine, N=113,		N=118	hamd, D1:23.2, D2:22.9, D3:23.0, PLC:23.1,	low
DeRubeis(21)	2005	180	MDD (DSM IV)	y	y	8	Paroxetine, N=120,				N=60	hamd, whole sample: 23.4	unknown/ high
Detke(22)	2002	245	MDD (DSM IV)	n	y	9	Duloxetine, N=123,				N=122	hamd, D: 21.42+4.11, PLC: 21.14+3.72,	unknown/ high
Detke(23)	2004	364	MDD (DSM IV)	n	y	8	Duloxetine, N=93,	Duloxetine, N=93,	Paroxetine, N=85,		N=93	hamd, D1:19.9, D2:20.2, P:20.3, PLC:19.9,	low
Dubé(24)	2010	176	MDD (DSM IV-TR)	n	y	8	Escitalopram, N=54,				N=122	n.s.	low
Dunlop(25)	2011	427	MDD (DSM IV)	y	y	12	Desvenlafaxine, N=285,				N=142	hamd, D: 22.0+4.2, PLC: 21.8+4.5,	unknown/ high
Elkin(26)	1989	119	MDD	n.s.	y	16	Imipramine, N=57,				N=62	hamd, I: 19.5 + 4.6, PLC: 19.5 + 4.6	low
Evans(27, 28)	1997	62	depression (GMS-AGECAT)	65 + only	n.s.	8	Fluoxetine, N=29,				N=33	hamd, F:20.5, PLC:21,	unknown/ high
Fava(29)	1998	128	MDD (DSM III-R)	n.s.	y	12	Paroxetine, N=55,	Fluoxetine, N=54,			N=19	hamd, P:23.1 + 3.4, F:23.9 + 3.8, PLC:23.7 + 2.7	low

Fava(30)	2005	90	MDD (DSM IV)	n	y	12	Fluoxetine, N=47,			N=43	hamd, F: 19.6 + 3.1, PLC: 19.9 + 2.9,	low
Feiger(31)	1996	120	MDD (DSM III-R)	y	y	8	Gepirone, N=41,	Imipramine, N=39,		N=40	MADRS: MED1: 28,26; MED2: 26,98; PLC: 26,88	unknown/ high
Feiger(32)	2006	257	MDD (DSM IV)	n	y	8	Selegiline transdermal, N=129,			N=128	hamd, S:28.3, PLC:28.6,	low
Feiger(33)	2009	235	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=117,			N=118	hamd, D:23.3, PLC:23.1	low
Ferguson(34)	1994	554	MDD (DSM III-R)	y	n.s.	9	Dothiepin, N=184,	Doxepin, N=184,		N=186	hamd, MED1: 23,9±3,3; MED2: 23,8±3,0; PLC: 23,6±3,1	unknown/ high
Forest(35)	2005	368	MDD (DSM IV)	y	n.s.	8	Escitalopram, N=124,	Citalopram, N=119,		N=125	hamd, E:24.8, C:25.0, PLC:25.0; MADRS, E:28.7, C:28.3, PLC:28.8,	low
GSK(36)	1991	663	MDD	n.s.	n	12	Paroxetine, N=272,	Fluoxetine, N=278,		N=113	n.s.	unknown/ high
GSK(37)	1993	565	MDD	n	n.s.	8	Bupropion SR, N=112,	Bupropion SR, N=114,	Bupropion SR, N=111,	Bupropion SR, N=111,	N=116	hamd, B1:34.3, B2:33.5, B3:34.1, B4:35.1, PLC:33.5	low
GSK(38)	1993	243	MDD+Anxiety (DSM III-R)	n	y	8	Paroxetine, N=120,				N=123	hamd, P:24.47, PLC:24.35,	low
GSK(39)	2000	92	double depression (DSM IV)	n	n.s.	8	Paroxetine, N=43,				N=49	n.s.	unknown/ high
GSK(40)	2003	235	MDD (DSM IV)	n	y	8	Paroxetine, N=117,				N=118	hamd, P:24.7, PLC:24.5,	low
GSK AK130927(41)	2004	397	MDD (DSM IV)	n	y	8	Bupropion XL, N=134,	Escitalopram, N=133,			N=130	hamd, MED1: 23,9±0,3; MED2: 23,3±0,3; PLC: 23,3±0,2	unknown/ high
GSK AK130926(41)	2004	388	MDD (DSM IV)	n	y	8	Bupropion XL, N=129,	Escitalopram, N=133,			N=126	hamd, 23,3±0,3	unknown/ high

GSK(42)	2005	414	MDD (DSM IV)	65 + only	n	10	Bupropion XL, N=210,			N=204	MADRS, B: 29.5 + 0.34, PLC: 29.8 + 0.34	unknown/ high
GSK(43)	2010	412	MDD (DSM IV-TR)	n	y	8	Paroxetine CR, N=158,	Paroxetine IR, N=83,		N=171	hamd, P1:22.7, P2:22.7, PLC:226	low
Goldstein(44)	2002	167	MDD or Bip II (DSM IV)	n	y	8	Duloxetine, N=66,	Fluoxetine, N=33,		N=68	hamd, D:18.4, F:17.9, PLC:19.2,	low
Goldstein(45)	2004	353	MDD (DSM IV)	n	y	8	Duloxetine, N=86,	Duloxetine, N=91,	Paroxetine, N=87,	N=89	hamd, D1:18.7, D2:17.9, P:17.8, PLC: 17.2,	low
Heiligenstein(46, 47)	1994	83	MDD or Bip II (DSM III-R)	n	n	8	Fluoxetine, N=41,			N=42	hamd, F:21.1 PLC:21.6,	unknown/ high
Heller(48)	1971	37	own criteria, severe depression	n.s.	n.s.	12	Imipramine, N=12,	Desipramine, N=11,		N=14	hamd, I: 26.6, D: 24.9, PLC: 25.6	unknown/ high
Heun(49)	2013	218	MDD (DSM IV-TR)	65 + only	y	8	Agomelatine, N=148,			N=70	hamd-17, A:26.9, PLC:26.8,	low
Hewett(50)	2009	569	MDD (DSM IV)	n	n.s.	8	Bupropion, N=187,	Venlafaxine, N=182,		N=197	MADRS, B:30.4, V:30.0, PLC:30.4,	unknown/ high
Hewett(51)	2010	581	MDD (DSM IV)	n	y	8	Bupropion, N=202,	Venlafaxine, N=193,		N=186	MADRS, B:30.6, V:30.1, PLC:30.6,	low
Hunter(52)	2011	23	MDD (DSM IV)	n	n.s.	8	Fluoxetine, N=12,			N=11	hamd, F:23.17, PLC:20.73,	unknown/ high
Hypericum Perforatum Depression Trial Study Group(53)	2002	225	MDD (DSM IV)	n	y	8	Sertraline, N=109,			N=116	hamd, S: 22.5 + 2.5, PLC: 22.7 + 2.7,	low
Iwata(54)	2013	699	MDD (DSM IV-TR)	y	y	8	Desvenlafaxine, N=232,	Desvenlafaxine, N=236,		N=231	hamd, D1:23, D2:23, PLC:23,	low

Jarrett(55)	1999	72	MDD (DSM III-R) +AD	n.s.	n.s.	10	Phenelzine, N=36,			N=36	hamd, P: 16.8 + 0.48, PLC: 17.4 + 0.5	low
Jefferson(56)	2006	270	MDD (DSM IV)	y	y	8	Bupropion XL, N=133,			N=137	IDS-C, B:44.5, PLC:43.9,	low
Kasper(57)	2005	514	MDD (DSM IV)	65 + only	y	8	Escitalopram, N=170,	Fluoxetine, N=164,		N=180	madrs, E:28.2, F:28.5, PLC:28.6,	low
Kasper(58)	2012	210	MDD (DSM IV-TR)	n	y	8	Escitalopram, N=139,			N=71	madrs, E:35.4, PLC:34.7,	low
Katona(59)	2012	446	MDD (DSM IV-TR)	65 + only	y	8	Vortioxetine, N=154,	Duloxetine, N=147,		N=145	hamd, V: 29.2, D:28.5, PLC:29.4,	low
Khan(60)	1998	353	MDD (DSM III-R)	n	n.s.	12	Venlafaxine, N=85,	Venlafaxine, N=90,	Venlafxine, N=83,	N=95	hamd, V75: 24.3, V150: 24.5, V200: 24.8, PLC: 25.1	unknown/ high
Koshino(61)	2013	564	MDD (DSM IV-TR)	y	y	8	Bupropion, N=190,	Bupropion, N=188,		N=186	n.s.	low
Lepola(62)	2003	468	MDD (DSM IV)	n	y	8	Escitalopram, N=155,	Citalopram, N=159,		N=154	MADRS, E:29, C:29.2, PLC:28.7,	unknown/ high
Lieberman(63)	2008	713	MDD (DSM IV)	n	n.s.	8	Desvenlafaxine, N=226,	Venlafaxine, N=127,	Venlafaxine, N=115,	N=245	hamd, D:25.4, V1:25.8, V2:25.1, PLC:25.5,	unknown/ high
Liebowitz(64)	2007	234	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=120,			N=114	hamd, D:23.7, PLC:23.7	low
Liebowitz(65)	2008	447	MDD (DSM IV)	n	y	8	Desvenlafaxine, N=150,	Desvenlafaxine, N=147,		N=150	hamd, D1:23, D2:23, PLC:23	low
Liebowitz(66)	2013	673	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=226,	Desvenlafaxine, N=224,		N=223	hamd, D1:23, D2:23, PLC:23	low
Loo(67)	2002	697	MDD or Bip II (DSM IV)	n	n	8	Agomelatine, N=136,	Agomelatine, N=146,	Agomelatine, N=135,	Paroxetine, N=144,	N=136	hamd, A1:27.9, A2:27.3, A3:27.4, P:27.3, PLC:27.4	low

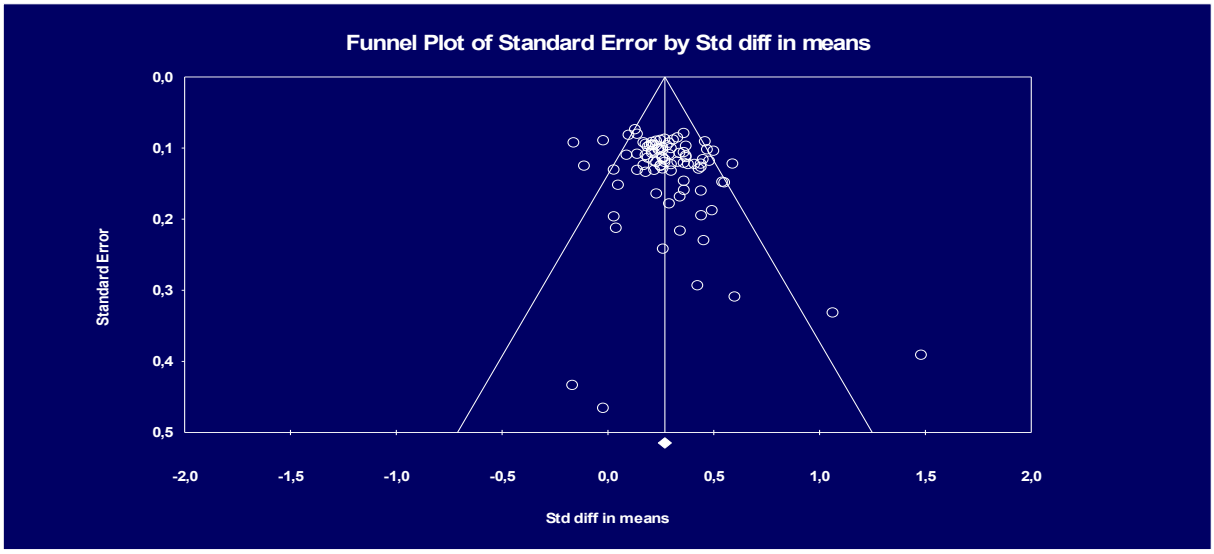
Lopez-Rodriguez(68)	2004	20	MDD (DSM IV), mild to moderate	n	n.s.	44	Fluoxetine, N=10,			N=10	hamd, F: 17.6, PLC: 17.2	unknown/ high
Lydiard(69)	1997	385	MDD (DSM III-R)	n	y	8	Sertraline, N=119,	Amitriptyline, N=104,		N=115	hamd, S:21.5, A:22.1, PLC:22.1,	low
Mahablesh warkar(70)	2013	597	MDD (DSM IV-TR)	y	n.s.	8	Vortioxetine, N=146,	Vortioxetine, N=153,	Duloxetine, N=149,	N=149	hamd, V1:29.8, V2:29.8, D:28.7, PLC:29.5	low
Malt(71)	1999	372	MDD (DSM III-R) mild to moderate	y	y	24	Mianserine, N=121,	Sertraline, N=122,		N=129	MADRS, M: 26.8 + 4.5, S: 26.8 + 4.4, PLC: 26.5 + 4.0	low
McGrath(72)	2000	154	MDD(DSM IV) + AD	n	y	10	Fluoxetine, N=49,	Imipramine, N=53,		N=52	n.s.	unknown/ high
Montgomery(73)	2013	553	MDD (DSM IV)	y	y	10	Levomilnacipran, N=276,			N=277	MADRS: L: 30.9 + 4.1, PLC: 30.5 + 3.7	low
Moreno(74)	2006	66	MDD (DSM IV)	n	y	8	Fluoxetine, N=20,			N=46	hamd, MED1: 15,42±1,09 ; PLC:16,43±1,09	unknown/ high
Mynors-Wallis(75)	1995	61	MDD, own criteria	n	n.s.	12	Amitriptyline, N=31,			N=30	hamd, A: 19.1 + 4.8 (N=27), PLC: 18.4 + 3.6 (N=26)	unknown/ high
Nierenberg(76)	2007	684	MDD (DSM IV)	n	y	8	Duloxetine, N=273,	Escitalopram, N=274,		N=137	hamd, D:17.6, E:17.8, PLC:17.7	low
Oakes I(77)	2012	316	MDD (DSM IV-TR)	n	y	8	Duloxetine, N=214,			N=102	hamd-17, D: 22.9, PLC: 22.8,	unknown/ high
Oakes II(77)	2012	330	MDD (DSM IV-TR)	n	y	8	Duloxetine, N=220,			N=110	hamd-17, D: 22.8, PLC: 22.9,	unknown/ high
Perahia(78)	2006	392	MDD (DSM IV)	n	y	8	Duloxetine, N=93,	Duloxetine, N=103,	Paroxetine, N=97,	N=99	hamd, D1:21.3 + 3.0, D2:21.4 + 4.4, P:21.0 + 3.4, PLC:20.6 + 3.7,	low

Philipp(79)	1999	151	moderate depression (ICD-10)	n	y	8	Imipramine, N=105,			N=46	hamd, I: 22.2 + 4.2, PLC: 22.7 + 4.0,	unknown/ high
Rapaport(80)	2003	319	MDD (DSM IV)	60 + only	y	12	Paroxetine CR, N=104,	Paroxetine IR, N=106,		N=109	hamd, P1: 22.1 + 3.45, P2: 22.3 + 3.15, PLC: 22.1 + 3.00	low
Rapaport(81)	2009	515	MDD (DSM IV)	60 + only	y	10	Paroxetine CR, N=168(163),	Paroxetine CR, N=177(173),		N=180 (179)	hamd, P1: 22.56 + 3.59, P2: 23.10 + 3.93, PLC: 22.73 + 4.0	low
Raskin(82)	2007	303	MDD (DSM IV)	65 + only	y	8	Duloxetine, N=201,			N=102	hamd, D:18.8 + 4.8, PLC: 18.9 + 4.5	unknown/ high
Reimherr(83)	1990	427	MDD (DSM III)	n	n.s.	8	Sertraline, N=142,	Amitriptyline, N=144,		N=141	hamd, S:23.28, A:23.18, PLC:23.43,	low
Reimherr(84)	1998	353	MDD (DSM III-R)	y	n.s.	8	Bupropion SR, N=120,	Bupropion SR, N=116,		N=117	n.s.	unknown/ high
Rickels(85)	1994	260	MDD or Bip (DSM III-R)	n	n	8	Nefazodone, N=96(safety-pop),	Imipramine, N=92(safety-pop),		N=95(safety-pop)	hamd, N:24.3, I:24.3, PLC:23.5	unknown/ high
Robinson(86)	2014	299	recurrent MDD (DSM-IV)	65 + only	y	12	Duloxetine, N=204,			N=95	Hamd-D maier subscale: D: 10.1 + 3.4, PLC: 9.96 + 3.1	unknown/ high
Roose(87)	2004	174	MDD (DSM IV)	75 + only	y	8	Citalopram, N=84,			N=90	hamd, C:24.4 + 4.3, PLC: 24.2 + 3.9,	low
Rudolph(88)	1999	295	MDD (DSM IV)	y	y	8	Venlafaxine XR, N=95,	Fluoxetine, N=103,		N=97	hamd, V:25, F:25, PLC:26	low
Sambunaris(89)	2013	429	MDD (DSM IV-TR)	y	y	8	Levomilnacipran, N=215,			N=214	MADRS, L:35.0, PLC:35.2,	low
Schatzberg(90)	2006	288	MDD (DSM IV)	65 + only	y	8	Venlafaxine IR, N=93,	Fluoxetine, N=99,		N=96	hamd, V:24, F: 24, PLC:23	unknown/ high

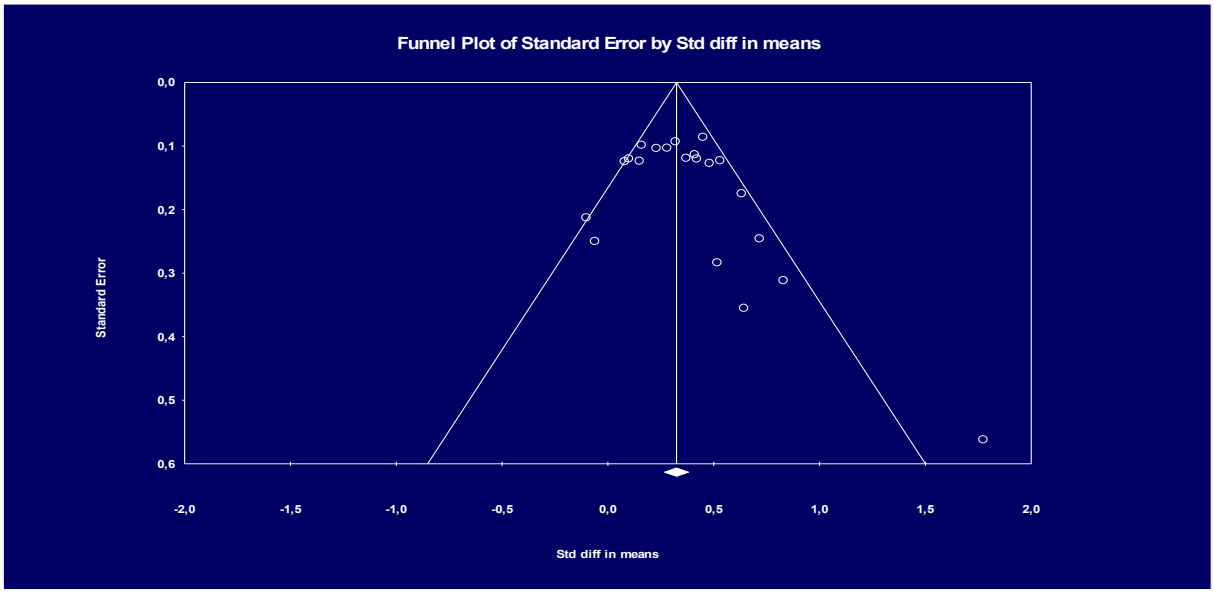
Schneider(91)	2003	728	MDD (DSM IV)	60 + only	y	8	Sertraline, N=360,				N=368	hamd, S:21.4 + 2.7, PLC:21.4 + 2.6,	low
Schweizer(92)	1998	172	MDD (DSM III-R)	65 + only	y	8	Imipramine, N=60,	Buspirone, N=54,			N=58	hamd, I:23.9 + 4.0, B:24.1 + 3.9, PLC:24.1 + 4.2,	low
Septien-Velez(93)	2007	369	MDD (DSM IV)	y	y	8	Desvenlafaxine, N=121,	Desvenlafaxine, N=124,			N=124	hamd, D1:24.8, D2:25.2, PLC:25.3,	low
Sheehan(94)	2009	406	MDD (DSM IV)	n	y	8	Trazodone, N=202,				N=204	hamd, T:23.2 + 4.2, PLC:22.4 + 4.4,	low
Silverstone(95)	1999	359	MDD (DSM IV)	y	y	12	Venlafaxine, N=122,	Fluoxetine, N=199,			N=118	hamd: V: 27.6 + 5.1, F: 27.0 + 4.6, PLC: 27.1 + 4.5	low
Sramek(96)	1995	144	MDD (DSM III-R)	n	y	9	Fluoxetine, N=72,				N=72	hamd, F: 28.2 + 4.1, PLC: 27.5 + 4.2	unknown/ high
Stahl(97)	2000	316	MDD (DSM IV)	n	y	24	Citalopram, N=103,	Sertraline, N=106,			N=107	hamd, C: 26.5, S: 26.6, PLC: 26.4	low
Stahl(98)	2010	482	MDD (DSM IV)	y	y	8	Agomelatine, N=158 (163),	Agomelatine, N=161 (167),			N=163 (165)	hamd: MED1: 26,8±3,28; MED2: 26,8±3,35; PLC: 26,4±2,92	low
Thase(99)	1997	191	MDD (DSM IV)	y	y	8	Venlafaxine XR, N=91,				N=100	hamd, V:25, PLC:24,	low
Thomson(100)	1982	59	MDD, own criteria	n	n.s.	12	Amitriptyline, N=31,				N=28	hamd, A: 17.4 + 4.9, PLC: 19.4 + 4.2,	low
Tourian(101)	2009	615	MDD (DSM IV)	n	y	8	Desvenlafaxine, N=148,	Desvenlafaxine, N=150,	Duloxetine, N=157,		N=160	hamd, D1:23 + 3, D2:23 + 3, Du:23 + 2, PLC:24 + 3,	low
Trivedi(102)	2004	447	MDD (DSM IV)	n	y	8	Paroxetine CR, N=153,	Paroxetine CR, N=148,			N=146	hamd, P1: 23.8 + 3.2, P2: 23.2 + 2.9, PLC: 23.5 + 3.3	low
Wade(103)	2002	377	MDD (DSM IV)	n	y	8	Escitalopram, N=188,				N=189	MADRS, E:29.2 + 4.2, PLC: 28.7 + 3.7,	low

Zajecka(104)	2010	484	MDD (DSM IV)	y	y	8	Agomelatine, N=156,	Agomelatine, N=161,	N=167	hamd, A1: 26.7 + 3.07, A2: 27.1 + 3.63, PLC: 27.1 + 3.71	low

Supplementary eFigure 2: ***Funnel Plot:*** *Primary Outcome Analysis 8 weeks*



Supplementary eFigure 3: ***Funnel Plot:*** *Primary Outcome Analysis 12 weeks*



1. Amsterdam JD: A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. in The Journal of clinical psychiatry2003. pp. 208-214.
2. Andreoli V, Caillard V, Deo RS, Rybakowski JK, Versiani M: Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. in Journal of clinical psychopharmacology2002. pp. 393-399.
3. Asnis GM, Bose A, Gommoll CP, Chen C, Greenberg WM. Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: A phase 3, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 2013;74:242-248.
4. Bakish D BA, Gommoll C, Chen C, Nunez R, Greenberg WM, Liebowitz M, Khan A. Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. J Psychiatry Neurosci. 2014 Jan;39:40-49.
5. Baldwin DS, Loft H, Dragheim M: A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). in European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology2012. pp. 482-491.
6. Barber J, Barrett M, Gallop R, Rynn M, Rickels K: Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. in J Clin Psychiatry2012. pp. 66-73.
7. Blumenthal J, Babyak M, Doraiswamy P, Watkins L, Hoffman B, Barbour K, Herman S, Craighead W, Brosse A, Waugh R, Hinderliter A, Sherwood A: Exercise and pharmacotherapy in the treatment of major depressive disorder. in Psychosomatic Medicine2007. pp. 587-596.
8. Bose A, Li D, Gandhi C: Escitalopram in the acute treatment of depressed patients aged 60 years or older. in The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry2008. pp. 14-20.
9. Boyer P, Montgomery S, Lepola U, Germain J, Brisard C, Ganguly R, Padmanabhan S, Tourian K: Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. in International Clinical Psychopharmacology2008. pp. 243-253.
10. Burke WJ, Gergel I, Bose A: Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. in The Journal of clinical psychiatry2002. pp. 331-336.
11. Clayton A, Zajecka J, Ferguson J, Filipiak-Reisner J, Brown M, Schwartz G: Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. in International Clinical Psychopharmacology2003. pp. 151-156.
12. Clayton AH, Kornstein SG, Dunlop BW, Focht K, Musgnung J, Ramey T, Bao W, Ninan PT. Efficacy and Safety of Desvenlafaxine 50 mg/d in a Randomized, Placebo-Controlled Study of Perimenopausal and Postmenopausal Women With Major Depressive Disorder. J Clin Psychiatry. 2013;74:1010-1017.
13. Cohn CK, Robinson DS, Roberts DL, Schwiderski UE, O'Brien K, Ieni JR: Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. in The Journal of clinical psychiatry1996. pp. 15-18.
14. Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RM, Houser TL, Ascher JA: Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. in Annals of

clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists1999. pp. 205-215.
15. Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, Ascher J, Batey S, Jamerson B, Metz A: A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. in Clinical therapeutics2001. pp. 1040-1058.
16. Cook IA, Leuchter AF, Witte E, Abrams M, Uijtdehaage SH, Stubbeman W, Rosenberg-Thompson S, Anderson-Hanley C, Dunkin JJ: Neurophysiologic predictors of treatment response to fluoxetine in major depression. in Psychiatry research1999. pp. 263-273.
17. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL: Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. in Depression and anxiety2000. pp. 58-65.
18. Croft H, Settle E, Houser T, Batey SR, Donahue RM, Ascher JA: A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. in Clinical therapeutics1999. pp. 643-658.
19. Cunningham L: Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. in Annals of Clinical Psychiatry1997. pp. 157-164.
20. DeMartinis NA, Yeung PP, Entsuah R, Manley AL: A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. in The Journal of clinical psychiatry2007. pp. 677-688.
21. DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, O'Reardon JP, Lovett ML, Gladis MM, Brown LL, Gallop R: Cognitive therapy vs medications in the treatment of moderate to severe depression. in Archives of general psychiatry2005. pp. 409-416.
22. Detke M, Lu Y, Goldstein D, Hayes J, Demitrack M: Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. in J Clin Psychiatry2002. pp. 308-315.
23. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I: Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. in European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology2004. pp. 457-470.
24. Dubé S, Dellva MA, Jones M, Kielbasa W, Padich R, Saha A, Rao P: A study of the effects of LY2216684, a selective norepinephrine reuptake inhibitor, in the treatment of major depression. in Journal of psychiatric research2010. pp. 356-363.
25. Dunlop B, Reddy S, Yang L, Lubaczewski S, Focht K, Guico-Pabia C: Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo. in Journal of Clinical Psychopharmacology2011. pp. 569-576.
26. Elkin I, Shea M, Watkins J, Imber S, Sotsky S, Collins J, Glass D, Pilkonis P, Leber W, Docherty J: National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. in Archives of General Psychiatry1989. pp. 971-982; discussion 983.
27. Evans M, Hammond M, Wilson K, Lye M, Copeland J: Treatment of depression in the elderly: effect of physical illness on response. in International journal of geriatric psychiatry1997. pp. 1189-1194.
28. Evans M, Hammond M, Wilson K, Lye M, Copeland J: Placebo-controlled treatment trial of depression in elderly physically ill patients. in International journal of geriatric psychiatry1997. pp. 817-824.

29. Fava M, Amsterdam J, Deltito J, Salzman C, Schwaller M, Dunner D: A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. in Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists1998. pp. 145-150.
30. Fava M, Alpert J, Nierenberg A, Mischoulon D, Otto M, Zajecka J, Murck H, Rosenbaum J: A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. in Journal of Clinical Psychopharmacology2005. pp. 441-447.
31. Feiger A: A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. in Psychopharmacology Bulletin1996. pp. 659-665.
32. Feiger AD, Rickels K, Rynn MA, Zimbroff DL, Robinson DS: Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. in The Journal of clinical psychiatry2006. pp. 1354-1361.
33. Feiger AD, Tourian KA, Rosas GR, Padmanabhan SK: A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder. in CNS spectrums2009. pp. 41-50.
34. Ferguson J, Mendels J, Manowitz N: Dothiepin versus doxepin in major depression: Results of a multicenter, placebo-controlled trial. in Journal of Clinical Psychiatry1994. pp. 258-263.
35. Forest L: Flexible-Dose Comparison of the Safety and Efficacy of LU 26-054 (Escitalopram), Citalopram, and Placebo in the treatment of Major Depressive Disorder [SCT-MD-02]. in Forest Laboratories - Clinical Study Register [wwwforestclinicaltrialscom]2005.
36. GlaxoSmithKline: A multicenter, randomized, double-blind, placebo-controlled comparison of paroxetine and fluoxetine in the treatment of major depressive disorder. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]1991.
37. GlaxoSmithKline: A multicenter dose-response evaluation of the safety and efficacy of bupropion HCI sustained-release versus placebo in depressed outpatients. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]1993.
38. GlaxoSmithKline: A Double-Blind, Randomized Trial of Paroxetine Versus Placebo In Patients With Depression Accompanied by Anxiety. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]1993.
39. GlaxoSmithKline: A multicentre, randomised, double-blind study to compare paroxetine versus placebo in the treatment of double depression. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]2000.
40. GlaxoSmithKline: An 8-week, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Fixed-Dose Study Comparing the Efficacy and Safety of a New Chemical Entity (NCE) or Paroxetine to Placebo in Moderately to Severely Depressed Patients with Major Depressive Disorder [GSK-NKD20006; NCT00048204]. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]2003.
41. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG: Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. in The Journal of clinical psychiatry2006. pp. 736-746.
42. GlaxoSmithKline: A Multi-Centre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible Dose Study to Evaluate the Efficacy, Safety and Tolerability of Extended-release Bupropion Hydrochloride (150mg-300mg once daily) in Elderly

Subjects with Major Depressive Disorder. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]2005.
43. GlaxoSmithKline: A Randomized, Double-blind, Placebo Controlled Trial to Evaluate the Clinical Effects of Controlled Release Paroxetine in the Treatment of Major Depressive Disorder. in GSK - Clinical Study Register [wwwgsk-clinicalstudyregistercom]2010.
44. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA: Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. in The Journal of clinical psychiatry2002. pp. 225-231.
45. Goldstein D, Lu Y, Detke M, Wiltse C, Mallinckrodt C, Demitrack M: Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. in Journal of Clinical Psychopharmacology2004. pp. 389-399.
46. Heiligenstein JH, Tollefson GD, Faries DE: Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo-controlled trial of fluoxetine versus placebo. in Journal of affective disorders1994. pp. 163-173.
47. Heiligenstein JH, Faries DE, Rush AJ, Andersen JS, Pande AC, Roffwarg HP, Dunner D, Gillin JC, James SP, Lahmeyer H: Latency to rapid eye movement sleep as a predictor of treatment response to fluoxetine and placebo in nonpsychotic depressed outpatients. in Psychiatry research1994. pp. 327-339.
48. Heller A, Zahourek R, Whittington H: Effectiveness of antidepressant drugs: a triple-blind study comparing imipramine, desipramine, and placebo. in The American journal of psychiatry1971. pp. 1092-1095.
49. Heun R, Ahokas A, Boyer P, Gimenez-Montesinos N, Pontes-Soares F, Olivier V. The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo-controlled study. J Clin Psychiatry. 2013;74:587-594.
50. Hewett K, Chrzanowski W, Schmitz M, Savela A, Milanova V, Gee M, Krishen A, Millen L, Leary MO, Modell J: Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. in Journal of psychopharmacology (Oxford, England)2009. pp. 531-538.
51. Hewett K, Gee MD, Krishen A, Wunderlich HP, Clus A, Evoniuk G, Modell JG: Double-blind, placebo-controlled comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. in Journal of psychopharmacology (Oxford, England)2010. pp. 1209-1216.
52. Hunter AM, Cook IA, Greenwald SD, Tran ML, Miyamoto KN, Leuchter AF: The antidepressant treatment response index and treatment outcomes in a placebo-controlled trial of fluoxetine. in Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society2011. pp. 478-482.
53. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. in JAMA : the journal of the American Medical Association2002. pp. 1807-1814.
54. Iwata N, Tourian KA, Hwang E, Mele L, Vialet C. Efficacy and safety of desvenlafaxine 25 and 5050% shaded blockmg/day in a randomized, placebo-controlled study of depressed outpatients. Journal of psychiatric practice. 2013;19:5-14.
55. Jarrett RB, Schaffer M, McIntire D, Witt-Browder A, Kraft D, Risser RC: Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial. in Archives of general psychiatry1999. pp. 431-437.
56. Jefferson JW, Rush AJ, Nelson JC, VanMeter SA, Krishen A, Hampton KD, Wightman DS, Modell JG: Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a

randomized, double-blind, placebo-controlled study. in The Journal of clinical psychiatry2006. pp. 865-873.
57. Kasper S, Swart H, Friis Andersen H: Escitalopram in the treatment of depressed elderly patients. in The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry2005. pp. 884-891.
58. Kasper S, Ebert B, Larsen K, Tonnoir B: Combining escitalopram with gaboxadol provides no additional benefit in the treatment of patients with severe major depressive disorder. in The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)2012. pp. 715-725.
59. Katona C, Hansen T, Olsen CK: A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. in International clinical psychopharmacology2012. pp. 215-223.
60. Khan A, Upton G, Rudolph R, Entsuah R, Leventer S: The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. Venlafaxine Investigator Study Group. in Journal of Clinical Psychopharmacology1998. pp. 19-25.
61. Koshino Y, Bahk W-M, Sakai H, Kobayashi T: The efficacy and safety of bupropion sustained-release formulation for the treatment of major depressive disorder: A multi-center, randomized, double-blind, placebo-controlled study in Asian patients. Edited by Cipriani CCFHHJKKLMMMPPRRST. New Zealand, Dove Medical Press Ltd.
New Zealand; 2013.
62. Lepola U, Loft H, Reines E: Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. in International Clinical Psychopharmacology2003. pp. 211-217.
63. Lieberman D, Montgomery S, Tourian K, Brisard C, Rosas G, Padmanabhan K, Germain J, Pitrosky B: A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder. in International Clinical Psychopharmacology2008. pp. 188-197.
64. Liebowitz M, Yeung P, Entsuah R: A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. in J Clin Psychiatry2007. pp. 1663-1672.
65. Liebowitz M, Manley A, Padmanabhan S, Ganguly R, Tummala R, Tourian K: Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder. in Current Medical Research and Opinion2008. pp. 1877-1890.
66. Liebowitz MR, Tourian KA, Hwang E, Mele L. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry. 2013;13:94.
67. Loo H, Hale A, D'Haenen H: Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT<inf>2C</inf> antagonist, in the treatment of major depressive disorder: A placebo-controlled dose range study. in International Clinical Psychopharmacology2002. pp. 239-247.
68. Lopez Rodriguez J, Lopez Butron MA, Vargas Terrez BE, Villamil Salcedo V: [Double blind study with antidepressant, brief psychotherapy and placebo in patients with mild to moderate depression]. in Salud Mental (Mexico City, Mexico)2004. pp. 53-61.

69. Lydiard R, Stahl S, Hertzman M, Harrison W: A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. in J Clin Psychiatry1997. pp. 484-491.
70. Mahableshwarkar AR, Jacobsen PL, Chen Y: A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. in Current medical research and opinion2013. pp. 217-226.
71. Malt U, Robak O, Madsbu H, Bakke O, Loeb M: The Norwegian naturalistic treatment study of depression in general practice (NORDEP)-I: randomised double blind study. in BMJ (Clinical research ed)1999. pp. 1180-1184.
72. McGrath P, Stewart J, Janal M, Petkova E, Quitkin F, Klein D: A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. in The American journal of psychiatry2000. pp. 344-350.
73. Montgomery SA, Mansuy L, Ruth A, Bose A, Li H, Li D. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: A randomized, double-blind, placebo-controlled, proof-of-concept study. Journal of Clinical Psychiatry. 2013;74:363-369.
74. Moreno R, Teng C, Almeida K, Tavares JH: Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. in Revista brasileira de psiquiatria (São Paulo, Brazil : 1999)2006. pp. 29-32.
75. Mynors-Wallis L, Gath D, Lloyd-Thomas A, Tomlinson D: Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. in BMJ (Clinical research ed)1995. pp. 441-445.
76. Nierenberg A, Greist J, Mallinckrodt C, Prakash A, Sambunaris A, Tollefson G, Wohlreich M: Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. in Current Medical Research and Opinion2007. pp. 401-416.
77. Oakes TM, Myers AL, Marangell LB, Ahl J, Prakash A, Thase ME, Kornstein SG: Assessment of depressive symptoms and functional outcomes in patients with major depressive disorder treated with duloxetine versus placebo: primary outcomes from two trials conducted under the same protocol. in Human psychopharmacology2012. pp. 47-56.
78. Perahia D, Wang F, Mallinckrodt C, Walker D, Detke M: Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. in European psychiatry : the journal of the Association of European Psychiatrists2006. pp. 367-378.
79. Philipp M, Kohnen R, Hiller K: Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. in BMJ (Clinical research ed)1999. pp. 1534-1538.
80. Rapaport M, Schneider L, Dunner D, Davies J, Pitts C: Efficacy of controlled-release paroxetine in the treatment of late-life depression. in J Clin Psychiatry2003. pp. 1065-1074.
81. Rapaport M, Lydiard R, Pitts C, Schaefer D, Bartolic E, Iyengar M, Carfagno M, Lipschitz A: Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial. in J Clin Psychiatry2009. pp. 46-57.
82. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, Rotz BT, Mohs RC: Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. in The American journal of psychiatry2007. pp. 900-909.
83. Reimherr F, Chouinard G, Cohn C, Cole J, Itil T, LaPierre Y, Masco H, Mendels J: Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-

controlled, multicenter comparison study in outpatients with major depression. in J Clin Psychiatry1990. pp. 18-27.
84. Reimherr F, Cunningham L, Batey S, Johnston J, Ascher J: A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. in Clinical Therapeutics1998. pp. 505-516.
85. Rickels K, Schweizer E, Clary C, Fox I, Weise C: Nefazodone and imipramine in major depression: a placebo-controlled trial. in The British journal of psychiatry : the journal of mental science1994. pp. 802-805.
86. Robinson M OT, Raskin J, Liu P, Shoemaker S, Nelson JC. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. Am J Geriatr Psychiatry 2014 Jan;22:34-45.
87. Roose S, Sackeim H, Krishnan K, Pollock B, Alexopoulos G, Lavretsky H, Katz I, Hakkarainen H: Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. in The American journal of psychiatry2004. pp. 2050-2059.
88. Rudolph R, Feiger A: A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. in Journal of Affective Disorders1999. pp. 171-181.
89. Sambunaris A, Bose A, Gommoll CP, Chen C, Greenberg WM, Sheehan DV. A Phase III, Double-Blind, Placebo-Controlled, Flexible-Dose Study of Levomilnacipran Extended-Release in Patients With Major Depressive Disorder. J Clin Psychopharmacol. 2013.
90. Schatzberg A, Roose S: A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. in The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry2006. pp. 361-370.
91. Schneider L, Nelson J, Clary C, Newhouse P, Krishnan K, Shiovitz T, Weihs K: An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. in The American journal of psychiatry2003. pp. 1277-1285.
92. Schweizer E, Rickels K, Hassman H, Garcia-España F: Buspirone and imipramine for the treatment of major depression in the elderly. in The Journal of clinical psychiatry1998. pp. 175-183.
93. Septien-Velez L, Pitrosky B, Padmanabhan S, Germain J, Tourian K: A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. in International Clinical Psychopharmacology2007. pp. 338-347.
94. Sheehan D, Croft H, Gossen E, Levitt R, Brulle C, Bouchard S, Rozova A: Extended-release trazodone in major depressive disorder: A randomized, double-blind, placebo-controlled study [NCT00775203]. in Psychiatry2009. pp. 20-33.
95. Silverstone PH, Ravindran A: Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. in Journal of Clinical Psychiatry1999. pp. 22-28.
96. Sramek J, Kashkin K, Jasinsky O, Kardatzke D, Kennedy S, Cutler N: Placebo-controlled study of ABT-200 versus fluoxetine in the treatment of major depressive disorder. in Depression1995. pp. 199-203.
97. Stahl S: Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. in Biological Psychiatry2000. pp. 894-901.
98. Stahl S, Fava M, Trivedi M, Caputo A, Shah A, Post A: Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. in J Clin Psychiatry2010. pp. 616-626.

99. Thase M: Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. in J Clin Psychiatry1997. pp. 393-398.
100. Thomson J, Rankin H, Ashcroft G: The treatment of depression in general practice: A comparison of L-tryptophan and amitriptyline with placebo. in Psychol Med (London)1982. pp. 741-751.
101. Tourian K, Padmanabhan S, Groark J, Brisard C, Farrington D: Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies. in Clinical Therapeutics2009. pp. 1405-1423.
102. Trivedi M, Pigotti T, Perera P, Dillingham K, Carfagno M, Pitts C: Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. in J Clin Psychiatry2004. pp. 1356-1364.
103. Wade A, Michael LO, Bang HK: Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. in International Clinical Psychopharmacology2002. pp. 95-102.
104. Zajecka J, Schatzberg A, Stahl S, Shah A, Caputo A, Post A: Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. in Journal of clinical psychopharmacology2010. pp. 135-144.