Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder

Ewgeni Jakubovski, M.A., Anjali L. Varigonda, M.D., Nicholas Freemantle, Ph.D., Matthew J. Taylor, Ph.D., Michael H. Bloch, M.D., M.S.

Objective: Previous studies suggested that the treatment response to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder follows a flat response curve within the therapeutic dose range. The present study was designed to clarify the relationship between dosage and treatment response in major depressive disorder.

Method: The authors searched PubMed for randomized placebo-controlled trials examining the efficacy of SSRIs for treating adults with major depressive disorder. Trials were also required to assess improvement in depression severity at multiple time points. Additional data were collected on treatment response and all-cause and side effect-related discontinuation. All medication doses were transformed into imipramine-equivalent doses. The longitudinal data were analyzed with a mixed-regression model. Endpoint and tolerability analyses were analyzed using meta-regression and stratified subgroup analysis by predefined SSRI dose categories in order to assess the effect of SSRI dosing on the efficacy and tolerability of SSRIs for major depressive disorder.

Results: Forty studies involving 10,039 participants were included. Longitudinal modeling (dose-by-time interaction=0.0007, 95% CI=0.0001–0.0013) and endpoint analysis (meta-regression: β=0.00053, 95% CI=0.00018–0.00088, z=2.98) demonstrated a small but statistically significant positive association between SSRI dose and efficacy. Higher doses of SSRIs were associated with an increased likelihood of dropouts due to side effects (meta-regression: β=0.00207, 95% CI=0.00071–0.00342, z=2.98) and decreased likelihood of all-cause dropout (meta-regression: β=−0.00093, 95% CI=−0.00165 to −0.00021, z=−2.54).

Conclusions: Higher doses of SSRIs appear slightly more effective in major depressive disorder. This benefit appears to plateau at around 250 mg of imipramine equivalents (50 mg of fluoxetine). The slightly increased benefits of SSRIs at higher doses are somewhat offset by decreased tolerability at high doses.

Am J Psychiatry 2016; 173:174–183; doi: 10.1176/appi.ajp.2015.15030331

While the efficacy of selective serotonin reuptake inhibitor (SSRI) medications and their widespread use is generally accepted in major depressive disorder (especially in more severe cases), there remains some uncertainty as to the optimal dose for SSRI pharmacotherapy of major depressive disorder (1–9). Current APA Practice Guidelines state that "optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached" (3). This recommendation is based on level-II evidence indicating that escalating antidepressant doses was "recommended based on moderate clinical confidence" (3).

Based on currently available evidence, the APA Practice Guidelines regarding antidepressant dosing appear reasonable. A previous meta-analysis examining dosing of antidepressant medications in major depressive disorder demonstrated a flat dose-response curve within the therapeutic range for antidepressant medications (≥100-mg imipramine equivalents) (10). Furthermore, the meta-analysis demonstrated a greater side effect burden at higher doses as evidenced by an escalating adverse events rate with increasing dosage of antidepressants (10). Although this meta-analysis employed quite advanced methodology for the time, the findings may be somewhat antiquated for use in clinical practice for several reasons. First, the authors grouped other classes of antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants, and atypical antidepressants) alongside SSRIs. Other antidepressants likely have a different dose-response relationship and tolerability profile with dose when compared with SSRIs. Second, the authors examined dose as a categorical rather than continuous outcome, which may reduce overall power to detect a dosing effect in the meta-analysis. In contrast, another meta-analysis, which was quite stringent in its inclusion criteria,

See related features: **Editorial** *by Dr. Trivedi (p. 105),* **Clinical Guidance** *(Table of Contents),* **AJP Audio** *(online), and* **Video** *by Dr. Pine (online)*

examined the dose-response of SSRI medication in only four fixed-dose and four dose-escalation trials in major depressive disorder. This meta-analysis demonstrated a weak positive association between higher doses and treatment response (11). This meta-analysis examining the dose-response curve in SSRI suggests the possibility that SSRIs may behave differently than other antidepressants.

The goal of the present meta-analysis is to improve the existing evidence-base regarding the dose-response relationship of SSRIs in major depressive disorder. Specifically, our goal is to determine whether there exists any evidence in SSRI trials of major depressive disorder to suggest that higher doses are associated with improved outcome. We conducted a meta-analysis and used meta-regression to examine the relationship between target SSRI dose in trials and the measured efficacy (and tolerability) of SSRI treatment compared with placebo.

METHOD

Search Strategy and Study Selection

A literature search was conducted on October 10, 2013 on PubMed and CENTRAL, The Cochrane Collaboration database of controlled trials (in the Cochrane Library). Published randomized controlled trials comparing all SSRIs versus placebo in short-term treatment of unipolar depression were sought by two reviewers (A.L.V. and M.H.B.), using the search term: ("SSRI"[MESH] OR "fluoxetine"[MESH] OR "fluvoxamine"[MESH] OR "citalopram"[MESH] OR "escitalopram"[MESH] OR "sertraline"[MESH] OR "paroxetine"[MESH]) AND "placebo"[MESH] AND "depression"[MESH]. Trials were included if 1) efficacy data were available for both SSRI- and placebo-treated participants for at least one time point other than baseline and endpoint and 2) they utilized standardized, validated outcome measurements of depression. Trials were excluded if 1) the age of participants was <19 years or >60 years; 2) a cross-over design was used; 3) psychiatric diagnosis other than major depressive disorder or a dual diagnosis was studied; 4) an SSRI was not studied; 5) not randomized; 6) not placebo-controlled; and 7) adjunctive psychotherapy was provided to the active or control group.

Data Extraction

Included trials provided depression ratings on the Hamilton Depression Rating Scale or the Montgomery-Åsberg Depression Rating Scale for at least three time points (baseline, endpoint, and at least one intermediate time point). If trials reported outcomes in a figure rather than in a table, a computer program (Dexter, German Astrophysical Virtual Observatory, University of Heidelberg, Heidelberg, Germany) was used to extract weekly data points from the figures (software available at http://dc.zah.uni-heidelberg.de/sdexter). Additionally, the number of treatment responders (as defined by study criteria) and the number of participants who discontinued during the course of the study (all-cause dropouts and dropouts due to side effects) were recorded. Additional data were collected on the type of SSRI, maximum dosage of medication, duration of the trial, and year of the trial. All SSRI doses were transformed into imipramine equivalent doses using previously described methodology (10).

Data Analysis

Data collection and preparation were conducted in Microsoft Excel 2007, and the effect of dose on time course of SSRI response was analyzed in SAS 9.3 (SAS Institute, Cary N.C.). We used generalized estimating equations to examine the effects of trial, treatment, modeling different forms of treatment effect, accounting for different periods within trials as repeated measures, and defining a new covariance structure for each trial by defining these as random effects. For each trial and week, the standardized mean difference in outcome scores between SSRI and placebo groups was calculated and weighted by the number of randomly assigned patients in the trial. Previous research has demonstrated that a logarithmic model provided the best fit for the time course of SSRI response compared with placebo (12, 13). The effects of SSRI were modeled using an autoregressive variance function, and the model with the lowest values on the Akaike Information Criterion was selected (14). Further details on this technique can be found elsewhere (13). We then examined the moderating effects of SSRI dosage using similar methodology. A mixed model was conducted that included the main effect of time and an interaction between SSRI dosage (in imipramine equivalents) and time. The main effect of SSRI dose was not included in the model, since this effect should be trivial. There should be no differences in depression severity (compared with placebo) at baseline. Differences should only be seen later when different SSRI doses start taking effect. Dose of SSRI was converted into imipramine equivalents based on previously defined methodology based on the therapeutic dose range of each medication (10, 15). Imipramine dose equivalents were chosen as the standard for antidepressants, since it was the first medication introduced in the class. For SSRI analysis, the dose equivalents were as follows: 100 mg of imipramine=120 mg of sertraline=100 mg of fluvoxamine=20 mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram. We additionally tested the SSRI dose model with an additional term to account for a delayed effect of SSRI dosing. We examined models in which the dosing effect of SSRI was only included after a lag of 2, 3, and 4 weeks and the initial model with no lag to see whether a modified log model can fit the data better. For this, we coded each week as a dummy variable and ran four models adding in a three-way-interaction between week, dose, and time. The goal of analysis was to determine whether the interaction between dose and time was significant, which would indicate that there exists a delayed effect of dose response relationship for SSRI in major depressive disorder.

As an alternative method of analysis, we also examined endpoint data from included trials. We examined 1) the standardized mean difference between endpoint depression scores and 2) the odds ratio of treatment response between SSRI and placebo using Comprehensive Meta Analysis,

Version 3 (Biostat, Englewood, N.J.). We conducted a meta-regression in Comprehensive Meta Analysis, Version 3, using a fixed-effects model that plotted the standardized mean difference (or odds ratio) for each trial against SSRI dose (in imipramine equivalents). A statistically significant meta-regression result would indicate an association between SSRI dose (in imipramine equivalents) and reported effect size of SSRI treatment compared with placebo. Additionally, in order to examine how our data replicated previous analysis in the area, we conducted an analysis examining previously utilized categories of SSRI dose. A stratified subgroup analysis was conducted using endpoint data with studies stratified by SSRI dosing (dose range categories: <100 mg, 100–199 mg, 200–250 mg, and >250 mg). This analysis examined the possibility that there might not be a linear association between SSRI dose and therapeutic response or that a linear relationship might exist but only up to or after a certain dose threshold. For clinician-friendly interpretation of the resultant data, we additionally converted all standardized mean difference outcomes to odds ratios in Comprehensive Meta Analysis, Version 3. We also calculated the number needed to treat or number needed to harm for each outcome based on the odds ratio and control event rate using the Center for Evidence-Based Medicine odds ratio to number needed to treat converter (16).

The analyses described thus far used all available data. The following sensitivity analyses were added to examine time and dose effects specific to intent-to-treat studies. The treatment effect was compared in intent-to-treat and completer studies both in the logarithmic model (by including an intent-to-treat status-by-time interaction) and in the endpoint data meta-analysis (via subgroup analysis). Furthermore, in the logarithmic model, the robustness of effect of dose (time-by-dose interaction) was tested by controlling for the intent-to-treat/completer study-by-time interaction. Finally, endpoint data from only intent-to-treat studies were used to conduct a meta-regression testing the effect of dose, as well as to conduct a subgroup analysis comparing the above-mentioned dose ranges.

We additionally examined the relationship between tolerability and SSRI dose in major depressive disorder trials using fixed-effects meta-regression in Comprehensive Meta Analysis, Version 2.2. Specifically, we examined the association between all-cause dropout (and dropouts due to side effects) as expressed in pooled odds ratios and SSRI dosage (in imipramine equivalents). A statistically significant meta-regression result would indicate an association between SSRI dose (in imipramine equivalents) and likelihood of participant dropout compared with placebo. Subgroup analysis was also performed between the four imipramine-equivalent SSRI dose ranges.

For all analyses, we conducted an additional sensitivity analysis excluding trials involving fluvoxamine. We chose to include fluvoxamine in our primary analysis, since fluvoxamine is an SSRI with an indication for major depressive disorder in many countries (e.g., the United Kingdom, Australia, and Russia). However, fluvoxamine does not possess a Food and Drug Administration indication for major depressive disorder and could have a different dose-response relationship compared with other SSRIs, and thus we decided to present our findings without fluvoxamine trials as a sensitivity analysis (see the figures in the data supplement accompanying the online version of this article).

RESULTS

Included Studies

A flowchart describing the selection of eligible trials is presented in Figure 1. Our search identified 1,707 studies, and an additional four studies were identified in references of other included trials and meta-analyses in the area. Forty studies met our inclusion criteria (17–55). The included studies reported 49 active treatment arms involving 10,039 adult patients with major depressive disorder. The characteristics of the included studies are summarized in Table S1 of the online data supplement. Six different SSRIs were studied in placebo-controlled trials with major depressive disorder: fluoxetine (k=9, N=2,386) (17, 21, 29, 31, 46, 47, 49, 51, 56), fluvoxamine (k=8, N=910) (18, 24, 27, 38, 39, 42, 45, 54), paroxetine (k=16, N=3,424) (19, 20, 22, 23, 25, 26, 28, 30, 33, 34, 36, 44, 48, 52, 55), sertraline (k=3, N=865) (43, 50, 57), citalopram (k=4, N=1,349) (32, 37, 40, 50), and escitalopram (k=3, N=1,105) (37, 41, 53).

SSRI Efficacy

Best-fitting model of SSRI response. The natural logarithmic ($\log_e$) model of SSRI treatment response had the best model fit. Based on Akaike information criterion, the logarithmic treatment model was significantly better than a model using the square root of week (χ^2=4.9, df=1, p=0.03). The estimate of treatment effect by log (week +1) from the final model was 0.32 (95% confidence interval [CI]=0.27–0.37; p<0.001). A $\log_e$ response curve indicates that the incremental SSRI benefit compared with placebo was greatest in the first week and gradually declined in magnitude as time persisted in short-term treatment trials. Models that introduced delayed treatment effects all produced similar (but worse or equivalent) model fits to when the dosing effect was introduced at baseline (week 2: χ^2=0, df=1, p=1; week 3: χ^2=0.6, df=1, p=1; week 4: χ^2=3.7, df=1, p=0.054).

Dose-response curve in continuous model of SSRI response. The logarithmic models at different imipramine equivalent dose isoquants are presented in Figure 2. There was significant effect of time (log [week +1]=0.23 [95% CI=0.13–0.33; p<0.0001]) and a significant interaction between dose and time (interaction=0.0007 [95% CI=0.0001–0.0013; p=0.0196]). This result indicates that higher doses of SSRIs were associated with a greater therapeutic response. In sensitivity analysis, the dose-by-time interaction remained significant when use of non-intent-to-treat analysis was adjusted for in the model (interaction=0.0007 [95% CI=0.0000–0.0014; p=0.00480]). Similarly, when fluvoxamine trials were excluded from the

analysis, there remained a significant dose-by-time interaction (interaction=0.0008 [95% CI=0.0002–0.0014; p<0.001]) (see Figure S2 in the online data supplement).

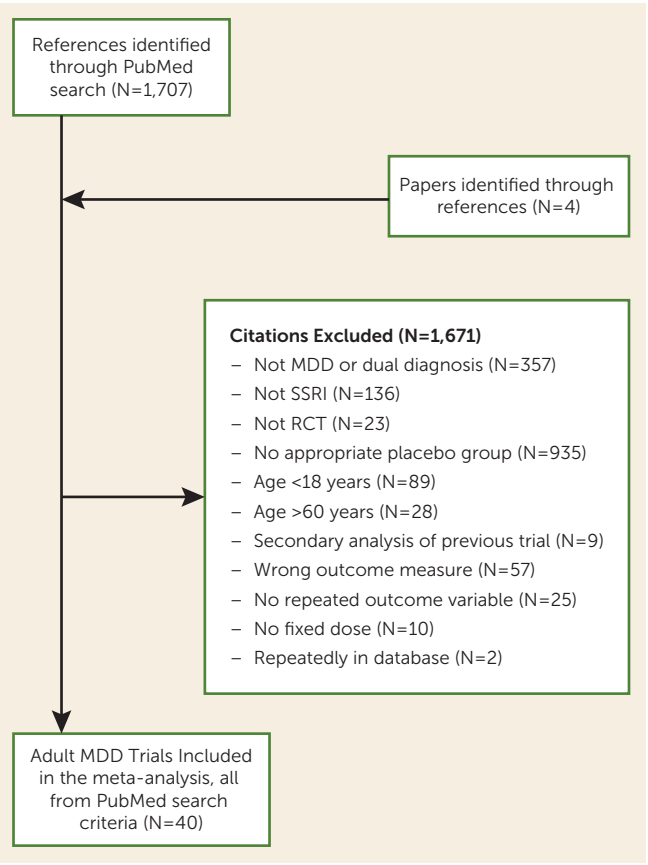
Traditional meta-analysis examining depression severity. Meta-regression described a significant association between SSRI dose (in imipramine equivalents) and measured efficacy of SSRIs in reducing depression severity (β=0.00053, 95% CI=0.00018–0.00088, z=2.98, p=0.0029). A scatterplot that depicts the relationship between imipramine equivalent dose of SSRIs and measured efficacy of SSRIs compared with placebo in terms of standardized mean difference is presented in Figure 3A. In sensitivity analysis, this result remained significant when restricted to trials using intent-to-treat analysis (β=0.00062, 95% CI=0.00025–0.00098, z=3.32, p=0.00090) but not when trials involving fluvoxamine were excluded (β=0.00029, 95% CI= –0.00010 to 0.00066, z=1.44, p=0.15) (see Figure S3A in the data supplement).

When SSRI dose was examined as a specific dosing category rather than as a continuous variable, there remained a significant effect of dose (test for subgroup differences: χ^2=54.4, df=3, p<0.001). The estimated efficacy of each SSRI dose category compared with placebo is described in Figure 3B. The greatest measured efficacy of SSRIs was observed in the dosing range of 200–250 imipramine equivalents. In sensitivity analysis, the differences between groups remained significant when restricted exclusively to trials employing intent-to-treat analysis (χ^2=56.2, df=3, p<0.001) or when fluvoxamine trials were excluded (χ^2=42.4, df=3, p<0.001) (see Figure S3B in the data supplement).

Traditional meta-analysis examining treatment response. Meta-regression demonstrated a significant association between SSRI dose (in imipramine equivalents) and measured efficacy of SSRIs with regard to the odds ratio of treatment response (β=0.0016, 95% CI=0.0005–0.0027, z=2.86, p=0.004). A scatterplot that depicts the relationship between imipramine equivalent dose of SSRIs and measured efficacy of SSRIs compared with placebo in terms of the odds ratio of treatment response is presented in Figure 3C. In sensitivity analysis, this result remained significant when restricted to trials using intent-to-treat analysis (β=0.00062, 95% CI=0.00025–0.00098, z=3.32, p=0.00090) and when trials involving fluvoxamine were excluded (β=0.0015, 95% CI=0.0003–0.0026, z=2.47, p=0.013) (see Figure S3C in the data supplement).

When SSRI dose was examined as a specific dosing category rather than as a continuous variable, there remained a significant effect of dose (test for subgroup differences: χ^2=14.5, df=3, p=0.002). The odds ratio of each SSRI dose category compared with placebo is presented in Figure 3D. The greatest measured efficacy of SSRIs was again observed in the dosing range of 200–250 imipramine equivalents. In sensitivity analysis, the differences between groups remained significant when restricted exclusively to trials employing intent-to-treat analysis (χ^2=56.2, df=3, p<0.001) or when fluvoxamine trials were excluded (χ^2=11.4, df=3, p=0.01) (see Figure S3D in the data supplement).

FIGURE 1. Flowchart of the Procedure for Selection of Eligible Trials From Identified References[a]

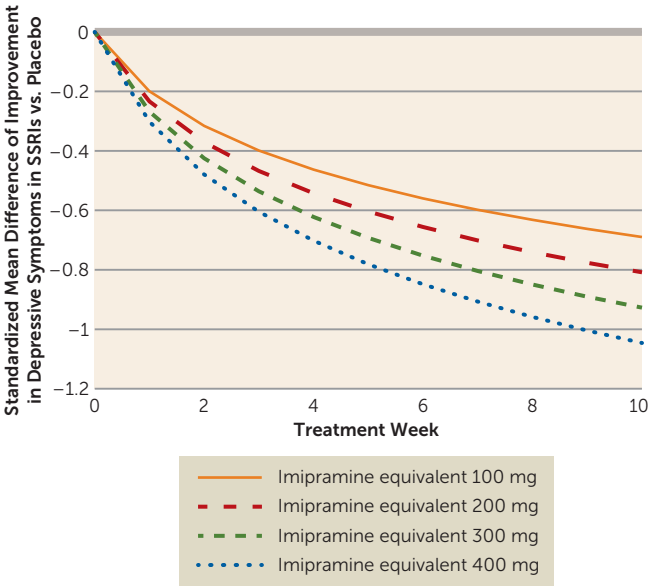


[a] MDD=Major depressive disorder; SSRI=selective serotonin reuptake inhibitor; RCT=randomized controlled trial

SSRI Tolerability

Higher SSRI dose was slightly, but significantly, associated with a lower likelihood of all-cause dropout (β=–0.00093, 95% CI=–0.00165 to −0.00021, z=−2.54, p=0.0110) in meta-regression analysis. The association between SSRI dose (in imipramine equivalents) and likelihood of all-cause dropout compared with placebo is presented in Figure 4A. However, when SSRI dose was divided into previously defined categories, there was no significant association between SSRI dose and likelihood of all-cause dropout (test for subgroup differences: χ^2=4.8, df=3, p=0.19). The likelihood of all-cause dropout compared with placebo was highest in the 100–200 imipramine-equivalent group and slightly, but not significantly, lower if the dose was lowered or raised from this dose. The association between SSRI dose and likelihood of all-cause dropout for each of the dosing categories is shown in Figure 4C. In the sensitivity analysis, excluding fluvoxamine trials, results remained similar for likelihood of all-cause dropout in the meta-regression (β=–0.00092, 95% CI=–0.00174 to −0.00010, z=−2.20, p=0.03), but became nonsignificant

FIGURE 2. Effect of Dosage on Longitudinal Response Curve of Selective Serotonin Reuptake Inhibitors (SSRIs)[a]



[a] The chart shows the effects of dosage on the longitudinal response curve examining the efficacy of SSRIs compared with placebo over time. Each line represents the typical improvement in depressive symptoms experienced over time in SSRIs compared with placebo at a dosage isoquant. Dosages are expressed in imipramine equivalents (100 mg of imipramine=120 mg of sertraline=100 mg of fluvoxamine=20 mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram).

in the subgroup analysis (χ^2=3.7, df=3, p=0.29) (see Figure S4 in the data supplement).

Meta-regression described a significant association between higher SSRI dose and increased likelihood of dropout due to side effects (β=0.00207, 95% CI=0.00071−0.00342, z=2.98, p=0.0028). A scatterplot demonstrating the relationship between SSRI dose and the likelihood of dropout due to side effects is presented in Figure 4B. Stratified subgroup analysis by SSRI dose category also demonstrated a significant association between SSRI dose and likelihood of dropout due to side effects. All dosing categories of SSRIs were associated with a greater likelihood of dropout as a result of side effects compared with placebo. Higher dosing categories of SSRIs were associated with a greater likelihood of dropout as a result of side effects. The association between SSRI dose and likelihood of dropout due to side effects for each of the dosing categories is shown in Figure 4B. In the sensitivity analysis, excluding fluvoxamine trials, results remained mostly unchanged for the likelihood of dropout due to side effects in the meta-regression (β=0.00249, 95% CI=0.00073−0.00425, z=2.77, p=0.006), but became nonsignificant in the subgroup analysis (χ^2=7.7, df=3, p=0.052) (see Figure S4 in the data supplement).

DISCUSSION

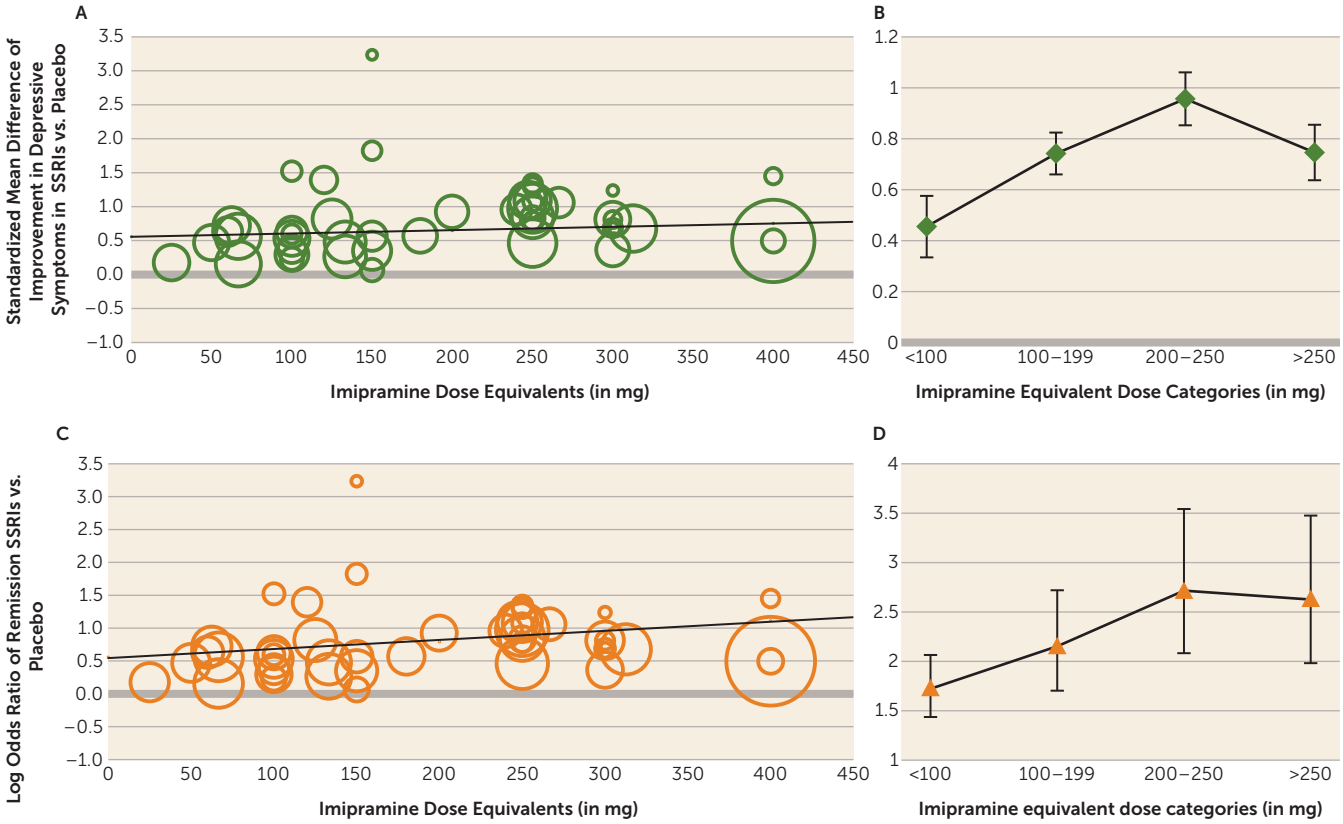
Meta-analysis demonstrated a significant association between higher SSRI doses and greater measured efficacy of SSRIs in placebo-controlled trials. This significant association between SSRI dose and measured efficacy was demonstrated in 1) longitudinal mixed-model meta-analysis, 2) endpoint meta-regression, and 3) stratified subgroup analysis by dose. These findings remained significant if the analysis was restricted to only data from studies employing intent-to-treat analysis and when fluvoxamine trials were excluded. Meta-analysis suggests that there may also be a consequence associated with escalating the dose of SSRI associated with reduced tolerability, as evidenced by a greater likelihood of dropout due to side effects with higher SSRI dose.

The results of this meta-analysis both extend upon and contradict a previous meta-analysis in this area (10). We replicated previous evidence suggesting a reduced tolerability of SSRIs at higher doses as evidenced by a higher likelihood of dropouts as a result of side effects. However, we demonstrated a significant positive association between SSRI dose and measured efficacy that flattened out only at the higher end of the recommended dosing range (greater than 250-mg imipramine equivalents). Specifically, meta-analysis demonstrates that using a higher dose of SSRI for major depressive disorder is associated with increased likelihood of response. Table 1 depicts odds ratio and number-needed-to-treat comparisons for different initial dosing strategies of SSRIs. Our results suggest a modest improvement in efficacy of high doses (200 mg–250 mg or >250-mg imipramine equivalents) compared with low doses (100 mg–200 mg imipramine equivalents), with odds ratios of approximately 1.3 and numbers needed to treat in the 14–16 range.

Previous meta-analysis and fixed-dose trials in this area have provided no evidence for escalating dose beyond the minimum recommended therapeutic dose (10, 57). Our meta-analysis differed in methodology in several important ways from this previous meta-analysis that likely explains the difference in results. First, we restricted our analysis to SSRI trials and did not include other antidepressants that likely have different dose-response and dose-tolerability curves. Second, we examined symptom improvement as a continuous measure rather than examining clinical improvement (yes/no) as the primary outcome of the meta-analysis. This decision likely increased power of the meta-analysis by increasing sensitivity of the primary outcome measure and reducing heterogeneity by eliminating differences in definition of therapeutic response. Third, we additionally examined the dosing effects of SSRIs not only with treatment response as a dichotomous outcome but also as a continuous measure. Meta-regression with a continuous measure is more sensitive to a change in SSRI benefit with dose. Fourth, we also included several trials published after the first meta-analysis. The additional trials provided more power to conduct this analysis.

Our meta-analysis demonstrates that there is substantial evidence for a modest increase in efficacy with higher doses of SSRIs starting from the point of initial titration. We also demonstrate that this benefit is at the cost of reduced

FIGURE 3. Effect of Dose on Measured Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) Compared With Placebo at Trial Endpoint[a]

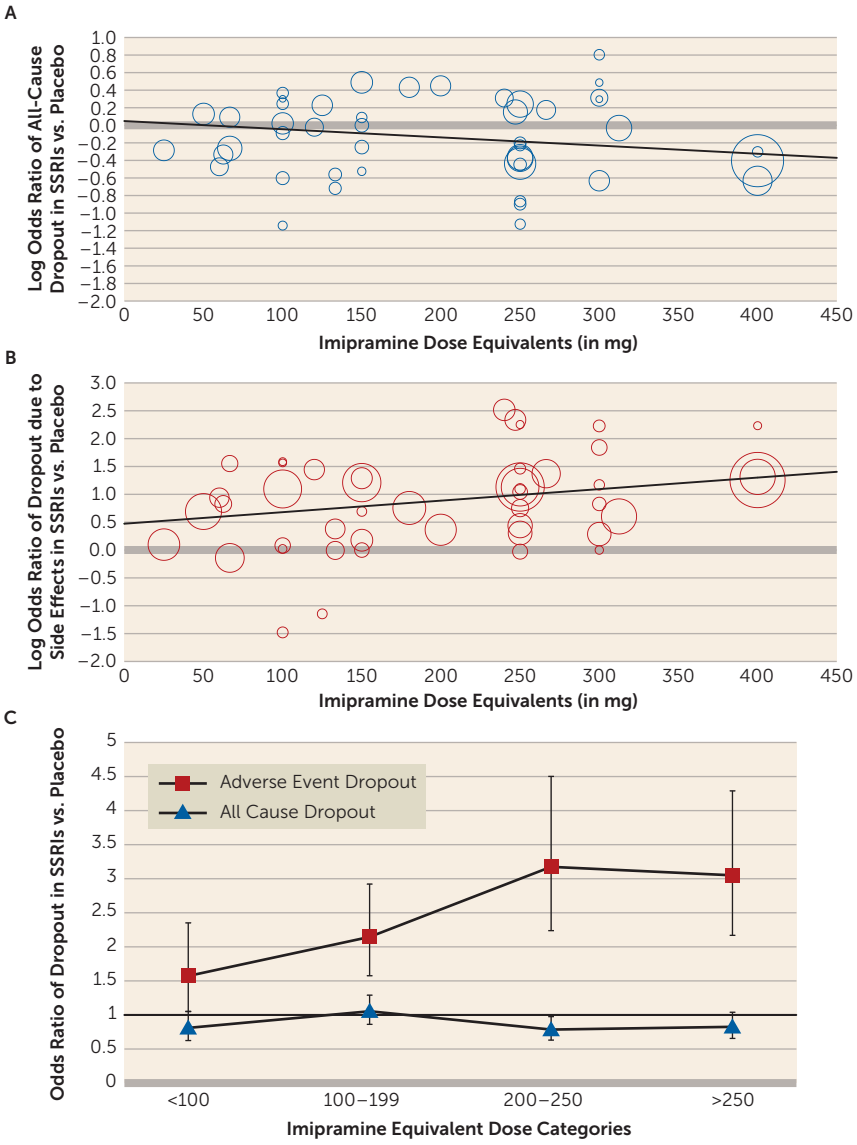


[a] The scatterplot A) depicts the association between SSRI dosage in imipramine equivalents and measured effect size of SSRIs compared with placebo (standardized mean difference). Within the scatterplot, circles represent individual studies, with the size of the circle corresponding to its weight in the meta-analysis. The regression line reflects the significant positive relationship between SSRI dosage and measured efficacy compared with placebo (β=0.00053, 95% CI=0.00018–0.00088, z=2.98, p=0.0029). A graph B) depicts the association between SSRI dose and measured effect size in four dose categories of SSRIs. The four chosen dose categories of SSRIs (<100 mg, 100 mg–199 mg, 200 mg–250 mg, and >250 mg) were based on a meta-analysis that failed to demonstrate a dose-response relationship in antidepressant medications (not exclusively SSRIs). Dosages are expressed in imipramine equivalents (100 mg of imipramine=120 mg of sertraline=100 mg of fluvoxamine=20 mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram). A second scatterplot C) depicts the association between SSRI dosage in imipramine equivalents and response in SSRIs compared with placebo (odds ratio). The regression line reflects the nonsignificant positive relationship between SSRI dosage and response compared with placebo (β=0.00029, 95% CI=−0.00010 to 0.00066, z=1.44, p=0.15). A second graph D) depicts the association between SSRI dose and response in four dose categories of SSRIs.

tolerability. Given this tradeoff between the risks and benefits, another potential prudent clinical strategy is to raise SSRI doses in nonresponders to low-dose treatment. Other systematic reviews have previously examined whether dose-escalation strategies are effective in nonresponders to low-dose antidepressant treatment. A systematic review that examined dose-escalation studies in low-dose SSRI nonresponders suggested that SSRIs have a flat dose-response relationship within the therapeutic range and that higher SSRI doses were only associated with a greater side-effect burden (58). By contrast, a later systematic review that examined the efficacy of dose escalation strategies in SSRI nonresponders suggested a modest benefit (number-needed-to-treat range: 12–82 in trials) of increasing to a higher-dose SSRI if subjects had received previous low-dose SSRI treatment for at least 4 weeks (59). This systematic review suggested that when the dose-escalation strategy was initiated before 4 weeks of SSRI treatment, there was no evidence of benefit to raising SSRI dose on likelihood of treatment response (59). Our results extend upon these previous dose-escalation studies and systematic reviews by demonstrating that the dose-response relationship of SSRI is mildly positive and not flat within the SSRI therapeutic range even when started from the initial point of treatment. Further research is needed to extend upon our results in order to 1) better gauge the risk/benefit of SSRI dose-escalation in low-dose SSRI nonresponders and 2) determine the ideal time point for starting SSRI dose escalation.

Given the potential clinical implications of the results of our meta-analysis, it is important to be clear in its limitations. Publication bias is a well-identified problem in trials involving antidepressant agents (6). We employed a comprehensive search strategy to try to identify all available published and unpublished trials of SSRIs. Given that our meta-analysis examined the difference in efficacy of different doses of SSRIs rather than the overall efficacy of the

FIGURE 4. Relationship Between Selective Serotonin Reuptake Inhibitor (SSRI) Dosage and Likelihood of Dropout[a]



[a] A scatterplot A) of a meta-regression analysis that examines the association between SSRI dose and likelihood of all-cause dropout is shown. Higher SSRI doses were associated with a lower rate of all-cause dropouts (β=−0.00093, 95% CI=−0.00165 to −0.00021), z=−2.54, p=0.0110). A second scatterplot B) of a meta-regression analysis that examines the association between SSRI dose and likelihood of dropout due to side-effects is also shown. Higher doses of SSRIs were associated with a higher rate of dropouts due to side effects (β=0.00207, 95% CI=0.00071–0.00342, z=2.98, p=0.0028). Within the scatterplot, circles represent individual studies, with the size of the circle corresponding to its weight in the meta-analysis. Lines represent the results of meta-regression analysis. A graph C) depicts the association between SSRI dose and all-cause dropouts and dropouts due to side effects in four dose categories. The four chosen dose categories of SSRIs (<100 mg, 100 mg–199 mg, 200 mg–250 mg, and >250 mg) were based on a meta-analysis that did not demonstrate a dose-response relationship in antidepressant medications (not exclusively SSRIs). Dosages are expressed in imipramine equivalents (100 mg of imipramine=120 mg of sertraline=100 mg of fluvoxamine=20 mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram).

underlying therapeutic class, it is not clear how publication bias could have influenced the relationship between SSRI dosing and measured efficacy. Assuming that the positive association between SSRI dose and measured efficacy is true, then publication bias, if present, would likely have dampened our measured association. Publication bias would have likely caused the suppression of negative trials, which based on the findings of this meta-analysis would be more likely to occur at lower SSRI doses, and potentially lead to a reduced measured association between dose and efficacy in the meta-analysis. Other limitations were present in our meta-analysis examining tolerability of SSRI agents at different doses. We would have liked to have analyzed the frequency of different side effects (e.g., .sexual dysfunction, nausea, sedation, etc.) at different SSRI doses. However, measurement and reporting of side effects have changed dramatically over the three decades during which these trials were published. Selective reporting of side effects in earlier manuscripts and changes in how side effects are screened for over time made this analysis not feasible. We would have also liked to examine how timing of dose titration affected likelihood of subject dropout in the trials employing higher SSRI doses, but titration schedules are variably reported in trials. Another general limitation is the generalizability to the community population. Most SSRI trials included in this meta-analysis had strict inclusion criteria. Therefore, many patients seen in typical clinical practice with depression, such as those with significant comorbid medical or psychiatric conditions or taking adjunctive medications, would be specifically excluded from these trials. Clinical patients with additional comorbid illness or concomitant medication use may respond differently to SSRI dose escalation both in terms of efficacy and side effects compared with clinical trials samples (11, 58, 59).

Our meta-analysis provides evidence to support clinical guidelines that recommend raising SSRI dose in adults with major depressive disorder who do not respond to SSRI medications at or below the lower end of the therapeutic

TABLE 1. Evidence-Based Medicine Estimates for Risks and Benefits of Selective Serotonin Reuptake Inhibitor (SSRI) Dosing Strategies for Major Depression[a]

Dose Category (and Daily Dosage)	Placebo		Subtherapeutic SSRI		Low-Dose SSRI	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Actual odds ratio of treatment response						
Subtherapeutic (<100 mg)	1.72	1.44–2.07				
Low-dose (100 mg–199 mg)	2.02	1.69–2.41	1.17	0.98–1.40		
Medium dose (200 mg–250 mg)	2.72	2.08–3.54	1.58	1.17–2.06	1.35	1.00–1.70
High dose (>250 mg)	2.65	2.22–3.17	1.54	1.29–1.84	1.31	1.07–1.52
Estimated odds ratio based on effect size						
Subtherapeutic (<100 mg)	2.23	1.91–2.62				
Low-dose (100 mg–199 mg)	3.16	2.76–3.62	1.42	1.24–1.62		
Medium dose (200 mg–250 mg)	5.07	4.34–5.91	2.27	1.95–2.65	1.60	1.37–1.87
High dose (>250 mg)	3.06	2.65–3.52	1.37	1.18–1.58	0.97	0.84–1.11
	N	Range	N	Range	N	Range
Actual number needed to treat of treatment response						
Subtherapeutic (<100 mg)	8	6–11				
Low-dose (100 mg–199 mg)	6	5–8	27	12–∞		
Medium dose (200 mg–250 mg)	4	3–6	9	6–27	14	8–∞
High dose (>250 mg)	4	4–5	10	7–17	16	10–64
Estimated number needed to treat based on effect size						
Subtherapeutic (<100 mg)	5	4–6				
Low-dose (100 mg–199 mg)	4	3–4	12	9–20		
Medium dose (200 mg–250 mg)	3	2–3	5	4–6	9	7–13
High dose (>250 mg)	4	3–4	13	9–26	No Benefit*	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Actual odds ratio of dropout due to side effects						
Subtherapeutic (<100 mg)	1.56	1.08–2.25				
Low-dose (100 mg–199 mg)	2.22	1.68–2.94	1.42	1.08–1.88		
Medium dose (200 mg–250 mg)	3.16	2.32–4.32	2.02	1.49–2.77	1.42	1.04–1.95
High dose (>250 mg)	3.08	2.29–4.14	1.97	1.47–2.65	1.39	1.03–1.86
Actual odds ratio of all-cause dropout						
Subtherapeutic (<100 mg)	0.82	0.67–1.01				
Low-dose (100 mg–199 mg)	1.09	0.92–1.29	1.33	1.12–1.57		
Medium dose (200 mg–250 mg)	0.80	0.68–0.95	0.98	0.83–1.16	0.73	0.62–0.87
High dose (>250 mg)	0.75	0.64–0.87	0.91	0.78–1.07	0.69	0.59–0.80
	N	Range	N	Range	N	Range
Actual number needed to harm of dropout due to side effects						
Subtherapeutic (<100 mg)	34	16–230				
Low-dose (100 mg–199 mg)	16	10–28	45	22–230		
Medium dose (200 mg–250 mg)	10	7–15	19	11–38	45	20–459
High dose (>250 mg)	10	7–15	20	12–40	48	22–611

[a] The data describe the odds ratios and number needed to treat/harm for SSRI dosing strategies compared with each other and with placebo. Doses are expressed in imipramine equivalents.

dose range. Higher doses of SSRIs are associated with increased efficacy (number needed to treat for treatment response range: 14–16) but also reduced tolerability as evidenced by a higher likelihood of dropouts due to side effects in trials (number needed to harm range: 22–24). However, overall dropout rates were reduced at higher doses of SSRIs, which is likely attributable to their greater efficacy. Further research needs to be performed to examine the ideal timing of dose escalation of SSRIs in major depressive disorder in order to maximize benefit while reducing unnecessary additional side effects caused by higher-dose SSRI treatment.

AUTHOR AND ARTICLE INFORMATION

From the Yale Child Study Center, New Haven, Conn.; the University of Vermont College of Medicine, Burlington, Vt.; Child Study Center and Department of Psychiatry, Yale University, New Haven, Conn.; the Department of Primary Care and Population Health, University College London; and the Department of Psychosis Studies, King's College London.

Address correspondence to Ewgeni Jakubovski (e.jakubovski@gmail.com).

The authors thank Jilian Mulqueen, B.A., and Catherine Coughlin, B.S., for their assistance in the preparation of this article.

Dr. Freemantle has received funding as a consultant for Lundbeck. Dr. Taylor has received compensation as a lecturer and for travel expenses from Bristol-Myers Squibb, Lundbeck, and Otsuka; he has served as a consultant to Sunovion; and a member of his family is an employee of GlaxoSmithKline. Dr. Bloch has received grant support from an American Academy of Child and Adolescent Psychiatry/Eli Lilly Junior Investigator Award, NARSAD, the National Institute of Mental Health (K23MH091240), the Rembrandt Foundation, and the Tourette Syndrome Association, as well as grant UL1 RR024139 from the National Center for Research Resources, a component of the National Institutes of Health, and NIH roadmap for Medical Research; he is also partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. All other authors report no financial relationships with commercial interests.

Received March 13, 2015; revision received June 29, 2015; accepted July 2, 2015; published online November 10, 2015.

REFERENCES

1. Kessler RC, Chiu WT, Demler O, et al: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 617–627
2. Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593–602
3. Gelenberg AJ, Freeman MP, Markowitz JC, et al: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Washington, DC, American Psychiatric Association, 2010
4. NICE: Depression: The Treatment and Management of Depression in Adults. London, National Institute for Health and Care Excellence, 2009
5. Marcus SC, Olfson M: National trends in the treatment for depression from 1998 to 2007. Arch Gen Psychiatry 2010; 67:1265–1273
6. Turner EH, Matthews AM, Linardatos E, et al: Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008; 358:252–260
7. Machado M, Iskedjian M, Ruiz I, et al: Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin 2006; 22: 1825–1837
8. Papakostas GI, Nelson JC, Kasper S, et al: A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. Eur Neuropsychopharmacol 2008; 18: 122–127
9. Entsuah AR, Huang H, Thase ME: Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 2001; 62:869–877
10. Bollini P, Pampallona S, Tibaldi G, et al: Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. Br J Psychiatry 1999; 174:297–303
11. Baker CB, Tweedie R, Duval S, et al: Evidence that the SSRI dose response in treating major depression should be reassessed: a meta-analysis. Depress Anxiety 2003; 17:1–9
12. Bloch MH, McGuire J, Landeros-Weisenberger A, et al: Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Mol Psychiatry 2010; 15:850–855
13. 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; 63:1217–1223
14. Akaike H: A new look at the statistical model identification. IEEE Trans Automat Contr 1974; AC–19:716–723
15. Benkert O, Szegedi A, Wetzel H: Minimum effective dose for antidepressants: an obligatory requirement for antidepressant drug evaluation? Int Clin Psychopharmacol 1996; 11:177–185
16. Centre for Evidence-Based Medicine Toronto: OR to NNT converter. Toronto, KT Clearinghouse
17. Byerley WF, Reimherr FW, Wood DR, et al: Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. J Clin Psychopharmacol 1988; 8:112–115
18. Claghorn JL, Earl CQ, Walczak DD, et al: Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. J Clin Psychopharmacol 1996; 16:113–120
19. Claghorn JL, Kiev A, Rickels K, et al: Paroxetine versus placebo: a double-blind comparison in depressed patients. J Clin Psychiatry 1992; 53:434–438
20. Cohn JB, Wilcox CS: Paroxetine in major depression: a double-blind trial with imipramine and placebo. J Clin Psychiatry 1992; 53(suppl): 52–56
21. Corrigan MH, Denahan AQ, Wright CE, et al: Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 2000; 11:58–65
22. DeRubeis RJ, Hollon SD, Amsterdam JD, et al: Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry 2005; 62:409–416
23. Detke MJ, Wiltse CG, Mallinckrodt CH, et al: Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol 2004; 14:457–470
24. Dominguez RA, Goldstein BJ, Jacobson AF, et al: A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry 1985; 46:84–87
25. Dunbar GC, Claghorn JL, Kiev A, et al: A comparison of paroxetine and placebo in depressed outpatients. Acta Psychiatr Scand 1993; 87: 302–305
26. Edwards JG, Goldie A: Placebo-controlled trial of paroxetine in depressive illness. Hum Psychopharmacol 1993; 8:203–209
27. Fabre L, Birkhimer LJ, Zaborny BA, et al: Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol 1996; 11:119–127
28. Fabre LF: A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. J Clin Psychiatry 1992; 53 (suppl):40–43
29. 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; 25:441–447
30. Feighner JP, Cohn JB, Fabre LF Jr, et al: A study comparing paroxetine placebo and imipramine in depressed patients. J Affect Disord 1993; 28:71–79
31. Feighner JP, Boyer WF, Merideth CH, et al: A double-blind comparison of fluoxetine, imipramine and placebo in outpatients with major depression. Int Clin Psychopharmacol 1989; 4: 127–134
32. Feighner JP, Overø K: Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. J Clin Psychiatry 1999; 60:824–830
33. Feighner JP, Boyer WF: Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry 1992; 53 (suppl):44–47
34. Golden RN, Nemeroff CB, McSorley P, et al: Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. J Clin Psychiatry 2002; 63:577–584
35. Heiligenstein JH, Tollefson GD, Faries DE: A double-blind trial of fluoxetine, 20 mg, and placebo in out-patients with DSM-III-R major depression and melancholia. Int Clin Psychopharmacol 1993; 8: 247–251

36. Kiev A: A double-blind, placebo-controlled study of paroxetine in depressed outpatients. J Clin Psychiatry 1992; 53(suppl):27–29
37. Lepola UM, Loft H, Reines EH: Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2003; 18:211–217
38. Lydiard RB, Laird LK, Morton WA Jr, et al: Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. Psychopharmacol Bull 1989; 25:68–70
39. March JS, Kobak KA, Jefferson JW, et al: A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. J Clin Psychiatry 1990; 51:200–202
40. Mendels J, Kiev A, Fabre LF: Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. Depress Anxiety 1999; 9:54–60
41. Nierenberg AA, Greist JH, Mallinckrodt CH, et al: Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin 2007; 23:401–416
42. Porro V, Fiorenzoni S, Menga C, et al: Single-blind comparison of the efficacy of fluvoxamine versus placebo in patients with depressive syndrome. Curr Ther Res 1988; 43:621–629
43. 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. Journal Clin Psychiatry 1990; 51(suppl B):18–27
44. Rickels K, Amsterdam J, Clary C, et al: A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. Acta Psychiatr Scand Suppl 1989; 350:117–123
45. Roth D, Mattes J, Sheehan KH, et al: A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression. Prog Neuropsychopharmacol Biol Psychiatry 1990; 14: 929–939
46. Rudolph RL, Feiger AD: A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord 1999; 56:171–181
47. Silverstone PH, Ravindran A: Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry 1999; 60:22–28
48. Smith WT, Glaudin V: A placebo-controlled trial of paroxetine in the treatment of major depression. J Clin Psychiatry 1992; 53(suppl): 36–39
49. Sramek JJ, Kashkin K, Jasinsky O, et al: Placebo-controlled study of ABT-200 versus fluoxetine in the treatment of major depressive disorder. Depression 1995; 3:199–203
50. Stahl SM: Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000; 48:894–901
51. Tollefson GD, Holman SL: How long to onset of antidepressant action: a meta-analysis of patients treated with fluoxetine or placebo. Int Clin Psychopharmacol 1994; 9:245–250
52. Trivedi MH, Pigotti TA, Perera P, et al: Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. J Clin Psychiatry 2004; 65:1356–1364
53. Wade A, Michael Lemming O, Bang Hedegaard K: Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002; 17:95–102
54. Walczak DD, Apter JT, Halikas JA, et al: The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. Ann Clin Psychiatry 1996; 8:139–151
55. Perahia DG, Wang F, Mallinckrodt CH, et al: Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry 2006; 21:367–378
56. 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. J Affect Disord 1994; 30:163–173
57. Fabre LF, Abuzzahab FS, Amin M, et al: Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. Biol Psychiatry 1995; 38:592–602
58. Adli M, Baethge C, Heinz A, et al: Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. Eur Arch Psychiatry Clin Neurosci 2005; 255:387–400
59. Ruhé HG, Huyser J, Swinkels JA, et al: Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: systematic review. Br J Psychiatry 2006; 189:309–316