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Less is More in Antidepressant Clinical Trials: A Meta-Analysis of the Effect of Visit Frequency on Treatment Response and Drop-out

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Abstract

Objective—We investigated how the number of follow-up visits affects response rates and drop-out among patients in antidepressant trials for Major Depressive Disorder (MDD).

Data Sources—Medline, PsycINFO, and PubMed were searched to identify trials contrasting antidepressants to placebo or active comparator in adults with depression. The index terms "depression—drug therapy," "depressive disorder—drug therapy," and "antidepressant agents," in addition to the class and individual generic name of all antidepressants were combined using the 'or' operator. Results were limited to 1) English language articles, 2) publication year 1985 or later, 3) age group ≥ 18, and 4) publication types including clinical trials, controlled clinical trials, meta-analysis, multi-center study, randomized controlled trial, or review.

Study Selection—Included articles reported trials of approved antidepressant medications for MDD in outpatients aged 18–65, were 6–12 weeks in duration, and had response rates specified using a standardized measure. Trials were excluded for enrolling inpatients, pregnant women, psychotic subjects, or those with treatment-resistant depression. These criteria allowed 9,189 articles identified in the literature review to be narrowed to 111 reports.

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Data extraction—Demographic characteristics, the number of study visits planned in each treatment cell, duration of active treatment, attrition rates, and response rates to medication and placebo were entered into a database.

Results—In a multilevel meta-analysis, active medication vs. placebo (OR 1.96, $p < 0.001$), active comparator vs. placebo-controlled study design (OR 1.82, $p < 0.001$), and longer vs. shorter duration (OR 1.87, $p < 0.001$) were associated with significantly increased odds of treatment response. After controlling for these variables, the number of study visits did not significantly influence response rates (OR 0.97, $p = 0.877$). The odds of drop-out were significantly decreased for active comparator vs. placebo-controlled trials (OR 0.67, $p = 0.002$) and longer vs. shorter duration trials (OR 0.54, $p = 0.035$), while increasing numbers of study visits significantly increased the odds of participant drop-out (OR 2.77, $p < 0.001$).

Conclusion—Visit schedules that are much more frequent than are commonly practiced in the community treatment of depression may increase the expense of clinical trials and make them less generalizable to standard clinical treatment.

INTRODUCTION

The aim of an antidepressant clinical trial is to test the specific efficacy of a medication to treat Major Depressive Disorder (MDD), but many non-pharmacologic components of antidepressant treatment also influence treatment response.[1] For example, participants in clinical trials receive lengthy screening evaluations and subsequently are followed via visits to a research clinic, where they meet extensively with physicians, nurses, social workers and research assistants. These treatment relationships are thought to be instrumental in helping patients comply with research procedures and may also have significant therapeutic effects.[2]

The high frequency of follow-up visits specified in most antidepressant clinical trials contrasts with antidepressant treatment practices in the community, where 73.6% of patients are treated exclusively by their general medical provider as opposed to a psychiatrist.[3] Less than 20% of patients have a mental health care visit in the first 4 weeks after starting an antidepressant,[4] and fewer than 5% of adults beginning treatment with antidepressant medications have as many as 7 physician visits in their first 12 weeks on the medication.[5] Thus, the administration of antidepressants in clinical trials, which form the evidence base for antidepressant treatments, bears little resemblance to clinical management of depression in the community.

In the single available study investigating the influence of clinic visits on antidepressant and placebo response, Posternak and Zimmerman (2007) calculated the change in depression severity scores over the first 6 weeks of treatment in 41 RCTs of antidepressants for MDD.[6] Studies having 6 weekly assessments (weeks 1–6) were compared to those having 5 (weeks 1–4 and 6) and 4 (weeks 1–2, 4, and 6) assessments. A cumulative therapeutic effect of additional follow-up visits on placebo response was found: between weeks 2 and 6, patients with weekly visits improved 4.24 HRSD points, while those with 1 fewer visit improved 3.33 points and those with 2 fewer visits improved 2.49 points. Participants receiving active medication also experienced more symptom change with increased numbers of follow-up visits, but the relative effect of this increased therapeutic contact was approximately 50% less than that observed in the placebo group. This study was limited by not testing the statistical significance of the differences found and by the restricted data set analyzed (only 41 studies), but the results suggest that visit frequency in an antidepressant trial may influence treatment response.

To better understand the effects of visit frequency, we conducted this multilevel meta-analysis to determine whether visit frequency significantly affects therapeutic response and

drop-out rates in antidepressant clinical trials. We improve upon previous investigations of visit frequency by collecting a much larger study sample, utilizing statistical methods that permit significance testing of the results obtained, and by analyzing drop-out rates in addition to treatment response. We hypothesized that after controlling for the effects of treatment assignment (medication vs. placebo), study type (placebo-controlled vs. active comparator), and study duration, an increasing number of study visits would significantly increase the odds of treatment response and decrease the odds of drop-out for a given study patient.

METHOD

Search strategy and selection criteria

A search of Medline, PsycINFO, and PubMed was conducted to identify RCTs contrasting antidepressants to placebo or active comparator in adults with depression. The index terms "depression—drug therapy," "depressive disorder—drug therapy," and "antidepressant agents," in addition to the class and individual generic name of all antidepressants were combined using the 'or' operator. Limiting these results to 1) English language articles, 2) publication year 1985 or later, 3) age group ≥ 18 (to be inclusive), and 4) publication types including clinical trials, controlled clinical trials, meta-analysis, multi-center study, randomized controlled trial, or review, which yielded 9,189 journal articles. The year 1985 was chosen to select trials utilizing more rigorous methods. Two authors (BRR and TMC) conducted a review of these titles to rule out those which were not clinical trials of antidepressants for depression, resulting in 2,559 titles.

Three judges (BRR, TMC, and SPR) reviewed the 2,559 titles, sequentially proceeding from article title to abstract and finally paper text, to determine whether they met inclusion or exclusion criteria (see Figure 1). These evaluations were pooled, and any differences between judges were resolved by discussion. To further ensure all relevant papers were reviewed, the references of all meta-analyses and review articles published since 2000 among the 9,189 journal articles were searched for pertinent references. In addition, the Cochrane Database of Systematic Reviews was electronically searched using the topic 'antidepressant.' This yielded 136 protocols and completed reviews, each of whose references was reviewed to ensure they were among the reviewed trials.

Inclusion criteria stipulated that articles report RCTs of a Food and Drug Administration (FDA) approved antidepressant medication for Major Depressive Disorder (MDD) in outpatient subjects aged 18–65. While meta-analyses were reviewed to identify studies, only data from individual RCTs were included in the analysis. Further criteria required trials to last between 6 and 12 weeks (inclusive), have comparison group of placebo or another FDA-approved antidepressant medication, be written in English, be published 1985 or later, and have response or remission rates specified using a standardized outcome measurement (e.g., Hamilton Rating Scale for Depression (HRSD)[7], Beck Depression Inventory (BDI)[8], Montgomery-Asberg Depression Rating Scale (MADRS)[9], Clinical Global Impression (CGI)[10]). Trials were excluded for enrolling inpatients, pregnant women, subjects who were psychotic, or those defined to have treatment-resistant depression. Also excluded were antidepressant augmentation studies and trials requiring as inclusion criteria a specific subtype of Major Depression, a specific medical illness, or an Axis I disorder other than depression.

Data extraction

For each included study, demographic characteristics of the participants, details of the treatment condition, duration of active treatment in each study, and response rates to

medication and placebo were entered into a database. We started counting the number of visits proscribed in each study with the initiation of treatment (i.e., we began with the week 1 visit and did not count evaluation or screening appointments). In most cases the visit schedule was stated in the methods section of the publication reporting each study. If this was not explicitly reported, we inferred the visit schedule from the number of data points in figures depicting the trajectory of symptom change over the course of the study. Since there was variability in the criteria different studies used to judge depression response, we standardized the response rate data to the extent that was possible. If studies reported multiple response rates based upon different outcome measures, we selected one response rate for extraction according to the following priority list: HRSD ≥ 50% decrease from baseline, MADRS ≥ 50% decrease from baseline, and CGI Improvement score of 1 or 2. Two judges (BRR and TMC) extracted the data, and any differences were resolved by consensus.

Data analyses

Data analyses followed those successfully implemented in four prior manuscripts, where the procedures are described in greater detail.[11–14] Mixed effects logistic regression models were used, similar to the approach taken by Bryk and Raudenbush,[15] Hox,[16] and Haddock, Rindskopf, and Shadish.[17] The multilevel logistic regression model is described by two equations: a within-studies equation and a between-studies equation, which accommodates the hierarchical structure of patients nested within medication conditions nested within studies. In the first set of models described below, the outcome variable was the reported response rate for each treatment cell (medication and placebo) in the studies comprising the sample.

The initial step was to determine whether there is significant variability in response rates across studies. To do this, we ignored the nesting within study and fit an unconditional model (Model 1). The within-studies equation for Model 1 is

$$\ln(p/[1-p]) = B_0$$

where ln (p/[1-p]) is the log odds of response and B_0 is a constant that is assumed initially to be the same for all groups within a study. At the between-studies level, the equation is

$$B_0 = G_{00} + U_0,$$

which describes the true response rates as varying around a grand mean (G_{00}) with error (U_0). To determine whether there were genuine differences between the studies (heterogeneity) or whether the variation in findings was compatible with chance alone (homogeneity), we examined the Birge ratio, which is calculated by dividing a chi-square by its degrees of freedom.[18] The value of the Birge ratio is near 1 when there is only random variation between studies, and as the value exceeds 1, the results of a set of studies lack homogeneity (i.e., they are more varied than expected based on sampling error alone).[19]

If there is significant variability in response rates across studies (i.e., Birge ratio $\gg 1$), it is possible to test whether the hypothesized predictors of treatment response explain a significant portion of this variability. First, we examined whether receiving active medication vs. placebo significantly influenced the odds of treatment response by including treatment assignment as a fixed effect in the within-studies equation (Model 2):

$$\ln(p/[1-p]) = B_1(\text{active}) + B_0$$

'Active' is a dummy variable coded one for antidepressant medication and zero otherwise. Using this method, odds ratios and estimated probabilities of response to treatment for patients receiving medication as opposed to placebo were computed.

Next, we proceeded to the between-studies level, where we added study type and study duration as fixed effects in the between-studies equation (Model 3):

$$B_0 = G_{00} + G_{01}(\text{comparator}) + G_{02}(\text{duration}) + U_0.$$

'Comparator' is a dummy variable coded one for comparator trials and zero otherwise, and 'duration' is the duration of treatment in each study, centered on the overall mean for duration in the sample. Using this method, odds ratios and estimated probabilities of response to treatment in the different study types and durations were computed. We wished to control for the effects of these variables prior to undertaking our primary analysis of interest given the findings of previous meta-analyses that study type and duration are significant predictors of antidepressant medication and placebo response.[11–12]

Finally, the analysis proceeded to test whether the number of study visits in which patients met with research staff influenced treatment response (Model 4). We added this variable to the between-studies equation, centered on the overall grand mean for number of study visits in our sample:

$$B_0 = G_{00} + G_{01}(\text{comparator}) + G_{02}(\text{duration}) + G_{03}(\text{visits}) + U_0.$$

We anticipated that the number of visits proscribed in an antidepressant clinical trial might be significantly correlated with the duration of treatment. However, we wished to disentangle the effects of study duration (which presumably influences treatment response via true medication effects, true placebo effects, and allowing time for spontaneous improvement) from the frequency of study visits.

Following our analysis of response rates, we conducted an analysis of drop-out rates in the studies comprising our sample. The drop-out analysis followed an identical structure to the response rate analysis, proceeding from an unconditional model (Model 1) to examine the influence of active treatment (Model 2), study type and duration (Model 3), and finally the frequency of follow-up visits (Model 4). All of the regression models were estimated using HLM 6.08. Differences in study characteristics, patient demographics, and clinical features across the different study types were investigated using two-tailed independent samples t-tests for continuous variables and chi-square (χ^2) tests for categorical variables (SPSS version 18).

RESULTS

Characteristics of included studies and participants

One hundred eleven studies comprising 62 placebo-controlled and 49 comparator trials met the inclusion and exclusion criteria (Table 1). As shown in Table 2, these included 126 medication conditions enrolling 13,676 participants in the placebo-controlled studies, 62 placebo conditions enrolling 6,750 participants in the placebo-controlled studies, and 99 medication conditions enrolling 8,734 participants in the comparator studies. Mean response

rates to medication ranged from 25–74% in the placebo-controlled trials and 29–95% in the comparator studies. For the purpose of comparison, mean response rates to placebo in the placebo-controlled trials ranged from 13–56%. Among the comparator trials, 6 out of 49 studies (12.2%) demonstrated significant differences in depression response rates between active treatment groups. Among the placebo-controlled trials, 51 out of 62 studies (82.3%) demonstrated significant differences in depression response rates between medication and placebo. Although we originally intended to analyze remission rates in addition to response rates, there was not sufficient information provided in the publications examined to permit this analysis.

As shown in Table 2, placebo-controlled studies in our sample had more patients per treatment arm ($t = 3.013$, df 285, $p = 0.003$), younger participants ($t = -2.646$, df 246, $p = 0.009$), and higher drop-out rates ($t = 4.468$, df 235 $p < 0.001$) relative to comparator studies, while the mean baseline depression severity score was significantly higher in comparator vs. placebo-controlled studies ($t = -2.646$, df 272, $p = 0.004$). Study duration ranged from 6–12 weeks in both placebo-controlled and comparator studies, and mean study duration was not significantly different between the study types ($t = 1.395$, df 285, $p = 0.164$). The number of study visits ranged from 3–12 in both placebo-controlled and comparator studies and was on average greater in placebo-controlled trials ($t = 6.137$, df 274, $p < 0.001$).

Analysis of response rates

Coefficients and odds ratios for the predictor variables in the models describing treatment response are tabulated in Table 3. In Model 1, the unconditional model of treatment response rates, variability between studies was over 16 times that expected by chance alone (Birge ratio: $\chi^2/df = 1772.6/106 = 16.7$). Therefore, the null hypothesis that response rates are homogeneous across studies was rejected, and the analysis proceeded with the conditional models.

Including treatment assignment (medication vs. placebo) in Model 2 accounted for 24.8% of the variability observed in response rates. The odds of responding to treatment for patients receiving antidepressant medication were 1.96 times higher compared to patients receiving placebo (95% CI 1.82 – 2.10, $p < 0.001$). The average medication response rate derived from Model 2 was 57.6%, compared to an average placebo response rate of 36.7%. In Model 3, including study type (placebo-controlled vs. comparator) and duration reduced the variability in response rates by an additional 40.7%. Across treatment assignments and durations, the odds of responding to treatment in comparator studies were 1.82 times greater vs. placebo-controlled studies (95% CI = 1.54 – 2.15, $p < 0.001$). Controlling for treatment assignment and study type, the odds of treatment response increased 1.87 times for each 1 week increase in study duration above the grand mean of the sample (95% CI = 1.42 – 2.46, $p < 0.001$). No significant interactions between study type and duration were found.

Adding the data on the number of study visits to create the full model (Model 4) did not explain additional variability in response rates over Model 3. Once treatment assignment, study type, and study duration were accounted for, the number of study visits did not significantly influence response rates in our sample (OR 0.97, 95% CI = 0.65 – 1.44, $p = 0.877$). We were interested in determining whether the effect of visit frequency might differ for patients receiving medication compared to placebo (i.e., visit frequency x treatment assignment interaction), but it is not possible to examine interactions between within-study variables (Active) and between-study variables (Visits) using this hierarchical modeling approach. As an alternative, we divided the data set into medication treatment cells and placebo treatment cells, then repeated the above analysis separately for each subset of the data. We found that the same pattern of results obtained for the medication and placebo data sets as was found in the combined sample. Treatment response was higher in comparator vs.

placebo-controlled studies and increased with study duration, but the number of study visits did not significantly influence response.

An additional subgroup analysis performed to assess the robustness of the results obtained was to limit the analyses to Selective Serotonin Reuptake Inhibitors (SSRIs). No change in the pattern of results obtained was found. Based on the rationale that the effect of study visits should be greatest for subjects completing the study (i.e., patients who drop-out are presumably unaffected by more or less visits later in the study), we repeated the analysis using response rate data for study completers rather than the ITT data set. For the 39/112 studies (35.1%) in the sample providing completer data, the duration of the study (OR 4.93, 95% CI = 1.26 – 19.3, p = 0.023) but not the number of visits (OR 0.42, 95% CI = 0.14 – 1.31, p = 0.133) significantly influenced the odds of treatment response.

Analysis of drop-out rates

Coefficients and odds ratios for the predictor variables in the models describing drop-out rates are tabulated in Table 4. In Model 1, the unconditional model of drop-out rates, variability between studies was over 19 times that expected by chance alone (Birge ratio: χ^2/df = 1938.2/98 = 19.7). Therefore, the null hypothesis that drop-out rates are homogeneous across studies was rejected, and the analysis proceeded with the conditional models.

Including treatment assignment (medication vs. placebo) in Model 2 did not account for substantial variability in drop-out rates. The odds of drop-out for patients receiving antidepressant medication were not significantly different from the odds of drop-out for patients receiving placebo (OR 0.96, 95% CI 0.89 – 1.05, p = 0.385). In Model 3, including study type and duration reduced the variability in response rates by 13.0%. Across treatment assignments and durations, the odds of drop-out in comparator studies were 0.67 times the odds in placebo-controlled studies (95% CI = 0.53 – 0.85, p = 0.002). Controlling for treatment assignment and study type, the odds of drop-out were reduced by a factor of 0.54 for each 1 week increase in study duration above the grand mean of the sample (95% CI = 0.30 – 0.96, p = 0.035). No significant interactions between study type and duration were found.

In the full model (Model 4), the number of study visits explained an additional 9.0% of the original variability in drop-out rates. Controlling for treatment assignment, study type, and study duration, the odds of drop-out increased 2.77 times for each 1 visit increase in the number of visits above the grand mean of the sample (95% CI = 1.66 – 4.63, p < 0.001). As in the response rate analyses, we investigated whether the effect of visit frequency on drop-out might differ for patients receiving medication compared to placebo. The pattern of results obtained for the medication and placebo data sets was again similar to the combined sample. The odds of drop-out decreased with increasing study duration (medication only: OR 0.35, 95%CI = 0.19 – 0.66, p = 0.002; placebo only: OR 0.19, 95%CI = 0.069 – 0.537, p = 0.003), whereas the odds of drop-out increased with increasing number of study visits (medication only: OR 2.95, 95% CI = 1.60 – 5.42, p = 0.001; placebo only: OR 1.84, 95% CI = 0.48 – 7.10, p = 0.368).

DISCUSSION

This meta-analysis examined the influence of follow-up visit frequency on treatment response and attrition rates in 111 studies of antidepressant medication for adult outpatients with MDD. Consistent with prior results reported by our group and others, the odds of treatment response in the studies we examined were significantly increased by receiving active medication as opposed to placebo, being in a comparator vs. placebo-controlled study, and being in a longer vs. shorter duration study. Taken together, these predictor variables

explained 65.5% of the variability observed in response rates among the treatment cells in our sample. Contrary to our hypotheses, visit frequency did not significantly influence the odds of response after accounting for treatment assignment, study type, and duration. We were also surprised to find that greater numbers of study visits significantly increased drop-out rates for participants in these antidepressant trials. Thus, for a given type of study and duration of treatment, greater numbers of study visits conferred no advantage in terms of response rates and actually posed a disadvantage to retaining patients in the study.

It has previously been argued that the intensive visit schedules found in antidepressant trials are necessary in order to maintain compliance with the study procedures, prevent dropout, and monitor the safety of participants randomized to placebo.[2] However, our findings suggest that more intense follow-up regimens are actually counterproductive when the goal is to maintain participants within a clinical trial, and this was true for both medication and placebo treatment. It may be the case that some subjects find the weekly visit schedule of many clinical trials to be onerous rather than supportive, making them more rather than less likely to drop-out over the course of the study. Visit schedules that are much more frequent than are commonly practiced in the community treatment of depression also contribute to the ballooning expense of Phase III clinical trials and make them less generalizable to standard clinical treatment. Therefore, decreasing the visit frequency of clinical trials has the potential to decrease the cost of new drug development, improve the retention of patients within studies, and facilitate the practice of evidence-based medicine.

In prior meta-analyses, we have shown that study duration significantly influences response to antidepressant medication,[11–12] but the result that increasing study duration is associated with decreased odds of drop-out was unexpected. This finding contradicts the commonly held view that longer studies typically have higher attrition rates and is consistent with recent reports of low drop-out rates in longer duration studies.[131] One possible explanation is that longer duration studies generally have lower frequencies of follow-up visits than shorter duration studies (e.g., 8-week duration trials in our sample skipped an average of 2.0 ± 1.1 visits, while 12-week duration trials skipped an average of 4.7 ± 1.7 visits). Since increased visit frequency is associated with higher drop-out rates, decreased visit frequency may explain the lower drop-out rates in longer duration studies. There may also be less investigator-initiated drop-out of participants who miss study visits in longer duration studies (i.e., investigators might be more flexible with visit non-compliance when there are greater numbers of study visits). Alternatively, participants may themselves feel reassured by having longer periods of follow-up and be willing to give study medication more time to work if they are not experiencing a positive response early in the study.

The findings that active comparator study designs (relative to placebo-controlled trials) have higher response rates to antidepressant medication and lower drop-out rates were also consistent with previous meta-analyses we have conducted of antidepressant clinical trials.[11–12,14] However, these results were even more striking in the present sample given that patients in the comparator trials had significantly higher baseline depression severity relative to patients in placebo-controlled trials. It may be the case that more severely ill individuals are unwilling to risk the possibility of receiving placebo and prefer to enroll in comparator-type studies. Subjects in comparator trials know they are receiving medications demonstrated to be effective for depression, while participants in placebo-controlled trials are aware they may be taking placebo. Higher expectations of improvement among these individuals in comparator trials may directly increase observed medication response via an enhanced placebo effect and may also lead subjects to form stronger therapeutic alliances, continue treatment during periods of clinical worsening or increased side effects, and report less severe symptoms. Alternatively, lower expectations for therapeutic gain in placebo-

controlled trials may decrease medication response rates in those trials and make enrolled subjects more likely to drop-out in the event of symptom worsening or non-improvement.

Finally, a number of limitations should be considered when interpreting the findings of this study. The use of trial-level summary data limited the data available for analysis in this study, as not all authors reported complete information about patient and trial characteristics in their published article. We were unable to test for associations between patient characteristics and the effects of visit frequency, which are potentially of great clinical interest if different types of patients may respond differently to follow-up visits. Additionally, publication bias may have affected which studies were included in these analyses, since RCTs failing to demonstrate significant differences between medication and placebo may not have been published. In our sample 82% of placebo-controlled trials showed a significant difference between at least one medication cell and placebo, which is higher than would be expected if all clinical trial data were published. However, it is not the efficacy of medication compared to placebo that was investigated in this analysis, so publication bias seems unlikely to have affected the overall patterns of response observed across trials.

A more significant limitation of this study is that we determined the number of visits based upon the designed visit schedule for each study rather than upon the actual number of visits that each participant attended. Missed study visits as well as participant drop-out likely resulted in alterations from the proscribed visit schedule in many cases. We performed analyses of completer data in order to explore for effects of drop-out, but not having access to patient-level data from each study made it the case that we were unable to determine the frequency of protocol violations. Finally, the number of study visits proscribed for a given study duration varied over a relatively modest range (i.e., from 3–8 visits in 8 week duration studies), which limits our ability to extrapolate these results to community settings in which visit frequency may vary even more widely. It is also possible that larger differences in visit frequency may have had a measurable effect on response rates. We believe that these limitations inherent to any retrospective review of visit frequency highlights the need to prospectively evaluate the influence of this variable on therapeutic response and medication/visit compliance in antidepressant clinical trials. Prospectively randomizing patients to different visit schedules would not only allow a more valid assessment of the effects of visit frequency but also may permit determination of patient characteristics moderating these effects.

In summary, results from this meta-analysis indicate that a weekly follow-up visit schedule in antidepressant clinical trials does not appreciably influence response to antidepressant medication or placebo but does significantly increase drop-out rates. Investigators should consider a less frequent visit schedule when designing future clinical trials, which may have the advantages of limiting expense and improving participant retention.

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CLINICAL POINTS

1. Clinicians may be advised to initiate a discussion of follow-up visit frequency with depressed patients at the beginning of treatment in order to integrate their recommendations with patients' expectations and preferences.
2. In the treatment of stable patients, clinicians may opt to evaluate patients every two weeks during the initiation of antidepressant medication and then taper visit frequency to monthly when clinically appropriate and in keeping with a given patient's preferences.

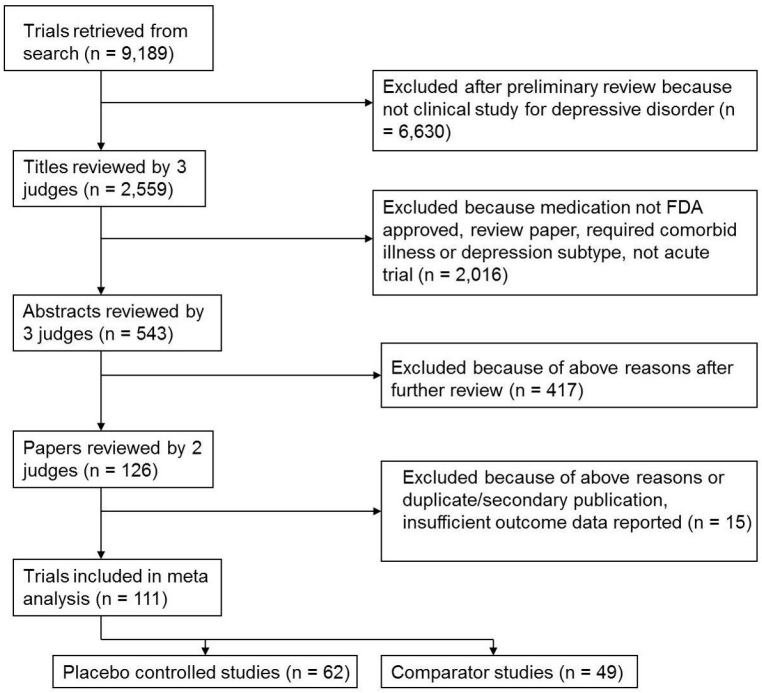

Figure 1.
Literature review and selection of studies.

Table 1

Summary of included studies and participants.

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Alves et al 1999[20]	venlafaxine fluoxetine	40 47	12	HRSD	.85 .75
Amsterdam et al 2003[21]	selegiline placebo	145 144	8	MADRS	.33* .21
Baldwin et al 1996[22]	nefazodone paroxetine	100 95	8	CGI	.55 .61
Beasley et al 1991[23]	fluoxetine trazodone	63 57	6	HRSD	.62 .69
Behnke et al 2003[24]	mirtazipine sertraline	171 168	8	HRSD	.68 .68
Benkert et al 2000[25]	mirtazipine paroxetine	127 123	6	HRSD	.58 .54
Bielski et al 2004[26]	escitalopram venlafaxine XR	97 98	8	HRSD	.61 .48
Bignamini et al 1992[27]	paroxetine amitriptyline	151 152	6	HRSD	.60 .65
Bodkin et al 2002[28]	selegiline TD placebo	88 88	6	HRSD	.33* .20
Bouchard et al 1987[29]	citalopram maprotiline	46 44	6	MADRS	.78 .73
Boyer et al 2008[30]	desvenlafaxine 50 desvenlafaxine 100 placebo	164 158 161	8	HRSD	.65* .63* .50
Burke et al 2002[31]	escitalopram 10 escitalopram 20 citalopram placebo	118 123 125 119		MADRS	.50* .51* .46* .28
Byerly et al 1988[32]	fluoxetine imipramine placebo	32 34 29	6	CGI	.43* .41* .13
Chouinard et al 1999[33]	paroxetine fluoxetine	100 98	12	HRSD	.67 .68
Christiansen et al 1996[34]	paroxetine amitriptyline	71 73	8	CGI	.65 .66

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Claghorn et al 1996[35]	fluvoxamine imipramine placebo	44 44 45	6	CGI	.48* .45* .27
Claghorn et al 1992[36]	paroxetine placebo	163 162	6	CGI	.42* .27
Cohn et al 1996[37]	nefazodone imipramine placebo	39 38 42	8	HRSD	.64* .64* .36
Cohn et al 1985[38]	fluoxetine imipramine placebo	54 54 58	6	HRSD	.72* .42 .30
Coleman et al 1999[39]	buproprion sertraline placebo	118 109 117	8	HRSD	.66 .61 .56
Coleman et al 2001[40]	buproprion fluoxetine placebo	136 146 145	8	HRSD	.56 .57 .50
Cosa e Silva et al 1998[41]	venlafaxine fluoxetine	196 186	8	CGI	.81 .84
Croft et al 1999[42]	buproprion sertaline placebo	116 116 116	8	HRSD	.66* .68* .47
Cunningham et al 1997[43]	venlafaxine venlafaxine XR placebo	92 87 99	12	CGI	.70* .52* .28
Cunningham et al 1994[44]	venlafaxine trazodone placebo	65 73 75	6	HRSD	.72* .60 .55
Dalery et al 2003[45]	fluvoxamine fluoxetine	86 91	6	HRSD	.60 .58
Davey et al 1988[46]	trazodone qd trazodone tid	95 87	6	CGI	.58 .60
DeMartinis et al 2007[47]	desvenlafaxine 100 desvenlafaxine 200 desvenlafaxine 400 placebo	114 116 113 118	8	HRSD	.51* .45 .48* .35
Detke et al 2002[48]	duloxetine placebo	121 115	9	HRSD	.45* .23

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Detke et al 2002[49]	duloxetine placebo	128 139	9	HRSD	.50* .35
Detke et al 2004[50]	duloxetine 80 duloxetine 120 paroxetine placebo	95 93 86 93	8	HRSD	.65* .71* .74* .44
De Wilde et al 1993[51]	paroxetine fluoxetine	37 41	6	HRSD	.68 .63
Debus et al 1988[52]	fluoxetine trazodone	18 17	6	HRSD	.50 .53
Dierick et al 1996[53]	venlafaxine fluoxetine	153 161	8	HRSD	.72* .60
Dunbar et al 1993[54]	paroxetine placebo	138 135	6	HRSD	.52* .22
Dunlop et al 1990[55]	fluoxetine 20 fluoxetine 40 fluoxetine 60 placebo	103 99 97 56	6	HRSD	.40 .40 .35* .26
Dunlop et al 2011[56]	desvenlafaxine placebo	285 142	12	HRSD	.61* .46
Fabre et al 1992[57]	fluvoxamine imipramine placebo	46 48 44	6	HRSD	.52 .52 .33
Fava et al 1998[58]	fluoxetine paroxetine placebo	54 55 19	12	HRSD	.57 .58 .53
Fawcett et al 1989[59]	fluoxetine amitriptyline	19 19	6	HRSD	.75 .78
Feighner et al 1991[60]	buproprion fluoxetine	59 60	6	HRSD	.63 .58
Feighner et al 1993[61]	paroxetine imipramine placebo	240 240 237	6	HRSD	.39* .38* .21
Feighner et al 1999[62]	citalopram 10 citalopram 20 citalopram 40 citalopram 60 placebo	131 130 131 129 129	6	MADRS	.48* .46* .61* .58* .32

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Feiger et al 1996[63]	nefazodone sertraline	71 72	6	HRSD	.59 .57
Feiger et al 2009[64]	desvenlafaxine placebo	117 118	8	HRSD	.39 .31
Fontaine et al 1994[65]	nefazodone low nefazodone high imipramine placebo	46 44 45	6	HRSD	.35 .57* .49* .31
Fournier et al 1997[66]	sertraline imipramine	43 45	8	HRSD	.71 .74
Gentil et al 2002[67]	venlafaxine amitriptyline	57 58	8	HRSD	.75 .76
Golden et al 2002[68]	paroxetine CR paroxetine placebo	206 211 205	12	HRSD	.60* .56 .48
Goldstein et al 2000[69]	duloxetine fluoxetine placebo	66 33 68	8	HRSD	.64 .52 .48
Goldstein et al 2004[70]	duloxetine 40 duloxetine 80 paroxetine placebo	86 91 87 89	8	HRSD	.44 .51* .40 .31
Hewett et al 2009[71]	bupropion XR venlafaxine XR placebo	187 182 197	8	MADRS	.57* .65* .46
Hewett et al 2010[72]	bupropion venlafaxine placebo	202 193 186	8	MADRS	.57 .66* .49
Hicks et al 2002[73]	nefazodone paroxetine	20 20	8	HRSD	.55 .80
Higuchi et al 2011[74]	paroxetine CR paroxetine IR placebo	158 83 171	8	HRSD	.63* .57 .46
Hong et al 2003[75]	mirtazipine fluoxetine	66 66	6	HRSD	.58 .51
Hsu et al 2011[76]	citalopram sertraline	21 21	6	MADRS	.41 .29
Hunter et al 2011[77]	fluoxetine placebo	12 11	8	HRSD	.50 .54

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Kasper et al 2005[78]	trazodone paroxetine	50 53	6	HRSD	.87 .91
Keegan et al 1991[79]	fluoxetine amitriptyline	18 19	6	HRSD	.63 .69
Khan et al 1998[80]	venlafaxine 75 venlafaxine 150 venlafaxine 200 placebo	83 89 81 93	12	HRSD	.52* .52* .60* .33
Khan et al 2007[81]	escitalopram duloxetine	136 126	8	HRSD	.61 .52
Khan et al 2011[82]	vilazodone placebo	231 232	8	HRSD	.44* .33
Lee et al 2007[83]	duloxetine paroxetine	238 240	8	HRSD	.61 .65
Leinonen et al 1999[84]	mirtazipine citalopram	136 133	8	MADRS	.85 .88
Lepola et al 2003[85]	citalopram escitalopram placebo	159 155 154	8	MADRS	.53 .64* .48
Liebowitz et al 2008[86]	desvenlafaxine 50 desvenlafaxine 100 placebo	150 147 150	8	HRSD	.54* .52 .45
Lineberry et al 1990[87]	buproprion placebo	110 106	6	HRSD	.51* .34
Lydiard et al 1989[88]	fluvoxamine imipramine placebo	17 18 17	6	HRSD	.53 .67* .30
Lydiard et al 1997[89]	sertraline amityptiline placebo	132 131 129	8	HRSD	.55* .53* .37
McPartlin et al 1998[90]	venlafaxine XR paroxetine	175 161	12	HRSD	.75 .70
Mehtonen et al 2000[91]	venlafaxine sertraline	75 72	8	HRSD	.73* .59
Mendels et al 1993[92]	venlafaxine low venlafaxine med venlafaxine high placebo	79 76 79 78	6	CGI	.60 .65 .68 .50

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Moller et al 2000[93]	sertraline amitriptyline	100 105	6	HRSD	.51 .68
Montgomery et al 2004[94]	escitalopram venlafaxine XR	146 142	8	MADRS	.77 .80
Moore et al 2005[95]	escitalopram citalopram	138 142	8	MADRS	.76* .61
Nemeroff et al 2007[96]	venlafaxine fluoxetine placebo	96 100 101	6	HRSD	.53* .45 .37
Nierenberg et al 2007[97]	duloxetine escitalopram placebo	273 274 137	8	HRSD	.43* .41 .32
Noguera et al 1991[98]	fluoxetine imipramine	60 60	6	CGI	.83* .50
Ohrberg et al 1992[99]	paroxetine imipramine	65 65	6	HRSD	.46 .39
Ontiveros et al 1997[100]	paroxetine fluoxetine	60 61	6	HRSD	.71 .67
Ou et al 2011[101]	escitalopram citalopram	115 117	6	HRSD	.72 .74
Owens et al 2008[102]	paroxetine CR venlafaxine XR	40 41	8	MADRS	.65 .71
Patris et al 1996[103]	citalopram fluoxetine	153 161	8	MADRS	.78 .76
Perry et al 1989[104]	fluoxetine trazodone	21 19	6	HRSD	.71 .82
Peselow et al 1989[105]	paroxetine imipramine placebo	40 36 42	6	HRSD	.48* .64* .33
Reimherr et al 1990[106]	setraline amitryptiline placebo	142 144 141	8	HRSD	.54* .60* .35
Rickels et al 1985[107]	fluvoxamine qd fluvoxamine bid	90 84	6	HRSD	.52 .52
Rickels et al 1994[108]	nefazodone imipramine placebo	86 86 86	8	HRSD	.52 .36 .31

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Rickels et al 2009[109]	vilazodone placebo	198 199	8	HRSD	.44* .33
Roth et al 1990[110]	fluvoxamine desipramine placebo	27 24 29	6	CGI	.63 .63 .38
Rudolph et al 1998[111]	venlafaxine 75 venlafaxine 225 venlafaxine 375 placebo	77 79 75 92	6	HRSD	.42 .50* .52* .30
Rudolph et al 1999[112]	venlafaxine fluoxetine placebo	95 103 97	8	HRSD	.57 .50 .42
Samuelian et al 1998[113]	venlafaxine clomipramine	52 46	7	HRSD	.59 .43
Sauer et al 2003[114]	venlafaxine amitriptyline	76 75	6	HRSD	.40 .47
Schweizer et al 1994[115]	venlafaxine imipramine placebo	64 71 78	6	HRSD	.60* .37 .35
Septien-Velez et al 2007[116]	desvenlafaxine 200 desvenlafaxine 400 placebo	121 124 124	8	HRSD	.60* .56* .38
Sheehan et al 2009[117]	trazodone placebo	202 204	8	HRSD	.54* .41
Shrivastava et al 1992[118]	paroxetine imipramine placebo	33 36 38	6	HRSD	.42* .25 .26
Smith et al 1992[119]	paroxetine placebo	33 33	6	HRSD	.45* .24
Swann et al 1997[120]	phenelzine desipramine	23 16	6	HRSD	.57 .57
Thase et al 1997[121]	venlafaxine placebo	91 100	8	HRSD	.58* .29
Tourian et al 2009[122]	desvenlafaxine 50 desvenlafaxine 100 duloxetine placebo	148 150 157 160	8	HRSD	.39 .49 .47 .38
Tylee et al 1997[123]	venlafaxine fluoxetine	147 156	12	HRSD	.65 .70

Study	Treatment	N (ITT)	Duration	Outcome measure	Response Rate
Wade et al 2002[124]	escitalopram placebo	188 189	8	MADRS	.55* .42
Wade et al 2007[125]	escitalopram duloxetine	141 146	8	MADRS	.69* .58
Walczak et al 1996[126]	fluvoxamine 25 fluvoxamine 50 fluvoxamine 100 fluvoxamine 150 placebo	144 144 144 144 144	8	HRSD	.42 .50 .59* .58* .38
Weisler et al 1994[127]	buproprion trazodone	59 52	6	HRSD	.56 .42
Wernicke et al 1988[128]	fluoxetine 5 fluoxetine 20 fluoxetine 40 placebo	94 91 92 77	6	HRSD	.46* .50* .48* .23
Wernicke et al 1987[129]	fluoxetine 20 fluoxetine 40 fluoxetine 60 placebo	97 97 103 48	6	HRSD	.39* .44* .30* .19
Yevtushenko et al 2007[130]	escitalopram citalopram 10 citalopram 20	108 106 108	6	MADRS	.95* .44 .83*

* $p < 0.05$ vs. comparison group

Table 2

Clinical characteristics of included patients and methodological features of studies included in the multilevel meta-analysis.

Characteristic	Placebo-Controlled Studies	Comparator Studies
N studies	62	49
N medication treatment groups	126	99
N patients in medication treatment groups	13,676	8,734
N placebo treatment groups	62	0
N patients in placebo treatment groups	6,750	0
Mean age	41.1 ± 2.5	42.1 ± 3.5
Mean drop-out rate	31.8 ± 14.1	24.0 ± 10.2
Mean N ITT[a]	108.9 ± 56.7	88.2 ± 52.3
Mean pre-treatment HRSD[b]	24.6 ± 3.6	26.1 ± 4.8

	N treatment conditions	N patients	N treatment conditions	N patients
Study duration				
6 wks	77	5,999	55	3,592
8 wks	92	12,169	36	4,218
12 wks	4	503	8	924
Study visits				
Weekly	66	4,750	20	1,148
Skip 1 visit	29	3,146	4	589
Skip 2 visits	55	8,088	32	2,611
Skip ≥3 visits	45	4,369	35	3,748
Meds used				
SSRI[c]	53	5,812	54	4,986
SNRI[d]	40	4,700	15	1,762
TCA[e]	16	1,096	12	733
Atypical AD[f]	15	1,835	17	1,230
MAOI[g]	2	233	1	23

[a] ITT = Intent to treat

[b] HRSD = Hamilton Rating Scale for Depression

[c] SSRI = Selective Serotonin Reuptake Inhibitor

[d] SNRI = Serotonin Norepinephrine Reuptake Inhibitor

[e] TCA = Tricyclic antidepressant

[f] Atypical AD = Atypical antidepressant (e.g., bupropion, nefazodone, mirtazipine, trazodone)

[g] MAOI = Monoamine Oxidase Inhibitor

Table 3

Coefficients and odds ratios for predictor variables at each step of the multilevel meta-analysis of response rates.

Variable	Model 1		Model 2		Model 3		Model 4	
	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)
Intercept	−0.018 (0.12)	0.98 (0.77–1.23)	−0.36 (0.70)	0.70 (0.55–0.90)	−0.55 (0.13)	0.57 (0.44–0.75)	−0.61 (0.054)	0.54 (0.49–0.60)
Active	--	--	0.43 (0.066)	1.54* (1.35–1.76)	0.42 (0.066)	1.52* (1.33–1.73)	0.65 (0.035)	1.92* (1.79–2.06)
Comparator	--	--	--	--	0.53 (0.19)	1.69* (1.12–2.55)	0.60 (0.085)	1.81* (1.53–2.15)
Duration	--	--	--	--	0.46 (0.36)	1.57 (0.73–3.39)	0.64 (0.14)	1.89* (1.43–2.50)
Visits	--	--	--	--	--	--	−0.031 (0.20)	0.97 (0.65–1.44)
Variance component	0.235		0.188		0.136		0.142	
X^2	299.9		237.7		147.3		859.7	
df	18		18		16		103	

* $p < 0.05$

Table 4

Coefficients and odds ratios for predictor variables at each step of the multilevel meta-analysis of drop-out rates.

Variable	Model 1		Model 2		Model 3		Model 4	
	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)	Coefficient (SE)	Odds Ratio (CI)
Intercept	−0.99 (0.065)	0.37 (0.33–0.42)	−0.96 (0.075)	0.38 (0.33–0.44)	−0.81 (0.089)	0.45 (0.38–0.53)	−0.85 (0.088)	0.42 (0.36–0.51)
Active	--	--	−0.036 (0.041)	0.96 (0.89–1.05)	−0.026 (0.97)	0.97 (0.90–1.06)	−0.026 (0.041)	0.97 (0.90–1.06)
Comparator	--	--	--	--	−0.40 (0.12)	0.67* (0.53–0.85)	−0.28 (0.11)	0.76* (0.61–0.95)
Duration	--	--	--	--	−0.62 (0.29)	0.54* (0.30–0.96)	−1.11 (0.33)	0.33* (0.17–0.63)
Visits	--	--	--	--	--	--	1.02 (0.26)	2.77 (1.66–4.63)
Variance component	0.391		0.389		0.340		0.305	
X^2	1938.2		1930.65		1620.2		1516.0	
df	98		98		96		95	

* $p < 0.05$