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

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ABSTRACT

Objective: We investigated how the number of follow-up visits affects response rates and dropout 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 classes and individual generic names 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 years, and (4) publication types including clinical trials, controlled clinical trials, meta-analysis, multicenter study, randomized controlled trial, or review.

Study Selection: Included articles reported trials of approved antidepressant medications for MDD in outpatients aged 18–65 years, 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.

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 versus placebo (OR = 1.96, $P < .001$), active comparator versus placebo-controlled study design (OR = 1.82, $P < .001$), and longer versus shorter duration (OR = 1.87, $P < .001$) 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, $P = .877$). The odds of dropout were significantly decreased for active comparator versus placebo-controlled trials (OR = 0.67, $P = .002$) and longer versus shorter duration trials (OR = 0.54, $P = .035$), while increasing numbers of study visits significantly increased the odds of participant dropout (OR = 2.77, $P < .001$).

Conclusions: 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.

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The aim of an antidepressant clinical trial is to test the specific efficacy of a medication to treat major depressive disorder (MDD), but many nonpharmacologic 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 less 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[6] calculated the change in depression severity scores over the first 6 weeks of treatment in 41 randomized controlled trials (RCTs) of antidepressants for MDD. 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 points on the Hamilton Depression Rating Scale (HDRS), 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

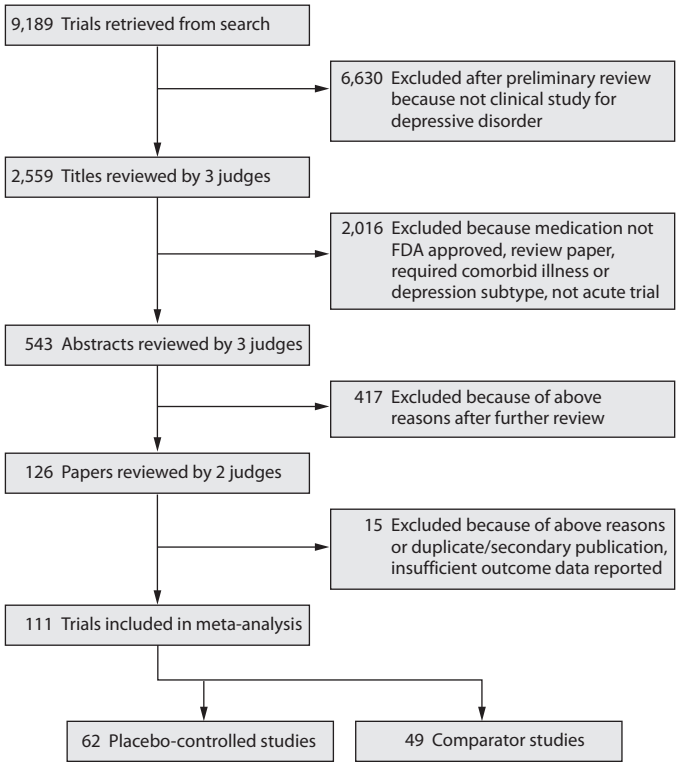
results suggest that visit frequency in an antidepressant trial may influence treatment response.

To better understand the effects of visit frequency, we conducted this multilevel meta-analysis to determine whether visit frequency significantly affects therapeutic response and dropout 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 analyzing dropout 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 dropout for a given study patient.

Clinical Points

- 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.
- In the treatment of stable patients, clinicians may opt to evaluate patients every 2 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



Abbreviation: FDA = US Food and Drug Administration.

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 classes and individual generic names 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 years (to be inclusive), and (4) publication types including clinical trials, controlled clinical trials, meta-analysis, multicenter study, RCT, or review, which yielded 9,189 journal articles. The year 1985 was chosen in order to select trials utilizing more rigorous methods. Two authors (B.R.R. and T.M.C.) conducted a review of these titles to rule out those that were not clinical trials of antidepressants for depression, resulting in 2,559 titles.

Three judges (B.R.R., T.M.C., and S.P.R.) reviewed the 2,559 titles, sequentially proceeding from article title to abstract and finally paper text, to determine whether the articles met inclusion or exclusion criteria (Figure 1). These evaluations were pooled, and any differences between judges were resolved by discussion. To further ensure that 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 search yielded 136 protocols and completed reviews, and for each of these, the references were reviewed to ensure they were among the reviewed trials.

Inclusion criteria stipulated that articles report RCTs of a US Food and Drug Administration (FDA)–approved antidepressant medication for MDD in outpatient subjects aged 18–65 years. 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 (eg, HDRS,[7] Beck Depression Inventory [BDI],[8] Montgomery-Asberg Depression Rating Scale [MADRS],[9] Clinical Global Impressions scale [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 (ie, 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. Because 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 on different outcome measures, we selected 1 response rate for extraction according to the following priority list: HDRS ≥ 50% decrease from baseline, MADRS ≥ 50% decrease from baseline, and CGI-Improvement score of 1 or 2. Two judges (B.R.R. and T.M.C.) extracted the data, and any differences were resolved by consensus.

Data Analyses

Data analyses followed those successfully implemented in 4 prior manuscripts, in which 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 et al.[17] The multilevel logistic regression model is described by 2 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 χ^2 value 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 (ie, they are more varied than expected based on sampling error alone).[19]

If there is significant variability in response rates across studies (ie, Birge ratio $>>1$), 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 versus 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 1 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 1 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 dropout rates in the studies comprising our sample. The dropout 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 (Scientific Software International; Skokie, Illinois). Differences in study characteristics, patient demographics, and clinical features across the different study types were investigated using 2-tailed independent samples *t* tests for continuous variables and χ^2 tests for categorical variables (using SPSS version 18; SPSS Inc; Chicago, Illinois).

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 of 49 studies (12.2%) demonstrated significant differences in depression response rates between active treatment groups. Among the placebo-controlled trials, 51 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, sufficient information was not 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 ($t_{285} = 3.013$, $P = .003$), younger participants ($t_{246} = -2.646$, $P = .009$), and higher dropout rates ($t_{235} = 4.468$, $P < .001$) relative to comparator studies, while the mean baseline depression severity score was significantly higher in comparator versus placebo-controlled studies ($t_{272} = -2.646$, $P = .004$). Study duration ranged from 6 to 12 weeks in both placebo-controlled and comparator studies, and mean study duration was not significantly different between the study types ($t_{285} = 1.395$, $P = .164$). The number of study visits ranged from 3 to 12 in both placebo-controlled and comparator studies and was on average greater in placebo-controlled trials ($t_{274} = 6.137$, $P < .001$).

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; $P < .001$). 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 versus placebo-controlled studies (95% CI, 1.54–2.15; $P < .001$). After 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; $P < .001$). 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; $P = .877$). We were interested in determining whether the effect of visit frequency might differ for patients receiving medication compared to placebo (ie, visit frequency × 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 was obtained for the medication and placebo data sets as was found in the combined sample. Treatment response was higher in comparator versus 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 (ie, patients who drop out are presumably unaffected by more or fewer 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 (34.8%) in the sample providing completer data, the duration of the study (OR = 4.93; 95% CI, 1.26–19.32; $P = .023$) but not the number of visits (OR = 0.42; 95% CI, 0.14–1.31; $P = .133$) significantly influenced the odds of treatment response.

Analysis of Dropout Rates

Coefficients and odds ratios for the predictor variables in the models describing dropout rates are tabulated in Table 4. In Model 1, the unconditional model of dropout rates, variability between studies was over 19 times that expected by chance alone (Birge ratio: $\chi^2/df = 1938.2/98 = 19.7$). Therefore,

Table 1. Summary of Included Studies and Participants

Study	Treatment	n (ITT)	Duration (wk)	Outcome Measure	Response Rate
Alves et al, 1999[20]	Venlafaxine	40	12	HDRS	.85
	Fluoxetine	47			.75
Amsterdam, 2003[21]	Selegiline	145	8	MADRS	.33*
	Placebo	144			.21
Baldwin et al, 1996[22]	Nefazodone	100	8	CGI	.55
	Paroxetine	95			.61
Beasley et al, 1991[23]	Fluoxetine	63	6	HDRS	.62
	Trazodone	57			.69
Behnke et al, 2003[24]	Mirtazapine	171	8	HDRS	.68
	Sertraline	168			.68
Benkert et al, 2000[25]	Mirtazapine	127	6	HDRS	.58
	Paroxetine	123			.54
Bielski et al, 2004[26]	Escitalopram	97	8	HDRS	.61
	Venlafaxine XR	98			.48
Bignamini and Rapisarda, 1992[27]	Paroxetine	151	6	HDRS	.60
	Amitriptyline	152			.65
Bodkin and Amsterdam, 2002[28]	Selegiline transdermal	88	6	HDRS	.33*
	Placebo	88			.20
Bouchard et al, 1987[29]	Citalopram	46	6	MADRS	.78
	Maprotiline	44			.73
Boyer et al, 2008[30]	Desvenlafaxine 50 mg	164	8	HDRS	.65*
	Desvenlafaxine 100 mg	158			.63*
	Placebo	161			.50
Burke et al, 2002[31]	Escitalopram 10 mg	118		MADRS	.50*
	Escitalopram 20 mg	123			.51*
	Citalopram	125			.46*
	Placebo	119			.28
Byerley et al, 1988[32]	Fluoxetine	32	6	CGI	.43*
	Imipramine	34			.41*
	Placebo	29			.13
Chouinard et al, 1999[33]	Paroxetine	100	12	HDRS	.67
	Fluoxetine	98			.68
Christiansen et al, 1996[34]	Paroxetine	71	8	CGI	.65
	Amitriptyline	73			.66
Claghorn et al, 1996[35]	Fluvoxamine	44	6	CGI	.48*
	Imipramine	44			.45*
	Placebo	45			.27
Claghorn et al, 1992[36]	Paroxetine	163	6	CGI	.42*
	Placebo	162			.27
Cohn et al, 1996[37]	Nefazodone	39	8	HDRS	.64*
	Imipramine	38			.64*
	Placebo	42			.36
Cohn and Wilcox, 1985[38]	Fluoxetine	54	6	HDRS	.72*
	Imipramine	54			.42
	Placebo	58			.30
Coleman et al, 1999[39]	Bupropion	118	8	HDRS	.66
	Sertraline	109			.61
	Placebo	117			.56
Coleman et al, 2001[40]	Bupropion	136	8	HDRS	.56
	Fluoxetine	146			.57
	Placebo	145			.50
Costa e Silva, 1998[41]	Venlafaxine	196	8	CGI	.81
	Fluoxetine	186			.84
Croft et al, 1999[42]	Bupropion	116	8	HDRS	.66*
	Sertraline	116			.68*
	Placebo	116			.47
Cunningham, 1997[43]	Venlafaxine	92	12	CGI	.70*
	Venlafaxine XR	87			.52*
	Placebo	99			.28
Cunningham et al, 1994[44]	Venlafaxine	65	6	HDRS	.72*
	Trazodone	73			.60
	Placebo	75			.55
Dalery and Honig, 2003[45]	Fluvoxamine	86	6	HDRS	.60
	Fluoxetine	91			.58
Davey, 1988[46]	Trazodone qd	95	6	CGI	.58
	Trazodone tid	87			.60
DeMartinis et al, 2007[47]	Desvenlafaxine 100 mg	114	8	HDRS	.51*
	Desvenlafaxine 200 mg	116			.45
	Desvenlafaxine 400 mg	113			.48*
	Placebo	118			.35
Detke et al, 2002[48]	Duloxetine	121	9	HDRS	.45*
	Placebo	115			.23
Detke et al, 2002[49]	Duloxetine	128	9	HDRS	.50*
	Placebo	139			.35
Detke et al, 2004[50]	Duloxetine 80 mg	95	8	HDRS	.65*
	Duloxetine 120 mg	93			.71*
	Paroxetine	86			.74*
	Placebo	93			.44
De Wilde et al, 1993[51]	Paroxetine	37	6	HDRS	.68
	Fluoxetine	41			.63
Debus et al, 1988[52]	Fluoxetine	18	6	HDRS	.50
	Trazodone	17			.53

(continued)

Table 1 (continued). Summary of Included Studies and Participants

Study	Treatment	n (ITT)	Duration (wk)	Outcome Measure	Response Rate
Dierick et al, 1996[53]	Venlafaxine	153	8	HDRS	.72*
	Fluoxetine	161			.60
Dunbar et al, 1993[54]	Paroxetine	138	6	HDRS	.52*
	Placebo	135			.22
Dunlop et al, 1990[55]	Fluoxetine 20 mg	103	6	HDRS	.40
	Fluoxetine 40 mg	99			.40
	Fluoxetine 60 mg	97			.35*
	Placebo	56			.26
Dunlop et al, 2011[56]	Desvenlafaxine	285	12	HDRS	.61*
	Placebo	142			.46
Fabre, 1992[57]	Fluvoxamine	46	6	HDRS	.52
	Imipramine	48			.52
	Placebo	44			.33
Fava et al, 1998[58]	Fluoxetine	54	12	HDRS	.57
	Paroxetine	55			.58
	Placebo	19			.53
Fawcett et al, 1989[59]	Fluoxetine	19	6	HDRS	.75
	Amitriptyline	19			.78
Feighner et al, 1991[60]	Bupropion	59	6	HDRS	.63
	Fluoxetine	60			.58
Feighner et al, 1993[61]	Paroxetine	240	6	HDRS	.39*
	Imipramine	240			.38*
	Placebo	237			.21
Feighner and Overø, 1999[62]	Citalopram 10 mg	131	6	MADRS	.48*
	Citalopram 20 mg	130			.46*
	Citalopram 40 mg	131			.61*
	Citalopram 60 mg	129			.58*
	Placebo	129			.32
Feiger et al, 1996[63]	Nefazodone	71	6	HDRS	.59
	Sertraline	72			.57
Feiger et al, 2009[64]	Desvenlafaxine	117	8	HDRS	.39
	Placebo	118			.31
Fontaine et al, 1994[65]	Nefazodone low dose	46	6	HDRS	.35
	Nefazodone high dose	44			.57*
	Imipramine	45			.49*
	Placebo	45			.31
Fournier, 1997[66]	Sertraline	43	8	HDRS	.71
	Imipramine	45			.74
Gentil et al, 2000[67]	Venlafaxine	57	8	HDRS	.75
	Amitriptyline	58			.76
Golden et al, 2002[68]	Paroxetine CR	206	12	HDRS	.60*
	Paroxetine	211			.56
	Placebo	205			.48
Goldstein et al, 2002[69]	Duloxetine	66	8	HDRS	.64
	Fluoxetine	33			.52
	Placebo	68			.48
Goldstein et al, 2004[70]	Duloxetine 40 mg	86	8	HDRS	.44
	Duloxetine 80 mg	91			.51*
	Paroxetine	87			.40
	Placebo	89			.31
Hewett et al, 2009[71]	Bupropion XR	187	8	MADRS	.57*
	Venlafaxine XR	182			.65*
	Placebo	197			.46
Hewett et al, 2010[72]	Bupropion	202	8	MADRS	.57
	Venlafaxine	193			.66*
	Placebo	186			.49
Hicks et al, 2002[73]	Nefazodone	20	8	HDRS	.55
	Paroxetine	20			.80
Higuchi et al, 2011[74]	Paroxetine CR	158	8	HDRS	.63*
	Paroxetine IR	83			.57
	Placebo	171			.46
Hong et al, 2003[75]	Mirtazapine	66	6	HDRS	.58
	Fluoxetine	66			.51
Hsu et al, 2011[76]	Citalopram	21	6	MADRS	.41
	Sertraline	21			.29
Hunter et al, 2011[77]	Fluoxetine	12	8	HDRS	.50
	Placebo	11			.54
Kasper et al, 2005[78]	Trazodone	50	6	HDRS	.87
	Paroxetine	53			.91
Keegan et al, 1991[79]	Fluoxetine	18	6	HDRS	.63
	Amitriptyline	19			.69
Khan et al, 1998[80]	Venlafaxine 75 mg	83	12	HDRS	.52*
	Venlafaxine 150 mg	89			.52*
	Venlafaxine 200 mg	81			.60*
	Placebo	93			.33
Khan et al, 2007[81]	Escitalopram	136	8	HDRS	.61
	Duloxetine	126			.52
Khan et al, 2011[82]	Vilazodone	231	8	HDRS	.44*
	Placebo	232			.33
Lee et al, 2007[83]	Duloxetine	238	8	HDRS	.61
	Paroxetine	240			.65
Leinonen et al, 1999[84]	Mirtazapine	136	8	MADRS	.85
	Citalopram	133			.88
Lepola et al, 2003[85]	Citalopram	159	8	MADRS	.53
	Escitalopram	155			.64*
	Placebo	154			.48
Liebowitz et al, 2008[86]	Desvenlafaxine 50 mg	150	8	HDRS	.54*
	Desvenlafaxine 100 mg	147			.52
	Placebo	150			.45

(continued)

Table 1 (continued). Summary of Included Studies and Participants

Study	Treatment	n (ITT)	Duration (wk)	Outcome Measure	Response Rate
Lineberry et al, 1990[87]	Bupropion	110	6	HDRS	.51*
	Placebo	106			.34
Lydiard et al, 1989[88]	Fluvoxamine	17	6	HDRS	.53
	Imipramine	18			.67*
	Placebo	17			.30
Lydiard et al, 1997[89]	Sertraline	132	8	HDRS	.55*
	Amitriptyline	131			.53*
	Placebo	129			.37
McPartlin et al, 1998[90]	Venlafaxine XR	175	12	HDRS	.75
	Paroxetine	161			.70
Mehtonen et al, 2000[91]	Venlafaxine	75	8	HDRS	.73*
	Sertraline	72			.59
Mendels et al, 1993[92]	Venlafaxine low dose	79	6	CGI	.60
	Venlafaxine medium dose	76			.65
	Venlafaxine high dose	79			.68
	Placebo	78			.50
Möller et al, 2000[93]	Sertraline	100	6	HDRS	.51
	Amitriptyline	105			.68
Montgomery et al, 2004[94]	Escitalopram	146	8	MADRS	.77
	Venlafaxine XR	142			.80
Moore et al, 2005[95]	Escitalopram	138	8	MADRS	.76*
	Citalopram	142			.61
Nemeroff et al, 2007[96]	Venlafaxine	96	6	HDRS	.53*
	Fluoxetine	100			.45
	Placebo	101			.37
Nierenberg et al, 2007[97]	Duloxetine	273	8	HDRS	.43*
	Escitalopram	274			.41
	Placebo	137			.32
Noguera et al, 1991[98]	Fluoxetine	60	6	CGI	.83*
	Imipramine	60			.50
Ohrberg et al, 1992[99]	Paroxetine	65	6	HDRS	.46
	Imipramine	65			.39
Ontiveros, 1997[100]	Paroxetine	60	6	HDRS	.71
	Fluoxetine	61			.67
Ou et al, 2011[101]	Escitalopram	115	6	HDRS	.72
	Citalopram	117			.74
Owens et al, 2008[102]	Paroxetine CR	40	8	MADRS	.65
	Venlafaxine XR	41			.71
Patris et al, 1996[103]	Citalopram	153	8	MADRS	.78
	Fluoxetine	161			.76
Perry et al, 1989[104]	Fluoxetine	21	6	HDRS	.71
	Trazodone	19			.82
Peselow et al, 1989[105]	Paroxetine	40	6	HDRS	.48*
	Imipramine	36			.64*
	Placebo	42			.33
Reimherr et al, 1990[106]	Sertraline	142	8	HDRS	.54*
	Amitriptyline	144			.60*
	Placebo	141			.35
Rickels et al, 1985[107]	Fluvoxamine qd	90	6	HDRS	.52
	Fluvoxamine bid	84			.52
Rickels et al, 1994[108]	Nefazodone	86	8	HDRS	.52
	Imipramine	86			.36
	Placebo	86			.31
Rickels et al, 2009[109]	Vilazodone	198	8	HDRS	.44*
	Placebo	199			.33
Roth et al, 1990[110]	Fluvoxamine	27	6	CGI	.63
	Desipramine	24			.63
	Placebo	29			.38
Rudolph et al, 1998[111]	Venlafaxine 75 mg	77	6	HDRS	.42
	Venlafaxine 225 mg	79			.50*
	Venlafaxine 375 mg	75			.52*
	Placebo	92			.30
Rudolph and Feiger, 1999[112]	Venlafaxine	95	8	HDRS	.57
	Fluoxetine	103			.50
	Placebo	97			.42
Samuelian and Hackett, 1998[113]	Venlafaxine	52	7	HDRS	.59
	Clomipramine	46			.43
Sauer et al, 2003[114]	Venlafaxine	76	6	HDRS	.40
	Amitriptyline	75			.47
Schweizer et al, 1994[115]	Venlafaxine	64	6	HDRS	.60*
	Imipramine	71			.37
	Placebo	78			.35
Septien-Velez et al, 2007[116]	Desvenlafaxine 200 mg	121	8	HDRS	.60*
	Desvenlafaxine 400 mg	124			.56*
	Placebo	124			.38
Sheehan et al, 2009[117]	Trazodone	202	8	HDRS	.54*
	Placebo	204			.41
Shrivastava et al, 1992[118]	Paroxetine	33	6	HDRS	.42*
	Imipramine	36			.25
	Placebo	38			.26
Smith and Glaudin, 1992[119]	Paroxetine	33	6	HDRS	.45*
	Placebo	33			.24
Swann et al, 1997[120]	Phenelzine	23	6	HDRS	.57
	Desipramine	16			.57
Thase, 1997[121]	Venlafaxine	91	8	HDRS	.58*
	Placebo	100			.29
Tourian et al, 2009[122]	Desvenlafaxine 50 mg	148	8	HDRS	.39
	Desvenlafaxine 100 mg	150			.49
	Duloxetine	157			.47
	Placebo	160			.38

(continued)

Table 1 (continued). Summary of Included Studies and Participants

Study	Treatment	n (ITT)	Duration (wk)	Outcome Measure	Response Rate
Tylee et al, 1997[123]	Venlafaxine	147	12	HDRS	.65
	Fluoxetine	156			.70
Wade et al, 2002[124]	Escitalopram	188	8	MADRS	.55*
	Placebo	189			.42
Wade et al, 2007[125]	Escitalopram	141	8	MADRS	.69*
	Duloxetine	146			.58
Walczak et al, 1996[126]	Fluvoxamine 25 mg	144	8	HDRS	.42
	Fluvoxamine 50 mg	144			.50
	Fluvoxamine 100 mg	144			.59*
	Fluvoxamine 150 mg	144			.58*
	Placebo	144			.38
Weisler et al, 1994[127]	Bupropion	59	6	HDRS	.56
	Trazodone	52			.42
Wernicke et al, 1988[128]	Fluoxetine 5 mg	94	6	HDRS	.46*
	Fluoxetine 20 mg	91			.50*
	Fluoxetine 40 mg	92			.48*
	Placebo	77			.23
Wernicke et al, 1987[129]	Fluoxetine 20 mg	97	6	HDRS	.39*
	Fluoxetine 40 mg	97			.44*
	Fluoxetine 60 mg	103			.30*
	Placebo	48			.19
Yevtushenko et al, 2007[130]	Escitalopram	108	6	MADRS	.95*
	Citalopram 10 mg	106			.44
	Citalopram 20 mg	108			.83*

*$P < .05$ vs comparison group.
Abbreviations: CGI = Clinical Global Impressions scale, CR = controlled release, HDRS = Hamilton Depression Rating Scale, IR = immediate release, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, XR = extended release.

Table 2. Clinical Characteristics of Included Patients and Methodological Features of Studies Included in the Multilevel Meta-Analysis

Characteristic	Placebo-Controlled Studies	Comparator Studies
No. of studies	62	49
No. of medication treatment groups	126	99
Patients in medication treatment groups, n	13,676	8,734
No. of placebo treatment groups	62	0
Patients in placebo treatment groups, n	6,750	0
Age, mean ± SD, y	41.1 ± 2.5	42.1 ± 3.5
Dropout rate, mean ± SD, %	31.8 ± 14.1	24.0 ± 10.2
N (ITT), mean ± SD	108.9 ± 56.7	88.2 ± 52.3
Pretreatment HDRS score, mean ± SD	24.6 ± 3.6	26.1 ± 4.8
Study duration (wk)	No. of Treatment Conditions / Patients, n	No. of Treatment Conditions / Patients, n
6	77 / 5,999	55 / 3,592
8	92 / 12,169	36 / 4,218
12	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
Medications used		
SSRI	53 / 5,812	54 / 4,986
SNRI	40 / 4,700	15 / 1,762
TCA	16 / 1,096	12 / 733
Atypical antidepressant[a]	15 / 1,835	17 / 1,230
MAOI	2 / 233	1 / 23

[a]Such as bupropion, nefazodone, mirtazapine, or trazodone.
Abbreviations: HDRS = Hamilton Depression Rating Scale, ITT = intent to treat, MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

the null hypothesis that dropout 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 dropout rates. The odds of dropout for patients receiving antidepressant medication were not significantly different from the odds of dropout for patients receiving placebo (OR = 0.96; 95% CI, 0.89–1.05; $P = .385$). 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 dropout in comparator studies were 0.67 times the odds in placebo-controlled studies (95% CI, 0.53–0.85; $P = .002$). Controlling for treatment assignment and study type, the odds of dropout 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; $P = .035$). 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 dropout rates. Controlling for treatment assignment, study type, and study duration, the odds of dropout 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; $P < .001$). As in the response rate analyses, we investigated whether the effect of visit frequency

Table 3. Coefficients and Odds Ratios for Predictor Variables at Each Step of the Multilevel Meta-Analysis of Response Rates

	Model 1		Model 2		Model 3		Model 4	
Variable	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% CI)
Intercept	0.16 (0.056)	1.17 (1.05–1.31)	−0.38 (0.058)	0.68 (0.61–0.76)	−0.61 (0.053)	0.54 (0.49–0.60)	−0.61 (0.054)	0.54 (0.49–0.60)
Active	…	…	0.67 (0.036)	1.96* (1.82–2.10)	0.65 (0.035)	1.92* (1.79–2.06)	0.65 (0.035)	1.92* (1.79–2.06)
Comparator	…	…	…	…	0.60 (0.084)	1.82* (1.54–2.15)	0.60 (0.085)	1.81* (1.53–2.15)
Duration	…	…	…	…	0.62 (0.14)	1.87* (1.42–2.46)	0.64 (0.14)	1.89* (1.43–2.50)
Visits	…	…	…	…	…	…	−0.031 (0.20)	0.97 (0.65–1.44)
Variance	0.314		0.236		0.140		0.142	
χ^2 component	1,772.6		1,368.9		858.9		859.7	
df	106		106		104		103	

*$P < .05$.

Table 4. Coefficients and Odds Ratios for Predictor Variables at Each Step of the Multilevel Meta-Analysis of Dropout Rates

	Model 1		Model 2		Model 3		Model 4	
Variable	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% CI)	Coefficient (SE)	Odds Ratio (95% 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	0.391		0.389		0.340		0.305	
χ^2 component	1,938.2		1,930.65		1,620.2		1,516.0	
df	98		98		96		95	

*$P < .05$.

on dropout 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 dropout decreased with increasing study duration (medication only: OR = 0.35; 95% CI, 0.19–0.66; $P = .002$; placebo only: OR = 0.19; 95% CI, 0.069–0.537; $P = .003$), whereas the odds of dropout increased with increasing number of study visits (medication only: OR = 2.95; 95% CI, 1.60–5.42; $P = .001$; placebo only: OR = 1.84; 95% CI, 0.48–7.10; $P = .368$).

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 versus placebo-controlled study, and being in a longer duration versus 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 dropout 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 3 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 dropout 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 dropout 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 (eg, 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). Because increased visit frequency is associated with higher dropout rates, decreased visit frequency may explain the lower dropout rates in longer duration studies. There may also be less investigator-initiated dropout of participants who miss study visits in longer duration studies (ie, investigators might be more flexible with visit noncompliance 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 dropout 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 nonimprovement.

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 1 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 on the basis of the designed visit schedule for each study rather than the actual number of visits that each participant attended. Missed study visits, as well as participant dropout, quite likely resulted in alterations from the proscribed visit schedule in many cases. We performed analyses of completer data to explore for effects of dropout, but because we did not have access to patient-level data from each study, 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 (ie, 3–8 visits in 8-week 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 highlight 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 not only would allow a more valid assessment of the effects of visit frequency but also may permit determination of patient characteristics that moderate 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 dropout 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.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others), vilazodone (Viibryd).

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