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Clinic Visits in Late Life Depression Trials: Effects on Signal Detection and Therapeutic Outcome

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Abstract

Objective—This meta-analysis investigated how the supportive care provided in antidepressant clinical trials for late life depression influences response and drop-out rates.

Method—Medline, PsycINFO, and PubMed were searched to identify trials contrasting antidepressants to placebo or active comparator in outpatients aged ≥ 60 years with Major Depressive Disorder (MDD). Hierarchical linear modeling was utilized to determine whether treatment assignment (medication vs. placebo), study type (placebo-controlled or comparator), study duration, and the number of study visits affected response and attrition rates.

Results—In the response rate analysis, a significant interaction was found between study visits and treatment assignment (OR 0.89, $t = -2.186$, $df = 36$, $p = 0.035$), such that each additional visit over the grand mean for the sample increased average placebo response by 2.5% while not significantly affecting medication response. Controlling for other variables, the effect of this interaction was to dramatically decrease average medication vs. placebo differences in trials having greater numbers of study visits. Neither the number of study visits (OR 0.96, $t = -0.468$, $df = 14$, $p = 0.646$) nor the treatment $\times$ visits interaction (OR 1.03, $t = 0.463$, $df = 35$, $p = 0.645$) influenced drop-out rates.

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Conclusion—Increased supportive care in the form of clinic visits leads to greater placebo but not antidepressant medication response in clinical trials for late life depression. Less frequent visit schedules may increase average medication-placebo differences in randomized controlled trials without appreciably increasing drop-out rates.

INTRODUCTION

Rising placebo response rates in clinical trials for many psychiatric disorders hamper efforts to bring new medications to market (1). In the case of Major Depressive Disorder (MDD), the average difference observed in published antidepressant trials between medication and placebo has decreased from an average of 6 points on the Hamilton Rating Scale for Depression (HAM-D) scale in 1982 to 3 points in 2008 (2). Increasing numbers of failed trials in recent years has made developing psychiatric medications progressively more time-consuming and expensive compared to medications for non-psychiatric indications (3). Consequently, several large pharmaceutical companies have reduced or discontinued research and development on medications for brain disorders (4).

The problem of failed trials is particularly acute in late life depression, where many large, well-conducted studies of antidepressant medications have not demonstrated a significant benefit compared to placebo (5). Even among published studies, less than 60% of placebo-controlled trials of antidepressant medications to treat late life depression report a significant drug-placebo difference (6). Consequently, many medications commonly prescribed for late life depression (escitalopram, bupropion, venlafaxine, among others) currently have no evidence for efficacy in geriatric patients.

One study design feature that has been implicated as a contributor to increased placebo response and reduced drug-placebo differences is the intensity of supportive care provided in an antidepressant trial. In adolescents with depression, a greater number of visits during the acute treatment period has been associated with significantly increased placebo response but not medication response (7). Similarly, an analysis of antidepressant clinical trials enrolling adults aged 18–65 years found a cumulative and positive therapeutic effect of additional follow-up visits on placebo response, but the effect of this increased therapeutic contact was approximately 50% less in the medication groups (8). A more recent meta-analysis of follow-up visits in antidepressant trials for adults reported no effect of visits on response rates, and more frequent visits for a given study duration appeared to increase attrition (9). While these data are mixed, they suggest that providing more supportive care to patients participating in an antidepressant clinical trial may have the effect of increasing placebo response and reducing drug-placebo differences.

From a therapeutic perspective, experienced clinical investigators have advocated frequent clinic visits, a multidisciplinary support team, and warm interpersonal contact as critical components of antidepressant clinical trials enrolling elderly patients (10). Individuals with late life depression frequently have medical comorbidities, numerous medications co-administered with antidepressants, and functional limitations that can affect participation in outpatient treatment (11). Interactions with research staff may help patients comply with and tolerate antidepressant treatment in these circumstances, and it is believed that unacceptably

high rates of non-compliance and drop-out would be observed in the absence of such support (12). Moreover, some investigators suggest that the “friendly familiarity” developing between research staff and patients during a trial has therapeutic effects by alleviating the social isolation and lack of community support that often are the case in older depressed patients (10).

Since different clinical management strategies and their relation to adherence and outcome have not been systematically studied in older adults, the objective of this study was to examine the costs and benefits to providing more supportive contact in clinical trials for late life depression. Specifically, we examined the influence of differing numbers of study visits on treatment response and attrition rates in antidepressant clinical trials for adult outpatients aged 60 or older. First, after accounting for other study variables known to influence response and drop-out rates, we hypothesized that we would find evidence for a treatment $\times$ study visits interaction in predicting treatment response. We anticipated that a greater number of study visits would be associated with increased placebo response but not medication response, which would have the effect of decreasing average drug-placebo differences. Second, we hypothesized that we would see a main effect of study visits on attrition, such that a greater number of study visits would be associated with decreased odds of drop-out across treatment conditions.

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 ≥ 60 , and 4) publication types including clinical trials, controlled clinical trials, meta-analysis, multi-center study, randomized controlled trial, or review, yielded 4,317 journal articles. The year 1985 was chosen to select trials utilizing more rigorous methods. Two authors (BRR and JT) conducted a review of these titles to rule out those which were not clinical trials of antidepressants for depression, resulting in 2,832 titles. These titles were sequentially examined from titles to abstracts and finally paper texts, to determine whether they met inclusion or exclusion criteria (see Figure 1).

Inclusion criteria stipulated that articles report an RCT of a Food and Drug Administration (FDA) approved antidepressant medication for Major Depressive Disorder (MDD) in outpatient subjects aged 60 years and older. 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., HAM-D (13), Beck Depression Inventory (BDI) (14), Montgomery-Asberg Depression Rating Scale (MADRS) (15), Clinical Global Impression (CGI) (16)). Trials were excluded for enrolling inpatients, 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). 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: HAM-D 50% decrease from baseline, MADRS 50% decrease from baseline, and CGI Improvement score of 1 or 2.

Data analyses

Data analyses followed those successfully implemented in several prior manuscripts, where the procedures are described in greater detail (6,7,9,17–18). We utilized a hierarchical linear modeling (HLM) approach to accommodate the nested structure of patients within medication conditions within studies (19–21).

First, we examined the heterogeneity in treatment response rates across studies by calculating H and I^2 statistics for an unconditional model. This model consists of a single level 1 (i.e., within study) equation that assumes the log odds of response in each treatment cell among the studies in the sample is equal to a constant. At level 2 (i.e., between studies) this constant can be described as varying around a grand mean with error. The H statistic ($H = \{X^2 / (df - 1)\}$) can be used to measure this variability in response rates, approximating 1 when there is only random variation between studies and progressively exceeding 1 as the results of a set of studies lack homogeneity (22). The I^2 statistic ($I^2 = \{H^2 - 1\} / H^2$) describes the proportion of total variation in response rates that is attributable to heterogeneity (23).

If there was significant variability in response rates across studies (i.e., the 95% confidence interval for H did not include 1), we proceeded to examine whether receiving active medication vs. placebo significantly influenced the odds of treatment response by including treatment assignment as a fixed effect in the level 1 equation. We also included study type (placebo-controlled vs. comparator) and study duration as fixed effects in the level 2 equation to control for the effects of these variables prior to undertaking our primary analysis of interest. Previous meta-analyses have reported that study type and duration are significant predictors of antidepressant medication and placebo response (6,17). Finally, we proceeded to test whether the number of study visits in which patients met with research staff influenced treatment response and whether there was evidence for a treatment $\times$ visits interaction. This yielded the final mixed model continuing a single level 1 predictor, three level 2 predictors, and the cross-level interaction between treatment assignment and visits.

Following our analysis of response rates, we conducted an identical analysis of drop-out rates in the studies comprising our sample. 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 (X^2) tests for categorical variables (SPSS version 20).

RESULTS

Characteristics of included studies and participants

Nineteen studies met the inclusion and exclusion criteria (Table 1). As shown in Table 2, these included 34 medication conditions enrolling 3,555 participants and 11 placebo conditions enrolling 1,854 participants. Mean response rates to medication ranged from 35–77% in these studies, while mean response rates to placebo ranged from 19–52%. Eight studies used an active comparator design, among which 0/8 studies (0%) demonstrated significant differences in depression response rates between treatment groups. Six of 11 placebo-controlled studies (54.5%) 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 treatment cells had significantly lower drop-out rates ($t = -2.673$, $df\ 41$, $p = 0.011$) relative to medication cells. Neither mean patient age ($t = 1.067$, $df\ 40$, $p = 0.292$) nor baseline depression severity score ($t = -0.702$, $df\ 43$, $p = 0.487$) were significantly different between the medication and placebo conditions. Study duration ranged from 6–12 weeks (mean 8.4 ± 2.2) in both placebo and medication treatment conditions and was not significantly different ($t = 0.802$, $df\ 43$, $p = 0.427$). Counting from the week 1 visit onward, the number of study visits ranged from 4–12 (mean 6.6 ± 1.8) in both placebo and medication treatment conditions and was not significantly different ($t = 0.018$, $df\ 41$, $p = 0.986$).

Analysis of response rates

In the unconditional model of treatment response rates, variability was over 4 times greater than expected by chance alone ($H = 4.2$, 95% CI 3.7–4.8), and the proportion of variability in response rates caused by heterogeneity rather than random error was 94% ($I^2 = 0.94$). This was strong evidence for true heterogeneity in response rates among the treatment cells comprising our sample, so the analysis proceeded with the conditional models.

Odds ratios and accompanying statistical tests for the predictor variables in the full models of treatment response rates are tabulated in Table 3. Assignment to medication vs. placebo accounted for 20.0% of the variability observed in response rates. Participants receiving antidepressant medication were significantly more likely to be responders compared to patients receiving placebo. Including study type (placebo-controlled vs. comparator) accounted for an additional 17.4% of the variance in response rates. Across treatment assignments and durations, the odds of responding to treatment in comparator studies were

significantly greater vs. placebo-controlled studies. In contrast, study duration was not a significant predictor of treatment response.

In the full mixed model, study visits and the active * visits interaction term explained an additional 8.5% of the original variability in response rates (sum variance explained 46.0%). Controlling for other variables, there was a significant interaction found between study visits and treatment assignment, while the number of study visits did not have a significant main effect on response rates. This interaction indicates that study visits had an effect on response rates that was dependent on whether a patient received medication or placebo. For each additional visit over the grand mean for the sample, average placebo response increased by 2.5%, while medication response remained approximately the same. Consequently, increasing the number of study visits for a given study duration has the effect of decreasing the average medication vs. placebo difference in response rates, with this difference entirely disappearing at higher visit frequencies.

To further investigate the robustness of these results, we divided the data set into medication cells in comparator trials, medication cells in placebo-controlled trials, and placebo cells in placebo-controlled trials and then repeated the above analyses of visit frequency. The pattern of results obtained was similar to the findings reported for the overall sample. Increasing visit frequency resulted in significantly increased placebo response in placebo-controlled trials (OR 1.35, $t = 6.140$, $df = 7$, $p < 0.001$) but had less influence on medication response (OR 1.18, $t = 2.165$, $df = 8$, $p = 0.062$ in placebo-controlled trials; OR 0.90, $t = -0.936$, $df = 5$, $p = 0.393$ in comparator trials). There was no significant effect of study duration on treatment response in any of the subgroups.

Analysis of drop-out rates

In the unconditional model of drop-out rates, variability between studies was nearly 3 times that expected by chance alone ($H = 2.9$, 95% CI 2.4–3.5), and the proportion of variability in drop-out rates caused by heterogeneity rather than random error was 88% ($I^2 = 0.88$). This result indicated true heterogeneity existed in drop-rates, so the analysis proceeded to examine the influence of predictor variables on drop-out rates.

As above, odds ratios and accompanying statistical tests for the predictor variables in the full models of treatment drop-out rates are tabulated in Table 3. Treatment assignment (medication vs. placebo) accounted for 15.6% of the variability in drop-out rates, and the odds of drop-out for patients receiving antidepressant medication were significantly greater than the odds of drop-out for patients receiving placebo. Including study type accounted for an additional 15.6% of the variance in drop-out rates. Across treatment assignments and durations, the odds of drop-out in comparator studies exhibited a trend toward being greater than the odds in placebo-controlled studies. No influence of study duration on drop-out rates was found, nor were any significant interactions between study type and duration were found.

In the full model, 'visits' and the 'active $\times$ visits' interaction term did not explain any additional variability in drop-out rates. Controlling for treatment assignment, study type, and study duration, the number of study visits did not have a significant main effect on drop-out

rates, and there was not a significant interaction between treatment assignment and study visits.

DISCUSSION

In this examination of the supportive care provided in antidepressant trials for late life depression, the primary finding was that offering patients more clinic visits significantly increased placebo response while leaving medication response generally unaffected. The effect of this treatment assignment $\times$ visits interaction was to dramatically decrease average medication vs. placebo differences with increasing visit frequency. For a given 12 week duration placebo-controlled study, providing 6 clinic visits resulted in an average medication response rate of 51.7% and placebo response rate of 39.5% (see Figure 2). Providing 8 clinic visits for the same duration study decreased the average medication response rate to 50.7% and increased placebo response to 44.4%, while providing 10 clinic visits resulted in a medication and placebo response of 49.7 and 49.3%, respectively. Thus, intensifying supportive care from 6 to 10 visits over 12 weeks resulted in a reduction of the average medication/placebo difference from 12.2% to 0.4%.

These results suggest that in the drug development setting it may be advisable to limit the frequency of visits proscribed in order to facilitate signal detection. There was no indication in the analyses reported that reducing study visits jeopardized retention of patients within studies, as there was no benefit of additional clinic visits on drop-out rates. It is certainly possible that intensive follow-up regimens characterized by frequent appointments, warm interpersonal relationships with health care staff, and family member involvement may benefit participants in late life depression trials, but decreased drop-out rates do not appear to be among these benefits.

The significance of these findings for the clinical treatment of patients with late life depression is more complex. While less frequent visit schedules in the RCTs we examined did not appear to have negative consequences for treatment outcome, the intensive follow-up provided in clinical trials is much greater than what depressed patients typically receive in the community (44–46). The least intensive visit schedule in a late life depression trial still entails more frequent follow-up than what most patients prescribed antidepressants receive in the community. For this reason our findings would not justify decreasing the frequency of visits provided in clinical practice, particularly since empirical support exists for the clinical benefits of adding collaborative care to treatment as usual for depressed patients treated in primary care settings (47).

In fact, the optimal clinical management strategy for depressed older patients receiving antidepressants is unknown, and the question compels further study. Given that patient characteristics have been reported to moderate placebo response (48), it seems likely that clinical and demographic variables affect how depressed patients respond to differing visit frequencies. Prospective, randomized studies of different visit schedules may allow patients who are likely to respond to more frequent therapeutic contact regimens to be differentiated from those who are not. Such information would facilitate the development cost-effective, personalized treatment strategies tailored to the needs of individual patients, which would

represent an improvement over the prevailing view of antidepressant clinical management as a “one-size-fits-all” intervention.

Data from this study are also germane to the important question of how to conceptualize the contribution of placebo response to medication response in psychopharmacologic treatments. The simplest model of this combination is to assume that medication effects are additive with placebo response (i.e., if placebo response in a clinical trial is 30% and medication response is 50%, then the specific effects of the medication account for $50\% - 30\% = 20\%$ of the observed response). This “assumption of additivity” would lead one to predict that visit frequency should contribute equally to medication and placebo response, resulting in no net change in medication-placebo differences with increasing visit frequency (49). At first glance, our results appear inconsistent with this assumption, since more study visits increased placebo but not medication response. However, this discrepancy might be explained by the presence of a group of patients in the studies examined who would not respond to medication or placebo and thus place a ceiling on medication response in an antidepressant clinical trial. An increase in placebo response beyond a certain threshold would then be expected to cause a corresponding decrease in the medication-placebo difference, which is what we found.

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, and we were unable to test for associations between patient characteristics and the effects of visit frequency. 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. 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, and 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. These limitations inherent to any retrospective review of visit frequency again highlight the need to prospectively evaluate the influence of this variable on therapeutic response in antidepressant clinical trials.

In summary, results from this meta-analysis indicate that more frequent follow-up visit schedules in antidepressant clinical trials enrolling older adults significantly increase placebo response and reduce observed medication vs. placebo differences. Both practicing clinicians as well as clinical researchers should consider tailoring follow-up visit frequency to the needs of the treatment context as well as the patient population being served.

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Figure 1.
Literature review and selection of studies.

Figure 2. a–b. Effect of differing study visits on medication and placebo response rates and the average medication vs. placebo difference

Response rates are estimated for a hypothetical 12 week duration, placebo-controlled trial using parameter estimates from the final hierarchical linear model.

Table 1

Summary of included studies and participants.

Study	Treatment	N (ITT)	Duration	Outcome Measure	Response Rate
Bondareff et al. 2000 (24)	sertraline	104	12	HRSD	.52
	nortriptyline	104			.41
Boseetal. 2008 (25)	escitalopram	129	12	HRSD	.46
	placebo	134			.38
Feighner & Conn 1985 (26)	fluoxetine	78	7	CGI	.49
	doxepin	79			.48
Forlenza et al. 1985 (27)	fluoxetine	28	6	MADRS	.61
	doxepin	27			.56
Guillibert et al. 1989 (28)	paroxetine	40	4	HRSD	.65
	clomipramine	39			.72
Hewettetal. 2010 (29)	bupropion	211	6	MADRS	.53
	placebo	207			.43
Hutchinson et al. 1992 (30)	paroxetine	58	7	HRSD	.60
	amitriptyline	32			.56
Kasper et al. 2005 (31)	escitalopram	173	4	MADRS	.46
	fluoxetine	164			.37
	placebo	180			.47
Nair et al. 1993 (32)	trimipramine	18	5	CGI	.67
	doxepin	19			.53
Newhouse et al. 2000 (33)	sertraline	116	8	HRSD	.73
	fluoxetine	118			.71
Rapaport et al. 2003 (34)	paroxetine CR	104	8	CGI	.72*
	paroxetine IR	106			.65*
	placebo	109			.52
Rapaport, et al. 2009 (35)	paroxetine 12.5mg	163	7	HRSD	.52*
	paroxetine 25mg	173			.58*
	placebo	179			.40
Raskin et al. 2007 (36)	duloxetine	207	4	HRSD	.37*
	placebo	104			.19
Roose et al. 2004 (37)	citalopram	84	7	HRSD	.41
	placebo	90			.38

Study	Treatment	N (ITT)	Duration	Outcome Measure	Response Rate
Schatzberg et al. 2002 (38)	mirtazapine	126	6	HRSD	.58
	paroxetine	120			.50
Schatzberg and Roose 2006 (39)	venlafaxine	93	6	HRSD	.44
	fluoxetine	99			.39
	placebo	96			.42
Schneider et al. 2003 (40)	sertraline	360	5	HRSD	.35*
	placebo	368			.26
Schweizer et al. 1998 (41)	imipramine	60	8	HRSD	.62*
	bupirone	54			.52*
	placebo	58			.36
Tollefson et al. 1995 (42)	fluoxetine	326	6	HRSD	.44*
	placebo	329			.32
Weihs et al. 2000 (43)	bupropion	48	6	HRSD	.71
	paroxetine	52			.77

* denotes $p < 0.05$ vs. comparator or placebo

Table 2

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

Characteristic	Assigned to medication	Assigned to placebo
N treatment groups	34	11
N patients	3,555	1,854
Mean age	70.3 $\pm$ 2.8	71.5 $\pm$ 3.5
Mean drop-out rate	28.4 $\pm$ 9.8*	20.1 $\pm$ 5.3*
Mean pre-treatment HRSD ^a	24.7 $\pm$ 2.6	24.1 $\pm$ 2.8

	N treatment conditions	N patients	N treatment conditions	N patients
Study duration				
6 wks	11	632	1	329
8 wks	13	1,595	6	896
10 wks	3	547	2	386
12 wks	7	781	2	243
Study visits				
6	17	1,692	4	897
7	5	760	4	610
8	10	1,103	3	347
Meds used				
SSRI ^b	20	2,516	0	0
SNRI ^c	2	344	0	0
TCA ^d	8	246	0	0
Atypical AD ^e	4	439	0	0

*
t = -2.673, df41, p = 0.011

^aHRSD = Hamilton Rating Scale for Depression

^bSSRI = Selective Serotonin Reuptake Inhibitor

^cSNRI = Serotonin Norepinephrine Reuptake Inhibitor

^dTCA = Tricyclic antidepressant

^eAtypical AD = Atypical antidepressant (e.g., bupropion, nefazodone, mirtazapine, trazodone)

Table 3

Multilevel meta-analysis of response and drop-out rates.

Variable	Response rates				Drop-out rates			
	OR(CI)	t	df	p	OR(CI)	t	df	p
Active	1.52 (1.33–1.74)	6.330	36	< 0.001	1.26 (1.08–1.48)	3.025	35	0.005
Comparator	1.70 (1.14–2.55)	2.809	15	0.014	1.49 (0.98–2.25)	2.054	14	0.059
Duration	1.06 (0.94–1.19)	1.056	15	0.308	1.02 (0.91–1.15)	0.388	14	0.703
Visits	1.11 (0.93–1.42)	1.288	15	0.217	0.96 (0.80–1.15)	–0.468	14	0.646
Active * Visits	0.89 (0.79–0.99)	–2.186	36	0.035	1.03 (0.91–1.17)	0.463	35	0.645

This table provides odds ratios and statistical tests for the predictor variables examined in the full model of treatment response and drop-out rates. 'Active' is a dummy variable coded one for antidepressant medication and zero otherwise. The odds ratio associated with 'Active' represents the odds of treatment response (or drop-out) for patients receiving medication compared to placebo, controlling for other study variables. 'Comparator' is a dummy variable coded one for comparator trials and zero otherwise, making the odds ratio associated with 'Comparator' the odds of treatment response in a comparator trial relative to a placebo-controlled trial. 'Duration' is the duration of treatment in each study, centered on the overall mean for duration in the sample (mean duration = 8.4 ± 2.2 weeks). 'Visits' denotes the number of clinic visits in each study, centered on the overall mean for visits in the sample (mean visits = 6.6 ± 1.8). The odds ratios associated with 'Duration' and 'Visits' provide the odds of response for 1 additional week duration or 1 additional visit over the grand mean for the sample, respectively, relative to the odds of response for the mean duration or number of visits.