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Relationship of Number of Clinic Visits to Response during Placebo-Controlled Antidepressant Trials in Late Life Depression

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Abstract

Objectives: To determine if the number of clinic visits affects placebo or drug response in antidepressant trials of late life major depression.

Method: A previous systematic review of placebo-controlled antidepressant trials in late life depression was updated. Selected trials randomized patients to antidepressant or placebo and included community dwelling patients aged 60 and older, with Major Depressive Disorder. The association of number of visits with response in the placebo and drug groups was examined adjusting for trial duration and the duration-visit interaction. Regressions were also performed to determine if the relationship between number of visits and response differed between treatment groups and to assess if lifetime duration of MDD influenced the visit-response relationship in the placebo group.

Results: Thirteen trials with 5028 patients were selected. After controlling for trial duration, number of visits was significantly associated response in the placebo group ($\chi2=4.69$, $p=0.03$) but not the drug group ($\chi2=0.38$, $p=0.54$); however, the association of response and number of visits did not differ significantly between the drug and placebo groups. Response rates appeared to increase with more visits in each group.

Conclusions: In late life depressed patients response rates increase with more frequent visits during placebo administration. Although this association was not significant in the group receiving antidepressants and clinical management, analysis of the interaction of several variables is limited by the small number of trials and we would be cautious about concluding that number of visits does not contribute to drug response.

Keywords: Antidepressants; Drug-placebo; Severity; Psychotherapy; MDD illness; MADRS

Introduction

Antidepressants are the mainstay of treatment for late life depression. Since their introduction, second generation agents have become most commonly employed. A meta-analysis of 10 placebo-controlled studies of second generation antidepressants in patients 60 years and older with major depression found that antidepressants were significantly more effective than placebo, but drug-placebo differences were modest with a number-needed-to-treat of 11 [1]. The magnitude of the drug-placebo difference is less than reported for in mixed aged samples [2]. The modest drug effect is in part related to high placebo response rates. A subsequent individual patient level meta-analysis [3] found very high rates of placebo-response in older depressed patients whose lifetime duration of depression was less than 2 years. In these patients the drug response rate barely exceeded the placebo rate (51.5% vs. 47.7%). Alternatively patients with a long history of MDD and at least moderate depression severity had robust drug effects (NNT=4).

Because placebo response plays such an important role in late life depression, understanding the factors that contribute to placebo response is important whether the aim is improving clinical treatment or designing clinical trials. The supportive care that is part of clinical management likely plays an important role in placebo response. In a recent meta-analysis of psychotherapy studies in late life depression we found that the magnitude of change within placebo control groups and supportive therapy control groups was substantial (Effect Size =0.9 and 1.1 respectively) while change within waitlist controls was minimal (Effect Size=0.11) [4]. We suspect that the supportive elements of supportive therapy and clinical management plus placebo explain the much larger effect of these active control groups.

Rutherford et al. [5] recently examined factors that might explain placebo response in late life depression. They hypothesized that the supportive care provided during trial visits would enhance response. In an analysis controlling for trial duration, they found response rates increased significantly with increasing number of visits in the placebo group but not the drug group. They also suggested that drug-placebo differences would become smaller as the number of visits increased. They hypothesized that trials with many clinic visits might have difficulty detecting antidepressant effects. Their work begins to address the important question of whether response to antidepressants is simply the additive effect of placebo, clinical management, and specific drug effects or the result of a more complex interaction in the drug group.

We undertook the current study to replicate the findings of Rutherford et al. but with an important difference in trial selection. We limited trials to those that randomized patients to drug and placebo. Rutherford et al. included comparison trials of two active drugs without a placebo along with placebo controlled trials. We

reasoned that examination of factors contributing to differences between drug and placebo response required randomization of patients to drug and placebo in order to account for other factors present in the samples that might influence outcome. Because lifetime duration of MDD illness affects placebo response rates, we also examined if the association of number of visits with response to placebo and clinical management varied in relation to lifetime duration of MDD. We hypothesized that because patients with a short lifetime history are more responsive to placebo and clinical management, they would show a greater effect of number of visits.

Methods

We previously performed a systematic search of the literature for placebo-controlled trials of second generation antidepressants in community dwelling patients aged 60 and older with major depression. [1] That search, reported previously, found 10 trials published before 2011. For the current study we conducted another search for randomized placebo-controlled trials of antidepressants published since the prior review and expanded the search to include all randomized placebo-controlled antidepressant trials in similarly defined samples. Like Rutherford et al. [5] we limited trials to those using FDA approved antidepressants and published since 1985 in order to ensure relatively comparable diagnostic definitions and study methods. Details of the methods for the prior search have been previously reported [1].

In the current study response was defined as 50% or greater improvement on the Hamilton Depression Rating Scale (HDRS) [6] or, if that was not available, on the Montgomery Asberg Depression Rating Scale (MADRS) [7] The number of visits was defined by each study protocol and included the screening visit, a baseline visit, and visits during the treatment phase of the trial. The trial duration was defined as the number of weeks of treatment. In trials with two drug arms, the drug groups were combined.

Statistical analysis: We first examined the correlation of number of visits with response rates, defined as the proportion in each study responding, weighted for sample size in each treatment group. We then examined the independent associations of number of visits, trial duration, and the visits-duration interaction with response rates in the placebo group and the drug treatment group using linear regression analysis. Number of visits, trial duration, and the visit-trial duration interaction were also entered in a single regression including both drug and placebo treated patients and with response as the dependent outcome. This analysis included a term for the treatment group and the interaction of number of visits with treatment group.

Next we determined if lifetime history of MDD interacted with the association of number of visits and response in the placebo group. Individual patient data for age of onset and response were previously obtained for 7 of the 13 trials, which included 2335 patients [3]. Lifetime duration of MDD was determined (current age-age of onset) and used to divide the sample into tertiles (lifetime duration <2 years, 2-10 years, and >10 years). We estimated and tested a regression model including number of visits, trial duration, lifetime duration of MDD, and the number of visits-lifetime duration interaction with response as the dependent outcome for the placebo group.

Results

In addition to the 10 trials identified in the previous search,[8-17] we found two additional trials in late life depressed patients published

since the prior review [18,19] and one placebo-controlled trial of imipramine meeting inclusion criteria [20].

Authors, year	MDD	Minimum Age, years	Trial Duration, weeks	Number of Visits	Treatment Group	Number of subjects
Tollefson et al. 1995 [8]	DSM III-R	≥ 60	6	8	Fluoxetine	325
					Placebo	329
Schweizer et al. 1998 [20]	DSM III-R	≥ 65	8	8	Imipramine	60
					Placebo	58
Schneider et al. 2003 [9]	DSM IV	≥ 60	8	6	Sertraline	360
					Placebo	368
Rapaport et al. 2003 [10]	DSM IV	≥ 60	12	10	Paroxetine CR	103
					Paroxetine IR	103
					Placebo	109
Roose et al. 2004 [11]	DSM IV	≥ 75	8	9	Citalopram	84
					Placebo	90
Kasper et al. 2005 [12]	DSM IV	≥ 65	8	8	Escitalopram	170
					Fluoxetine	164
					Placebo	180
Schatzberg et al. 2006 [13]	DSM IV	≥ 65	8	8	Venlafaxine IR	93
					Fluoxetine	99
					Placebo	96
Raskin et al. 2007 [14]	DSM IV	≥ 65	8	7	Duloxetine	201
					Placebo	102
Bose et al. 2008 [15]	DSM IV	≥ 60	12	9	Escitalopram	129
					Placebo	134
Rapaport et al. 2009 [16]	DSM IV	≥ 60	10	9	Paroxetine CR 12.5 mg/d	163
					Paroxetine CR 25 mg/d	173
					Placebo	179
Hewett et al. 2010 [17]	DSM IV	≥ 65	10	9	Bupropion XL	207
					Placebo	203
Katona et al. 2012 [18]	DSM IV-TR recurrent	≥ 65	8	7	Vortioxetine	156
					Duloxetine	151

					Placebo	145
Robinson et al. 2014 [19]	DSM IV-TR recurrent	≥ 65	12	7	Duloxetine	204
					Placebo	95

Table 1: Trial characteristics of placebo-controlled random assignment trials of second-generation antidepressants in community dwelling older patients with nonpsychotic, unipolar Major Depressive Disorder

These 13 trials included 5028 patients of whom, 2942 received an antidepressant plus clinical management and 2086 received placebo plus clinical management (Table 1). Number of visits ranged from 6 to 10. Trial duration ranged from 6 to 12 weeks.

Association of number of visits with response

Response rates increased with number of visits in each group (r = 0.58, df = 11, p = 0.04 in the drug group and r = 0.55, df = 11, p = 0.05 in the placebo group). When we controlled for trial duration and the visit-duration interaction, number of visits was significantly associated with response rate in the placebo group (Table 2). The regression model accounted for 47% of the variance in response (the adjusted R^2) in the placebo group. In the drug group response rate was not significantly associated with number of visits once trial duration was accounted for. The regression model accounted for 32% of the variance in response in the drug group.

Next we explored if the association between number of visits and response differed in the drug and placebo groups. Figure 1 show the relationship between the number of visits and response in the drug and the placebo groups when trial duration and the visit-duration interaction are accounted for the slope of the linear regressions indicates that with each visit response rates would increase by 5.6 percentage points in the drug group and 3.5 percentage points in the placebo group.

In the placebo group		
Variable	**Likelihood Ratio χ2**	**P**
Number of visits	5.10	0.024
Trial duration	4.99	0.025
Visits by duration	4.15	0.042
In the drug group		
Variable		
Number of visits	0.21	0.64
Trial duration	0.33	0.57
Visits by duration	0.63	0.43
Note: All tests have 1 df		

Table 2: Association of number of visits, trial duration, and the visit by duration interaction with response in the placebo group.

In the regression comparing the number of visits and response in the drug and placebo groups combined, the interaction term (number of visits with treatment group) was trivial (χ^2=0.16, p=0.69) indicating that the relationship of number of visits with response did not differ by treatment group.
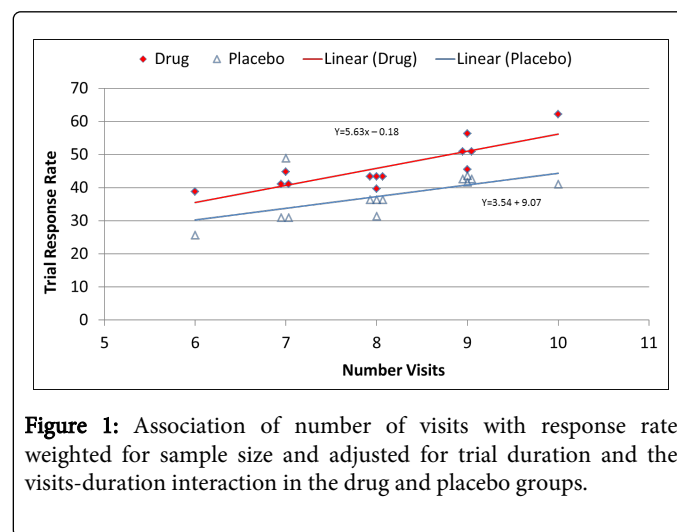

Figure 1: Association of number of visits with response rate weighted for sample size and adjusted for trial duration and the visits-duration interaction in the drug and placebo groups.

Interaction of number of visits with lifetime duration of MDD

In the regression model that included lifetime duration of MDD and number of visits, trial duration, and interaction terms for visits by trial duration and visits by lifetime duration of MDD with response as the outcome in the placebo group, illness duration was the only variable significantly associated with response (z=2.22, df=1, p=0.03). The interaction of number of visits with illness duration did not reach significance (z=1.71, df=1, p=0.09).

Discussion

Our data partially replicate the findings of Rutherford et al. in late life depression.[5] Total number of visits significantly contributed to response rates in the placebo group after controlling for trial duration and the visits-duration interaction. Similar to Rutherford we did not find a significant association of number of visits with response in the drug group once trial duration was controlled; however, we would be cautious about concluding there is no relationship. The failure to find a significant relationship of visits and response in the drug group does not indicate that no relationship exists. Furthermore, a trial level analysis of 13 trials has limited power to detect differences that might exist especially when examining the interaction of several variables. We found no significant difference in the relationship of visits with response between treatment groups. Further, unlike Rutherford et al., Figure 1 suggests response rates increase as number of visits increase in both the drug and placebo groups and there is no indication that drug-placebo differences in response rates would decline with additional visits.

Studies of the relationship of clinic visits to response in mixed aged samples have produced mixed results. Posternak and Zimmerman examined 41 six-week placebo-controlled antidepressant trials that included four, five, or six visits during the treatment period [21] They found that response rates increased with each additional visit in both the drug and placebo group. Rutherford et al. examined 62 placebo controlled antidepressant trials in depressed patients aged 18-65 years of age [22]. When other factors were controlled, they did not find a significant effect of number of visits on response.

Our findings do not provide support for our hypothesis that the relationship of number of visits and response in the placebo group would be stronger in those within short lifetime duration of MDD. Lifetime duration of MDD was related to response, but the interaction of lifetime MDD duration with number of visits and response failed to reach significance (p=0.09). Again the power of this analysis is limited by the number of trials.

Our analysis differs from the Rutherford et al. analysis in late life depression [5]. The most important difference is that we limited trial selection to placebo-controlled randomized trials. This is critical to assuring that other factors not accounted for but which might influence outcome are randomly distributed in the two groups. Rutherford et al. included 9 double-blind comparison trials without a placebo in their analysis.

Limitations

The primary limitation of our analysis is the limited number of trials. This small number increases the chance of a type II error (concluding no difference when there is one). In our trial level analysis the number of visits was determined by study protocol. It is likely some patients had fewer visits than planned although completion rates were fairly high (74% in the drug groups and 79% in the placebo groups). Without individual patient data for number of visits, we cannot assess the effect of actual number of visits on response. Finally while we included all of the published placebo-controlled trials of antidepressants in older depressed adults published since 1985, these trials commonly employed exclusion criteria that limit the generalizability of the findings.

In summary our data partially replicate the findings of Rutherford et al. [5] and Posternak and Zimmerman [21]. During a clinical trial response rates increase in the placebo group as clinic visits increase independent of trial duration. Unlike Rutherford, we did not find evidence that the relationship of number of visits and response differed in the drug and placebo groups or that drug-placebo differences in response would become smaller as number of visits increased. Although we could not confirm a clear association of number of visits with response in the drug group, we think it is premature to conclude that number of visits is not related to response during antidepressant treatment. From a clinical trial design perspective if a greater number of visits increases placebo response and high placebo response rates make it difficult to detect drug-placebo differences [23] then fewer visits should enhance signal detection. The conflicting data about whether more frequent visits enhance response during antidepressant treatment pose a dilemma for clinicians. Clinicians are likely to prescribe antidepressants, not placebo. Currently in primary care, where most depressed patients are seen, follow-up visits are infrequent [24,25]. Yet meta-analyses of collaborative care trials, indicate an advantage of collaborative care (which usually involves more patient visits) over usual antidepressant treatment; [26,27] however, collaborative care usually involves several elements, not just more frequent visits. Clinical management during antidepressant treatment is not likely to change without more careful study of the elements of clinical practice that effect change.

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