



Published in final edited form as:

*J Clin Psychopharmacol*. 2010 June ; 30(3): 323–327. doi:10.1097/JCP.0b013e3181dc6b3e.

## Survey of Investigators' Opinions on the Acceptability of Interactions With Patients Participating in Clinical Trials

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### Abstract

**Introduction**—There is growing concern about the ability of clinical trials to reliably detect differences between active drugs and placebo. To date, little attention has focused on how interactions between clinical trial investigators and patients may influence study outcomes. We sought to explore what types of interactions with patients investigators considered to be appropriate during placebo-controlled pharmacotherapy studies of major depressive disorder.

**Methods**—Questionnaires describing 26 specific types of clinician-patient interactions were administered to principal investigators (PIs) attending an investigators meeting for a phase 3 clinical trial of an antidepressant medication. Principal investigators were asked to rate the acceptability of each intervention. They were also asked to report the mean time they spent with patients at a midstudy visit. Principal investigators were grouped according to previous trial experiences (participation in <20 or ≥20 prior trials).

**Results**—Principal investigators generally agreed that physical health recommendations and nonspecific interactions with study patients were acceptable. Relating the investigator's personal experiences and siding with the patient on interpersonal conflicts were consistently rated as unacceptable. Less-experienced PIs were significantly more likely to view as acceptable cognitive, behavioral, and emotionally supportive interventions compared with more-experienced PIs. Forty-two percent of PIs reported spending at least 20 minutes with patients at midstudy visits.

**Conclusions**—There is significant variability between PIs in what are considered to be appropriate interactions with patients participating in clinical trials. Greater standardization of these interactions is required to reduce placebo response rates and to strengthen the ethical conduct of clinical trials.

### Keywords

clinical trial; placebo; major depressive disorder; ethics; antidepressant

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The results of clinical trials constitute the foundation of evidence-based medicine. For psychiatric illnesses, there is increasing concern about the ability of trials to adequately detect differences between active compounds and placebo.<sup>1,2</sup> Placebo response is increasing in clinical trials and is highly variable between trials.<sup>3,4</sup> High placebo response rates in clinical trials are of great concern because they increase the likelihood of both type 1 (in active comparator trials) and 2 (in placebo-controlled trials) errors in assessing new compounds.<sup>5</sup> Such failed trials, in which placebo response obscures the true drug effects,

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### AUTHOR DISCLOSURE INFORMATION

Mr Vaughan has no disclosures.

entail a significant waste of resources and may pose threats to the public health through their impact on the evidence base of treatment efficacy.

To date, most emphasis on reducing placebo response in trials has focused on improving the accuracy and reliability of the clinician-administered rating scales to assess outcomes.<sup>6</sup> Although failure of raters to comply with standardized quality administration training has been frequently documented, little published data currently exist demonstrating that improving rater quality improves detection of drug-placebo differences.<sup>7</sup> Other potential causes for the increasing placebo effects observed in major depressive disorder (MDD) trials include problems with the validity of rating scales (even when administered reliably), the heterogeneity of depressive syndromes, and recruitment through advertisements that may differentially select for patients particularly responsive to nonspecific clinical interactions.<sup>3</sup>

In contrast to the emphasis on rater quality, very little attention has focused on the impact on outcomes resulting from interactions between the investigator and the clinical trial patient. The potential influence of the prescriber's role in pharmacotherapy outcomes was first explored in the 1960s.<sup>8,9</sup> In particular, the strength of the therapeutic alliance, encapsulating concepts such as empathy, compassion, a helpful attitude, and sympathetic listening, may be a particularly powerful influence on outcomes with drug treatment.<sup>10</sup>

One study that did attempt to standardize the role of investigators in a trial was the Treatment of Depression Collaborative Research Program (TDCRP): a National Institute of Mental Health-sponsored study of cognitive therapy, interpersonal therapy, imipramine and placebo treatment of MDD. For this protocol, Fawcett et al<sup>11</sup> composed a clinical management manual for pharmacotherapists to follow. The primary goal of the manual was to standardize imipramine/placebo administration during TDCRP. The manual proposed that visits during the study be limited to 20 to 30 minutes and discouraged sessions shorter than 15 minutes. Among other recommendations, the manual emphasized the need to preserve “*empathy, support and those naturally spontaneous and more casual exchanges that permit treatment to be carried out in a warm and truly human way*”; (italics in original; p. 313). It specifically prohibited the use of specific psychotherapeutic techniques and “open-ended inquiry into or discussion of interpersonal relationships” (p. 313). The manual also recommended focusing on target symptoms, which aids in the structure of sessions.

Analysis of the TDCRP data found that a greater proportion of the variance in outcomes with imipramine or placebo treatment derived from the effect of the pharmacotherapist rather than from the treatment assignment.<sup>12</sup> Moreover, objective evaluations of therapeutic alliance in the TDCRP found that the strength of the alliance correlated with outcome across all conditions, including pharmacotherapy. This variability in the physician-patient relationship was suggested to be a leading cause for the variability in drug-placebo differences in studies of tricyclic antidepressants.<sup>13,14</sup>

Today, other than the general guidance that investigators should not conduct psychotherapy with participants in trials, there is very little standardization of investigator-patient interactions. Examples of variability that may be of concern include the amount of time the investigator spends with the patient at each visit and the types of verbal and nonverbal interactions that occur in the setting of a clinical trial. Here, we report the results of a questionnaire exploring these issues that was administered to principal investigators (PIs) in a phase 3 placebo-controlled trial for MDD.

## MATERIALS AND METHODS

Use of the questionnaire was approved by the Emory Institutional Review Board. The questionnaire was distributed to PIs attending the investigators meeting for a 12-week, phase

3b, randomized, fixed-dose, placebo-controlled clinical trial of a Food and Drug Administration–approved serotonin norepinephrine reuptake inhibitor for the treatment of MDD, conducted in 2009 at sites in the United States and Canada. Primary inclusion criteria for participation in the trial were ages 18 to 75 years, meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for a current major depressive episode, and a minimum Montgomery-Åsberg Depression Rating Scale score of at least 25 at both screening and baseline visits. Key exclusion criteria were previous failure to respond in the past 3 years to 3 or more antidepressants, 2 adequate courses of psychotherapy, or 1 course of electroconvulsive therapy; current clinically significant suicide risk; substance abuse, post-traumatic stress disorder, or obsessive–compulsive disorder in the past year; current clinically significant medical illness; and lifetime diagnosis of bipolar or psychotic disorder. The results from this clinical trial have not yet been published.

Principal investigators attending the meeting were asked to complete a questionnaire exploring the nature of their interactions with patients participating in clinical trials. No personally identifying information of the respondents was collected. Investigators were informed that the questionnaire was solely for the purpose of research into their attitudes regarding appropriate interactions with patients in clinical trials. The investigators were advised that their participation was completely voluntary; completing the survey reflected consent to participate in the research. The questionnaire asked for the number of studies for which the investigator had performed Clinical Global Impression (CGI) ratings and the usual amount of time they spend with a clinical trial patient at a midstudy visit when evaluating response (including CGI) and tolerability of the study medication. This question was posed as a multiple-option question, with the categories of <10, 10–19, 20–29, and 30 minutes.

Investigators were then asked about the acceptability of 26 specific kinds of interactions that could occur between the investigator and the patient participating in a placebo-controlled clinical trial. On the questionnaire, the investigators were instructed to “Consider yourself to be conducting a visit at week 4 of an 8-week placebo-controlled trial of a medication for the treatment of major depressive disorder.” The questionnaire asked the investigator to rank the acceptability of the interactions from 1 to 4, where: 1, never acceptable; 2, sometimes acceptable; 3, usually acceptable; and 4, always acceptable. The interactions were grouped into 7 categories: (1) cognitive and (2) behavioral interventions, (3) emotional support, (4) psychological advice giving, (5) general health recommendations, (6) resource referrals, and (7) nonspecific interactions. The interactions listed on the questionnaire were presented in an unstructured, mixed order, and their interaction category was not listed.

## Statistical Analysis

Questionnaire data were entered into SPSS version 16.0 (SPSS Inc, Chicago, Ill) for analysis. Means and SDs were computed for continuous data, and categorical data were assessed as frequencies. Principal investigators were grouped into more- and less-experienced categories based on whether they had conducted CGI ratings in at least 20 or less than 20 previous studies, respectively. Comparisons of means between these groups were conducted with Mann-Whitney *U* test, due to the highly skewed distribution of the number of previous trials among the investigators.

## RESULTS

Nineteen PIs (18 Medical Doctors and 1 Doctor of Osteopathic Medicine) completed the survey. Three PIs did not report the number of studies for which they had previously conducted CGI ratings. Of the remaining 16, the number of studies in which the PIs had

previously performed CGI ratings ranged from 0 to 150, with a mean of 55.8. Splitting the data into those PIs who had performed CGI ratings in fewer than 20 trials ( $n = 6$ ) versus those that had done so in at least 20 trials ( $n = 10$ ), the respective means were 4.5 and 86.5 ( $P < 0.001$ ).

With respect to the mean time spent with a depressed patient at a midstudy visit, 4 (21%) spent less than 10 minutes; 7 (37%) spent 10 to 19 minutes; 7 (37%) spent 20 to 29 minutes; and 1 (5%) spent at least 30 minutes. These proportions were not significantly different between more- and less-experienced PIs.

The acceptability ratings of the specific interactions are shown in Table 1. Table 2 provides summed acceptability scores for the items within each category. Less-experienced PIs were significantly more likely to consider as acceptable behavioral ( $P = 0.042$ ) and cognitive interventions ( $P = 0.016$ ), psychological advice ( $P = 0.042$ ), and emotional support ( $P = 0.016$ ). Nonspecific interactions, health recommendations, and financial resource referrals did not differ by PI experience level. Specific interventions that received consistently low acceptability ratings included the physician relating personal experiences and taking sides on issues relating to employment and family conflicts.

## DISCUSSION

These questionnaire data indicate important discrepancies between PIs regarding what types of interactions they consider acceptable during study visits with patients in placebo-controlled trials for major depressive disorder. There is high variability between PIs regarding the amount of time they spend with patients and for specific types of interactions. Forty-two percent of PIs spent 20 minutes or more with trials patients at a midstudy visit.

The finding that less-experienced investigators considered it acceptable to provide behavioral and cognitive interactions is significant in that these differences may impact study outcome. The efficacy of cognitive behavioral therapy (CBT) for MDD and anxiety disorders is well established.<sup>15</sup> Although full recovery from MDD with CBT usually takes at least 12 hourly sessions of therapy, smaller reductions in depressive symptoms from CBT interactions may be sufficient to obscure drug-placebo differences on psychiatric rating scales.

Less-experienced investigators were also more willing to provide psychological advice or emotional support, which strengthen the therapeutic alliance and may thereby increase nonspecific response to treatment. On the other hand, too little supportive work may increase patient dropout and thereby harm the signal-detection level of the study. Among community psychiatrists in Germany, provision of verbal support reduced rates of treatment discontinuation among depressed patients receiving an antidepressant.<sup>16</sup> In clinical trials, patient retention and drug-placebo separation may be enhanced through appropriate instruction to patients regarding their research role in helping to determine whether a drug is effective or not, and by explaining that definitive treatment for their illness is provided upon completion of their participation.<sup>17</sup>

That less-experienced PIs endorsed interactions to support the therapeutic alliance is in keeping with the recommendations of the TDCRP manual.<sup>11</sup> Specifically, the manual emphasized warmly greeting the patient and using “special effort...to reinforce the patient’s continued hope and optimism regarding improvement” (p. 315). Moreover, “any tendency to administer the pharmacotherapy condition mechanically, to maintain inappropriate distance, to relate in a perfunctory way is antitherapeutic and must be avoided” (p. 319). Limitations on psychotherapy interventions should “not result in the patient’s receiving limited emotional support” (p. 320). Among the permitted interventions by psycho-pharmacologists

were to (1) develop a positive and meaningful relationship with the physician; (2) provide psychological support via conveying a sense of hope and optimism, especially early in treatment; (3) provide education and information about the illness and medication; (4) provide simple advice, including promoting exercise and socialization; and (5) allow for ventilation and abreaction within the time limits and if it is thought to enhance the therapeutic relationship. Quite at odds with the standard in placebo-controlled trials today, the manual emphasizes the pharmacotherapist should “clearly communicate an expectation that the patient will improve” (p. 314).

The results of the survey also raise issues related to the ethics of the treatment of patients in clinical trials. Specifically, what kinds of education and advice would it be unethical to withhold from patients in trials, in the name of minimizing placebo response? For example, the questionnaire revealed disagreement about whether providing written information to patients about depression was acceptable. Moreover, there were discrepant opinions about providing standard recommendations for sleep hygiene and exercise, a basic educational component of depression treatment.<sup>18</sup> This tension between minimizing placebo response and providing ethical treatment to study patients is worthy of further exploration.<sup>5</sup>

Severely curtailing physician-patient interactions in placebo-controlled trials may raise questions of external validity of study’s findings. If a study medication only demonstrates efficacy over placebo under conditions that do not reflect routine clinical care, then the actual effectiveness of the drug in clinical practice may be quite weak.

There are several limitations to this initial work exploring investigators’ opinions about specific interactions in clinical trials. First, investigators’ opinions and attitudes may not correlate with their own personal actions as an investigator. That is, investigators may perform certain interactions more or less frequently than they indicated was “acceptable” on the questionnaire. Second, the survey sample was relatively small, and although the range in trial experience was broad, conducting similar surveys with more investigators (including subinvestigators), and investigators involved in trials for other illnesses, such as psychotic disorders, would be instructive. Finally, for reasons of anonymity, we did not collect any demographic information, but such information may have been helpful in identifying whether age, sex, or other variables could have provided greater explanatory power to the diverse findings.

In summary, the results of this survey indicate significant variability in PIs’ attitudes regarding interactions with study patients. The findings from this survey suggest that just as there is need for standardization of raters before the initiation of a clinical trial, there also ought to be some mechanism for generating agreement and standardization between investigators regarding the nature of interactions with study patients.

## Acknowledgments

No external source directly funded this work. Dr Dunlop has research support from AstraZeneca, Forest, Glaxo-Smith- Kline, Organon, Wyeth, and NIH and served as consultant for Imedex LLC, Digitas Health, and MedAvante.

Dr Dunlop is supported (in part) by a K12 grant from the National Institutes of Health National Center for Research Resources, K12 RR 017643 and 1KL2RR025009.

## REFERENCES

1. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLOS Med.* 2008; 5:260–268.

2. Turner E, Matthews A, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Eng J Med*. 2008; 358:252–260.
3. Walsh B, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002; 287:1840–1847. [PubMed: 11939870]
4. Sysko R, Walsh BT. A systematic review of placebo response in studies of bipolar mania. *J Clin Psychiatry*. 2007; 68:1213–1217. [PubMed: 17854245]
5. Dunlop BW, Banja J. A renewed, ethical defense of placebo-controlled trials of new treatments for major depression and anxiety disorders. *J Med Ethics*. 2009; 35:384–389. [PubMed: 19482985]
6. Kobak KA, Kane JM, Thase ME, et al. Why do clinical trials fail? The problem of measurement error in clinical trials: time to test new paradigms? *J Clin Psychopharmacol*. 2007; 27:1–5. [PubMed: 17224705]
7. Kobak KA, Feiger AD, Lipsitz JD. Interview quality and signal detection in clinical trials. *Am J Psychiatry*. 2005; 162:628. [PubMed: 15741493]
8. Rickels, K. *Non-Specific Factors in Drug Therapy*. Springfield, IL: Charles C. Thomas; 1968.
9. Uhlenhuth EH, Rickels K, Fisher S, et al. Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia*. 1966; 9:392–418. [PubMed: 4872909]
10. Schweizer E, Rickels K. Placebo response in generalized anxiety: its effect on the outcome of clinical trials. *J Clin Psychiatry*. 1997; 58(suppl 11):30–38. [PubMed: 9363046]
11. Fawcett J, Epstein P, Fiester SJ, et al. Clinical management—imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. *Psychopharm Bull*. 1987; 23:309–324.
12. McKay KM, Imel ZE, Wampold BE. Psychiatrist effects in the psychopharmacological treatment of depression. *J Aff Disord*. 2006; 92:287–290.
13. Krupnik JL, Sotsky SM, Simmens S, et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health treatment of depression collaborative research program. *J Consult Clin Psychol*. 1996; 64:532–539. [PubMed: 8698947]
14. Blatt SJ, Zuroff DC. Empirical evaluation of the assumptions in identifying evidence based treatments in mental health. *Clin Psychol Rev*. 2005; 25:459–486. [PubMed: 15893862]
15. Butler AC, Chapman JE, Forman EM, et al. The empirical status of cognitive behavioral therapy: a review of meta-analyses. *Clin Psychol Rev*. 2006; 26:17–31. [PubMed: 16199119]
16. Linden M, Dierkes W, Munz T. Non-pharmacological treatment of psychiatrists in addition to the prescribing of an antidepressant drug. *Eur Psychiatry*. 2007; 22:419–426. [PubMed: 17482798]
17. Zimbroff DL. Patient and rater education of expectations in clinical trials (PREECT). *J Clin Psychopharmacol*. 2001; 21:251–252. [PubMed: 11270933]
18. Dunlop BW, Self RL. Exercise for depression: efficacy, safety and clinical trial implications. *Psychopharm Bull*. 2008; 42:5–20.

**TABLE 1**  
Acceptability Ratings of 19 PIs for Potential Interactions With Study Patients

Item No.	Category	Interaction	Acceptability Scores					Mean	SD
			Never (1), n (%)	Sometimes (2), n (%)	Usually (3),n (%)	Always (4), n (%)			
1	H	Recommending follow-up with a primary care provider regarding a patient's medical concern	1 (5)	2 (11)	6 (32)	10 (53)	3.32	0.89	
2	E	Expressing condolences regarding the patient's recent loss of a loved one	1 (5)	4 (21)	3 (16)	11 (58)	3.26	0.99	
3	N	Offering a handshake before and/or after a visit	1 (5)	2 (11)	8 (42)	8 (42)	3.21	0.86	
4	H	Recommending a patient who has 3 alcohol drinks per day to reduce their alcohol intake	4 (21)	6 (32)	4 (21)	5 (26)	2.53	1.12	
5	N	Providing printed educational materials about the patient's disorder	5 (26)	4 (21)	6 (32)	4 (21)	2.47	1.12	
6	H	Recommending a change toward a healthier diet	7 (37)	2 (11)	4 (21)	6 (32)	2.47	1.31	
7	P	Praising the patient for making a positive life change or health behavior change	6 (32)	3 (16)	6 (32)	4 (21)	2.42	1.17	
8	N	Advising a patient who has not improved or worsened at week 4 in an 8-wk trial that more time is needed to assess efficacy	2 (11)	8 (42)	5 (26)	3 (16)	2.37	1.07	
9	R	Identifying government or private financial/social resources for a low-income patient	5 (26)	4 (21)	9 (47)	1 (5)	2.32	0.95	
10	B	Suggesting a change in sleep behavior in accord with sleep hygiene practices	6 (32)	5 (26)	5 (26)	3 (16)	2.26	1.10	
11	B	Recommending starting some form of routine exercise program	7 (37)	4 (21)	5 (26)	3 (16)	2.21	1.13	
12	E	Encouraging a patient to vent their feelings about a current stressor	7 (37)	7 (37)	4 (21)	1 (5)	1.95	0.91	
13	R	Referring a patient with significant financial stressors to a consumer credit counseling service	8 (42)	7 (37)	4 (21)	0 (0)	1.79	0.79	
14	C	Suggesting an alternative way of thinking about a stressor they are experiencing	9 (47)	6 (32)	3 (16)	1 (5)	1.79	0.92	
15	B	Suggesting activities for the patient to engage in, to increase their level of socialization	9 (47)	7 (37)	2 (11)	1 (5)	1.74	0.87	
16	P	Suggesting alternative ways to address a conflict with a coworker	11 (58)	5 (26)	1 (5)	2 (11)	1.68	1.00	
17	C	Suggesting techniques the patient could use to distract themselves from sad or anxious feeling states	11 (58)	4 (21)	4 (21)	0 (0)	1.63	0.83	
18	P	Suggesting alternative ways of discussing contentious issues with spouse/significant other	10 (53)	7 (37)	1 (5)	1 (5)	1.63	0.83	
19	R	Providing the patient with ideas to help them find employment or change employment	10 (53)	7 (37)	1 (5)	1 (5)	1.63	0.83	
20	P	Suggesting alternative ways to respond to troublesome behavior by the patient's children	10 (53)	7 (37)	2 (11)	0 (0)	1.58	0.69	
21	P	Suggesting a solution for a psychosocial problem the patient is facing	10 (53)	7 (37)	2 (11)	0 (0)	1.58	0.69	
22	C	Encouraging the patient to focus on positive rather than negative events or memories	11 (58)	5 (26)	3 (16)	0 (0)	1.58	0.77	
23	E	Placing an arm around a patient's shoulder after a particularly emotional visit	11 (58)	6 (32)	2 (11)	0 (0)	1.53	0.70	
24	P	Recommending quitting a job you believe is deleterious to the patient	11 (58)	7 (37)	1 (5)	0 (0)	1.47	0.61	
25	E	Endorsing that the patient's boss or spouse does seem to be treating them unfairly	12 (63)	6 (32)	1 (5)	0 (0)	1.42	0.61	

Item No.	Category	Interaction	Acceptability Scores				Mean	SD
			Never (1), n (%)	Sometimes (2), n (%)	Usually (3),n (%)	Always (4), n (%)		
26	E	Relating your own personal experience in coping with a stressor that was similar to one that the patient is now experiencing	13 (68)	6 (32)	0 (0)	0 (0)	1.32	0.48

Categories of interactions: B indicates behavioral intervention; C, cognitive intervention; E, emotional support; H, general health recommendation; N, nonspecific interaction; P, psychological advice giving; R, resource referral.

**TABLE 2**

Summed Acceptability Ratings for Categories of Inhibition Between More- and Less-Experienced PIs

Interaction Category	Questionnaire Item Numbers	Acceptability Score, Mean (SD)		<i>P</i> *
		Less-Experienced PIs (n = 6)	More-Experienced PIs (n = 10)	
Behavioral interventions	10, 11, and 15	8.3 (2.9)	5.7 (1.8)	0.042
Cognitive interventions	14, 17, and 22	7.5 (2.6)	4.1 (1.3)	0.016
Emotional support	2, 12, 23, 25, and 26	15.0 (3.7)	11.1 (2.8)	0.042
Health recommendations	1, 4, and 6	9.3 (2.4)	8.5 (2.4)	0.64
Nonspecific items	3, 5, and 8	8.3 (1.2)	8.3 (1.9)	0.71
Psychological advice	7, 16, 18, 20, 21, and 24	11.3 (3.5)	6.7 (2.1)	0.016
Resource referral	9, 13, and 19	7.0 (2.8)	5.4 (1.7)	0.26
All	All	66.8 (17.7)	49.8 (11.9)	0.06

\* *P* value calculated from Mann-Whitney *U* test.