

## Patient expectations in placebo-controlled randomized clinical trials

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### Abstract

**Objective** To explore participants' experience in placebo-controlled randomized clinical trials (RCTs) specifically in relationship to their expectations. **Background** Aspects of being in RCTs, such as informed consent, perception of benefit and understanding of randomization, have been examined. In contrast, little is known concerning the formation of patient expectations before and during trials. **Methods** Qualitative methods using in-depth interviews with a semi-structured interview guide of nine patients from four different RCTs. Data analysis was conducted using a codebook format arranging participant responses under broad analytical headings. The interviewer used a semi-structured interview guide to direct the conversation from one broad topic to the next within the context of the ongoing conversation. A checklist of topics encouraged participants to describe their experiences in RCTs. Narratives concerning expectation, blinding and placebo were compared to identify common themes. **Results** Patient anticipatory processes were influenced and modified both before and during the trial from multiple inputs. Such factors as past experiences in RCTs, past experiences of ineffective treatment, stress of being off regular medications, fear of being a 'placebo responder', input of non-study doctors or other health professionals, the experience of other participants, measurements of health parameters made during the trial and the presence or absence of side-effects all affected patient expectation. **Conclusion** Expectations in RCTs are not fixed and instead may be viewed as continuously shaped by multiple inputs that include experience and information received both before and during the trial. Variability in placebo response observed in previous studies may be related to the fluid nature of expectations. Trying to control and equalize expectations in RCTs may be more difficult than previously assumed.

### Introduction

The extensive literature on randomized controlled trials (RCTs) has primarily been from the perspective of researchers and the needs of the medical community for rigorous and unbiased evidence; questions of methodology and interpretation of

results have been the central focus (Spilker 1996). The systematic study of participants' experience in RCTs has lagged behind (Hudmon *et al.* 1996). Such knowledge is critical in order to ensure that patients' rights and needs are being respected (Stanley *et al.* 1984; Leach *et al.* 1999; Stein & Pincus 1999), to help insure patient recruitment and retention (Cassileth

*et al.* 1982; Llewellyn-Thomas *et al.* 1991; Welton *et al.* 1999), and finally to consider the possibility that the context of RCTs may have unique impacts on patients and consequently on the outcome of the trials (Simes *et al.* 1986; Kleijnen *et al.* 1994; Kaptchuk 2001).

Recently, a growing body of research has begun to study participants' experiences in RCTs. Studies on the quality of subjects understanding of informed consent have been most prominent (Appelbam *et al.* 1982; Benson *et al.* 1985; Kent 1996) but patient motivation to join RCTs (Henzlova *et al.* 1994; Schron *et al.* 1997), patient perception of benefits received in RCTs (Cassileth *et al.* 1982; Mattson *et al.* 1985), and patient perspectives on the meaning of random allocation (Snowdon *et al.* 1997; Featherstone & Donovan 1998) have also appeared. Few studies have examined the construction of patient expectation before and during a double-blind placebo-controlled trial. Such information concerning cognitive frameworks could inform the extensive literature on the impact of expectation on health outcomes (Flood *et al.* 1993; Leedham *et al.* 1995; Montgomery *et al.* 1998; Crow *et al.* 1999; Kirsh 1999; Di Blasi *et al.* 2001) and patient satisfaction (Ross *et al.* 1987; Llewellyn-Thomas *et al.* 1992; Thompson & Sonol 1995; William *et al.* 1995) in RCTs and regular practice. Just as important, because expectancy is considered a critical underlying mechanism of the placebo effect (Kirsch 1985; Jensen & Karoly 1991; Sutton 1991; Mitchell *et al.* 1996), empirical knowledge of patient anticipatory processes could critically inform placebo theory and research. Previous discussions of cognitive frameworks and placebo response in RCTs have tended to make assumptions about expectations without empirical information. A normative perspective has accepted expectation as a relatively stable and predictable phenomenon that is thought to involve patients' hope for improvement or cure (Goldstein 1962; Shapiro & Shapiro 1997; Spiro 1998). The purpose of this pilot study is carefully to examine expectation in double-blind RCTs. By asking past trial participants to describe their experiences, this study allows an exploration of the phenomenon of expectation as it arises in specific contexts related to participating in a clinical trial, for example, participants' reasons for entering the trial, their experiences with prior treatments, their initial

expectations, and their expectations and reflective self-monitoring as the trial proceeded. Many of these influences fall short of what might be said to constitute patient 'unblinding' (which is a related question with its own literature) (Moscucci *et al.* 1987; Swartzman & Burkell 1998); nevertheless, these influences may give investigators concerns that expectation and its relation to health outcomes such as placebo response may be poorly understood.

## Participants and methods

The study was conducted at a large urban tertiary care teaching hospital. Participants were sought from all recently completed double-blind placebo-controlled pharmacological trials. The hospital's clinical trial unit identified five such studies, completed within the previous year. Investigators for these studies were asked to allow their past participants to be contacted for the present study. Three investigators, conducting four trials, agreed to contact their patients. Letters under the investigators' cover were sent to 53 past participants asking those interested in participating in an interview study concerning their experiences in a clinical trial to return an enclosed card indicating their willingness to be contacted. Twelve cards were returned and nine interviews were conducted (in the other three cases, logistical issues prevented interviews from being made).

Data were collected by in-depth interviews conducted by D.S. and C.K. using a semi-structured interview guide. The purpose of the guide format is to foster a conversation about the participants' experiences, allowing them the freedom to discuss in greater detail or at greater length, aspects of their experiences that they feel are important or noteworthy and to frame those discussions in their own terms. The interviewer directs the conversation from one broad topic to the next within the context of the ongoing conversation. Topics covered in the interview guide included background information about the participants and their family, their general health, their experience with the trial (how they became involved, their experiences and feelings regarding recruitment, consent, randomization, blinding, and their participation in the trial), their reasons for participating, and their expectations upon entering and throughout the course of the trial. Specific probes

were asked when participants failed to address one of the study concerns in the course of the more open conversation. Interviews took place either at the hospital or in the participant's home; they each lasted roughly 1 hour and were tape-recorded for later analysis. Analysis for this pilot study focused on issues pertaining to the participants' expectations upon entering the trial and throughout its course and their feelings and experiences with regard to being in a 'blinded' situation. Data analysis was conducted using a codebook format (Lincoln & Denzin 2000), arranging participant responses under broad analytical headings (e.g. reasons for participating; expectations upon entering the trial; feelings about being blinded; differences between the blinded study situation and the unblinded experience of being treated by their doctors). D.S. conducted initial coding; T.K. then reviewed the coding for accuracy and completeness.

The nine participants range in age from 34 to 65 years. Five are male, all are middle class, and most (eight of nine) had post-high school education. Participants were drawn from four trials: four came from a trial of a collagen preparation for rheumatoid arthritis, others came from trials of risedronate for bone loss in lupus, LJP 394 to treat kidney function in lupus, and remacemide for Parkinson's disease.

Results from the participant interviews are presented below, grouped according to salient themes that arose from the data pertaining to the issues of expectation and blinding. Verbatim quotations are provided in order to assist the reader in following our interpretations.

## Results

### Reasons for entering the study

Six of the nine participants cited their general desire to gain improvement in the course of their disease as one of the reasons for participating in a trial. Only one, a patient with rheumatoid arthritis, specifically cited symptom relief: 'to find a better way to control the pain of the arthritis' (E.V.). Three said they participated for altruistic reasons, as E.H. said, for example, 'he (the study doctor) brought it up in a very subdued way ... in fact (he said) these studies probably won't help you, directly, but indirectly the whole

class of Parkinson's could learn more.' One woman (W.S.) said, 'I wanted to try the newest thing in arthritis, that was all', while one man (C.T.), who participated in a trial of risedronate's ability to prevent bone loss, did so because his doctor told him he would receive 'additional examinations'.

### Initial expectations

In discussing their reasons for entering a trial, the participants were asked what expectations they had as they entered the study. Contrary to the 'normative' assumption that patients enter clinical trials expecting improvement or cure, only one of the nine participants stated that he had real expectations of physical benefit from participating in the trial. Of the remaining eight, five made distinctions in their statements between hoping they would achieve *some* benefit from participation in the trial vs. having any *real* expectation of improvement (Uhlmann *et al.* 1984). The remaining three participants stated that their anticipatory thoughts regarding participation in the trial focused on fears of harmful side-effects as opposed to positive expectations of benefit. Three participants expressed a fact that was common to all the participants in our sample, namely, that their chronic conditions were such that their experiences with prior treatments led them to expect failure. Indeed, for some participants in our study, failure of prior treatments to improve their condition was part of the eligibility criteria, as it is for many such studies. Finally, some of the participants noted that being required by the study protocol to 'go off' medications they were currently taking in order to participate in the study was stressful and a source of concern to them. Compiled below are participants' most salient remarks regarding their initial expectations:

B.J.: My fantasy would be, hey, this would be a magic pill, la di da, end of this disease. But I knew better. I had enough of a perspective to realize that, well, its probably not going to do much of anything ... It's not going to cure this disease, we all knew that.

K.P.: I guess everybody looks at it as grandeur, you know, saying, 'wow, I'll take this pill and everything will stop, I can write again, you know'.

HL: All the other medications I'd been on failed over time. . . I'd lost all confidence in all physicians in my area.

W.S.: Even when I went to the doctor and he gave me something I had no more confidence that that would work than this experiment. (In her own history) nothing had worked yet.

H.L.: In the midst of all this, I had to stop all my other meds, I had to stop the med that I was on that was helping my arthritis and I was stressed about that, because this was the only drug that I could take that was working.

E.H.: I kept thinking that I was taking the placebo because I wasn't having any side-effects. But, in fact, I was taking a mild form of the medication. (INT: Did your belief that you were on the placebo change your attitude?) yeah, I felt more confident about the outcome, as one of my goals was that it wasn't going to have an adverse effect on me.

V.E.: I don't picture going to a doctor and having him say, this is what you need to feel better and him giving it to me as a real given that that's going to happen. And so maybe there's a lot more uncertainty to the result for me going to a doctor than for other people, so that when I came to the study, it wasn't a dramatic difference from going to a doctor. . . I've also gone to the doctor and been given lots of anti-inflammatories that haven't helped me too.

J.B.: I was positive it would help me. I was positive going in and I was positive through the whole thing.

#### Expectation during the course of the trial and the experience of being 'blinded'

All of the participants we interviewed said they self-monitored during the trial. For some this meant paying attention to daily symptom changes; for others, especially those in studies of bone loss or kidney function, for whom symptoms of their illness were not expected to change, this meant paying attention to changes in lab values or discussions with study staff or doctors about changes in their condition or changes in the conditions of other study participants. For most this meant changes in thoughts, feelings, and expectations about whether or not they were

receiving a real drug or a placebo. Listed below are excerpts from participants' recollections of their initial expectations:

V.E.: Went with the basic assumption, I think, that I couldn't be lucky enough to get the right strength. Went in with the, almost fear, that I was going to be the type of person . . . where I would assume that any positive was coming from the drug and I really wanted to try to be rational about if I felt better was it truly the drug that was doing that or was I feeling better just because I was on something. I didn't want to be the placebo that felt better . . .

B.J.: my sense was that there was a mild attenuation of symptoms. (His hypothesis that he was on the drug) may have waxed and waned. It's a very tenuous hypothesis . . . nothing dramatic ever occurred, there was a guess, based on the fact that I had some side-effects (dry mouth, headaches). . . Both feet planted firmly in mid-air. . . My expectations were, boy it would be nice if I didn't get the placebo because I'd like to find out first hand if there's a powerful effect. And hopefully, I can sort that out from a placebo effect. That would be one expectation. On the other side, working against that is, hey you fool, you know placebo effects are very powerful and you're not going to be able to sort this out without getting the word from the pharmacist in New York when the time comes.

H.L.: (When the study physician reported) no change in blood work results. Half way through, maybe three quarters of the way through the study, I asked my doctor, I go well? he goes, 'you look really good how do you feel?' I says, well I feel alright, so he said, 'well I think you got the drug', and I says I don't think so . . . I thought I'd get that feeling where you feel better all the sudden. . . Three quarters of the way through the study, I says yeah, I probably got the placebo, I mean because I didn't feel any different.

W.S.: I was very hopeful that something would happen . . . I was told that other people were doing better . . . you know that everything you're trying works for some people but doesn't work for others . . . Early on I considered the possibility that I was (a placebo responder) and I thought that would be great. I don't care what it

takes ... Initially I did (have heightened expectations), placebo or not I didn't care, I was really hoping it would make a difference ...

K.P.: Probably even halfway through the study, I said, you know, I asked the doctor how things were going and a lot of people were complaining of dizziness and headaches and I said, well that's a dead give away right there that I must have the sugar pill 'cause I got neither. No nausea no headaches, no dizziness'.

## Discussion

In this study, eight of nine subjects asked to describe their expectations upon entering an RCT indicated that they did not expect to experience significant improvement in their condition. This finding, which directly contradicts common assumptions regarding expectation and the placebo effect and the role of expectation in clinical trials, is notable not because the study's conclusions are immediately generalizable to the population of all RCT participants, but because our investigation was designed to explore qualitatively and in depth the experience of participating in a clinical trial.

The participants in this study describe a number of contexts that are common to trial participants, for example, joining a trial because nothing else has worked (as this is a requirement of many types of trials), participating for reasons other than the study's outcomes, being required to discontinue current medications, participating in order to get additional (or free) medical attention. From these common and recognizable contexts, this study links participants' lack of a positive expectation to broader constructs emerging from their own reasoning processes. Not only were many of them convinced they would not experience the kind of benefit that is assumed to explain the placebo effect, several participants expressed negative expectations related to their fear of harmful side-effects from the real drug (E.H.: I kept thinking that I was taking the placebo because I wasn't having any side-effects. But, in fact, I was taking a mild form of the medication. ... [O]ne of my goals was that it wasn't going to have an adverse effect on me).

Taken together, the commonness of the contexts described by the study participants and the reason-

ableness evident in their discussions of their expectations suggest the need for larger studies. The assumption that patients' positive expectations of benefit may be driving placebo effects in RCTs may require additional, and more direct, evidence.

A second finding of this study is that expectations are subject to change during the course of a trial as a result of self-monitoring. However, because these expectation processes occur below the threshold of unblinding, they may remain invisible to investigators. Given the limits of our study, this finding may not be immediately generalizable; as a pilot study, however, it does suggest potential avenues of further study in the areas of the RCT design, the role of expectation in the placebo effect and in the interpretation of trial results. Specifically, some of the factors identified by participants as affecting expectation and changing during the course of the trial may merit further exploration. These include:

- fear of side-effects of real drug;
- past experiences of ineffective treatments both within previous RCTs and in regular clinical encounters with personal doctors (resulting in a lack of expectation in study treatment);
- stress of being off one's regular medications;
- change in expectation when no improvement is felt;
- change in expectation when no side-effects are experienced;
- fear of being a 'placebo responder', and
- never being sure whether one can trust what one's body is saying, 'it may be placebo effect'.

Participants in this study also indicated a number of ways in which their expectations could be influenced during the course of the study by information they were able to obtain. These include the following:

- input, positive or negative from their non-study doctor or other health professionals outside the study;
- change in expectation upon learning that others in the study are having experiences (improvement, worsening, or side-effects) this patient is not experiencing, and
- change in expectations based on results of study measurements (e.g. blood tests).

A third finding of this study was that participants used complex qualitative language to describe their anticipatory processing, suggesting that a more phe-



nomenological approach that focuses closely on patient experience may be a useful way of understanding contextual factors within RCTs. Such studies may be conceptually framed in ways analogous to anthropological studies of 'illness experience' and 'illness narratives' (Kleinnman 1989; Good 1993; Mattingly 1998). By using 'trial experience' and 'trial narratives' as foci of investigation rather than the more narrowly targeted notion of 'expectation', investigators may be able to elicit a broader range and more extensive descriptions of patients' anticipatory thinking (Spilker 1996). A subsequent study by our group, within an ongoing RCT currently underway in irritable bowel syndrome, takes this approach: we interview a randomly selected subsample of patients as they are participating in an RCT (these patients' results are withheld from the quantitative study because of the unknown effects of the interviews on outcomes). Our aim is to collect data on the ways in which participants form expectations and judgements about the treatment they are receiving. As we follow participants through the trial we will capture changes in their expectations as well as their immediate assessments of treatment and treatment assignment.

This study sheds light on processes that may potentially affect the validity of RCTs. For example, in the sample of patients interviewed for this study, it is clear that some patient expectations changed after randomization and over the course of the trial. Given the unique and idiosyncratic ways that expectation was modulated and the amount of self-monitoring taking place, some changes in expectations in RCTs after randomization may be unequally distributed in comparative arms (Kaptchuk 1998). In this same vein, one might question whether the purported beliefs and motivations of the self-selected population of those who choose to join RCTs (e.g. altruism and/or increased expectation of benefit or practitioner attention) are generalizable to the larger population suffering from the disease (MacMahon & Trichopoulos 1996). Because none of these practices rise to the level of explicit bias involving unblinding or self-selection, they would formally go unnoticed and unreported by investigators. Clearly, however, participants in our study were sufficiently aware of their own processing to be able to remember and describe their

expectations as influencing their perceptions and their beliefs.

The observed high variability in placebo effects found in RCTs (Kleinnman 1989; Shetty *et al.* 1999; Moerman 2000) is another threat to the validity of the RCT that may be related to the fluidity of patient expectations that we observed here. This variability may be a result of some combination of contextual factors at work in an uncontrolled fashion across multiple studies that may be affecting patients' processes of expectation in unpredictable ways. The significance of our findings is further enhanced by the fact that both Parkinson's disease and rheumatoid arthritis (two of the four disease clinical trial groups from which we drew our study participants) have been identified in previous studies (Pincus & Stein 1997; Goetz *et al.* 2002) as conditions where strong placebo effects are often observed in clinical trials [in the case of Parkinson's disease, further neuroimaging studies (de la Fuente-Fernandez & Stoessel 2002) have demonstrated a physiological basis for such a placebo response]. In such potentially 'placebogenic' conditions, a study of how patients' expectations are formed and how they evolve over the course of an RCT may also shed light on patients' therapeutic responses to placebo.

## Conclusions

Our finding that patients' expectation and motivations for joining placebo-controlled trials are highly variable and do not resemble the typical 'normative model' may help explain the variability that placebo researchers have observed. Such variability suggests that trying to control and equalize expectations in the comparative arms of an RCT may be more difficult than assumed. Additional study into the impact of these modifiers of expectation may therefore be warranted.

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