**Describing Placebos in Patient Information Leaflets: Effects on Patients’ Beliefs**

**Running head: Placebos in Patient Information Leaflets**

**Word count: 1864**

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**Keywords**

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**Abstract**

Background

There are ethical shortcomings to current standard practices regarding the provision of information about placebos in clinical trials. Written information about placebos for clinical trial participants can be incomplete and even misleading. We aimed to develop accurate yet accessible written information about placebos for patients who might participate in clinical trials, and to test the effects of such information on patients’ beliefs about placebos.

Methods

With input from 22 patients and public volunteers, a new, “elaborated” information leaflet was developed to provide accessible and evidence-based information about placebos and their possible effects. A “standard” leaflet was also produced which gave a neutral but incomplete description of placebos. In an online experiment 328 participants with chronic health conditions were randomised to read either the elaborated or the standard leaflet. Participants completed validated measures of the credibility and expected effectiveness of placebo treatment for pain and intentions, attitudes, perceived behavioural control, and subjective norms towards taking part in a placebo-controlled trial.

Results

The elaborated leaflet had a significant positive effect on participants’ ratings of the credibility (t(326)=-2.78, p<.01) and effectiveness (t(326)=-2.59, p<.05) of placebo treatment for pain. It had no effect on intentions to take part in placebo-controlled clinical trials.

Conclusions

The elaborated leaflet provided more comprehensive information about placebos than is commonly provided in current clinical trials. Such a leaflet appears to have greater ethical validity and might increase the magnitude of placebo effects. Further research is needed with participants who are actively considering enrolling in a placebo-controlled trial.

**Introduction**

Placebo-controlled randomised clinical trials remain the gold standard method of choice for medical research evaluating the efficacy of new drugs. Such trials must be conducted in accordance with Good Clinical Practice guidelines and ethical principles as per the Declaration of Helsinki ([1](#_ENREF_1)). One important aspect of these guidelines is that patients should be fully informed about the interventions they might receive and give written informed consent. However, in a recent analysis of the content of participant information leaflets (PILs) used in placebo-controlled trials, written information about placebos was typically incomplete and at times misleading ([2](#_ENREF_2)). For example, despite numerous demonstrations of placebo effects and mechanisms in the scientific literature,([3-6](#_ENREF_3)) only 1 of 45 leaflets explicitly stated that patients might experience beneficial effects from the placebo ([2](#_ENREF_2)). This suggests patients may have inadequate understandings of the potential clinical effects of placebo interventions, which jeopardises the validity of informed consent. Indeed, evidence suggests that clinical trial participants often have false beliefs about and limited understanding of placebos and their possible effects ([7-9](#_ENREF_7)).

Poor communication about placebos may also be confounding study outcome. PILs typically do not explicitly tell patients that they might experience health changes when receiving a placebo intervention ([2](#_ENREF_2)). However, patients who believe placebos are likely to be ineffective tend to interpret symptoms or symptom relief experienced during a trial as indicators that they are receiving the verum treatment and can experience “placebo anxiety,” modulating their reporting of subjective outcomes if they are concerned they might look foolish for reporting benefits from placebo treatments ([10](#_ENREF_10), [11](#_ENREF_11)). If trial participants expect placebos to have no effect, this could reduce the actual measured effect of placebos because placebo analgesia is produced at least in part via expectancy ([12-14](#_ENREF_12)). Consistent with this, when study participants know they are likely to receive a placebo, the placebo effect size is reduced ([15](#_ENREF_15)). When trial participants know they are likely to receive the verum, the placebo effect size is increased ([16-18](#_ENREF_16)). In two recent U.S. trials placebo pills elicited clinically meaningful benefits when presented to participants positively and with a credible rationale ([4](#_ENREF_4), [19](#_ENREF_19)). Providing more positive information about placebos in clinical trials could thus increase patients’ expectations of benefit and increase the size of placebo effects.

The inter-relationships between information about placebos and study outcome are undoubtedly complex and empirical work is needed to untangle them. A useful first step is to develop written information which describes placebos in different ways to clinical trial participants. We aimed to develop accurate yet accessible written information about placebos and placebo effects for patients who might participate in clinical trials. The objectives were to identify whether, compared to a standard leaflet about placebos, such information could (a) trigger more positive beliefs about placebos and (b) increase willingness to participate in a placebo-controlled clinical trial. We included the latter objective because evidence suggests different people might be encouraged to ([20](#_ENREF_20)) or deterred from ([21](#_ENREF_21)) taking part in trials that use placebo controls; it is therefore important to examine the impact on recruitment of new information about placebos.

**Methods and Materials**

There were two phases to the study: development and testing the leaflet. Approval was obtained from the university’s research ethics committee (ERGO reference:5616).

Developing the Leaflet

Two leaflets were developed: a ‘standard’ leaflet and an ‘elaborated’ leaflet (see Supplementary Material). The standard leaflet was based on an existing leaflet produced by the National Institute for Health Research (NIHR: ‘Clinical Trials: What they are and what they’re not Version 2’, October 2010) and provided basic, neutral information about placebos and their effects, consistent with the PILs most commonly used in UK clinical trials ([2](#_ENREF_2)). The elaborated leaflet provided more detailed evidence-based information about placebos and their possible effects, drawing on reviews of placebo effects ([3](#_ENREF_3), [5](#_ENREF_5), [6](#_ENREF_6)) and a study of open-label (i.e. non-deceptive) placebo prescribing ([4](#_ENREF_4)). Four main points were conveyed: the placebo effect is powerful; placebos can work through conditioning mechanisms, as illustrated by Pavlov’s dogs; a positive attitude can enhance placebo effects; and engaging with a placebo treatment faithfully is vital. Anonymous comments on the elaborated leaflet were obtained from 22 members of the public and patients interested in health research (recruited through “People in Research” and similar networks). This feedback helped us to simplify the language and make the leaflet attractive, informative and accessible.

Testing the Leaflet

*Design and Hypotheses*

A 2-group design tested the effects of the elaborated leaflet compared to the standard leaflet on (a) credibility and outcome expectations of placebo treatment of pain (theoretical precursors to placebo analgesia responses) and (b) intentions towards taking part in a placebo-controlled clinical trial (theoretical precursor to volunteering for a clinical trial according to the theory of planned behaviour, an established theory of volitional behaviour ([22](#_ENREF_22))). The elaborated leaflet was expected to produce higher scores on these constructs.

*Procedure*

Inclusion criteria were adults (>16 years) self-reporting a chronic illness. Participants were recruited through web-based adverts to patient support groups including Asthma UK, Action on Pain, Pain Concern, the National Rheumatoid Arthritis Society, the IBS Network, People in Research, an online participant pool, and the university community. The study was presented online. Web-based adverts included a link to the study webpage where interested individuals could read an information page before ticking a consent box. Simple randomisation assigned participants the elaborated or standard leaflet. Three very simple true/false questions tested whether participants had read the information. Participants then completed the validated questionnaires described below.

*Measures*

The credibility expectancy questionnaire (CEQ) measured placebo credibility and expectancy using two 3-item subscales ([23](#_ENREF_23)). Example items for these constructs are as follows: “At this point in time, how logical does a placebo treatment seem?” (credibility); “By the end of a course of placebo treatment, how much improvement in your pain do you think would occur?” (expectancy). Items have a mix of 9 and 11 item response scales and subscale scores were computed by aggregating item z-scores. High scores indicate higher perceptions of credibility of placebo treatments and more positive expectations of placebo treatment’s effects on pain.

A theory of planned behaviour questionnaire measured intentions, attitudes, subjective norms and perceived behavioural control related to taking part in a hypothetical placebo-controlled clinical trial ([24](#_ENREF_24)). Participants answer all items using 7-point rating scales with item-specific anchors. Example items for these constructs are as follows: “I want to take part in a placebo-controlled trial if I get the chance” (agree-disagree anchors, intentions); “Taking part in a placebo-controlled trial is…” (good-bad anchors, attitudes); “If given the chance, it is expected of me that I take part in a placebo-controlled trial” (agree-disagree anchors, subjective norms); “If I had the chance to, whether I decide take part in a placebo-controlled trial is completely up to me” (agree-disagree anchors, perceived behavioural control). Scale scores were computed by aggregating component item scores; high scores indicate positive inclinations towards taking part in placebo controlled trials.

*Statistical Methods*

Descriptive statistics and between groups t-tests compared the effects of standard and elaborated leaflets on continuous outcomes. Cohen’s d effect size for between group comparisons was computed (d=0.8, large effect; d=0.5, medium effect; d=0.2, small effect) ([25](#_ENREF_25)). Between group comparisons were repeated with and without those participants (n=80) who answered the simple true/false questions incorrectly.

**Results**

Participants

408 people with chronic illness completed the study, but 80 answered the comprehension questions incorrectly. Three hundred and twenty eight participants were included in the main analyses, aged 17 to 75 years (Mean = 32.69, SD = 12.46). The most commonly reported chronic conditions were : depression (n=65, 19.82%), asthma (n=43, 13.11%), back pain (n=38, 11.59%), anxiety (n=29, 8.84%), migraine (n=27, 8.23%), chronic pain (n=23, 7.01%), arthritis (n=22, 6.71%), heart disease or high cholesterol (n=22, 6.71%), and fibromyalgia (n=20, 6.10%). There were no significant differences between the elaborated and standard leaflet groups on demographic or clinical variables (see Table 1).

*Insert Table 1 Here*

Effects of the Elaborated Leaflet

Participants who had read the elaborated leaflet rated placebo treatment of pain as significantly more credible and significantly more effective than participants who had read the standard leaflet (Table 2). There were, however, no differences in intentions to take part in a placebo-controlled clinical trial between participants who had read the elaborated leaflet vs those who had read the standard leaflet. Similarly, the elaborated leaflet had no effect on participants’ attitudes towards, subjective norms about, and perceived control over taking part in a placebo-controlled clinical trial.

*Insert Table 2 Here*

These analyses were repeated including the 80 participants who failed the simple true/false questions indicating they might not have read the leaflets. The results followed the same pattern: the elaborated leaflet group rated placebo treatment of pain as significantly more credible (t(406) = -2.161, p=.03) and marginally more effective (t(406) = -1.770, p=0.08) and their intentions to take part in a trial were no different compared to the standard leaflet group.

**Discussion**

In this study a leaflet was developed with input from patients and the public that provided an accurate accessible evidence-based description of placebos and placebo effects. Compared to a standard leaflet, the elaborated leaflet is more consistent with the scientific evidence base regarding placebo effects. In this way, it could be said to have greater ethical validity.

As hypothesised, when compared to the standard leaflet the elaborated leaflet had a significant but small positive effect on credibility and expectancy scores: patients perceived placebo treatment for pain as more credible and more likely to be effective. This is likely to have knock-on effects if the elaborated leaflet were to be used in a placebo-controlled clinical trial. A large body of literature suggests that if patients expect placebos to be more effective, then placebos will actually be more effective ([5](#_ENREF_5), [12](#_ENREF_12), [14](#_ENREF_14)). Although not tested here, if placebos are perceived as more credible this might also enhance the magnitude of placebo effects; a more credible treatment is also likely to be a more meaningful treatment which would augment meaning response processes involved in placebo effects ([9](#_ENREF_9), [26](#_ENREF_26)). In a placebo-controlled clinical trial, increasing the placebo effect will likely have implications for comparisons between the placebo and treatment groups. Future studies should test the extent to which providing better information about placebos to trial participants results in larger placebo effects in the placebo and/or treatment groups.

Contrary to our hypothesis, the elaborated leaflet did not influence variables related to taking part in a placebo-controlled trial such as intentions, attitudes, subjective norms, and perceived behavioural control. This suggests providing more information about placebos might neither enhance nor adversely affect recruitment to trials, although it must be remembered that our participants were not contemplating taking part in an actual placebo controlled trial. Future studies might also consider the effect of the elaborated leaflet on other relevant variables, such as informed choice ([27](#_ENREF_27)).

We have developed a more comprehensive evidence-based information leaflet about placebo-controlled trials than is commonly used in current clinical research. Our leaflet appears to have greater ethical validity and might increase the magnitude of placebo effects, without affecting patients’ willingness to volunteer for trials. Larger-scale research involving patients considering enrolment in an actual trial is needed to investigate the ethical and scientific consequences of different methods of informing patients about placebos and their effects.

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**Competing Interests**

The Authors declare that there are no conflicts of interest.

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**Table 1. Participant Characteristics (N = 328)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristic | Participants | | Elaborated leaflet  (n=172) | | Standard leaflet  (n=156) | | Between group comparison |
|  | Percentage | n | Percentage | n | Percentage | n |  |
| *Gender* |  |  |  |  |  |  | χ2 (1) = 0.60, p=.44 |
| Female | 66.3% | 216 | 63.9% | 110 | 67.9% | 106 |  |
|  |  |  |  |  |  |  |  |
| *Self-Rated Health* |  |  |  |  |  |  | χ2 (4) = 3.82, p=.43 |
| Very good | 8.9% | 29 | 9.3% | 16 | 8.3% | 13 |  |
| Good | 46.9% | 153 | 44.2% | 76 | 4.9% | 77 |  |
| Fair | 35.6% | 116 | 37.2% | 64 | 3.3% | 52 |  |
| Bad | 7.7% | 25 | 6.9% | 12 | 8.3% | 13 |  |
| Very bad | 0.9% | 3 | 1.7% | 3 | 0 | 0 |  |
|  |  |  |  |  |  |  |  |
| *Education* |  |  |  |  |  |  | χ2 (3) = 2.81, p=.42 |
| Graduate school | 25.1% | 81 | 25.0% | 43 | 24.4% | 38 |  |
| College | 54.2% | 175 | 50.6% | 87 | 56.4% | 88 |  |
| High school | 20.4% | 66 | 22.7% | 39 | 17.3% | 27 |  |
| Less than high school | 0.3% | 1 | 0 | 0 | 0.6% | 1 |  |
|  |  |  |  |  |  |  |  |
| *Country* |  |  |  |  |  |  | χ2 (3) = 1.81, p=.61 |
| USA | 85.8% | 273 | 80.8% | 139 | 85.9% | 134 |  |
| UK | 9.4% | 30 | 11.0% | 19 | 7.1% | 11 |  |
| Canada | 2.8% | 9 | 2.9% | 5 | 2.6% | 4 |  |
| Other | 4.9% | 16 | 5.2% | 9 | 4.5% | 7 |  |
|  |  |  |  |  |  |  |  |
| Previous experience in an RCT | 7.9% | 26 | 9.3% | 16 | 6.4% | 10 | χ2 (1) = 0.94, p=.33 |
|  |  |  |  |  |  |  |  |
| Chronic condition limits activities | 77.7% | 255 | 73.3% | 126 | 82.7% | 129 | χ2 (1) = 3.93, p=.07 |
|  |  |  |  |  |  |  |  |

**Table 2. Effects of the elaborated leaflet on expectancy, credibility, and willingness to take part in placebo-controlled trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Mean (SD) | |  |  |
|  | Cronbach’s alpha | Elaborated leaflet (n=172) | Standard leaflet (n=156) | t (326) | Cohen’s d |
| Expectancy | 0.90 | 0.11 (2.53) | -0.64 (2.74) | -2.59\* | 0.29 |
| Credibility | 0.78 | 0.19 (2.44) | -0.56 (2.45) | -2.78\*\* | 0.31 |
| Intentions | 0.96 | 4.77 (1.74) | 4.55 (1.72) | -1.15 | 0.13 |
| Attitudes | 0.87 | 4.73 (1.28) | 4.67 (1.16) | -0.43 | 0.05 |
| Subjective Norms | 0.63 | 3.11 (1.46) | 3.11 (1.40) | 0.05 | 0 |
| Perceived Behavioural Control | 0.66 | 5.37 (1.16) | 5.39 (1.06) | 0.13 | 0.02 |

\*p<.05, \*\*p<.01