What trial participants need to be told about placebo effects to give informed consent: a survey to establish existing knowledge among patients with back pain

John Hughes,1 Maddy Greville-Harris,2 Cynthia A Graham,2 George Lewith,3 Peter White,4 Felicity L Bishop2

ABSTRACT

Introduction Patients require an accurate knowledge about placebos and their possible effects to ensure consent for placebo-controlled clinical trials is adequately informed. However, few previous studies have explored patients’ baseline (ie, prettrial recruitment) levels of understanding and knowledge about placebos. The present online survey aimed to assess knowledge about placebos among patients with a history of back pain.

Design A 15-item questionnaire was constructed to measure knowledge about placebos. Additional questions assessed sociodemographic characteristics, duration and severity of back pain, and previous experience of receiving placebos.

Setting Participants recruited from community settings completed the study online.

Results 210 participants completed the questionnaire. 86.7% had back pain in the past 6 months, 44.3% currently had back pain. 4.3% had received a placebo intervention as part of a clinical trial and 68.1% had previously read or heard information about placebos. Overall knowledge of placebos was high, with participants on average answering 12.07 of 15 questions correctly. Few participants correctly answered questions about the nocebo effect (31.9% correct) and the impact of the colour of a placebo pill (55.2% correct).

Conclusions The findings identified key gaps in knowledge about placebos. The lack of understanding of the nocebo effect in particular has implications for the informed consent of trial participants. Research ethics committees and investigators should prioritise amending informed consent procedures to incorporate the fact that participants in the placebo arm might experience adverse side effects.

INTRODUCTION

Placebos are an essential component of randomised controlled trials (RCTs). They are used to control for bias, contextual and psychological components of treatment and thus isolate the specific effects of the intervention under investigation. Administering placebos to patients can elicit both beneficial and adverse (‘nocebo’) effects. Many factors are now known to impact on the strength of the placebo response, including factors associated with the healthcare professional administering treatment, the patient receiving treatment and their therapeutic relationship.1–4 Characteristics of the intervention itself, such as medication colour, the form and frequency of administration also influence the strength of placebo response.5–8 Nocebo effects are typically linked to patient expectations derived from side-effect warnings and can be conditioned from previous adverse events.9 Common nocebo effects include nausea, stomach pains, itching, bloating, depression and sleep problems.10

It is important that potential trial participants know about placebo and nocebo effects. At minimum an accurate knowledge of the possible benefits and adverse effects of placebos is necessary to ensure consent to take part in an RCT is adequately informed. In addition, people’s understanding of, and attitudes towards, placebos may influence their willingness to participate in placebo-controlled RCTs11 12 and thus could have implications for fair access. However, information leaflets used in RCTs often provide incomplete or inaccurate information about placebos. Bishop et al found that only 1 of 45 participant information leaflets used in major RCTs in the UK mentioned that placebos may elicit beneficial effects and only four mentioned that placebos can elicit adverse effects.13

It is necessary to assess people’s baseline knowledge of placebos (ie, before participating in any trial recruitment activities) in order to identify common gaps in knowledge and thus specify the placebo characteristics that should be prioritised for inclusion in participant information leaflets. However, little is known about the public’s knowledge of placebos and placebo effects. We surveyed people with back pain to examine current levels of placebo knowledge and identify knowledge gaps. To the authors’ knowledge this is the first such study. The objective was to inform improvements to informed consent procedures.

METHODS

Design and measures

A web-based cross-sectional survey was conducted. Fifteen true-false items assessed knowledge of placebos (for items, see table 1). Items were developed after consulting with experts in placebo research and examining relevant literature. The questionnaire was pretested with 10 lay volunteers and modified based on their feedback. The survey also assessed demographic characteristics; experience of/sources of knowledge about placebos (to permit an initial assessment of the validity of our knowledge questionnaire); and history and severity of back pain and its impact on daily living, using the validated reliable Chronic Pain Grade

To cite: Hughes J, Greville-Harris M, Graham CA, et al. J Med Ethics Published Online First: [please include Day Month Year]. doi:10.1136/medethics-2016-103964
Questionnaire. Participants also completed a 15-item acupuncture questionnaire (reported separately). Participants also completed a 15-item acupuncture questionnaire (reported separately).

**Participants**

We surveyed adults with a history of back pain, as back pain is prevalent and placebos have demonstrated pronounced effects in chronic pain conditions.

**Procedure**

Ethical approval was given by the University of Southampton Psychology Ethics Committee. Fifteen UK universities invited staff and students to participate via email. The study was also advertised on social media sites pertaining to back pain and to local businesses. Adults who had ‘had back pain’ were invited to take part in a ‘short (10 min) online quiz’ about alternative treatments for back pain. On clicking a link participants reached an information page presenting study details and a tick-box to indicate consent. Participants then completed the survey.

Data were imported into SPSS V.22 and summarised using descriptive statistics. Analysis of variance, t-test, $\chi^2$ test and Spearman’s correlation test assessed whether knowledge of placebos was related to previous experience of receiving placebos, having previously read or heard about placebos, via friends and family, school/university, general knowledge, books, media and/or the internet.

**RESULTS**

**Participant characteristics**

Two hundred and twenty-six people participated between July and October 2014. Data were excluded from 16 individuals who failed to complete any placebo knowledge items, leaving 210 participants. One hundred and thirty-six participants were female (67.7%) and 65 were male (32.3%), aged 18–74 years (M=35, SD=14.05) (9 skipped these items). All participants reported back pain: 100% ever had back pain, 86.7% (n=182) in the past 6 months and 44.3% (n=93) currently. Of those reporting current back pain, average pain intensity was mild (M=3.4, SD=2.16) (see table 2 for additional characteristics).

**Experiences of placebos**

Only nine participants (4.3%) had previously received a placebo as part of an RCT, but 68.1% (n=143) reported having previously read or heard about placebos, via friends and family, school/university, general knowledge, books, media and/or the internet.

**Knowledge**

Participants answered between 4 and 15 knowledge items correctly (M=12.07; SD=2.35) (see table 1). Key gaps in placebo knowledge were identified; 31.9% knew that a placebo pill can have side effects and 55.2% knew that the colour of a placebo pill can change how effective it is.

The nine participants who had previously received placebo treatment as part of an RCT (M=12.22, SD=1.64) had similar knowledge scores to the 201 who had not (M=12.06, SD=2.39) (p=0.841). However, the 143 participants who reported previously reading or hearing about placebos had significantly higher scores (M=12.55, SD=2.15) than the 67 who indicated they had not read or heard about placebos (M=10.97, SD=2.49) (t=4.663, df=205, p<0.001).

There were just two differences in knowledge by sociodemographic and clinical characteristics. Participants who identified as white British had higher placebo knowledge scores than other ethnicities combined (M=12.47, SD=2.18) and M=11.33 (SD=2.50), respectively; t=3.422, df=208, p=0.001). Participants who reported less intense pain during the previous 6 months and 44.3% (n=93) currently. Of those reporting current back pain, average pain intensity was mild (M=3.4, SD=2.16) (see table 2 for additional characteristics).
Table 2  Participant characteristics

<table>
<thead>
<tr>
<th>Gender*</th>
<th>Number (n)</th>
<th>Per cent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>136</td>
<td>67.7</td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
<td>32.3</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>137</td>
<td>65.2</td>
</tr>
<tr>
<td>Other White background</td>
<td>39</td>
<td>18.6</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>9</td>
<td>4.3</td>
</tr>
<tr>
<td>Chinese</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>7.7</td>
</tr>
<tr>
<td>Preferred not to state ethnicity</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>66</td>
<td>31.4</td>
</tr>
<tr>
<td>Administrator/secretary</td>
<td>27</td>
<td>12.9</td>
</tr>
<tr>
<td>Academic</td>
<td>25</td>
<td>11.9</td>
</tr>
<tr>
<td>Postgraduate student</td>
<td>21</td>
<td>10.0</td>
</tr>
<tr>
<td>Researcher</td>
<td>19</td>
<td>9.0</td>
</tr>
<tr>
<td>Teaching</td>
<td>12</td>
<td>5.7</td>
</tr>
<tr>
<td>Healthcare professional</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>Currently not working/retired</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>Technician/programmer</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>Care work</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Engineering</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>5.7</td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>Some college</td>
<td>31</td>
<td>14.8</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>50</td>
<td>23.8</td>
</tr>
<tr>
<td>Master’s degree</td>
<td>58</td>
<td>27.6</td>
</tr>
<tr>
<td>Doctoral degree</td>
<td>44</td>
<td>21.0</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>8.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain in past 6 months†</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>4.23</td>
<td>1.96</td>
</tr>
<tr>
<td>Interference in daily activities</td>
<td>3.83</td>
<td>2.57</td>
</tr>
<tr>
<td>Interference in recreational activities</td>
<td>3.08</td>
<td>2.70</td>
</tr>
<tr>
<td>Interference in work activities</td>
<td>2.93</td>
<td>2.61</td>
</tr>
</tbody>
</table>

*Nine participants did not specify their gender.
†Items answered on a 0–10 scale, where 10 indicates highest levels of pain intensity/interference.

months had higher placebo knowledge scores than those who reported more intense pain ($r_s = −0.210; p<0.01$).

DISCUSSION

Placebos are an important component of RCTs used to elucidate the specific effects of an intervention under investigation. For informed consent to be valid, trial participants need an accurate knowledge of placebos; this should minimally include an understanding that placebos can have both beneficial and adverse effects. Our community-based survey of people with back pain found relatively high knowledge overall but only a small minority of participants knew that placebos could have adverse, that is, nocebo, effects. Evidence from meta-analysis suggests as many as 52% of RCT participants receiving a placebo may experience nocebo effects. However, just 31.9% of our participants knew that a placebo can have side effects. Earlier studies elsewhere reported similar findings: 4.8% of general practitioner patients in New Zealand agreed that placebos can cause bad side effects and 7.7% of patients recruited from a rheumatology clinic in France believed placebos can induce adverse effects. Our study updates and extends this work, suggesting that the UK patients would also benefit from receiving information about nocebo effects before taking part in a placebo-controlled RCT.

A lack of placebo knowledge among potential trial participants has implications for the ethical principle of autonomy, and consequently participants’ ability to provide full informed consent. Respect for autonomy requires potential participants to have sufficient information to enable them to make an informed decision regarding participation. In particular, the Declaration of Helsinki requires volunteers to be informed about the potential benefits and harms of participation. The knowledge gaps identified within the present study, combined with the limited descriptions of placebos in participant information sheets found previously, suggest that in many cases participants do not have an adequate understanding of the potential benefits and harms of placebos before consenting to placebo-controlled RCTs. This would appear to violate the principle of autonomy, and may question the ethical validity of consent.

There is increasing awareness that ethical practices, such as the content of participant information sheets, should be grounded in empirical data. However, there remains a dearth of published research to inform investigators and research ethics committees. This study was strengthened by using evidence-based items to assess placebo knowledge objectively. The fact that participants who had previously read or heard about placebos scored higher than other participants provides initial evidence for the construct validity of the knowledge questionnaire.

Selection bias is a limitation; participants were more highly educated than the general UK population (almost 50% possessed a postgraduate qualification). This may have driven the high placebo knowledge scores and a more representative sample might have exhibited less knowledge; indeed, even lower levels of knowledge about nocebo effects have been reported by others. However, educational attainment was not related to placebo knowledge in this sample.

Research ethics committees and investigators should prioritise amending informed consent documentation and procedures to explain that participants in the placebo arm might experience beneficial and adverse effects. Our findings suggest that while volunteers may have some existing knowledge that placebos can elicit beneficial effects, they are far less likely to appreciate their potential to elicit adverse effects. Adding information about nocebo effects to participant information sheets and associated discussions might therefore increase participants’ capacity to provide ethically valid informed consent. Future research could evaluate placebo knowledge gaps in other patient groups and develop resources and guidelines to improve the provision of patient information about placebo and nocebo effects. In the meantime, we recommend that research ethics committees apply greater scrutiny to the description of placebos in participant information sheets.

Acknowledgements The authors would like to thank participants for completing the online questionnaire.

Contributors MGH and FB conceived and designed the work, with input from CG, GL and PW. MGH collected the data. JGH analysed the data and drafted the manuscript. All authors contributed to data interpretation, revised the work for important intellectual content, approved the version to be published and are accountable for the work.
Funding  The study was funded by a grant from Arthritis Research UK (grant reference 20113).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Psychology Ethics Committee, University of Southampton, UK.

Provenance and peer review  Not commissioned; externally peer reviewed.

Data sharing statement  The data reported in this paper may be requested from the corresponding author.

Open Access  This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

What trial participants need to be told about placebo effects to give informed consent: a survey to establish existing knowledge among patients with back pain

John Hughes, Maddy Greville-Harris, Cynthia A Graham, George Lewith, Peter White and Felicity L Bishop

*J Med Ethics* published online June 29, 2017

Updated information and services can be found at:
[http://jme.bmj.com/content/early/2017/06/29/medethics-2016-103964](http://jme.bmj.com/content/early/2017/06/29/medethics-2016-103964)

These include:

**References**

This article cites 23 articles, 5 of which you can access for free at:
[http://jme.bmj.com/content/early/2017/06/29/medethics-2016-103964#BIBL](http://jme.bmj.com/content/early/2017/06/29/medethics-2016-103964#BIBL)

**Open Access**

This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See:
[http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Open access (110)

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)