

## Placebos and placebo effects in medicine: historical overview

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*J R Soc Med* 1999;92:511-515

In modern medical research placebos constitute an important methodological tool. Placebos are given to controls in a clinical trial with the intention of mimicking some experimental intervention. Although the most frequently used placebo is the 'sugar pill' in drug trials, placebos can be and have been used for all kinds of interventions, ranging from placebo ultrasound in the treatment of pressure ulcers and placebo surgery in the treatment of osteoarthritis to sham traction in the treatment of low back pain and placebo oestrogen implants in the prevention of menopause symptoms.

### ETYMOLOGY

The word placebo (Latin, 'I shall please') was first used in the 14th century<sup>1</sup>. In that period, it referred to hired mourners at funerals. These individuals often began their wailings with *Placebo Domino in regione vivorum*, the ninth verse of psalm cxiv, which in the Latin Vulgate translation means 'I shall please the Lord in the land of the living'. Here, the word placebo carries the connotation of depreciation and substitution, because professional mourners were often stand-ins for members of the family of the deceased. Around the same time, in the late 1300s, Geoffrey Chaucer in his *Canterbury Tales* (Merchant's Tale) depicts a man named Placebo. Like the hired mourners, the man is associated with wicked behaviour and is portrayed as a sycophant.

The first documented medical use of the word placebo dates from the late 18th century<sup>1</sup>. In the 1785 *New Medical Dictionary*, placebo is described as 'a commonplace method or medicine'<sup>2</sup>. In 1811, the revised *Quincy's Lexicon-Medicum* defines placebo as 'an epithet given to any medicine adapted more to please than to benefit the patient'<sup>3</sup>.

### PLACEBOS IN CLINICAL PRACTICE BEFORE WORLD WAR II

Until the first half of the 20th century the use of placebos seems to have been widespread in medicine. In 1807 Thomas Jefferson, recording what he called the pious fraud, observed that 'one of the most successful physicians I have ever known has assured me that he used more bread pills, drops of colored water, and powders of hickory ashes, than of all other medicines put together'<sup>4</sup>. About a hundred years later, Richard Cabot, of Harvard Medical School, described how he 'was brought up, as I suppose every physician is, to use placebo, bread pills, water subcutaneously, and other devices'<sup>5</sup>.

Only a few physicians considered the bread pill a threat to the integrity of medicine, and most ethical codes endorsed 'necessary deception'. A 'polychromatic assortment of sugar pills' was routinely quaffed by patients<sup>6</sup>. However, placebos were thought to bring only comfort to the patient, with no impact on pathophysiology<sup>7</sup>. The value of placebo was thought inversely related to the intelligence of the patient; the use of a medical ritual was more effective and necessary for 'unintelligent, neurotic, or inadequate patients'<sup>8</sup>.

### PLACEBOS IN CLINICAL RESEARCH

Until 1950, most therapies were judged to be efficacious on the basis of pathophysiological rationales provided by authoritative experts rather than by documented observations and comparative research<sup>9</sup>. The bulk of clinical knowledge was based on noncomparative research, though there are some exceptions<sup>10</sup>.

In 1801, John Haygarth reported the results of what may have been the first placebo-controlled trial<sup>11</sup>. A common remedy for many diseases at that time was to apply metallic rods, known as Perkins tractors, to the body. These rods were supposed to relieve symptoms through the electromagnetic influence of the metal. Haygarth treated five patients with imitation tractors made of wood and found that four gained relief. He used the metal tractors on the same five patients the following day and obtained identical results: four of five subjects reported relief. It is clear that Haygarth had the notion of a placebo effect when he stated that 'an important lesson in physic is here to be

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learnt, the wonderful and powerful influence of the passions of the mind upon the state and disorder of the body. This is too often overlooked in the cure of diseases'. He further wrote that the experiment 'clearly prove[d] what wonderful effects the passions of hope and faith, excited by mere imagination, can produce on disease'. In fact, Haygarth had not abandoned the Renaissance idea that imagination was the major mediator between body and mind<sup>12</sup>.

In 1863, Austin Flint tried to understand whether drugs given for articular rheumatism changed the natural history of disease<sup>13</sup>. Flint placed 13 patients 'on the use of a placebo which consisted, in nearly all the cases, of the tincture of quassia, very largely diluted. This was given regularly, and became well known . . . as the *placeboic remedy* for rheumatism'. Flint, in accord with the understanding at his time, had no idea of concurrent control, but concluded that 'the disease does end from self limitation' and that inert treatment worked. The explanation was fitted into prevailing dogma. Placebo was a fraud and deception that had the 'moral effect of a remedy given specially for the disease', but placebos did not affect the natural course of disease; they were *a priori* excluded from having such an impact. Placebos were therapeutic duds to manage patients, or, as in the Flint investigation, a camouflage behind which to watch nature take its course.

In the beginning of this century, the German physician Adolf Bingel performed a large-scale comparative clinical trial to assess the specific effect of diphtheria antitoxin serum in the treatment of diphtheria<sup>13</sup>. Bingel was concerned whether the antitoxin in the serum was responsible for the effect or whether treatment with serum not containing the antitoxin would give comparable results. He alternately allocated 937 patients to either diphtheria antitoxin serum or normal horse serum (the placebo) and assessed the effect. He concluded that treatment with normal horse serum achieved a similar clinical outcome to that with the antitoxic serum.

In the 1930s, several important papers were published with regard to the introduction of placebos in clinical research. Evans and Hoyle<sup>14</sup> and Gold and colleagues<sup>15</sup> actually used the word placebo for the inert treatment given to controls in an experimental situation. Both papers assessed the value of drugs used in the treatment of angina pectoris in cross-over experiments and deceptively administered placebos to the 'no-treatment' comparison group. Various drugs were given, interspersed with periods of placebo administration. In both trials the drugs were judged to exert no specific action that might be useful in the treatment of angina. Gold and colleagues tried to explain why inert interventions might work: their points included 'confidence aroused in a treatment', the 'encouragement afforded by a new procedure' and 'a change of medical advisor'<sup>15</sup>.

In 1938, the word placebo was first applied in reference to the treatment given to concurrent controls in a trial<sup>16</sup>. In previous years, uncontrolled observations had given promising results with vaccines in preventing colds. Controlled experiments, with persons in the control group receiving no treatment, had also given favourable results. The efficacy of cold vaccines was evaluated in several placebo-controlled trials. The authors reported that

'the students in the control groups were treated in exactly the same manner as those in the experimental groups but received placebos instead of vaccine. The subjects in this group were given lactose-filled capsules which were indistinguishable from the capsules containing the vaccine. They were prescribed with exactly the same instructions as the capsules containing the vaccine.'

The trial gave negative results, although the results in the vaccine-treated groups were comparable with those in previously reported experiments. It was the substantial improvement in the placebo group that made the findings negative. The conclusion reads

'one of the most significant aspects of this study is the great reduction in the number of colds which the members of the control groups reported during the experimental period. In fact these results were as good as many of those reported in uncontrolled studies which recommended the use of cold vaccines'.

The placebo effect was born.

#### FROM 'HUMBLE HUMBUG' TO 'POWERFUL PLACEBO'

The view on placebos until the 1950s was that 'it cannot harm and may comfort the patient'<sup>17</sup>. The placebo was considered a 'humble humbug'<sup>18</sup>. While using placebos in research, clinicians began to recognize the therapeutic value of administering inert preparations to patients in control groups of trials. Henry Beecher was one of the first researchers to note this phenomenon. In his 1955 landmark article 'The Powerful Placebo', he reviewed 15 placebo-controlled trials and concluded that, on average, the magnitude of the placebo effect was 35.2%<sup>19</sup>. In retrospect, it is difficult to understand the large impact this paper had since 13 of the 15 papers reviewed did not include no-treatment groups. They could therefore not distinguish between changes caused by the natural course of disease and those caused by placebo. Remarkably, in the two studies that included no-treatment controls no differences were observed between the no-treatment group and the placebo group. Beecher made the mistake many still make: effects

observed in the placebo-treated group were solely attributed to the placebo. Anyhow, the paper has certainly had great impact on the concept of placebo<sup>14</sup>, and may be responsible for the misconception that a fixed fraction (one-third) of patients respond to placebos. Kienle and Kiene lately pointed to at least nineteen other possible reasons for the changes in the placebo-treated groups in Beecher's review<sup>20</sup>.

### **SURGERY AS PLACEBO**

At the end of the 1950s, several reports suggested that a surgical procedure, ligation of the internal mammary artery, alleviated heart disease. At that time collateral vessels were believed to originate from the internal mammary artery; thus, ligation of the artery would increase coronary blood flow through collateral vessels proximal to the point of ligation. Some researchers were sceptical about the efficacy of the operation, and the technique was evaluated in two very small randomized clinical trials<sup>21,22</sup>. All patients in both trials were actually operated on, but the artery was ligated in only half of them in one trial<sup>21</sup>, one-third in the other<sup>22</sup>. In both trials the rates of improvement were the same in ligated patients and those who received skin incision. Subsequently the treatment was abandoned, although neither trial had the statistical power to demonstrate equivalence. In 1961, Beecher used the data of these trials to calculate an overall improvement rate<sup>23</sup>. Interestingly, he found the average rate to be 37%, and stated that 'its average magnitude is the same as other average placebo effects encountered in disease'.

More recently, clinical trials of fetal dopamine cell implants for Parkinson's disease have been conducted. In these studies, one half of patients received the cell implants while the other half had placebo surgery.

### **PLACEBO RESPONDERS AND PLACEBO NON-RESPONDERS**

In the 1950s, researchers became interested in whether there were personality factors that would identify placebo responders (i.e. those who react exceptionally well to placebo treatment<sup>24</sup>). If it were possible to separate placebo responders from non-responders before the start of a trial, on the basis of personality characteristics, trials would become more efficient. Numerous experiments were conducted and many indicated certain personality characteristics in responders; however, such findings could not be replicated in separate studies and the personality of a placebo responder was never determined<sup>25</sup>.

### **DEFINITION OF PLACEBO AND PLACEBO EFFECT**

Because of the scientific interest in placebos and placebo effects, definitions were needed. In the early 1960s, Shapiro

defined placebo as 'any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated'<sup>26</sup>. Brody defined it as 'an intervention designed to simulate medical therapy, that at the time of use is believed not to be a specific therapy for the condition for which it is offered'<sup>27</sup>. Hornung has pragmatically defined placebo as 'an empty preparation or intervention imitating an effective preparation or intervention where one must decide on the "emptiness" of the preparation in each particular situation'<sup>28</sup>.

There has been considerable debate over the definition of the placebo *effect*. Shapiro defined it as 'the psychological or psychophysiological effect produced by placebos'<sup>26</sup>. Brody proposed a wider definition. He considered the placebo effect as 'a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property'<sup>27</sup>. Note that, according to this definition, a placebo effect does not require a placebo. Gøtzsche defined the placebo effect as 'the difference in outcome between a placebo treated group and an untreated control group in an unbiased experiment'<sup>29</sup>. Anderson prefers to define the placebo effect by inclusion rather than by exclusion and suggests 'an effect in which individually or culturally based expectations for a treatment cause are contributory to physical or psychological improvement after such a treatment'<sup>30</sup>.

From a theoretical point of view, we think that Gøtzsche's definition of the placebo effect is correct. However, it is difficult, if not impossible, to conduct unbiased experiments with a placebo-treated and an untreated control group because the treatment allocation can not be masked. Brody's definition is conceptually clear, but presents difficulties in operation. Methodologically, the purpose of masking treatment allocation is to make extraneous factors influencing the clinical course comparable between groups. These extraneous factors include the placebo effects as defined by Brody, but also include lifestyle adjustments and use of co-medication. Gøtzsche clearly refers to the latter concept. In psychologically oriented research on placebo effects, Brody's definition is frequently used. However, in the methodological work, Gøtzsche's definition is more common. This has led to some confusion in the past. We consider Brody's definition the more appropriate.

### **HAWTHORNE EFFECT**

The Hawthorne effect was described in the 1930s after investigations on the relation between illumination and industrial efficiency at the Hawthorne plant of the Western Electric Company in Chicago. According to legend, worker productivity at the plant improved not only when the

illumination was increased but also, later, when it was decreased. The reason was supposed to be the attention paid to the workers by the researchers and not the lighting itself. Although subsequent investigations revealed that improvements in efficiency had probably resulted from other factors<sup>31</sup>, the term 'Hawthorne effect' has survived to describe the phenomenon whereby a subject's performance changes simply because he or she is being studied. The Hawthorne effect is not part of the placebo effect<sup>32</sup>.

### **NOCEBOS AND NOCEBO EFFECT**

In 1961, Kennedy introduced the term *nocebo* to distinguish the pleasing and salubrious effects of an empty preparation from its noxious effects<sup>33</sup>. A few years later, the concept of *nocebo* was elaborated by Kissel and Barrucand<sup>34</sup>. Hahn has lately proposed that *nocebo* effects are in fact placebo side effects<sup>35</sup>. Kennedy and Kissel and Barrucand distinguished placebos from *nocebos* only in terms of positive and negative outcomes. Hahn proposes a definition of *nocebo* effect in which the expectation of the recipient is accounted for. This means that, if one expects a negative effect and this effect indeed occurs, it will be called a true *nocebo* effect. Knowledge of *nocebo* effects is hindered by ethical concerns<sup>36</sup>. First, as with studies into the placebo effect, experimental studies of *nocebo* effects involve deception of participants. Thus, participants cannot participate with full information, which makes informed consent difficult. Second, such studies into *nocebo* effects are expected to result in detrimental outcomes. Both these drawbacks make research into *nocebo* effects difficult.

### **WORKING MECHANISMS OF THE PLACEBO EFFECT**

Though sound scientific evidence is lacking, we believe that placebo effects exist across all disciplines of medicine. It seems therefore unlikely that a single universal theory can explain all placebo effects. Currently, several theories are taken seriously as possible explanations for the placebo effect, among them classic conditioning, response expectancy and a psychoneuroimmunological response. Classic conditioning considers the placebo response as a conditioned Pavlovian-type learned response that has its basis in experience<sup>37</sup>. Inert substances, procedures, people or treatment setting can all act as a conditioned stimulus for the alleviation of symptoms, if they have been repeatedly associated with powerful unconditioned stimuli. This theory focuses on the input; the placebo effect arises because it is stimulus-expected. The second theory, response expectancy<sup>38</sup>, is the anticipation of one's own automatic reactions to various situations. Response expectancy is different from stimulus expectancy in that it focuses on the output rather than the input. Neither theory, however, offers a

physiological mechanism, whereby the placebo effect is manifested. There is some experimental evidence that the placebo response in experimental pain is associated with conditioning<sup>39</sup> while other work points to the response expectancy model as more plausible<sup>40</sup>. Moreover, there is some evidence that endogenous opioids are implicated in placebo analgesia<sup>41</sup>, though how they would act in the proposed mechanisms remains unclear. In other disease models, a psychoneuroimmunological response has been suggested<sup>42</sup>.

### **CURRENT STATUS OF PLACEBOS IN CLINICAL TRIALS**

A frequent misconception is that a placebo-controlled trial is equivalent to a trial in which the control group receive no treatment. If experimental treatment is complementary to standard care, it can be given on top of standard treatment. Then, blinding is implemented by giving placebo-controlled treatment. If the treatment under study is competitive with established therapy, experimental treatment is contrasted with regular treatment. In this situation, blinding is established via a double-dummy technique. This means that patients in the experimental group receive a placebo for control treatment, and patients in the reference group receive a placebo for the experimental treatment. In the evaluation of treatment strategies, placebos are generally not indicated. Here, cointerventions and behavioural changes are part of the strategy under study. This situation, however, is prone to bias in assessment of patient outcome. Measures such as outcome adjudication by a blinded adjudication committee should then be taken.

Before a drug can be registered, the legal requirement is proof of efficacy in 'adequate and well-controlled trials'. Many groups have interpreted this rule as mandatory comparison with an untreated placebo group, but this interpretation is at odds with the ethical requirement that established therapy may not be withheld from patients. Attention has been drawn to the unjustified use of placebos in some clinical research<sup>43</sup>.

### **METHODOLOGICAL CONSIDERATIONS AND FUTURE DIRECTIONS**

A research design that can validly investigate components of the placebo effect is the balanced placebo design<sup>44</sup>. A good example is the study conducted by the general practitioner K B Thomas<sup>45</sup>. Thomas randomly assigned 200 symptomatic patients in whom no definite diagnosis could be made to one of four treatment arms—a consultation conducted in a 'positive' manner, with and without treatment; and a consultation conducted in a 'negative' manner, with and without treatment. Two weeks after consultation, he found a significant difference in patient satisfaction between the

positive and negative groups, but not between the treated and untreated groups.

By use of the balanced placebo design, we shall be able to identify important factors contributing to the placebo effect and to assess the impact of extraneous factors on specific treatment effects<sup>44</sup>. Thus, we should be helped to provide optimal treatment to individual patients and to discover the extent to which results of placebo-controlled trials can be generalized. Knowledge of the components of placebo effects in different disease models will contribute to both of these issues. Hence, there is a need for investigations to identify the most important non-specific factors. When these factors and the mechanisms of action have been uncovered, we shall have to debate their implications for medical research and clinical practice.

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