Concept of true and perceived placebo effects

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We often and wrongly equate the response seen in the placebo arm of a clinical trial with the placebo effect. In order to obtain the true placebo effect, other non-specific effects can be identified by including an untreated control group in clinical trials. A review of the literature shows that most authors confuse the perceived placebo effect with the true placebo effect. The true placebo effect is highly variable, depending on several factors that are not fully understood. A distinction between the perceived and the true placebo effects would be helpful in understanding the complex phenomena involved in a placebo response.

Interest in complex issues relating to the placebo effect has recently increased, and in 1994 most major general medical journals focused on the subject.¹⁻⁴ Some of the complexities are addressed in this wry definition: placebo is the "most effective medication known to science, subjected to more clinical trials than any other medicament yet nearly always does better than anticipated. The range of susceptible conditions appears to be limitless."⁵

This paper sets out to differentiate between the perceived and the true placebo effect. The former is what we commonly assume the placebo effect to be: the response observed in the placebo group of a randomised controlled trial. The true placebo effect equals this response minus other effects that often determine the outcome in all treatment groups of such studies.

Concepts

The response to the application of a placebo in a clinical trial (such as a new antihypertensive drug) is commonly equated with the placebo response—an average drop of 5 mm Hg seen in the placebo arm at the end of the treatment phase will almost automatically be attributed to the placebo effect. This is not necessarily correct. Undoubtedly a placebo effect may have contributed to the change in blood pressure, but several other factors could also have played a role.

Natural course of disease—We all appreciate that a disease or symptom may, over time, change in either direction. If, in our above example, the blood pressure would naturally decrease, such a change might exaggerate the perceived placebo effect. If it increased, the change would (partly) occlude the perceived placebo effect.

Regression towards the mean—Most biological variables fluctuate. In situations where end point variables are first measured while they are likely to be at or near a peak a second measurement would probably give a lower reading. In other words the blood pressure may, on average, be relatively high at entry and lower at the end of a treatment, quite unrelated to effects of treatment or placebo. Even though at first glance this phenomenon seems unlikely, it is very real indeed. Patients often see their doctor

because their complaint is at a peak. In clinical trials patients are often included because their symptom is present to a predefined degree (such as systolic blood pressure >160 mm Hg). In both cases a second visit would probably show that the blood pressure had fallen, thus contributing substantially to the perceived placebo effect.

Other time effects—To assume that the effect observed by administering a placebo for a given time (say four weeks) equals the placebo effect is to assume that all other factors influencing the outcome variable have remained constant. There are, however, several other potential effects that, depending on the clinical situation and setting, may change. For example, the skill of the investigator may have increased between the first and the last measurement. This may lead to detection of larger (or smaller) pathological changes than before, which can thus decrease (or increase) the perceived placebo effect. There also may be time effects related to the patients. For example, "white coat hypertension" could decrease as patients become used to having their blood pressure measured, which would spuriously increase the perceived placebo effect. In short term studies there may also be seasonal changes in blood pressure, which again could affect the size of the perceived placebo effect.

Unidentified parallel interventions—It is possible that patients, once included in a trial, become sensitised to the problem under investigation and contribute, either deliberately or unconsciously, to the clinical outcome. Hypertensive patients could, for example, reduce their salt intake, try to avoid stress, or adopt other modifications of lifestyle.

TRUE PLACEBO EFFECT

The perceived placebo effect is thus a function of several factors and cannot be equated with the true placebo effect. In trials with a parallel untreated group (no placebo or other intervention, as with "waiting list controls") these other non-specific effects would produce the same response as in a placebo group (except, of course, for the true placebo effect). If one therefore subtracted the effects observed in such a group from those in the placebo group the true placebo effect would be identified (fig 1).

The size of the perceived placebo effect in relation to the true placebo effect is variable. The perceived placebo effect is equal to the true placebo effect if no effect is observed in the untreated control group, but if

FIG 1—Differentiation of true placebo effect from perceived placebo effect

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the perceived placebo effect is of the same size in the untreated and the placebo control group the true placebo effect is zero.

The above concept is not relevant to estimating the size of the treatment effect in placebo controlled trials. Its estimation is usually done by subtracting the perceived treatment effect from the perceived placebo effect, which results in the true treatment effect (fig 2).

FIG 2—Differentiation of true treatment effect from perceived treatment effect

The concept may, however, be of crucial importance for the development of treatment strategies in clinical practice: the optimal benefit of a given intervention is based upon optimisation of both the specific treatment effect and the true placebo effect.^{4,6} It is therefore interesting that often no distinction is made between effects seen in placebo groups from those in untreated controls.

"Placebo" in the literature

We conducted a Medline literature search for all clinical trials and meta-analyses published during 1986-94 that included the words "placebo" and "untreated" in their summary. We read all 318 abstracts independently. Of these, 52 articles seemed (according to their abstracts) to contain both an untreated and a placebo group, and these we read in full. In fact only 12 of these did have both placebo and untreated groups. We now report on those studies that contained ratings of pain as a clinical endpoint.⁷⁻¹²

The table summarises key data from these publications. Generally, placebo treatment was effective in alleviating pain compared with no treatment. To elicit a true placebo effect patients must be conscious: in one trial placebo was administered directly postoperatively to sleeping patients, and no difference in pain ratings was observed between the placebo group and untreated controls.¹¹ Objective variables may also respond to placebo treatment: this occurred in trials where swelling and C reactive protein concentration after tooth extractions were significantly different in the placebo and the untreated groups.^{8,9} "Physical"

placebos such as detuned ultrasound equipment^{8,9} and sham acupuncture¹⁰ seem to be associated with more powerful true placebo effects than simple oral placebos.¹²

Comment

It is surprising how few studies with placebo and untreated controls could be retrieved. Other search strategies were tried (such as "non-treatment" or "waiting list" in addition to "untreated") but were not fruitful. Many authors of clinical trials simply do not make a clear distinction between the terms placebo and untreated but use these as synonyms. Clearly, this is misleading, ignores the complexity of the issue, and perpetuates widespread misconceptions about the placebo effect.

The cumulative effects of regression towards the mean, spontaneous remission, and other factors can be substantial. All may vary depending on the clinical situation and the design of the study. Our findings suggest that procedures intimately involving the patient and those that are invasive, like acupuncture or ultrasound treatment, are associated with more powerful true placebo effects than oral drug treatment. Similar findings have been shown in a recent comparative experiment: when patients were treated for primary varicose veins a topical placebo was shown to have more beneficial effects than an oral one, on both subjective and objective end points.¹³

A placebo response has been claimed to be a fixed constant amounting to about 30% of any given treatment effect.¹⁴ This is misleading. Neither the true nor the perceived placebo effect is such a constant. The extent of the true placebo effect depends on, among other factors, the attitude of the doctor or therapist (towards the treatment and the patient), on the attitude of the patient (towards his or her own health, the doctor or therapist, the type of treatment), on the conditioning of the patient (his or her suggestibility), and on the type of treatment (its mechanism as well as impressiveness, invasiveness, perceived plausibility, experience, cost, etc).¹⁵

Several other observations often made about the placebo effect seem to be debatable. True placebo effects are not inevitable and may be totally absent in certain clinical situations. They may not only affect subjective variables (such as pain) but also objectively quantifiable ones (such as C reactive protein concentration^{8,9}). However, placebo effects on pain have repeatedly been shown to be greater than those on other symptoms.¹⁶ Placebo effects are not

Summary of results of trials including a placebo group and an untreated control group

Study	Study design	Sample size	Indication	Interventions	Results in			Estimated true placebo effect
					Placebo groups	Untreated control groups	Experimental group	
Holroyd <i>et al</i> ⁷	Meta-analysis of 60 clinical trials	20 Placebo groups* 17 Untreated groups	Recurrent migraine	Propranolol or relaxation v various placebos	Average subject improvement 14.3%	Average subject improvement 2.1%	Average subject improvement 43.3% or 43.7%	Substantial
Hashish <i>et al</i> ⁸	Double blind controlled trial with five parallel groups (two not detailed in table)†	150	Tooth extraction	Ultrasound treatment v detuned ultrasound equipment	Postoperative pain score of 16	Postoperative pain score of 30	Postoperative pain score of 16	Substantial
Ho <i>et al</i> ⁹	Double blind controlled trial with five parallel groups (two not detailed in table)†	79	Tooth extraction	Ultrasound treatment v detuned ultrasound equipment	Postoperative pain score of 40.2	Postoperative pain score of 58.5	Postoperative pain score of 49.9	Substantial
Helms <i>et al</i> ¹⁰	Randomised controlled trial with four parallel groups (visitation, controls not detailed in table)	43	Primary dysmenorrhoea	Acupuncture v sham acupuncture at wrong points	Average pain score decreased by 52	Average pain score decreased by 19	Average pain score decreased by 115	Substantial
Sinclair <i>et al</i> ¹¹	Randomised double blind trial with three parallel groups†	3×10	Postoperative pain after hernia repair	Lignocaine spray on surgical wound v placebo spray	Pain score of 37‡	Pain score of 38‡	Pain score of 22‡	None
Nyboc-Andersen (1990) ¹²	Randomised double blind trial with three parallel groups†	62	Breast tenderness after abortion	Oral bromocriptine (2.5 mg twice daily) v oral placebo	Pain score of 35§	Pain score of 25§	Pain score of 7.2§	Marginal

*Not necessarily from the same trials.

†Double blind refers to experimental and placebo groups.

‡Estimated mean of pain scores during first 24 hours after surgery.

§During first 24 hours after abortion.

always beneficial and may present unwanted reactions (nocebo effects).

Conclusion

Although essential in most clinical trials, a clear distinction is still lacking between placebo and untreated control groups as well as between perceived and true placebo effects. When describing a placebo response, one must account for the natural course of the disease, the regression towards the mean, and other non-specific effects. The resulting true placebo response is highly variable between studies and may, in many cases, be substantially smaller than the perceived placebo effect. More research should be directed towards better understanding of the complex boundary conditions that may interact and determine the true placebo effect. The best way to achieve this is the inclusion of a second, untreated control group in placebo controlled trials provided that there are no ethical objections.

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Thromboembolic occlusion of a pulmonary arteriovenous malformation

A very unusual pulmonary embolism

Pulmonary embolism is a common medical emergency, typically associated with hypoxia secondary to a ventilation perfusion mismatch. Pulmonary arteriovenous malformations are rare and cause hypoxia due to direct arterial venous shunting. We present the case of a woman with both pulmonary embolism and a pulmonary arteriovenous malformation in whom an embolus fortuitously occluded the malformation leading to a paradoxical improvement in oxygenation.

Case history

A 74 year old woman was admitted to her local hospital with a history of rapidly worsening shortness of breath over the preceding few weeks. She had been suffering from slowly progressive dyspnoea for one to two years, and over the past six months her friends had noticed that her lips and fingers were bluish. Recently she had also become short of breath at rest. She had smoked 40 cigarettes a day for 55-60 years, and chronic bronchitis had been diagnosed several years before. Five years ago, after a minor episode of haemoptysis, plain chest radiography had shown a probable pulmonary arteriovenous malformation. She refused further investigation or treatment of this. She had no history of nose bleeds or overt gastrointestinal bleeding and no neurological symptoms.

On admission to her local hospital she was hypoxaemic and mildly hypercapnic on air (arterial oxygen pressure 6.6 kPa and alveolar carbon dioxide pressure 6.1 kPa). The hypoxaemia was unresponsive to oxygen therapy, suggesting the presence of a right to left shunt. Chest radiography again confirmed the presence of a possible pulmonary arteriovenous malformation. Four weeks after admission she was transferred to this hospital.

On admission she was cyanosed, with a respiratory

rate of 30 breaths/min, pulse of 100 beats/min, and blood pressure of 130/80 mm Hg. She had no telangiectases and no family history of hereditary haemorrhagic telangiectasia. The lungs were hyperinflated with occasional wheeze. She had no cor pulmonale and no cardiac murmurs or pulmonary bruits. Full blood count was normal (haemoglobin concentration 15.5 g/l). Pulmonary function tests showed a reduced vital capacity (65% of predicted) and a ratio of forced expiratory volume in one second to vital capacity of 0.50, consistent with chronic airflow obstruction. The electrocardiogram showed small inferior Q waves, and the chest x ray film showed an apparent pleural shadow in the left mid-zone but no obvious pulmonary arteriovenous malformation. Measurements of arterial blood gas pressures on air and oxygen showed a normal alveolar carbon dioxide pressure but an arterial oxygen pressure on air of 8.1 kPa rising to 14.6 kPa on 35% oxygen (fig 1)—consistent with ventilation perfusion mismatch rather than shunting. To look for the presence of pulmonary shunts, a lung perfusion scan was performed with technetium labelled macroaggregates of albumin with additional γ camera images over the right kidney. When intrapulmonary shunting is present, labelled aggregates may pass through to the systemic circulation, and the size of the shunt is then calculated from the amount of radioactivity detected in the right kidney compared with the amount injected. The scan in this patient showed no intrapulmonary shunt but showed multiple perfusion defects highly suggestive of pulmonary emboli. A ventilation scan confirmed that the defects were not matched. No source of thromboembolism was found despite investigations including Doppler ultrasound of the leg and iliac veins.

The patient was treated with heparin then warfarin, with an initial improvement in symptoms. Eight days

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