Just what is a placebo?

JOHN ELLARD AM, RFD, FRACP, FRANZCP, FRCPsych, MAPsS

Placebos have demonstrated many powerful effects. Clearly they are not inactive, and like all active substances produce side effects. But how do we define them?

Cognitive dissonance is an uneasy state of mind that arises when one tries to maintain two directly opposed beliefs. I experienced it first-hand about half a century ago, in this way.

I had been to a course in statistics and had learned about the double-blind experimental technique in which the medication under investigation is compared with a substance believed to be inactive – a placebo. Since the placebo given to the control group would do nothing at all, any benefits or harms in the active group would represent the effects of the medication. It was as simple as that – placebos were inactive.

Then it occurred to me that in my outpatients' duties I was using placebos and achieving very good results. There were virtually no useful psychotropic drugs in those days, and there were sufferers who needed 'something to take', rather than more complex psychological help. I made much use of the alkaline mixture of gentian, which I knew could do no harm. I wove a web of comfort and hope around it and many ingested these advantages with the mixture.

What then was a placebo? The one certain thing was that placebos were not inactive, so the first question was, what could they do? Notice I am evading the question of how to define a placebo – I shall come to that last.

The power of placebos

In the 1950s it had been suggested that if you ligated the internal mammary artery, blood would be diverted to the heart, and angina relieved thereby. The operation was done and the patients reported substantial improvement. Then a double-blind series was conducted in which some patients had the artery ligated and the others had no more than a skin incision. Both procedures produced very encouraging and equal benefits. This is particularly significant because angina does not have a tendency towards spontaneous remission.[1]

There is a long history of surgical operations achieving popularity for the cure of particular conditions even though there is no logical reason to believe that the surgery had any specific effect. Oophorectomy for hysteria, colectomy for 'toxic' diseases such as epilepsy, and the hitching up of various organs described as 'floating' come to mind. Johnson's review of surgery as a placebo is well worth reading – it is not easy to do double-blind trials in the area of surgery.[2]

A few more examples of the activities of placebos will suffice – the list is virtually endless. Placebos have been found to produce clinically significant changes in the pulmonary function of asthmatics[3] and significant benefits in the treatment of hypertension,[4] duodenal ulcers,[5] and migraine.[6] Given intrathecally, placebos have benefited patients with severe spasticity of cerebral origin.[7]

A trial in which the arteriogenic compound VEG 165 was administered by both intracoronary and intravenous infusion produced a strong sustained benefit in exercise time and the relief of angina. These results were matched by the infusion of placebo.[8] I could go on, but I believe that one must accept that placebos can be very powerful.

There have been many attempts to define those who will react to placebos. The literature is large and occasionally contradictory. The probability is that there is no such thing as a 'typical placebo reactor'.

The biological actions of 'inert' substances

Now we come to another problem. If you have condition X and I give you active substance Y, and then you improve significantly, we may be able to give some sort of physiological and pharmacological account of the processes involved. If next I give you a placebo (without telling you that it is a placebo) and you achieve a similar remission, then once more biological mechanisms are involved – to lower your blood pressure, heal your duodenal ulcer, diminish your spasticity, or whatever.

Now in some cases our 'placebo' produces measurable biological changes and improvement – just as is the case with the active substance administered. It is not easy to give a precise account of the difference between the two actions and to say that one is active and the other a placebo, for the latter in this case has produced quantifiable changes by quantifiable mechanisms.

The situation is complicated when the placebo is known not to

Dr Ellard is the Editor of Medicine Today, and a consultant psychiatrist, Sydney, NSW.

be inert. Suppose that the 'active' compound has some atropine-like side effects that would make the double-blind trial difficult to achieve. We could add a trace of atropine to our placebo, which is now of course active as well. And consider the agents that have been used widely in disorders which most would regard as having no pharmacological indication. Some of them are thyroid hormone, cyanocobalamin, vitamins, trace elements and the like. Here it is sometimes difficult to know whether the patient, the doctor, or both the participants in the process are manifesting the placebo effect.

There are two other points to be made in this context. The first is that placebos can cause side effects. Look at the statistical material accompanying any properly examined medication and you will see that those in the placebo group will develop many complaints, ranging from anorexia to xerostoma.

Take a preparation at random – for example, in trials with selegiline in Parkinson's disease. In the early stage of a trial involving 157 patients, those in the actively treated group reported side effects as follows: fatigue 26.1%, palpitations 10.8%, vertigo 25.5% and insomnia 26.8%. The corresponding figures for the placebo group were 19.7%, 8.9%, 22.3% and 20.4%. The differences are not striking.[9]

It is not surprising that a few patients have become addicted to 'inert' placebos: one took 10,000 placebo tablets in a year.[10,11]

So, what is a placebo?

To put it simply, it seems that two processes contribute to the effects of many therapeutic acts. The first can be understood, at least partially, in terms of the scientific knowledge of the day, and an extension of that knowledge can be expected to lead to advances in therapy. The second process in most cases is not as powerful, but it is pervasive and worthwhile. It may well be that it enters, to some degree, into most therapeutic encounters. It is difficult to know its limits: think of the hundreds of painless amputations performed in mesmeric sleep, before the development of effective anaesthetic agents.[12]

The history of response to placebos is so well documented – and their actions are so familiar to me from personal experience. Thus I was amazed to read in a recent *New England Journal of Medicine* article that detailed statistical analysis caused the authors to report that they found '... little evidence in general that placebos had a powerful clinical effect'.[13] The editorialist on this topic thought their conclusions 'just a bit too sweeping'.[14] I think it was Sir Peter Medawar who said that if you need statistics to prove your case, then you are probably wrong.

Obviously the process is psychological. If, unobserved, I slip a placebo into your coffee I would not expect it to relieve your migraine. We have words like 'suggestion' to describe the process, but we are doing little more than giving names to our ignorance.

Science is a technique essential in particular areas – we must pursue it and use it. It is not much use if one is writing sonnets, composing symphonies or trying to become the President of the USA. Some of medicine is like that. What we do for our patients, the way in which we do it, and the environment in which it is done gives our actions significance and that significance can have very beneficial effects. This is not a definition of a placebo but I suspect that the definition is somewhere in that direction. MT

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