Hyperbaric medicine and the placebo effect

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Abstract

(Bennett MH. Hyperbaric medicine and the placebo effect. *Diving and Hyperbaric Medicine*. 2014 December;44(4):235-240.) The placebo in medicine has a long and interesting history. Despite the widespread use of placebo medication and sham interventions in clinical research, surprisingly little is known about how placebos work. There is evidence the administration of placebo preparations can induce measurable changes in physiology including the production of endorphins. Placebos usually involve some form of deception, but have been shown to work even when their lack of 'active' ingredients is declared to the patient. The relevance of the nature of placebo effects has become a central debate in the field of hyperbaric medicine with the recent suggestion that 131 kPa of air may be an active therapeutic intervention rather than a convenient and convincing sham. This paper discusses the nature of placebo and participation effects and the implications for hyperbaric oxygen therapy if low-pressure air is regarded as therapeutic.

Key words
Placebo, research, hyperbaric research, evidence, general interest

Introduction

With the rising profile of evidence-based medicine over the last 30 years, physicians have an increasing appreciation of the advantages of high-quality evidence in clinical decision making. In this context, it is generally accepted that for the assessment of efficacy of new treatments, appropriately powered, blinded, randomised controlled trials (RCTs) are the design least prone to bias. This design is, therefore, the least likely to lead to false conclusions. Indeed, the very word 'random' has taken on a talismanic quality such that some investigators have included this descriptor even when it is inappropriate.

When well-planned and conducted, RCTs with blinding and allocation concealment have many advantages. Most importantly, they eliminate bias in the allocation of subjects to the alternative treatment arms. That is to say, a properly random allocation method ensures the only reason for differences between the subjects in each treatment group at the start of a trial are those due to random chance. The magnitude of this chance is dependent on sample size and is measureable using standard statistical approaches. An RCT that also ensures allocation concealment (where the individual responsible for enrolling the subjects cannot be aware of the group to which any individual will be allocated) and the blinding of subjects, investigators and outcome-assessors to the actual treatment received by each individual is even less likely to be subject to bias. In these trials, the outcome cannot be systematically affected by the conscious or subconscious bias of either the subject or the investigators because there is no way they can be aware what treatment any individual is receiving.

Of course few, if any, trials are in practice perfect in design and implementation. It is the job of well-informed critical appraisal to determine the reliability of a trial outcome and, therefore, the degree to which those outcomes should influence practice. Apart from a meticulous and thorough investigation of the methods and conduct of a trial, one further way to appraise treatment outcomes is to evaluate the robustness of apparent treatment effects (good or bad) across a range of studies in similar populations. This is the aim of systematic review and meta-analysis – both of which require appraisal of their design and conduct.

Except in rare circumstances where deliberate misconduct can be demonstrated, we have little choice as consumers of studies than to accept that trials are performed as described. Even given this, we should appreciate there are a number of subtle influences that only meticulous trial design and execution can avoid. This is particularly true of trials of human subjects where important outcomes are either subjective or require interpretation by outcome assessors.

One fascinating aspect of human trials is the potential for biases due to expectations about the effectiveness of treatments and the way in which they are administered. In particular, there are three well-described potential such influences – the 'placebo effect', the 'Hawthorne effect' and the 'nocebo effect'. They are sometimes summarised by the umbrella term 'participation effects'. These effects can make the interpretation of randomised trials problematic unless exemplary trial design is employed and the potential for participation effects acknowledged.

This paper will discuss the interaction of these effects and trial design with particular reference to how one may avoid systematic bias and misinterpretation of outcomes.

The placebo effect

A placebo has been defined as "*a substance or procedure… that is objectively without specific activity for the condition*

being treated".[1] Inherent in the concept of the placebo is an intention to deceive the patient and sometimes the investigator and the outcome assessor engaged in a trial. Often, patients given a placebo treatment will have a perceived or actual improvement in a medical condition; this is commonly called the 'placebo effect'. The placebo effect is simply the patient response that cannot be attributed to an investigational intervention. While most often thought of in terms of 'the power of the mind', there are a number of potential explanations, any of which may be operating singly or in combination. These include a direct effect of altered levels of hormones or endorphins, expectancy effects, regression to the mean and a flawed trial methodology.

HISTORY

The word placebo has an interesting origin. Derived from the Latin *placēbō*, meaning "*I shall please*", the use of this term began with St. Jerome's translation of the bible from the 'Old Latin' to that in use in the Christian church in the fourth century (the translation came to be known as the *Vulgate Bible*, referring to the use of the 'common' form of Latin). Here Jerome chose to translate the Hebrew *ethalec*, previously rendered as "*I shall walk with*", as "*I shall pleas*e" – *placebo* in Psalm 114:9. By the eighth century, this psalm was an integral part of the *Office of the Dead*, and verse 9 was the first response from the congregation: "*Placebo Domino in regione vivorum*" – "*I will please the Lord in the land of the living*".

In France, it was the custom for the mourning family to distribute largesse to the congregation immediately following the ritual. Often, distant relatives and even total strangers would attend the ceremony, singing the placebo response while feigning great anguish, in the expectation of receiving a satisfying repast. These 'placebo singers' were thus fakers and by the eighteenth century had given their name to fake remedies designed to fool the patient.[2]

At that time, and well into the nineteenth century, placebo remedies were described as 'commonplace methods or medicine', perhaps reflecting the relative lack of effective pharmacological agents. The term was not always pejorative. Placebos were used by even the most eminent practitioners. In his 1998 review of the subject, Kaptchuk quotes an 1811 definition as "*any medicine adapted more to please than to benefit the patient, sometimes with a derogatory implication but* ***not with the implication of no effect***" (my emphasis).[3] By the early twentieth century, the practice of deliberately administering therapies known to be inactive was becoming more questionable, with the famous US physician, Richard Cabot, saying that while he had been trained to use placebos, he had concluded "*I have not yet found any case in which a lie does not do more harm than good*".[4]

That placebos could have salutary effects was clear to practitioners from the start. The first 'proof' was published in 1799 by the British physician Haygarth, when he gave an account of the effectiveness of wooden sham devices designed to mimic the popular (and expensive) metal device called a 'Perkins tractor' at 'drawing out' rheumatism and inflammation in the head and face.[5]

Despite continuing to be the shady resort of charlatan practitioners, placebos have, however, found an enduring place in human clinical research. By the 1960s, placebo-controlled trials became the norm for trials designed to test new pharmaceuticals where no effective alternative was available, and in many jurisdictions such trials are required for the approval of new medications. In contrast to the placebo effect, inert substances may also produce unpleasant or harmful effects. The term 'nocebo' was coined by Walter Kennedy in 1961 to describe this phenomenon.[6] Kennedy chose the Latin word *nocebo* ("*I shall harm*") because it was the opposite of the Latin word *placebo*, and used it to denote the counterpart of the placebo response.

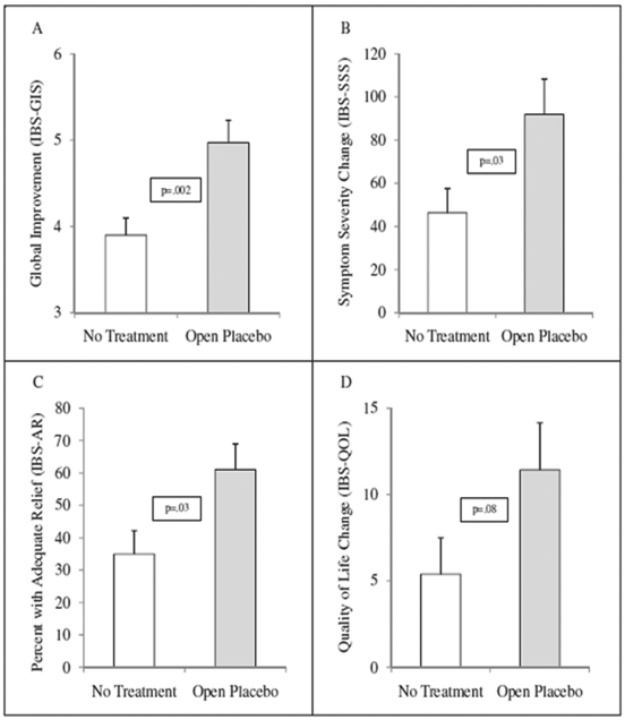
One might expect from a phenomenon with such a venerable lineage that we would now know a great deal about the mechanisms by which placebos can produce apparently beneficial effects. In fact, surprisingly little is known about what has become a fascinating area of study for some. Indeed, in 2011, the Harvard Medical School formally declared their ongoing interest with the establishment of the *Program in Placebo Studies*.[7]

EVIDENCE OF THE PLACEBO EFFECT

Common placebos include inert tablets, vehicle infusions, sham surgery and other procedures based on false information.[8] Whether we choose to call it a 'sham compression' or a placebo, an exposure to a hyperbaric chamber environment that is designed to mimic a true session of hyperbaric oxygen treatment (HBOT) clearly falls within this definition. A problem arises, however, if such a 'sham' actually has a therapeutic effect. Put simply, if a placebo actually has demonstrable and reproducible efficacy with clinically important effects, then it would cease to be a placebo and become an effective treatment. It seems a simple distinction, but herein lies the nub of a modern hyperbaric controversy.

Commonly, trials are designed to compare a putatively active therapy against a well-designed placebo or sham; well designed in the sense that the patient cannot distinguish one from the other. The purpose is to demonstrate whether or not the trial treatment can demonstrate effects over and above those produced by an inactive substance. Universally accepted placebos can have a surprisingly positive effect on a patient, and the degree to which a placebo may demonstrate benefit is discussed more fully below. However effective, the principle is that, if an 'active' therapy is no more effective than a 'placebo' therapy, then there is no ethical justification for using the 'active' agent. The most common rationale

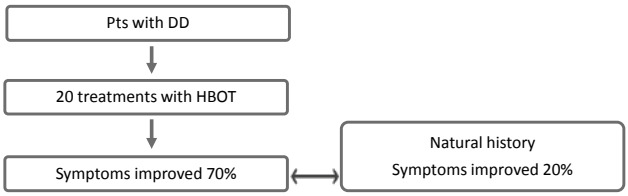
Figure 1
Improvement in four subjective measures of bowel health and quality of life in patients with irritable bowel syndrome (IBS); in all cases an openly declared placebo was superior to a no-treatment control group in this randomised trial (from Kaptchuck, 2010[10])



behind this is that the 'active' agent is less safe or more expensive and inconvenient than the placebo alternative.

This concept is not novel, and the medical literature is full of such examples. One such example relevant to hyperbaric practice for its physical nature is the well-known sham surgery trial of Dimond.[9] In this randomised study, an experienced cardiac surgeon performed either an internal mammary artery ligation for angina pectoris or a sham procedure through a similar incision with exposure of the vessels but no ligation. The patient and the cardiologist measuring the outcomes were blinded to the allocation. Both groups of patients reported statistically significant improvements in chest pain and used less nitroglycerine for pain relief, but there were no clinically significant differences between the groups. Electrocardiographic signs of ischaemia on exercise were unchanged before and after the procedures in either group. Although one could conclude that both the sham and the 'real' operative procedure were truly efficacious, Dimond preferred the interpretation that this was evidence of a participation effect. As he remarked in this paper "*The frightened, poorly informed man with angina, winding himself tighter and tighter, sensitizing himself to every twinge of chest discomfort, who then comes into the environment of a great medical center and a powerful positive personality and sees and hears the results to be anticipated from the suggested therapy is not the same total patient who leaves the institution with the trademark scar.*"

Figure 2
A case series describing the use of HBOT to treat hypothetical Davis Disease (DD)



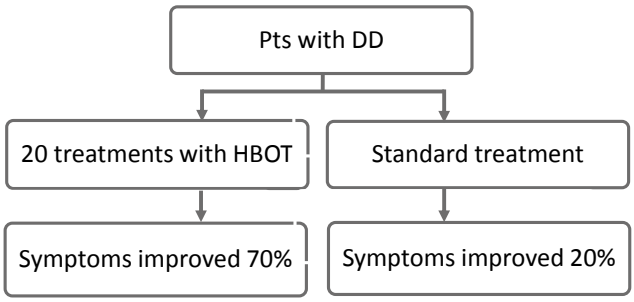
What is less well known is that placebos can have such effects even when the patient knows the given 'treatment' is without any active drug, as compared with a control group who knowingly did *not* get a placebo.[10] In this randomised trial, Kaptchuk tested placebo (with reinforcement) against a no-treatment control, with no attempt at deception or concealed administration. Patients were randomized to three weeks of either open-label placebo pills presented as "*placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes*" or no-treatment controls with the same quality of interaction with providers. There were widespread improvements in placebo over no treatment (Figure 1).

It has been known for some time that placebo effects can be exhibited through specific physiological pathways. In 1978, Levine published a fascinating example using the relief of dental pain with opiates as a model.[11] In a blinded, randomised, controlled trial using pain assessed with a visual analogue scale as the primary outcome, patients were given either naloxone or a placebo at three and four hours after dental extractions. Some given the placebo reported an improvement in pain scores and were identified as 'placebo responders'. The relevant finding for us is that on subsequent injection of naloxone, the placebo responders reported an increase in pain. The conclusion is that this particular placebo response is mediated through opiate receptors; placebo responders in this model produced endorphins that could subsequently be antagonised by naloxone.

Hyperbaric oxygen and the placebo effect

Imagine we are reviewing clinical work designed to demonstrate the effect of a course of HBOT for the hypothetical, chronic, incurable neurological condition 'Davis Disease' (DD), named for the first patient in whom it was described. The first piece of evidence we locate is a simple case series as represented in Figure 2. Case series are regarded as poorly reliable clinical proof because of the many potential sources of bias that may be present. For example, these patients may all have a mild form of the disease where symptoms wax and wane over time, or may not all truly have DD because of improperly applied diagnostic testing. One

Figure 3
A non-random comparative trial of HBOT versus 'standard treatment' for hypothetical Davis Disease (DD)



further source of bias is that they were all highly selected and motivated, and the improvement seen is a participation effect rather than a true pharmacological effect of HBOT. Whatever the 'truth', there are three potential conclusions: HBOT improved the symptoms of DD in this group of patients; these patients are different in some way from the usual patient with DD and this is the true expected rate of improvement for such a group; or the improvement is due to a placebo or participation effect. On the information given we simply do not know which of these options is the most likely.

We continue our review of the evidence and find the non-random, cohort study represented in Figure 3. Here a group of patients have been studied, some of whom were selected to have HBOT and some of whom continued to have the standard treatment available. Although the method and circumstances of this selection is of great importance in determining what biases may be more likely in this trial (e.g., those getting HBOT are willing to pay for it, or they are those mobile enough to attend the chamber), the fact is that any non-random selection method is subject to potential bias. Put simply, we cannot guarantee the two groups are exactly comparable in all respects except that one group received HBOT. In fact, our interpretation as to the 'true' effect of HBOT is almost unchanged. HBOT may improve the symptoms of DD, the patients who got HBOT may be different in some way that makes them more responsive, or a participation effect is operating. How likely the second option is to be true will depend on how truly comparable the two groups are; close examination of the methods used, the size of the cohort and the results of any subgroup or propensity analyses may influence our estimation of this likelihood. We still need more reliable information.

The next trial we look at is represented in Figure 4. Now we have found a randomised, blinded, controlled trial where HBOT is compared to a sham therapy involving compression to 131 kPa, breathing air. Importantly, neither the patients nor the investigators were aware of the group to which any individual had been allocated.

The results of the major outcome are reproduced in Figure 5. Both groups have improved in their 'badness' score

Figure 4
A randomised controlled trial of HBOT versus a sham therapy for hypothetical Davis Disease (DD); the sham was 131 kPa breathing air

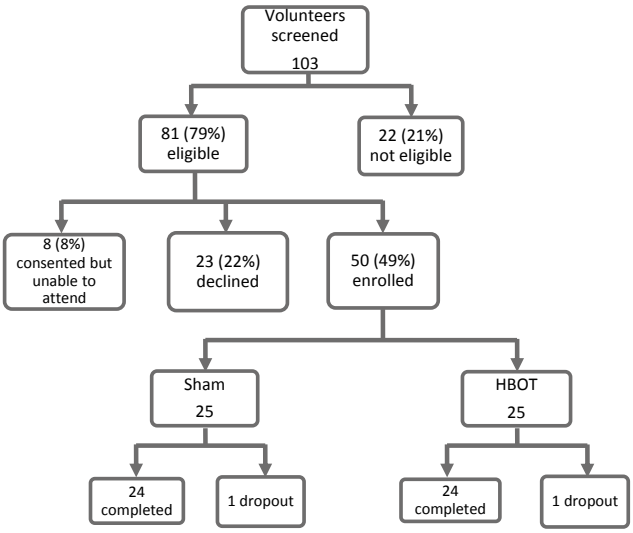
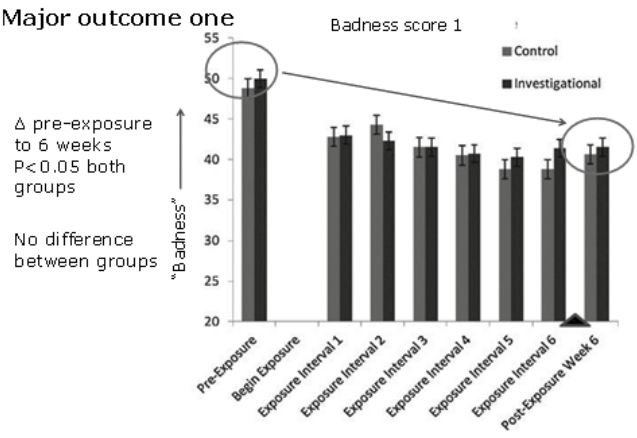


Figure 5
Results of the major outcome in the two randomised groups from the trial shown in Figure 4; the circles highlight the reduction in 'badness' scores in both groups; there are no between-group differences that reach statistical or clinical significance (figure modified from 12)



for this outcome, but there are no important differences between the groups at any time. The difference now is that we have effectively eliminated the potential conclusion that the observed effects are due to differences between the groups. These patients have been randomised, and we rely on this process to evenly distribute all important patient characteristics. Often, authors will publish the proportion of patients in each group who have known potential confounders for the outcome (or the mean value of such a factor), in order to demonstrate there are no important differences between groups, at least for those factors. This is a form of reassurance that the random schedule has performed as expected.

There are now only two potential conclusions – either both therapies work equally well, or there is no true efficacy for HBOT because it performs no better than sham. In the latter case, the improvement must be due to a placebo or participation effect. Which option you prefer will depend on your willingness to accept that the sham therapy is actually an effective treatment in its own right.

HBOT AND MILD TRAUMATIC BRAIN INJURY

In fact, these results come from a recent paper investigating the use of HBOT for the treatment of mild traumatic brain injury with ongoing symptoms of post-traumatic stress disorder or post-concussion symptoms.[12] The authors chose to accept the conclusion that a placebo effect was at work: "*Given that HBO_2, in this controlled study, demonstrates no therapeutic value, requires long treatment series, is expensive, exposes patients to potential side effects, and has limited availability, clinical usage is not warranted…*"

While this is the position accepted by the majority of practitioners in the field, there are a small number of practitioners and scientists who prosecute the alternative hypothesis.[13] Suggesting the sham here has a 'real' therapeutic effect invokes one (or more) of three mechanisms. Breathing air at 131 kPa may be therapeutic because of the pressure exposure or minor increases in the inspired partial pressure of oxygen or of the nitrogen in air. One disturbing consequence of this position is that it may not be possible to truly sham a hyperbaric oxygen session at all. Any convincing 'pretend' treatment will inevitably involve some positive pressure above ambient in order to seal the doors of the chamber and produce the need to equalize the middle ear. Efrati has suggested this leaves us with no alternative but to use open-label, randomised evidence as the best possible design in hyperbaric medicine (Efrati SB-JE, personal communication, 2014).

For the majority, the lack of evidence for a therapeutic effect of either the small amount of increase in inspired oxygen (equivalent to about 27% oxygen at 101.3 kPa) or the small increase in environmental pressure and inspired nitrogen means the 'participation effect' alternative is simply the much more likely proposition. This assumption is often referred to as *Occam's razor* or *lex parsimoniae* after William of Occam who popularised this approach in the fourteenth century. Put simply in modern English, Occam suggested that among competing explanations, the one with the fewest assumptions should be selected. While other, more complicated solutions may ultimately prove correct, the fewer assumptions that are made, the better.

Conclusions

The placebo effect is under active study and has proved to be both widespread and surprising in scope. Clinical trialists need to be wary of participation effects and in particular are urged to adopt RCTs with sham controls in order to tease out the true benefit of therapies above those that could be ascribed to placebo.

Once again we find ourselves at a fascinating point in the history of hyperbaric medicine. The long-running arguments within the field concerning the efficacy or otherwise of HBOT for a range of chronic neurological conditions have been hampered until recently by a lack of methodologically rigorous human trials. Sham-controlled trials in multiple sclerosis,[14–16] cerebral palsy,[17] post-concussion syndrome[12,18,19] and autism spectrum disorder (ASD)[20,21] have somehow moved this debate from 'does HBOT work?' to 'do both low-level compression breathing air and HBOT work?'. Of particular methodological interest in this regard is the small trial of Granpesheeh et al, who found no evidence in children with ASD of a difference in outcome between 'active' HBO at 131 kPa breathing 24% to 28% oxygen and ambient air using airflow noise to simulate compression.[21]

It is my opinion this is not a helpful debate and may be difficult to resolve. I have no certainty to offer here. The repeated demonstration that we can expect the same results with HBOT and trivial exposures while breathing air (and a number of other versions of sham therapy) seems much more likely owing to the placebo effect than an as yet unexplained mechanism. But it remains possible (if unlikely) that time will prove me wrong. At present, I cannot see how those on the other side of this debate can prove their assertions, given that shamming HBOT is not possible in their interpretation of the world. Interestingly, most protagonists of this interpretation of the evidence still advocate 100% oxygen breathing at 152 kPa rather than the safer, cheaper alternative of 131 kPa air.[22,23] This suggests they still believe in the benefits of HBOT over air-breathing despite the results of the trials referred to above. The impression given is that the goal posts are being moved.

Perhaps the best those of us who have taken Occam's approach can do is proceed with caution and await some form of convincing evidence that confinement in a chamber at minimal pressure really does have significant healing potential for the human brain. It is a fascinating possibility with great ramifications for the future of hyperbaric medicine. It is also very unlikely.

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The database of randomised controlled trials in hyperbaric medicine maintained by Michael Bennett and his colleagues at the Prince of Wales Hospital Diving and Hyperbaric Medicine Unit, Sydney is at:
<http://hboevidence.unsw.wikispaces.net/>

Assistance from interested physicians in preparing critical appraisals is welcomed, indeed needed, as there is a considerable backlog. Guidance on completing a CAT is provided. Contact Associate Professor Michael Bennett: <m.bennett@unsw.edu.au>