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Do medical devices have enhanced placebo effects?

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Abstract

Although the placebo in a clinical trial is often considered simply a baseline against which to evaluate the efficacy of a clinical intervention, there is evidence that the magnitude of placebo effect may be a critical factor in determining the results of a trial. This article examines the question of whether devices have enhanced placebo effects and, if so, what the implications may be. While the evidence of an enhanced placebo effect remains rudimentary, it is provocative and therefore worthy of further study. Suggestions are made, therefore, for how such an effect can be investigated without violating the principles of informed consent.

Keywords: Placebo effects; Medical devices; Effect enhancement; Clinical trial design

1. Introduction

In modern medicine, the placebo plays an indispensable but largely supportive role as a baseline from which to compare the efficacy of a drug or other therapy. Yet beyond providing a "no treatment" group, the placebo response itself may be important because its magnitude may influence the interpretation of a randomized controlled trial (RCT). For example, when an analysis was made of all the RCTs that examined the effectiveness of H2 blockers, it was found that drug effectiveness was demonstrated only in those studies whose placebo responses were relatively small [1,2]. In other words, the results of these trials depended on the magnitude of the response to the placebo, as well as the response to the active drug.

These findings suggest that the placebo response may also influence the results of other types of trials. A comparison between a drug in pill form and a device or surgery would be subject to a similar effect if, for example, the overall response to a device or surgery includes a greater placebo component than does the pill to which it is compared. Under such circumstances, a difference between two treatments might result from differences in their placebo effects rather than differences in the therapies themselves. If the placebo can influence the outcome or interpretation of a therapeutic trial in this way, it is important to determine what factors may modify the "placebo dose" and ask if different sham controls have different effects.

It is generally accepted that the strength of a drug placebo's response is related to its route of administration. In 1955, Louis Lasagna, an early investigator of the placebo effect, noted that "an injection is thought to be more effective than something taken by mouth" [3]. And it was said that "for universal patient acceptance nothing can approach the psychotherapeutic impressiveness of puncture of the integument by a hollow needle. The placebo substance introduced via the needle is usually second in importance to the needle stick [itself]" [4].

The notion of an "enhanced" [5] or "mega-placebo" [6] effect is probably applicable to interventions such as surgery or devices, if, as claimed, the placebo effect is influenced by elaborate rituals [7], appeals to mysterious powers [8], or high technology [9]. Indeed, acceptance of an enhanced placebo effect underlies the opinion that practicing physicians may "choose treatment whose appearance or route of administration is known to be associated with strong placebo effects" [10]. But do we know whether heightened placebo effects actually exist? As Lasagna states, "the art of the placebo" is "based not on any systematic investigation of the facts but on impressions" [3].

This article examines the evidence for the existence of an enhanced placebo effect for devices and discusses its implications for the design and interpretation of clinical trials. A heightened placebo effect may be particularly influential in determining the outcome of trials that compare a device ei-

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ther to a sham device or to a pill, or trials that compare a surgical procedure to medical management.

2. Evidence for an enhanced placebo effect

The documentation of an enhanced placebo effect is based on both direct evidence and meta-analysis. While some placebo research is recent, much of what is described below was performed between the mid-1950s and the late 1960s when the widespread adoption of the double-blind placebo-controlled RCT called attention to the significant effects of the placebos (and attempted to remove its distorting influence) [11]. This early period of placebo inquiry ended when the ethical requirement for patient protection in the form of informed consent put a formidable barrier in the way of placebo research.

2.1. Trials designed to detect an enhanced placebo effect

At least six clinical trials have investigated whether a device or procedure produces a heightened placebo effect. One of the earliest studies was motivated by a desire to define a "baseline under controlled conditions" for oral and parenteral placebos that could be used for future comparisons of antihypertensive agents given by these different routes [12]. The study was a four-arm, double-blind RCT in which 74 subjects received either parenteral ergotoxine alkaloids or parenteral placebo and another 60 subjects received either oral ergotoxine or oral placebo. Follow-up continued for up to 143 weeks. In an attempt to make treatment arms comparable with regard to the amount of time spent with the clinic nurse (what the researchers called "tender loving care"), patients receiving injections visited the clinic every 2 weeks whereas those in the two oral arms made weekly visits. Tablets were taken three times daily. The result was a dramatic lowering of both systolic and diastolic blood pressure in the two groups receiving parenteral interventions. In fact, no difference was detectable between parenteral drug and parenteral placebo. Furthermore, neither oral drug nor oral placebo had any effect on blood pressure. Although the different effects of oral and parenteral ergotoxine provide support for an enhanced placebo effect, the lack of effect on blood pressure of oral ergotoxine may also be explained by poor bioavailability of ergotoxine's oral dosage form. Nevertheless, the study's failure to exclude this possibility does not compromise its conclusion that "parenteral placebo is more effective than the oral placebo" [12].

Two early experiments on patients with arthritis were also influential in fostering the notion of an enhanced placebo effect. The first describes 88 highly refractory patients with rheumatoid arthritis who had "been exposed to an almost unbelievable number of nostrums, cultists, chemicals and physical agents, all of which [had] failed" [13]. When these patients received placebo pills for up to 4 weeks, 50% of them improved according to subjective criteria devised by the investigators. (By contrast, such objective measures of disease activity as erythrocyte sedimentation rate improved more slowly.) If patients did not respond to the oral placebo, or had only a transient response, their treatment was changed by the investigators to injections of normal saline. Sixty-four percent of those resistant to placebo tablets responded to injections and 82% of all placebo-treated patients had some benefit, which lasted for "2 to 20 months." The authors concluded that injections "are the best placebo," noting that injections seemed to be effective even for patients with "higher degrees of placebo resistance." The study is obviously flawed by lack of concurrent control subjects, and the results are likely to be influenced by selection bias because outcomes were reported for only 60% of placebo-treated patients. (The others appear to have been lost to follow-up.) Nevertheless, this report and a related study with similar results by the same investigators on 128 patients with degenerative arthritis [14] provided support for the belief in a graded placebo response.

Another early study of 39 patients with arthritis of the knee (21 with osteoarthritis and 18 with rheumatoid arthritis) seemed to confirm this belief. The subjects in this study had recently completed a three-arm double blind RCT comparing steroid injections of two types with an inert aqueous vehicle. Benefits in the three groups were indistinguishable. All patients were then given a week's supply of placebo tablets, and the success of this placebo was compared to that of the previous placebo injection. The authors found that the earlier placebo injections were statistically significantly more effective than the subsequent placebo tablets and that more clinical deterioration occurred with the placebo tablets. Their conclusion was that "in the comparison between the injection trial and the tablet trial, we are inclined to think that the ratio of 3:2 which favors improvements with injections, and the more striking fact that four times as many patients claim deterioration with tablets, are due to the different methods of administrating the placebos. In the case of the injection course, the whole paraphernalia of the aseptic ritual can hardly fail to impress suggestible patients, whereas the mere prescribing of tablets is surrounded by no such aura" [15]. These conclusions are open to question for a variety of reasons, among them the effect of order: the oral placebo was invariably administered after the parenteral placebo. Furthermore, the placebo tablets were administered only after a long, unsuccessful trial, which doubtless left many participants discouraged.

A trial that might be used to argue against the greater power of a parenteral placebo was conducted on hospitalized schizophrenic patients. This study, which had a complex study design, compared the effects of placebo pills or placebo injections on the level of activity of 64 schizophrenic patients on two wards who were matched on the basis of activity observed during a 10-day period. Patients were alternately assigned to one of two groups: one instructed to "heighten their activity" and the other to "lower their ward activity" [16]. Patients then received a daily pla-

cebo treatment that was supposed to help them follow these instructions. On one ward, patients in both the active and idle groups received oral placebo pills, while in the other ward both groups received intramuscular injections of sterile water. Ward behavior was monitored by aides who were blinded to the assigned treatment. Contrary to the hypothesis, neither placebo produced changes from baseline. It is hard to draw conclusions from this study because neither arm exhibited a placebo effect and, in any event, it would be hard to interpret the significance of the results.

An RCT performed in Germany, just before informed consent became mandatory in 1990, examined how a placebo's route of administration influenced therapeutic outcomes in a group of patients with varicose veins. In this study, 61 patients were randomized to receive either an oral placebo or a topical placebo to be applied to both legs. The latter was considered by the researchers to be a more elaborate placebo ritual. Treatment was given daily for 24 days. Subjective outcomes, quantified by having the patient mark visual analogue scales between two extremes, included cramps, stabbing pain, paraesthesias, heaviness of legs, itching, leg pain during standing or sitting, and need to elevate legs during the day. Objective measures included venous refill time as measured by light reflex rheography, foot volume by water plethysmography, and minimal leg circumference at the ankle measured with a standard tape. All evaluations were performed by a blinded investigator. Improvement was between 30% and 70% for each of the outcome measures. For six of the seven subjective symptoms (the exception being itching), the topical placebo was significantly more effective than the oral placebo. Light reflex rheography improved significantly more for the topical than for oral placebo group, and the other two objective measures followed this trend without reaching statistical significance. These results were published in a paper entitled: "Placebo treatment for varicosity: don't eat it, rub it!" [17]. Unfortunately, the authors could not exclude the possibility that rubbing had a beneficial effect on the microcirculation and hence on the disease outcomes they measured.

Another relatively recent experiment unintentionally provided evidence for an enhanced placebo effect. This was a randomized crossover trial that compared the benefits of acupuncture or diazepam in 44 patients with chronic cervical osteoarthritis of more than 6 months' duration [18]. Each patient was randomized to the order in which the different treatments (acupuncture, sham acupuncture, diazepam, and placebo) would be received. Pain intensity was measured before and 2 h after the treatment. Real acupuncture, sham acupuncture (with real needles at sham acupuncture points), and diazepam all produced equal results, and each was significantly superior to placebo pill.

Most of the studies just described lacked sufficient statistical power, and had other methodological weaknesses. Nonetheless, the results are intriguing and consistent with the hypothesis that some placebos are more powerful than others.

2.2. Evidence for an enhanced placebo effect from meta-analysis

One study pooled trials and performed a meta-analysis in an attempt to determine whether there is a difference between injected and oral placebos. A total of 35 RCTs were found that met inclusion criteria for comparing an oral and a parenteral drug for the treatment of acute migraine headache [19] of which the results of 22 trials could be combined. Thirteen trials were not included because of such problems as allowing rescue medication within 2 h of randomization or incomplete data. A total of 865 patients received an oral placebo, of whom 26% experienced pain relief, and 862 received a parenteral placebo, of whom 32% got relief. The "better" result with parenteral placebo, which was statistically significant, remained after adjusting for treatment setting and severity of headache at baseline. Adjustments were not made for such potentially confounding factors as other baseline differences in patient characteristics or differences in the way pain severity was assessed. Nonetheless, the authors concluded that subcutaneous placebo administration is associated with an enhanced placebo effect in the acute treatment of headache.

A second meta-analysis focused on determining the magnitude of the placebo effects of procedures under conditions that the researchers assumed would heighten expectations. The study examined peer-reviewed case series describing the results of "innovative" procedures, initially accepted by the medical community and subsequently found to be unsupported by RCTs [20]. The enthusiastic reports included glomectomy as a treatment for bronchial asthma, levamisole for herpes simplex virus (HSV), photodynamic inactivation for HSV infections, organic solvents (ethyl ether and chloroform) for HSV, and gastric freezing for duodenal ulcer. Outcomes were analyzed for a total of 6931 patients, treated in uncontrolled clinical trials by one of these five methods. Pooled data from these reports found that 2783 subjects (40%) had excellent outcomes 2049 (30%) good outcomes, and 2098 (30%) poor outcomes. In other words, a beneficial effect was found in 70% of subjects receiving these procedures, which the authors considered to be an estimate of the magnitude of the placebo effect under conditions of heightened expectations. Obviously, it is impossible to know to what extent this estimate is increased by bias due to such factors as unblinded reporting.

3. Implications of an enhanced placebo effect

Although scientific evidence for an elevated placebo effect remains inconclusive, it is worth considering the potential implications of such a phenomenon. Indeed, failure to do so in the past may well have contributed to errors in the design of some RCTs and misinterpretations of the results of others.

The most important implications of an enhanced placebo effect relate to the tendency to ignore how the placebo base-

line may influence the results of an RCT. In the placebo-controlled RCT, attention is usually focused on the active intervention (verum) [9]. Yet, the outcome depends on the difference between the verum and the dummy; hence, the effects of both dummy and verum must be accorded equal consideration.

An analysis of 117 RCTs that tested the efficacy of cimetidine or ranitidine in the treatment of peptic ulcer disease found a correlation between the magnitude of the placebo effect and the drug–placebo difference. The latter is usually considered to be a measure of the verum's (active drug) effectiveness. Thus, whether a trial has a positive or negative outcome partially depends on the magnitude of the placebo response. A bigger placebo response favors a negative outcome, whereas a smaller placebo response favors a positive outcome [1,2].

Because the placebo effect influences the magnitude of the baseline for the measurement of a therapeutic effect, it also influences the statistical power of a study. Thus, if a sham device tends to produce a greater placebo response than a pill, a RCT designed to prove the efficacy of a device may require more subjects if the control is a sham device than if it is a placebo pill. To avoid the problem of insufficient sample size in RCTs [21,22], sample size calculations should be based on realistic estimates of the differences between expected effects of verum and control arms. Three types of RCTs must be considered: device versus sham device, device versus pill, and surgery versus medical management. Let us consider the results of studies in each of these categories.

3.1. Trials that compare devices to sham devices

That so many RCTs comparing a device to a sham device in the control of pain yield equivocal results [23,24] may reflect an enhanced placebo effect of the sham device. Studies examining the effectiveness of acupuncture are a case in point. More than 500 RCTs of acupuncture, approximately half of them sham controlled, have been performed for a variety of conditions [25,26]. Yet, "disappointingly little has been achieved by literally hundreds of attempts to evaluate acupuncture scientifically" [27]. Thus, it must be asked whether inordinately high placebo effects contributed to the inconclusive nature of this research by weakening the statistical power of these trials. In an attempt to tease apart "placebo effects" from the "natural history" of the condition, one study examined only the results of acupuncture RCTs for various pain syndromes that included a "no treatment" control arm as well as both acupuncture and sham acupuncture arms. This study concluded that "acupuncture . . . treatment is associated with more powerful true placebo effects than oral drug treatment" [28]. Unfortunately, however, this study contained no quantitative data.

Because sham acupuncture needling is rarely compared to a placebo pill, it is uncertain whether the placebo response is truly "enhanced." It is also possible, of course, that "sham acupuncture" (needling at a false point or random needling, for example) may have counter-irritation properties that initiate neurological processes or stimulates other physiological mechanisms (such as the release of neurotransmitters). In fact, a vexing problem in the study of acupuncture, and other devices, is to select a placebo that mimics the verum and yet is a bona fide placebo! [29]. Nonetheless, an unusual result in one RCT acupuncture trial illustrates how a pure placebo effect may obscure a possible effect of the verum. In this study of 51 dental operative patients who received either real or sham acupuncture, blinding of patients was accomplished by hiding both the real and sham needles in a tube. The sham needle, however, never touched the skin because it became embedded in plastic on the undersurface of the holder. The result was that both real and sham acupuncture produced "100% success and high levels of patient acceptance" [30].

A high placebo effect is also found when transcutaneous electrical nerve stimulation (TENS) is evaluated for treating the kinds of pain for which acupuncture was evaluated. Placebo response rates, in many of these studies, range from 40% to more than 60% [31–33]. (Some TENS studies, however, have smaller placebo effects, comparable to those found with oral placebos [34,35].) As with acupuncture, however, the absence of comparisons between the TENS sham device and an oral placebo makes it impossible to distinguish between "usual" and "enhanced" placebos effects. Nonetheless, inordinately high placebo effects may contribute to the problem, often noted, of demonstrating the efficacy of TENS [34–38]. Similar considerations may help to explain the equivocal results obtained in studies evaluating therapeutic ultrasound for treating musculoskeletal pain [28,39–41] and epidural corticosteroids for treating sciatica [42,43].

High placebo responses have also been found in the few RCTs that have compared surgery to sham surgery [9] for such diverse conditions as angina pectoris, asthma, osteoarthritis of the knee, and Parkinson's disease [44–48]. Again, such studies provide only limited support for the notion of an enhanced placebo effect because the sham surgery was never compared to another kind of placebo intervention.

3.2. Trials that compare a device to a pill

Enhanced placebo effects may have important implications for RCTs that compare the effectiveness of a device to a pill. In this case, the placebo effect is imbedded in the results of two verum treatments. A differential placebo effect will confound a comparison unless the two possibly different placebo effects are controlled. Thus, trials comparing different routes of administration of the same drug or two drugs necessarily administered by different routes often use a "double dummy" or "double placebo," in which all subjects always receive both a pill and an injection (only one of which is verum). The justification given for this design, however, is the prevention of detection bias; the issue of controlling for placebo effects is rarely mentioned [49,50]. Yet this method of controlling for differential placebo ef-

fects is not always used. For example, a recent review of RCTs that compared NSAIDS given by different routes found the technique was used in only 65% of studies [51].

3.3. Trials that compare surgery and medical management

Clarification of the possibility of an enhanced placebo effect may help in refining judgments about the results of RCTs that compare surgical with medical (pharmacological) management. Such trials usually neglect the placebo effect by making a direct comparison of surgical intervention and medical management, thereby assuming that any placebo effect imbedded in the treatment arms is equal. If surgery or a device produces a greater placebo response than pills, then the likelihood of a Type I error increases when surgery or a device appears to outperform pills, whereas the likelihood of Type II error increases when both appear equally effective. This potential problem may be overlooked, for example, when comparisons were made between medical and surgical management of coronary artery disease [52–54], a disease in which placebos may have a striking effect [55–57]. Concrete evidence of an enhanced placebo effect may help to redefine the interpretation of such trials.

4. Designing studies to elucidate an enhanced placebo effect

It seems clear that the demonstration of an enhanced placebo effect would have a large impact on the interpretation of many completed RCTs and on the design of new ones, particularly those involving a comparison of two different types of therapeutic modalities. Were it not for ethical constraints, one might hope to demonstrate an enhanced placebo effect simply by conducting a RCT that compares the effects of a sham device and an oral placebo pill. A more ethically acceptable trial, however, would be done with four arms: two active treatments (a pill and a device, for example) and two placebos (an oral placebo pill and a sham device) [18]. A challenge for such a study design, however, would be to enroll enough subjects to assure sufficient statistical power.

Another approach would be a trial with a “parallel run-in period” in which all potential subjects are treated with placebo. A run-in period has been used as a means of identifying “placebo responders,” who then are disqualified from a subsequent RCT. A RCT from which placebo responders have been eliminated presumably becomes more efficient because it is limited to individuals with persistent symptoms and diminished placebo response rates [58–60]. The value of this approach, however, is disputed. Some argue that it has no value [61,62], while others argue that it is crucial for detecting efficacy in conditions with high placebo responses [63]. The method nevertheless remains in use for such diverse conditions as depression and hypertension.

We have not found a trial of a device in which a placebo run-in period has been used. If, however, a condition were identified that could legitimately be treated by either a device or a drug, a double run-in period of patients randomized to either placebo pill or sham device would provide an opportunity to test for an enhanced placebo effect. Of course, such a run-in period would be ethically acceptable only if all patients entering the trial subsequently have the opportunity to participate in a more familiar RCT, which offers patients a chance to receive either the device or the verum pill therapy. For example, subjects might enter a second phase of study after the run-in, in which each of the original placebo arms would be randomized to receive either continued placebo or its respective verum therapy. This second phase would provide additional, but less statistically powerful, data relating to the possibility of an enhanced placebo effect. In a sense, the proposed design consists of two separate studies: the first, a simple comparison of two placebos; the second, a conventional four arm RCT. The parallel run-in first phase provides a direct comparison of two types of placebos, but allows patients to be informed about the trial in general terms without jeopardizing the concealment that is obligatory for a placebo controlled study. To be sure that all patients have an opportunity to receive a verum treatment, those who want it could receive their choice of treatment at the conclusion of the trial.

Carpal tunnel syndrome, a condition with increasing prevalence that is becoming a major public health concern [64], provides a concrete example of how the study design might be employed. Both acupuncture and amitriptyline are being used as treatments, although the effectiveness of neither has been well demonstrated. One poorly designed RCT supports the use of acupuncture [65]; justification for the use of amitryptiline comes largely from its clinical success in treating fibromyalgia [66]. Thus, a RCT is justified both by the lack of scientific support for either treatment and a design that does not unjustly deny appropriate treatments [67,68]. When entering the trial, patients would be told they could receive acupuncture, sham acupuncture, amitriptyline, or placebo pill. In the “parallel” run-in phase trial, they would actually be randomized to receive either sham acupuncture or placebo pill. In the second phase, those in the placebo acupuncture group would be randomized to receive either verum or sham acupuncture, and those taking placebo pill would be randomized to receive either amitriptyline or its placebo. Furthermore, at the end of the study all patients, could be granted their choice of treatment.

This trial design should be ethically acceptable both in terms of informed consent and not denying available effective treatment. In addition, the risk of harm is minimal to all participants because sham acupuncture has the same benign risk profile as genuine acupuncture [69–71]. Sham acupuncture should not raise the same ethical issues as sham surgery [72,73].

5. Conclusion

The evidence for the existence of an enhanced placebo effect for devices and procedures is intriguing but by no

means conclusive. Most studies on the subject were conducted before the era of obligatory informed consent and suffer from methodological flaws that cast doubt on their validity. Yet, the phenomenon cannot be ignored because its existence has important implications for the interpretation of many influential RCTs. Suggestions have been made for how the enhanced placebo effect might be investigated without violating the principles of informed consent.

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