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THE CASE OF VERTEBROPLASTY TRIALS: PROMOTING A CULTURE OF EVIDENCE-BASED PROCEDURAL MEDICINE

Franklin G. Miller, Ph.D. and
Department of Bioethics, National Institutes of Health

David F. Kallmes, M.D.
Department of Radiology, Mayo Clinic

Abstract

Two independent, randomized controlled trials of vertebroplasty for the relief of pain associated with vertebral fractures demonstrated that this procedure was no better than a sham intervention. Publication of the trial results prompted strong, critical commentaries by practitioners and professional societies. In this article we offer a psychological explanation of this dismissive response to rigorous scientific evidence, which appeals to the "placebo reactions" of physicians when dramatic improvement is noted in patients' symptoms following administration of invasive procedures. We argue that the story of the response to the vertebroplasty trials underscores the need to develop a culture of evidence-based procedural medicine.

Vertebroplasty is a widely used procedure to treat pain associated with vertebral fractures. Initially developed in the 1980s for treatment of spinal tumors, it was subsequently introduced into practice for treatment of painful, osteoporotic vertebral compression fractures based on published case series [1–2]. Although the exact mechanism of action remains unclear, most practitioners believe that vertebroplasty relieves pain through stabilization of microfractures. Two recently published, randomized, placebo-controlled trials demonstrated that, in terms of pain relief and improvement in function, vertebroplasty was equivalent to a sham intervention that did not involve injection of cement [3–4]. The publication of these trial results stimulated the publication of a number of editorial commentaries in which vertebroplasty practitioners and their professional societies questioned the validity of these two studies [5–7]. Criticisms were primarily focused on patient selection and whether or not the studies utilized a true "placebo," since local anesthesia was used in the control arm.

In the current article we propose a diagnostic explanation of the critical response to the two placebo-controlled vertebroplasty trials and also offer a prescribed remedy to these types of responses. The diagnostic explanation highlights the idea of the physician as "placebo reactor," a psychological dynamic that reinforces clinicians' belief in the value of procedures that they recommend or administer and perceive to be beneficial. The term "placebo reactor" in this discussion refers to the reaction on the part of physicians to the observed clinical outcomes in their own patients. As a result of this psychological dynamic clinicians face cognitive dissonance when their clinical experience conflicts with clinical trial results. The prescribed remedy we offer is to develop the culture of evidence-based procedural medicine, which corrects the biases naturally produced by clinical experience.

Address Correspondence to: Franklin G. Miller, Ph.D., Department of Bioethics, National Institutes of Health, Building 10, Room 1C118, Bethesda, MD 20892-1156, (301) 435-8719, fmiller@nih.gov.

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The Physician as Placebo Reactor

In his classic text on the sociology of medicine, Freidson described the "clinical mentality" of physicians [8]. Written before the advent of evidence-based medicine, Freidson's account remains pertinent today. The clinical mentality reflects the disposition of physicians to take an activist orientation to treating patients and puts a premium on clinical experience. Freidson observes that "the practitioner is likely to have to *believe in what he is doing* in order to practice —to believe that what he does, does good rather than harm, and that what he does makes the difference between success and failure rather than no difference at all. He is, himself, a placebo reactor who is developing faith in his remedies and so modifying his behavior toward his patient" [8, p.168]. In a later passage Freidson notes that the physician's "commitment to his sense of effectiveness in treating the illness he sees is sustained by the uncontrolled role of his own placebo reactions in clinical practice" [8, p. 329].

The clinical mentality and associated tendency of physicians to become placebo reactors to their own treatments are apt to be all the more strongly operative in those areas of medicine that use invasive procedures to treat suffering patients, especially when dramatic improvement is observed shortly after procedural intervention, as in the case of vertebroplasty. A recent commentary of a spine surgeon who performs vertebroplasty, written in reaction to the placebo-controlled trials, is consistent with this hypothesis of the physician as placebo reactor: "On a personal level, most of us became proponents of these procedures because we saw dramatic results—usually unequivocal. Most patients report significant improvement in pain immediately after the procedure, and many bedridden patients are able to leave the hospital within hours" [9, p. 9]

The concept of physicians as placebo reactors is likely to be resisted by physicians because the placebo response is viewed as a phenomenon manifested exclusively by patients. Moreover, the scientifically trained practitioner may feel embarrassed by the characterization of himself as a placebo reactor. Although it is well understood that the physician-patient relationship can promote placebo responses, little attention has been devoted to the psychological dynamics of the physician that are analogous (but not identical) to the placebo response in patients. To be sure, physicians receive no therapeutic benefit from the treatments that they provide, but they do develop expectations and beliefs relating to the value of their treatments that are similar to placebo responses in patients—therapeutic benefit attributed to the context of the clinical encounter rather than the pharmacological or physiological properties of specific treatments.

An important explanatory approach to the placebo response in patients is what Brody calls "a meaning model" [10]. He analyzes this model as containing at least three generic components: "providing an understandable and satisfying explanation of the illness; demonstrating care and concern; and holding out an enhanced promise of mastery or control over the symptoms" [10, p.79]. Consistent with the first and third components of Brody's meaning model, physicians find and respond to meaning in their clinical practice. (Obviously, the second component of receiving a demonstration of care and concern applies only to the patient, not to the physician.) Scientifically trained physicians administer treatments on the basis of a therapeutic rationale that links the nature of the procedure with the correction of pathophysiology or anatomical injury. When these procedures are associated with marked patient improvement in symptoms, they provide physicians with an understandable and satisfying explanation of therapeutic success. It is instructive in the case of vertebroplasty practitioners critical of the placebo-controlled trials that they emphasize the putative mechanism of action of "microfracture stabilization," even though such an association has yet to be proved.

In addition to the link to pathophysiology, the observed therapeutic success gives the clinician a "promise of mastery or control over the [patient's] symptoms." Cognitive and emotional factors on the part of the physician contribute to the psychological dynamics of creating and reinforcing physicians' belief in the value of their therapeutic procedures, analogous to the formation of placebo responses in patients. Placebo responses in *patients* that represent genuine therapeutic benefit can be produced by "inert" interventions and accompany and augment the responses to known beneficial treatments [11]. Similarly, *physicians* can become placebo reactors to the treatments they prescribe or administer irrespective of whether they actually work to produce therapeutic benefit based on their pharmacological ingredients or procedural components.

Clinical experience naturally produces placebo reactions in physicians, which reinforce their belief in the value of the treatments they prescribe or administer. This experience is often unable, however, to determine whether treatments are effective by virtue of their pharmacological or procedural components, whether they work only by means of the patient's placebo response, or whether they do not work at all. The reason for this is an elementary principle of logic: association does not imply causation. The assumption of causation is an example of the logical fallacy of *post hoc ergo propter hoc* (after that, therefore because of that). In other words, the fact that therapeutic benefit follows the administration of a treatment intervention does not entail that the intervention caused the benefit. The clinician observes the patient before and after delivering a treatment but has no direct basis of comparison with untreated patients in order to assess *causality*.

The observed benefit that appears in clinical experience may be the result of true procedural efficacy, but may also result from the natural history of the condition, regression to the mean, or the patient's placebo response. Randomized controlled trials are typically necessary to determine whether medical interventions *cause* beneficial outcomes. When the outcomes are subjective, such as relief of pain, rigorous demonstration of causality demands placebo-controlled trials in which the patients and the outcome assessors are masked regarding what treatments patients receive. In other words, clinical experience leads to biased assessments of treatment effectiveness by virtue of creating placebo reactions in clinicians, which reinforce their beliefs in the therapeutic value of the treatments that they prescribe or administer. Evidence-based medicine is necessary to correct the biases that naturally arise from clinical experience.

Cognitive Dissonance

Evidence-based medicine is the ruling academic approach to clinical practice, but it is at loggerheads with the "clinical mentality." Abundant clinical experience, reflected in published case series, promotes the belief that vertebroplasty is an effective treatment for pain caused by vertebral fractures. However, the placebo-controlled trials of vertebroplasty imply, but do not definitively prove, that this procedure does not itself work to produce therapeutic benefit. As such, the trials suggest that the observed benefit is at least partially mediated through the placebo response. The conflict between these two sources of evidence, that is, clinical practice versus evidence-based medicine, causes cognitive dissonance.

It is noteworthy that the critics of the vertebroplasty trials did not take the stance that randomized, placebo-controlled trials are irrelevant to assessing treatment efficacy. In an era of evidence-based medicine, this would be seen as patently unscientific. Virtually all clinicians seem committed to evidence-based medicine, at least by paying lip service to the need for evidence from well-designed randomized trials. Instead, the critics focused on potential scientific flaws within the two published placebo-controlled trials. Commenting on the placebo-controlled trials, Orr noted, "My first instinct was to pick through the papers for flaws

that would invalidate the results" [9, p. 9]. Focusing on potential weaknesses in study design and performance dissipates the intense cognitive dissonance stimulated by the trial results.

Instead of rejecting, or at least seriously questioning, the therapeutic value of vertebroplasty, the critics rejected the evidence of the published trials. Had these trials not been judged to be methodologically flawed, commitment to evidence-based medicine would have required calling vertebroplasty itself into question. In other words, the cognitive dissonance between clinical experience and trial results could have been resolved in two different ways: judging the procedure to lack efficacy or, alternatively, judging the trials to lack validity. The critics took the latter stance, which may at least in part reflect the strength of clinicians' placebo reactions to the procedures that they administer and the weak commitment to evidence-based medicine. If the trials were flawed, as the critics contend, then clinicians can rest comfortably with continuing to administer vertebroplasty based on the psychologically compelling "evidence" of clinical experience and the methodologically weak evidence of unblinded randomized trials comparing this procedure with conservative medical therapy.

The methodological objections to the two placebo-controlled trials of vertebroplasty have been addressed in detail elsewhere and will not be repeated here [12–13]. We believe that these objections singly and together have no merit in challenging the conclusions of each of these trials that vertebroplasty is no more effective than a sham intervention without injecting cement in producing pain relief caused by vertebral fractures. All trials have methodological limitations. Nevertheless, the consistent results of these two placebo-controlled trials place a very heavy burden of proof on advocates of vertebroplasty. Owing to inherent biases, the accumulated clinical experience has very little evidentiary force as compared with the trial results.

Promoting a Culture of Evidence-Based Procedural Medicine

We have traced the deeply entrenched phenomenon of the physician as placebo reactor to the psychological dynamics of medical care, which is accentuated in those domains of medicine that administer invasive procedures. It is doubtful that the placebo reactivity of physicians can be eradicated or even that this would be desirable, on balance. On the one hand, we have pointed out the biases in assessing treatment effectiveness that this psychological tendency creates. More skepticism about therapeutic effectiveness of procedures that have not been rigorously evaluated might be salutary in correcting the unwarranted aggressiveness of medical intervention and the potential iatrogenic consequences, as well as reducing the costs of non-beneficial procedures. On the other hand, we want physicians to believe in the value of the treatments they provide, so that they can confidently assume the challenging professional responsibilities of medical care. Moreover, there is reason to think that the placebo reactivity of physicians may contribute to promoting positive placebo responses in patients. Clinicians' beliefs in the value of the treatments they recommend and administer are likely to help promote patients' expectations of therapeutic benefit, which in turn can enhance therapeutic responses.

In any case, we contend that the appropriate and most effective remedy for the deleterious consequences of physicians relying on clinical experience and associated placebo reactions is to develop the culture of evidence-based medicine. In the domain of procedural medicine, this is hampered by the fact that there is no regulatory requirement to validate experimental treatments by rigorous randomized controlled trials before they are introduced into standard medical practice. The FDA has authority to approve and regulate the marketing of pharmaceuticals and medical devices. It has no authority to regulate the practice of medicine. Hence, procedures are often introduced into clinical practice based on weak evidence from case series. FDA's requirements for approving medical devices are generally much less rigorous than for pharmaceuticals. This regulatory environment seems unlikely to change. To

date, payors in the United States have shown little interest in requiring rigorous evidence from randomized trials before covering invasive procedures. This may change in the future in the wake of growing societal concern about the escalating costs of medical care and the interest in comparative effectiveness research. Coverage with evidence development, in which promising but not yet validated treatments receive health insurance coverage only in the context of clinical trials to evaluate their effectiveness, deserves greater attention by Medicare and other payors [14].

Apart from systemic changes in regulation of medicine or insurance coverage, academic medicine and professional societies should take the lead in embracing and teaching evidence-based medicine. The training of physicians in procedural medicine, in residency programs and continuing medical education, should emphasize the principles of evidence-based medicine and the importance of validating innovative procedures by means of well-designed randomized trials. Especially disappointing to us has been the reaction of professional societies to the placebo-controlled vertebroplasty trials [6]. The placebo reactivity of individual clinicians is understandable. A higher standard should be expected of professional societies. Otherwise, they function as no more than trade associations dedicated to promoting the financial interests of their constituents.

Conclusion

Commitment to evidence-based medicine has yet to penetrate deeply into those domains of clinical practice that rely on invasive procedures. It has been deemed acceptable to introduce invasive procedures into practice without rigorous evaluation by means of randomized controlled trials. The response of clinicians and professional societies to the two placebo-controlled trials of vertebroplasty testifies to how thin the culture of evidence-based medicine is in interventional radiology and other medical specialties whose practitioners perform this procedure. This story may stand out in the intensity of the controversy generated by trial results, but it is far from unique. In this article we have endeavored to explain the defensive, critical response to the recent vertebroplasty trials in terms of the psychological dynamics of placebo reactivity among clinicians. To remedy the biases created by this “clinical mentality” we need to strengthen the culture of evidence-based procedural medicine. Cognitive dissonance between clinical experience and randomized trial results is inevitable; however, it is neither necessary nor desirable that this dissonance is resolved in favor of clinical experience.

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