Using Placebo Responses in Clinical Practice:

Is there a there, there? What do we need to know?

January 19-20, 2012
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Introduction

This meeting included expert presentations on the various issues of importance in the current world of placebo and each of those is summarized herein. But the heart of the conference was discussion of the challenges and opportunities for applying the new knowledge in the clinic and in the field. Extensive informal discussions among the speakers and other audience members followed immediately after each presentation, and again more formally at the end of each day. While these discussions cannot be reported here in their entirety, this report attempts to capture the spirit of those discussions, as well as highlighting the most important issues.

Physicians and other healers have made use of placebo effects, and have prescribed inert pills, throughout history. By the middle of the 20th century the phenomenon began to come under systematic scientific scrutiny. In the past few decades there has been an explosion of knowledge—biochemical and experimentally verifiable knowledge—about the basis of placebo effects. Today, our understanding has reached a level where placebo effects are candidates for entering standard medical practice in a more established and uniform way. But there have always been problems associated with the use of placebos and, therefore, with the institutionalization of the placebo effect. Chief among these problems are (1) the inherent ethical challenges associated with a physician’s being less than fully candid with a patient while “prescribing” a procedure that has no explicit medical basis; (2) the variability across patients (and even cultures) of placebo effectiveness; and (3) the existence of so-called “nocebo effects,” which are adverse reactions whose underlying etiology is the same as that for placebo effects.

What are the mechanisms underlying placebo effects? How do we understand them biochemically, neurophysiologically, and psychosocially? While there are no complete answers, a great deal has been learned in the recent past. This report concludes with a discussion of the future challenges associated with making placebo-based treatments a more regular part of medical training and treatment.

For readers interested in a more extensive scientific presentation of these issues, there is a special issue of the Transactions of the Royal Society of London (June 27, 2011, vol 336, pages 1781-1930) devoted to the topic “Placebo effects in medicine: mechanisms and clinical implications.”
Charting the path forward

Jack Killen

Dr. Jack Killen, Deputy Director of the National Center for Complementary and Alternative Medicine (NCCAM), gave the first formal presentation, speaking about National Institutes of Health (NIH) perspectives on the conference.

A growing body of evidence, much of it supported by the NIH, is elucidating the neurobiological and psychological mechanisms underlying placebo and nocebo effects. That evidence is providing fascinating insights into a variety of neurobiological processes. It is also prompting re-examination of important questions about intentional utilization or manipulation of placebo or nocebo effects in clinical practice. Can and should placebo or nocebo effects ever be used intentionally in clinical care? Under what – if any – circumstances might such use be medically and ethically appropriate? How does current understanding of placebo and nocebo effects influence the structure and context of the clinical encounter? These questions are particularly important given that much of what we know about placebo is built around normal volunteers and short term effects.

The hope of the NIH sponsors of the workshop is that discussion following very brief background presentations summarizing the current state of research will inform a forward-looking agenda of research aimed at providing the evidence needed by clinicians and policy makers in addressing such questions. The title of the workshop, which is play on Gertrude Stein’s famous quip about returning to her childhood home in Oakland after 50 years, is intended to capture the current state of uncertainty about whether placebo-based approaches can and should ever be employed in clinical practice.

Placebo and healing: Implications for practice, research & policy

Wayne B. Jonas

Dr. Wayne B. Jonas, President and CEO of Samueli Institute, used the stories of two patients to illustrate the opportunities and challenges that research on placebo and nocebo creates. One was a 56-year-old man who asked about acupuncture to help with his lower back pain. His wife had recommended acupuncture treatment, but he was unsure, and asked “Does it work, doctor? Or is it all just placebo?” The very form of these questions embodies an inherent problem on how to talk with patients about placebo. The conscientious physician looks into the literature and finds evidence that acupuncture is superior to the best current conventional therapy (see Figure 1), but sham acupuncture (where the needle locations and placements do not follow acupuncture theory) produces largely the same improvement. Thus, the most honest, direct and straightforward answers to this patient’s questions are: “Yes, it often works” and “Yes, it appears to be a placebo,” or as Dr. Jonas prefers, “It works via meaning and context (MAC) effects.” Given the way the patient came to the clinic, given how he asked the question, and given the likelihood that, if told acupuncture is placebo, the patient would not spend the time and money on it, and given that acupuncture would likely significantly help the patient, what communication and recommendation should the physician provide?

The second patient was a Marine who arrived carrying a bag of dietary supplements. He wanted to know about supplements for performance enhancement including something called “super-oxygenated (SO) water.” Many of his friends used such supplements (including SO Water) and were eager to try anything that might boost their performance so he had a lot of group reinforcement for these beliefs from his peers. He had a bag of supplements and wanted to get my advice on them. Upon analysis of the contents of that bag of supplements, it turned out that some contained the toxic metals arsenic and mercury, others (such as vitamin E) were self-administered in doses that could be harmful, and most of the rest had little or no evidence that they were useful for enhancing performance. Nevertheless, the harmless supplements might still, in fact, be “effective” in improving performance, but this effect would be due to placebo. In searching the literature on “super-oxygenated water” a randomized, placebo-controlled study was found in which tap water was given to two groups. In one group the water was labeled “super-oxygenated water,” and that group showed improved performance compared to the group given water that was labeled plain water. What should the physician tell this patient, given the social and peer context in which he operated?

These two examples illustrate the need to consider placebo and nocebo in the context of real-world encounters with patient needs. How do we address these issues in an ethical and evidence-based manner? Thirty years ago the prescribing of inert (e.g., sugar) pills was common. A physician could write a prescription for “Obecalp” (placebo spelled backwards) and pharmacists would know what to do. Today this is considered unethical. But many physicians still want to use the placebo effect to enhance healing. So instead of prescribing sugar pills, they prescribe actual medicines they believe are relatively effective.
harmless, even though those medicines are known to be ineffective for the condition at hand and may produce adverse effects. Such behavior by physicians who want to harness the power of placebo is understandable, but still unfortunate. Is this more ethical than giving sugar pills? Yet, deception, (of either the patient or the clinical) is unethical. We need better ways to engage the power of placebo (which we should reframe as meaning and context effects) in the service of healing.

**Memory for drug action: A key mechanism in placebo responsiveness**

*Fabrizio Benedetti*

Dr. Benedetti is one of the world’s leading researchers focusing on placebo effects. He gave a brief summary of several important findings that address the “memory” for drug actions, and their connection to placebo effects that mimic the drug actions.

What are the mechanisms that underlie the collection of effects that we call “placebo”? In descriptive terms, placebo can be driven by classical conditioning, expectation, and social observation. In terms of the neurophysiology, mechanisms for some forms of placebo rely on opioid receptors; others rely on non-opioid receptors; and some rely on the higher level cognitive functions associated with the frontal lobe. Disrupting any one of these pathways will decrease or eliminate the placebo effect.

Genetics, expectation, and several forms of learning are psychobiological factors that control reactions to placebo-based treatments. Within “learning,” there are also subdivisions, including social learning, reinforced expectations, and classical (“Pavlovian”) conditioning. Dr. Benedetti’s presentation focused on conditioning in the context of analgesic drugs to promote pain tolerance. Actual analgesic drugs (morphine or ketorolac) are used to demonstrate the behavioral consequences of analgesia when performing an increasingly painful endurance task. When other drugs are given to block the action of the analgesics (naxolone to block morphine receptors, or rimonabant to block ketorolac-activated cannabinoid receptors), the behavioral increases in pain tolerance and endurance go away. When placebos are given after several days of the drug-induced analgesia, strong effects are seen—but critically, these effects also go away if the blocking drugs are given. Thus, it is clear that the physiology of placebo-induced analgesia operates through the very same channels that decrease pain via drugs.

Analogous effects seen in mice suggest there are parallels between the mouse and human physiology that may foster future research into these effects.

Pain research is challenging for many reasons and one is that it is difficult to measure objectively. Subjective pain may be the most commonly studied phenomenon in association with placebo, but it is not the only one. There are placebo effects that can be measured more directly, using neurophysiological tools. In Parkinson’s disease, changes based on drugs (apomorphine), can be demonstrated behaviorally (via a measure of arm rigidity) and also via direct subcortical recording of an implanted electrode (in patients for whom this invasive procedure is justified clinically). These same behavioral and neurophysiological changes are seen on days when a placebo is used instead of the apomorphine, again demonstrating the close link between the physiological mechanisms for drug and placebo induced changes (as illustrated in Figure 2).

Importance is also attached to the distinction between “placebo effects” — any changes seen in a placebo group of subjects — and “placebo responses” — which are limited to changes due to the placebo/psychological manipulation itself. These two can now be experimentally separated using “hidden interventions,” wherein a treatment is administered without the subject’s knowing. If the treatment normally elicits analgesic effects, but those effects disappear when the treatment is performed without the subject’s knowing, one can safely deduce that those effects were caused by psychological factors, rather than caused by the treatment (as illustrated in Figure 3).

We can use this collection of experimental tools to ask questions that are new to placebo research. (1) What happens if the therapeutic rituals are eliminated? In the case of painkillers, we can ask this...
question by eliminating the “rituals of the therapeutic actions” (RTA). With hidden injection (and in the absence of ritual), pain reduction effects are eliminated or much weakened. This creates a situation where we can see a placebo effect with no placebo! This leads to the next question: (2) Do we need a placebo? Perhaps a sub-therapeutic dose of a drug can be used, leading to improvement via placebo effects? And in the cases where we know that the mechanism is based on memory for a given drug, can we (3) increase drug memory? By analogy to vaccination? Can we use these kinds of mechanisms to increase placebo effectiveness?


Conditioning and placebo responses: Lessons from mechanistic & clinically oriented research

*Luana Colloca & Ulrike Bingel*

Dr. Luana Colloca is a researcher at NCCAM, NIH. She spoke primarily about animal studies using classical conditioning in contexts where the effects seen could be interpreted as placebo effects in animals. Studies in the 1960s and 1980s with rats revealed that substituting placebos for active drug treatments delayed the onset of an autoimmune disorder (lupus, in lupus-prone mice). A recent replication showed similar effects in mice for a different disorder. The conclusion was that substituting conditioning stimuli (i.e., stimuli which themselves are not inherently therapeutic and therefore are examples of placebos) can lead to the delay of onset and decrease in severity of an autoimmune disorder in mice while using a cumulative amount of drug that would be ineffective by itself. A more recent study (using the immunosuppressant drug cyclosporin-A) looked directly at the changes in the physiology and metabolism of mice undergoing an analogous experimental procedure.

Of course, the point of doing these animal studies is to guide applications with humans. Dr. Colloca then presented the application of similar experimental protocols in humans. Cyclosporin-A affects the immune system in humans as well as mice. Two objective physiological measures were used to see the effects of the drug when it was actually presented. Cyclosporin-A blocks production of IL-2 (interleukin-2, a drug produced by lymphocytes that is part of the body’s immune response system) and also has interactions with IFN-γ (interferon-gamma, another important chemical in the immune system). By pairing actual administration of cyclosporin-A with a conditioning cue, the conditioning cue alone came to elicit similar (though less strong) changes in IL-2 and IFN-γ when presented in the absence of cyclosporin-A. Thus, the placebo conditioning experiments with mice have a direct correspondence with humans.

The sequence of events needed for application is illustrated to the right (Figure 4): Molecular and animal research, to enable a full understanding of the biochemical pathways for conditioned placebo responses; laboratory research with healthy subjects and patient subjects; clinical-randomized control trials, to proof efficacy of a therapeutic approach; and finally, routine clinical practice. Dr. Colloca’s primary message here was that these kinds of conditioning studies—using drugs and animal models followed by analogous testing in humans—could make a substantial contribution to our scientific understanding, and possible future use, of placebo effects.
Dr. Ulrike Bingel is a neurologist and Professor of Pain and Cognition at the Institute for Systems Neuroscience in Hamburg, Germany. Her presentation focused on conditioned responses in the pain system of the body. She began by reminding the audience that in most neuroimaging studies on placebo analgesia “conditioning,” is not studied separately from “expectation” but used in combination to maximize the induced placebo analgesic response. As illustrated below, in these studies “expectation” is induced by verbal communication (instruction) from the experimenter and reinforced by a conditioning procedure. A typical paradigm is illustrated at right (Figure 5). Both the “control” and the “placebo” groups of subjects are given a painful stimulation (indicated by the ‘80s) during the initial pain presentation session, and later they are given the same set of stimuli during the final testing session. In between, there is a “conditioning” or expectation manipulation session. In some studies, no verbal suggestions are given about the effectiveness of the “treatment,” while in others expectancy is explicitly modulated. In this paradigm here the participants were informed that “this cream will decrease your pain during the coming painful stimuli.” This verbal suggestion is accompanied (unbeknownst to the subject) by a substantial decrease (indicated by the 40) in the painful stimulation on the placebo treated skin area during that session.

Work from Luana Colloca comparing the effects of verbal suggestion alone and a combination of verbal suggestion and conditioning show that placebo responses are stronger and more sustainable when expectation is reinforced by conditioning.

In the group receiving the verbal suggestion alone, only a slight decrease in perceived pain is subsequently noted. But in the group getting both the suggestion and the conditioning experience with objectively decreased pain stimulation, the effect is much stronger, and a greater reduction in perceived pain is reported during the testing session at the end.

Of course, it is possible to use instructions that lead the subjects to expect increased pain, rather than decreased pain (“hyperalgesia” instead of “analgesia”). A manipulation of that sort can be called a “nocebo” effect in this context. Interestingly, research has shown that the use of verbal suggestion alone is just as strong as verbal suggestion plus conditioning (by changing the pain stimulus) in this hyperalgesic nocebo effect. This means that a physician telling a patient that they are likely to experience pain (or other unpleasant side effects) is much more likely, by itself, to cause the patient to have increased pain; while telling the patient that a treatment will decrease pain does not have nearly as much effect. On the other hand, including a conditioning procedure with a known effective drug or objective decrease in a pain stimulus will strongly enhance the positive placebo effect.

In addition to behavioral evidence for the changes in subjective pain during placebo analgesia, there is also evidence from functional brain imaging. Indeed, a 2009 study by Dr. Bingel and colleagues in the premier journal Science demonstrates changes down to the level of the spinal cord. As was mentioned by other speakers, the analgesic effects of opioid drugs can be demonstrated using functional Magnetic Resonance Imaging (fMRI) to illustrate changes in physiological activity of the nervous system (that is, changes in blood flow based on neural activity). Now there is additional evidence from brain imaging of metabolic activity using Positron Emission Tomography (PET). And, as Dr. Benedetti described in detail, it is not just the opioid receptor systems that are sensitive to placebo, but also other pathways including those relying on cannabinoid receptors. Dr. Bingel emphasized the value of imaging studies in addressing one of the traditional objections to placebo research, namely that subjects might be responding in ways to “please” the experimenter—perhaps reporting more change than they truly feel. Now that we can see objective changes in brain activity in parts of the brain and spinal cord known to be involved in pain processing, it is not likely that the effect is solely an artifact of trying to please the experimenter.
While this presentation looked only at the immune and pain systems, there is clear evidence that these effects influence other systems of the body as well. Dr. Bingel closed with mention of the use of interspersed placebos: the use of placebo to reduce drug delivery after a period of conditioning. Working out the optimal protocol for using the actual drug at first, and then gradually replacing some fraction of the drug administration with placebo is an obvious opportunity for animal studies of conditioning.

Discussion after this presentation was guided by questions that Dr. Bingel and Dr. Colloca presented at the very end: How long do the conditioned responses last? What are the optimal protocols? Are the protocols substance-specific? Can we quantify the presumed value of interspersed placebo administration—does this have benefits beyond cost reduction, such as reducing toxicity of side effects? How do we address for placebo (or any other treatment) the reality of individual differences in effectiveness?


Beliefs, expectancy and clinical outcome

Irving Kirsch

Dr. Irving Kirsch is the Associate Director of the Program in Placebo Studies and the Therapeutic Encounter at the Beth Israel Deaconess Medical Center and Harvard Medical School.

Expectancy, argued Dr. Kirsch, is the heart of cognitive functioning. We are trying to anticipate what will happen in the world so that we can adjust our behavior accordingly. Expectancy can be a conscious and slow process, as when trying to decide how to invest money, or it can be automatic and fast, as when a baseball player anticipates where they ball will be in order to be able to catch it. Expectancy can also affect perception. There is a famous “ambiguous picture” that can be seen as either a man or a mouse, and if it is presented after showing a series of animals, people are more likely to see it as a mouse, but if it is presented after showing a series of human faces, it is seen as a face. Placebo effects are examples of such expectancies.

In most instances, the effects of classical conditioning are mediated by expectancy. Dr. Kirsch described a study in which investigators surreptitiously reduced the intensity of a painful stimulus after administering a placebo cream to the arm where the pain stimulus was being given. Subsequently, when the full pain stimulus was returned, subjects experienced less pain with the cream than without—a clear placebo effect. Dr. Kirsch and colleagues repeated this experiment with the important difference that the subjects were told that the pain stimulus was being lowered during the training trials, so that they need not attribute the pain reduction to the effect of the cream. The idea was that if this placebo effect was an automatic process—one not mediated by cognition—then the pain reduction should still occur. But this did not happen. As shown in Figure 6, telling people that the pain stimulus was being lowered completely blocked the effect of conditioning on both the amount of pain people expected (left side of Figure 6) and the amount of pain they experienced (right side of Figure 6). In the same experiment, the correlation between expectancy and placebo pain reduction was measured to be .70. This was the correlation also found during a clinical study of irritable bowel syndrome (IBS). Taken together, these data show that the effects of conditioning depend on people’s expectations.

Figure 6. Left graph shows subjects’ predictions of how much pain they will experience when told (“informed conditioning”) or not told (“surreptitious conditioning”) that the intensity of pain stimuli during training trials was actually being reduced. Subjects predicted improvement significantly only when they were not informed of the manipulation. As seen on the right, those predictions were accurate. Subjects receiving the information that the stimulus intensity was being reduced during training showed no subsequent pain reduction.

Figure 7. Graph showing the increased effectiveness of placebo when accompanied by increased caring interactions between physician and patient.
Dr. Kirsch then discussed other ways in which expectancy and the placebo effect can interact. In particular, he described a study by Ted Kaptchuk and colleagues on IBS in which there were three treatment groups: a “wait listed” group, a group given a placebo treatment, and a group given the same placebo treatment but with much more time and apparent interest and comforting concern of the doctor. As shown in the slide at right (Figure 7), this combination of placebo treatment with increased physician-patient interaction in a caring way led to a greater response rate.

More recent studies are being designed to disentangle the roles of the therapeutic relationship and expectation. This will be done by having four groups in a 2x2 design. One group will have high expectancy of effect (because they are being treated) compared to the group who is put on a wait list (and will therefore have low expectancy of change). Each of these two groups will be subdivided, with one receiving perfunctory, brief encounters with the therapist (and thus presumably developing a weak therapeutic relationship) and the other half experiencing a much more engaged and obviously concerned therapist.

Dr. Kirsch closed with a discussion of hypnosis. Hypnosis could be thought of as a kind of “extra-strength” non-deceptive placebo. It is significantly correlated with expectancy and with the placebo effect, and it is effective with the same kinds of clinical conditions for which placebo are effective. Hypnosis is more effective, in general, than placebo pills; it is not deceptive; and it can and should be used as an adjunct to standard treatments. In meta-analyses of IBS hypnosis produced as powerful a response as active medications and a better response than placebo controls for those medications. Interestingly, both “enhanced placebo” (i.e., a placebo treatment augmented by a more substantial therapeutic relationship) and “open label placebo” yielded responses comparable to hypnosis and the drug treatments.

Placebo effects and implications for the doctor-patient relationship

Howard Brody

Dr. Brody is the Director of the Institute for Medical Humanities of the University of Texas. His presentation described some of the best and worst medical uses of placebos in current medical practice. The good news is that physicians have a healthy respect for the powers of mind-body interactions in medical practice. The bad news is that many physicians feel justified in prescribing drugs with potentially serious side effects in order to stimulate a placebo response. Such drugs include antibiotics, analgesics, and sedatives.

Dr. Brody reminded the audience of one basic dichotomy within placebo-based treatment: Is it the critical component the physician-patient relationship? Or is it the use of a pill? The answer, if one exists, would have direct impact on how placebo effects should be generated and used. The most likely answer is that both approaches work, and that the best placebo effects are elicited by making use of both: Have a caring and mutually respectful, engaged relationship with the patient; and use some of the other ritualized trappings of placebo (such as inert pills or other formal treatment protocols like acupuncture) to further engage the patient’s own healing mechanisms.

The example of “Marcus Welby, MD,” a successful medical drama television series of the 1970s, was used iconically to represent the caring physician who went out of his way to make good use of the doctor-patient relationship. This idea, “the doctor as a therapeutic agent” represents one key view of placebo. The second view, of course, is based on the use of impersonal rituals, as iconically represented by inert pills. Both are known to be effective, and their combination is apparently best. In one study it was shown that a warm supportive relationship between physician and patient adds to the measured placebo effects in a sham treatment of irritable bowel syndrome (IBS). And, importantly, this interpersonal relationship requires no misleading or deceptive use of medications. On the other hand, it takes a significant amount of time, energy and sensitivity for a doctor to create and maintain such a relationship with each patient.

There are several reasons that the “pill” approach to generating placebo effects continues to be popular. It is concrete and easy to implement. It is a natural belief on the part of the physician that the associated deception is a necessary part of the process. As was mentioned by Dr. Brody and several others during the conference, this last idea may simply be wrong. A recent study by Prof. Ted Kaptchuk and colleagues suggests that “open label placebos” (that is, placebo pills given to the patient with the explicit statement that they are placebo pills) can be effective for creating relief from some conditions. Today, the deceptive prescription of placebo pills is generally considered unethical. If one cannot prescribe a pill called “placebo” (or “obecalp”), then physicians may instead prescribe other pills which they expect will do little or no harm to their patients, while serving as the “placebo” to elicit and harness the appropriate effects.

Dr. Brody elaborated each of the two approaches in the spirit of this conference: how is the placebo effect best exploited and moved to standard medical practice? For “the doctor as a therapeutic agent” the key question becomes: How does a physician ideally stimulate a maximum, positive placebo response without using pills or other ritualized treatments? This question is close to Dr. Brody’s central personal concerns as a practicing physician, and he connects it to a “meaning model.” In that context the themes become clear, and are clearly entwined with both interpersonal and cultural contexts. All the approaches to building that relationship involve processes that are simultaneously simple, dyadic
interpersonal interactions, but also require a shared cultural world.

One component is “learning to listen,” especially when that listener is a person of authority who is taking significant time to interact directly and exclusively with the patient, while letting the patient “tell their story.” Research has shown that being put on a “waiting list for treatment” has better therapeutic effectiveness than being put in a “no treatment” group — even though there is no formal treatment in both cases. Expectation is clearly one component of such an effect, but Dr. Brody speculated that it may be enhanced by the form of the interactions associated with being put on the waiting list.

A second component is the delivery of a “meaningful explanation” from the authority figure to the patient, after listening to their story. The important thing is to convey the idea that the authority believes he or she has an understanding of what might be the problem. In medicine, the “meaningful explanation” is often a diagnosis. (Dr. Brody said that in the 19th century Oliver Wendell Holmes said something like: “congestion of the liver’ always works;” in other words, it can be more helpful to give a completely fictitious diagnosis than to appear to have no idea what is wrong with the patient.*)

A third component is the communication of “care and concern.” In the modern world of medicine, not only the physician’s presence, but the surrounding accouterments of a modern medical office convey the seriousness with which the establishment is taking the patient’s story. Of course, that is not nearly as important as the behavior of the physician during the interactions with the patient, but it does add gravis.

The last component is “mastery and control”: conveying the idea that something can be done, and that someone knows how to do it. Independent of the objective truth of the situation, a patient being told by his team of oncologists that “we simply don’t know what is going on” or “we don’t know what to do about this,” leads to a very different experience than being told “we’ve identified the critical problem and know what the best treatment is.” The latter can elicit both relief and the engaged energy of the patient.

Dr. Brody lamented the lack of research addressing the above beliefs about the best way to use a “meaning model” to improve healing. There are very few carefully controlled studies documenting the success of this strategy in clinical practice. There is an abundance of conclusive evidence that the placebo effect exists and is strong; but there is very little evidence about the best ways to harness it.

Returning to the second view, “pill as placebo,” there is a similar paucity of data about how best to exploit it (even ignoring for the moment the ethical issues).

Dr. Brody added a few more slides that he created during the workshops earlier presentations and discussions, for an inspiring closing summary. There is no “choice” about whether or not to “use” the placebo (and nocebo) effects. Those effects are going on in every medical encounter between patient and physician. They exist whether we want them to or not; whether we are consciously exploiting them or not. The “choice” is about how we go about using them: well or poorly, blindly or thoughtfully. Moreover, the time for having more research to help guide these decisions is NOW. The time is right for several reasons. We know more about the biological mechanisms underlying placebo. We have a better understanding of how to design empirical tests, because as researchers we were appropriately taken to task by our colleagues for logical flaws and alternative explanations in earlier placebo research. We have a better handle on the some of the problematic concepts whose careful articulation eluded previous generations of placebo researchers.

Practical challenges for moving forward with the best placebo research include: How do we assemble and support interdisciplinary research teams? How do we come to grips with the fact that a placebo
works primarily on “illness” (i.e., how you feel) and not on disease (what is going wrong in your body). This is not to say that there will never be research showing placebo effects directly on disease processes; it is only saying that we are not there yet. We are encouraged in hoping this will change by the clear demonstrations that some placebo effects use the same biochemical pathways as effective drugs. And this observation about the distinction between affecting illness versus disease, that is, affecting how you feel, is not meant in any way to be disparaging of the importance of helping patients feel better. That is, after all, the reason they come to us.

And finally, how do we incorporate the necessary qualitative components into research design—things like meaning, ritual and other difficult to quantify things that are nonetheless crucial aspects of the placebo process? What does it mean to say that a patient “expects” something? How do we incorporate that notion in our research designs?

Placebos and rituals

Ted Kaptchuk

Prof. Ted Kaptchuk is the Director of the Program in Placebo Studies and the Therapeutic Encounter at the Beth Israel Deaconess Medical Center and Harvard Medical School. He began his presentation by examining the role of rituals in placebo effects. This discussion was used as a lead-in for presenting patients’ own words about how they experienced being subjects in an experiment where they didn’t know if they were getting the real medical treatment or a placebo. Their comments led Prof. Kaptchuk to design and conduct some experiments using “open-label placebo” groups: that is, groups of subjects who are given placebos and are told very clearly that they are being given placebos, and what that means.

The term “ritual” is important and unique for the world of placebo research in its own right. “Ritual” does not assume or specify a mechanism. It is highly descriptive: it is not only expectation, it is not only conditioning, it is not only anxiety reduction, though it interacts with all of those mechanisms. Because of its unique features, attempting to understand the role of “rituals” in placebo helps us generate new hypotheses.

“Medical Ritual” has its own set of shared rules and assumptions. When one goes to the doctor for an ailment, there is waiting outside the examination-interview room; being measured for vital signs before entering the interview area; having a conversation with the doctor who then tells you to remove your clothes (which you do); and then being touched and peered at in ways that are not normally permitted outside a doctor’s office. You are told to put your clothes back on; another conversation ensues; and typically some medicines and procedures are prescribed for you before leaving. This ordinary encounter, which we do many times in our lives, is extraordinary in terms of comparison with most other interpersonal interactions. The fact that the patient and doctor share a set of assumptions and expectations about the coming events makes this a “medical ritual”:

- A prescribed and repetitive set of behaviors of more or less invariant sequences not entirely encoded by the participants and performed with the intention of promoting health.

As is typical for virtually all forms of ritual, there are associated cultural concepts of power; there is a narrative and a performance structure; it is a multi-dimensional and multi-sensory experience involving affect, cognition, morals and aesthetics; and it typically involves a “healer” with technical expertise and a charismatic presence.

Is modern medicine purely a ritual? No. By the criteria specified for randomized controlled trial (RCT) experiments, the effectiveness of a treatment is defined to be its effect after all the components associated solely with ritual (i.e., placebo effects) are removed. And yet, the very existence of placebo effects represents an unexpected revelation that ritual still has potency even within the modern de-mythologized and rational world of biomedicine.

How do patients in a RCT study think about placebo? Prof. Kaptchuk and colleagues interviewed a collection of such subjects at various points during an extended RCT study. What they learned was that patients thought a great deal about whether they were (for instance) getting a real acupuncture treatment or a sham acupuncture treatment. Note that the quality of sham acupuncture is now so good that about 85 percent of the subjects could not tell whether the needles were puncturing their skin or not. But that didn’t stop the patients from wondering and worrying about it. “Maybe I’m making the whole thing up” was a frequent comment from people who subjective health was improving; they didn’t know whether the improvement was “real” or “just due to placebo.”
It was then clear that patients in RCTs were actively thinking and worrying about whether they were in the placebo or “real treatment” groups. How could this new variable be addressed? Prof. Kaptchuk took the unusual approach of designing a new study in which the investigators were simply telling the patients which group they were in! It was advertised (during the subject recruitment phase) as a study of mind-body therapy for irritable bowel syndrome. When prospective subjects phoned the study group, they were told that it was a study using “placebo,” and they were asked if they had heard of the “placebo effect.” Then it was explained that this was a study involving two groups: a no-treatment control group and a placebo group. Prospective subjects were given an extensive explanation of the design of the experiment; and each subject was strongly encouraged to stay in the study even if they were ultimately in the no treatment group. At the end of the interview and explanation, an envelope was opened and the subjects were randomly assigned to the no treatment or placebo group. If they were in the placebo group, they were given a container of pills and told to take two pills a day for the experimental period.

This is the first study that ever randomized patients to open-label placebo and a no-treatment control. (There was a study in 1965 that treated 15 “neurotics” with open-label placebo but it did not have a no-treatment control. There has also been a dose-extension study in pediatric attention deficient disorder treated patients that combined open-label placebo with drugs; the study intervention was therefore more than open-label placebo. Kaptchuk and colleagues showed statistically significant differences between the placebo group and the no-treatment group. In effect, this is saying that the ritual by itself was enough to cause changes, even when the placebo-procedure was explained openly to the subjects."

Prof. Kaptchuk was careful to say that it is not clear how much this study should guide placebo research. But it is likely that there will be attempts to replicate it, as is always the case in science when a newly reported finding forces people to rethink their basic assumptions.


Kaptchuk TJ. Placebo studies and ritual theory: A comparative analysis of Navajo, acupuncture and biomedical healing [theoretical-philosophical analysis]. Philosophical Transactions of the Royal Society B

Nocebo research: Implications for clinical trials and practice

Luana Colloca

Dr. Luana Colloca is a researcher at the National Institutes of Health’s National Center for Complementary and Alternative Medicine (NIH’s NCCAM) in the Department of Bioethics and at the Clinical Center. She spoke about “nocebo” effects in research and practice. The same processes that create placebo effects can cause adverse effects “nocebo” effects. By “adverse effects” we mean any of a number of undesirable outcomes, such as the creation of painful side effects, dropping out of an experimental study, or discontinuing an active medication. One of the surprisingly clear findings, across a number of studies, is that verbal suggestions inducing nocebo effects (e.g., telling a subject that they are likely to experience pain or other negative side effects) are more powerful and longer-lasting than analogous suggestions for a positive placebo response. While there are ethical issues with some forms of nocebo effects, there are many for which physician behavior can be adjusted to avoid the nocebo effects, without any ethical problems.

A single verbal interaction can lead to long-lasting nocebo effects. In a study of the subjective experience of a specific, physically painful stimulus, delivered at the same time of each day over a period longer than a week, two groups of subjects were given different verbal information. Some subjects were told that “Repeated pain over several days will increase your pain sensation over time, e.g., from day to day.” The other group was not given such information. Without the information, pain ratings from the stimulus decreased over time (blue in Figure 8 at right), but for subjects given the above “information,” the pain did not habituate, and stayed high (red line in Figure 8.) throughout the study. These subjective reports were further verified via functional brain imaging data for the same subjects.

Nocebo effects are of great importance in RCTs (random controlled trials) for clinical research. For instance, in the placebo arm of anticonvulsant drug trials, subjects reported adverse events including anorexia, memory difficulties, paraesthesia (prickly or itchy skin sensations) and upper respiratory tract infections—all of which are adverse events reported for the drugs themselves. In another experiment, the presence of informed consent raised the number of adverse effects for the placebo control, relative to the active drug.

One of the important practical consequences of adverse events in RCTs is the dropout rate in clinical trials. Dr. Colloca showed quantitative placebo responses across a collection of studies ranging from 18 percent to 74 percent, leading to dropout rates between 2 and 10 percent.
Expectation effects—for example, saying things to a patient that leads them to expect or anticipate the possibility of pain—strongly increases the number of pain reports, even when in a placebo condition. In a study of headache subsequent to lumbar puncture, one group of subjects was told to expect a headache after the procedure. Of the 15 subjects so treated, seven reported headaches (almost 50 percent). Of the 13 subjects undergoing the same procedure, but not being told to expect headaches, none reported having had a headache when asked later. In 1981 (when this study was conducted) it was possible for the authors to suggest that patients not be told to expect a headache, even though such headaches are not uncommon side effects to the procedure. Today, a discussion of possible side-effects to any medical procedure is virtually mandatory.

One of the more striking studies was a report of nocebo effects in infants. Objective measures of infant pain response to a series (over days) of blood tests requiring a needle (venipuncture) showed an increase in anticipatory pain. The infants, who had previously not reacted to the gentle cleaning of the skin prior to the start of the series of venipunctures, began to exhibit such behavior as the days went on. They were apparently reacting to the previously neutral stimuli, in anticipation of the coming pain, (which made the procedure more painful than it might otherwise have been.

In adults, the knowledge that a pain-reducing procedure is being interrupted creates a greater increase in pain than the same interruption without conscious knowledge. In patients scheduled to receive a dose of morphine at a given time, the clinician is interrupted and explains this to the patient. The comparison is to a patient receiving morphine without active delivery by a clinician, so that the delivery can be surreptitiously interrupted. The graph at the right (Figure 9) shows, with blue circles, the increase in reported pain after an open interruption. The red circles indicate the almost flat pain level after a surreptitious interruption. Clearly, knowledge of the situation has substantially increased the patient’s suffering.

This collection of studies raises ethical issues in what would have seemed a straightforward question: Should the clinician discuss possible side-effects of a treatment with patients? There is a consensus today that the answer is almost always “yes,” but it is clearly the case that this procedure also entails additional pain and suffering for many patients.

Placebo: Clinical and Research Implications

Josephine P. Briggs

Dr. Josephine P. Briggs, Director of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) provided closing comments addressing overarching concepts associated with placebo.

Dr. Briggs shared with attendees her thoughts on a theme that is inter-related with placebo—the “over-activity” of our health care system. This concept contends that the United States medical system is doing too much, especially in terms of testing and treatment, and that this over-activity is not in the best service of healing. These concerns have been triggered by claims of overuse of diagnostic testing; the questionable validity or appropriateness of widely used tests for surgical decision making (e.g., the prostate specific antigen (PSA) test); potential dangers of prophylactic use of aspirin; and other examples, which have sparked controversy and criticism in the press. This concept of over-activity is, in some respects, an opposite side of the coin to placebo. Dr. Briggs noted that though a placebo may have enormous effects on subjective measures there are ethical concerns of deception, just as there are ethical concerns with over-treating. So, how do we harness the potential power of placebo, and how do we tease apart the complex language surrounding this concept to help inform a research agenda?

NCCAM began tackling this concept very early in its existence when it co-sponsored in 2000 a workshop, The Science of the Placebo: Toward an Interdisciplinary Research Agenda, to help untangle the concept of placebo from its historic trappings and look at it from a research and clinical perspective.

The word placebo has been in use in a medical context for hundreds of years, but what does it really mean? In today’s culture it is almost synonymous with something fake or the concept of quackery. However, many would contend that when we talk about placebo we are actually referring to contextual effects and meaning that often surround the patient-provider interaction and the rituals of care. Thus, the negative cultural definition of placebo is unfortunate as the medical community begins, perhaps for the first time, to seriously consider the potential utility of placebo in a clinical setting. And, it is unclear whether a word with such a deeply entrenched meaning can be recast or even abandoned.

This highlights the importance of words and of symptoms in thinking about the future utility of placebo. Indeed, the concept of symptoms holds some similar issues as we consider the distinction between illness—how you feel—and disease—what is wrong in your body—and how important that distinction is when evaluating placebo-related research Most patient-doctor interactions are, at least initially, oriented around symptoms—asking the person how they feel. While this information is useful, and an important guide to treatment; Western medicine is often more focused on understanding the underlying biological processes in the body, or disease-focused. Thus, placebo research, especially as reported during these workshops, can be seen in many respects as being at the boundary between illness and disease.

An excellent example of this is research done by Dr. Kaptchuk and his team. The team studied the effects of the drug, albuterol, versus various controls—placebo, sham acupuncture, and no-intervention—on asthma symptoms. They demonstrated that there was a striking dichotomy between subjective measures (e.g., Are you feeling better?) and objective measures (e.g., the maximum forced expiratory volume). While only albuterol had an effect on the objective measures, both placebo and sham acupuncture, in contrast to the no-treatment group, had effects almost as large as that of albuterol on subjective reports of improvement. Thus, this research highlighted that while placebo had
an effect on the subjective measures of illness or symptoms, it did not have effects on the objective measures of disease, which is a critical distinction to make and it helps us consider where the utility of placebo may lie clinically.

Dr. Briggs pointed out that this kind of reporting is essential if NIH and other funders are to make sensible decisions in the realm of placebo research. She reminded the members of the community the importance of reporting all research—positive or negative. This unbiased reporting will address the concern that only studies which find the desired effects are published, and that studies that don’t find the desired effects are not. Systematic non-reporting of completed studies for this reason raises not only huge challenges for funding agencies, but also would be a disservice to the important field of placebo research.
