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# Placebo Effects in Guidelines, Practice, and Patient Choice:

Beginning a Conversation about an  
Under-recognized Therapeutic Tool

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# Executive Summary

**For much of the modern era of medicine, the placebo has been largely viewed as a useful control in clinical trials. However, clinical research has demonstrated that placebo has powerful effects of its own. Despite this mounting evidence, providers rarely consider placebo effects in clinical management or treatment guidelines. The failure of providers to appreciate placebo effects represents a significant gap in care and is inconsistent with fully informed consent.**

Over the past few decades a variety of studies have demonstrated the effect of placebo in different clinical conditions, mainly for self-reported outcome measures and global ratings of improvement. Although requiring further replication, early studies have demonstrated the effectiveness of the placebo treatment even when it is administered without deception. The “placebo effect” encompasses a wider spectrum of effects than the results associated with the use of a sugar pill in a clinical trial. It comprises all the influences that surround the therapeutic experience, such as expectancy, the patient-provider interaction, trust, empathy, compassion, and the ritual surrounding pill taking.

It has become clear that there is not just one placebo effect. Psychological experiments have implicated conscious expectancy, classical conditioning, the patient-clinician encounter, and anxiety reduction as playing a role in the placebo response in different situations. Researchers also are beginning to delve more deeply into the mechanisms of the placebo effect and have demonstrated a neurobiological basis for clinical improvement induced by placebo.

In an effort to encourage discussion about placebo as a potential therapeutic tool, [the Robert Wood Johnson Foundation \(RWJF\)](#) funded a [five-part series](#) facilitated by [the Program in Placebo Studies at Beth Israel Deaconess Medical Center](#). The second event in the series, which was held on December 9–10, 2013 in Boston, included a public evening program and a one-day working group meeting to discuss the potential role of placebo in clinical guidelines, clinical practice, and shared decision making.

Participants in the working group discussed the many areas of uncertainty that exist regarding the placebo effect, including terminology, the magnitude of placebo responses and the factors that enhance it in different conditions, the underlying causes of the placebo effect, the potential roles for the use of placebo, ethical considerations, framing effects, the relationship of placebo to shared decision making, and consideration in clinical research and clinical practice guidelines. An important outcome of the working group meeting was a new consideration of the placebo effect in each participant’s area of focus; many participants had been unaware of many aspects of the placebo effect prior to the conference.

The participation of a patient and his spouse added a unique perspective to the working group discussion. As an individual with a chronic condition for which mainstream treatments do not alleviate all symptoms, he shared his view that the priorities of patients and scientists differ in several aspects.

## Based on presentations and discussion, the working group created a preliminary set of recommendations:

1. Raise the awareness of clinicians about the placebo effect, including its physiologic underpinnings and the existing evidence base (e.g., through letters to the editor, review articles in clinical journals, or additional reporting about placebo responses in drug clinical trial reports).
2. Develop a standard taxonomy for the placebo effect, including terms such as placebo, placebo effect, context, ritual, nocebo, and nocebo effect.
3. To move the awareness and use of placebo enhancing behaviors into the mainstream of clinical care, invest in studies to build the evidence base and work with organizations to build the harnessing of placebo effects into standard practice.
4. Conduct mechanistic studies of placebo that include patients (rather than healthy volunteers) and evaluate longer term outcomes.
5. Fund research to better understand these aspects of the placebo effect.
6. Where appropriate, build placebo into the analytic framework for clinical research (i.e., include both a placebo arm and a no intervention arm in addition to the active treatment arm).
7. To ensure that the variability of placebo effect is taken into account, encourage stratification by severity of illness in clinical trials.
8. Expand acceptance of the use of subjective measures, especially in light of the heightened focus on improving the patient experience.
9. Encourage clinicians to discuss with patients both the efficacy of drugs relative to placebo and the absolute response rate, or effectiveness of the drugs.
10. Replicate open-label placebo studies.
11. Ensure that measurement of the placebo effect assesses meaningful clinical improvement, whether as functional status metrics, or symptom scores changes.
12. Develop standard outcomes measures and a standard database for collection of results to enable patient-level meta-analysis.
13. Work with the Agency for Healthcare Research and Quality and National Institutes of Health to ensure that evidence-based practice center (EPC) reports include placebo use and the responses to questions about data on the placebo response.

While these early recommendations require refinement and expansion, they represent a preliminary blueprint for the steps to close the gap that currently exists in clinical practice related to the consideration and use of placebo.

## Acknowledgements

We would like to thank the Robert Wood Johnson Foundation for funding this event, Diane W. Shannon, MD, MPH for her writing services, and Deborah Grose and the rest of staff of the Program in Placebo Studies for administrative support.

# The Placebo Effect: Powerful Yet Under-Recognized

For much of the modern era of medicine, the placebo has been largely viewed as a useful control in clinical trials. However, a growing body of evidence demonstrates that placebo has powerful effects of its own. For example, a 2008 trial demonstrated that placebo effects could be administered in a dose-dependent manner to provide adequate relief for up to 62 percent of patients with irritable bowel syndrome.<sup>1</sup> A 2014 comparison trial of rizatriptan and placebo for acute migraine documented that when the drug was labeled as placebo its efficacy was similar to that of placebo labeled as the drug.<sup>2</sup> In the same study, researchers calculated that placebo accounted for more than 50 percent of the effect of the migraine drug and concluded that the ritual of pill taking and the information provided to patients are integral components of the treatment effect.

Despite the mounting evidence of the power of the placebo effect, providers rarely consider placebo effects in clinical management or treatment guidelines. For example, the federally maintained website [www.clinicaltrials.org](http://www.clinicaltrials.org) includes no mention of studies directly studying the placebo effect. (Harold Sox, personal communication, December 9, 2013) Similarly, a search of the clinical guidelines clearinghouse maintained by the Agency for Healthcare Research and Quality (AHRQ) results in no entries for treatments or interventions that attempt to harness placebo effect or include placebo directly.<sup>3</sup>

The failure of providers to appreciate placebo effects represents a significant gap in care: the potential for placebo to enhance pharmaceutical effects or serve as a therapeutic tool in its own right is currently being overlooked, and thus a potentially effective therapy is underutilized. In addition, the data on the placebo effect are not widely discussed with patients, creating an ethical dilemma. Withholding information about how effective therapies compare to placebo or about placebo effects in general is not consistent with fully informed consent and may preclude an effective shared decision-making process. In short, providers are currently failing to consider and inform patients of a potentially important treatment option.

## Encouraging Conversations about Placebo

Recognizing the ethical and clinical implications of the lack of consideration of placebo as a potential therapeutic tool, [the Robert Wood Johnson Foundation \(RWJF\)](#) funded a [five-part series](#) facilitated by [the Program in Placebo Studies at Beth Israel Deaconess Medical Center](#), which is affiliated with Harvard Medical School, to further the discussion of the placebo effect in clinical medicine. The second event in the series, which was held on December 9-10, 2013 in Boston, included a public evening program and a one-day working group meeting to discuss the potential role of placebo in clinical guidelines, clinical practice, and shared decision making.

The goal of the event was to raise awareness and advance the discussion about the failure to consider placebo in clinical care. Rather than providing answers, the event was aimed at raising important questions about the current thinking regarding placebo. The approach taken by RWJF is summed up in this statement from their web page on the power of the placebo effect, “If the placebo effect is to become a legitimate addition to the clinician’s toolbox, then we must better understand its underlying mechanisms and the circumstances in which it is most effective.”<sup>4</sup>

Experts from a variety of medical fields were invited to participate in the working group, as was a patient with a long history of advocating for the interests of patients with chronic illness. Importantly, invitees had not previously studied the placebo effect. Instead, their attendance represented an important step toward encouraging the consideration of placebo by leaders in a range of disciplines. (See the [appendix](#) for a list of participants.)

## A Clinical Epiphany

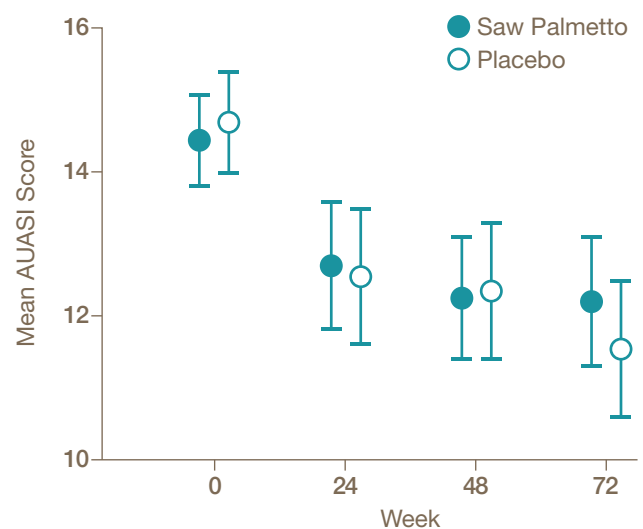
Michael Barry, MD, clinical professor of medicine at Harvard Medical School and president of the Informed Medical Decisions Foundation, opened the public evening program by describing his epiphany about the placebo effect—an experience that presaged those of many attendees of the two-part event.

In the late 2000's, Dr. Barry and colleagues conducted a large, randomized, placebo-controlled, double-blind trial that compared placebo with saw palmetto in the management of lower urinary tract symptoms (LUTS) in men.<sup>5</sup> The men had American Urological Association (AUA) symptom index scores of 8 to 24, which indicate moderate symptom severity. The primary outcome was the change in AUA symptom index scores from baseline to study completion at 72 weeks.

After screening, 369 men were randomized to receive either saw palmetto in escalating doses up to three times the standard dose or placebo pills that were similar in appearance. After 72 weeks, about half (48.9 percent) of the group that received saw palmetto experienced a drop of 3 point in AUA symptom index scores, compared with 52.5 percent of the placebo group. The difference was not statistically significant. There were virtually no side effects attributable to saw palmetto (saw palmetto was associated with significantly more minor injuries, such as strains and sprains, which may have been due to chance, as multiple comparisons were made). The researchers concluded that saw palmetto was no more efficacious than placebo in the management of LUTS (see Figure).

However, Dr. Barry began to assess the data from a different perspective. The data indicated that although there was no difference between the placebo and active treatment groups in terms of efficacy (i.e., the effect seen with the drug in a controlled research setting, subtracting the placebo effect from the drug effect), both treatments demonstrated effectiveness (i.e., the

Figure: Mean AUA Symptom Index Scores for Saw Palmetto and Placebo Groups From Baseline to 72 Weeks\*



### NO. OF PATIENTS

Saw Palmetto	176	172	164	164
Placebo	181	177	172	170

\* Error bars indicate 95% confidence interval

Source: Barry MJ, Meleth S, Lee JY, et al. Effects of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial. *JAMA*. 2011; 306:1344-1351.

percentage of men responding as would be seen in the real-world setting). About half of the men in *both* groups experienced an improvement from baseline of 3 points, which is a change that is considered “clearly perceptible” to patients, and therefore clinically meaningful.

Based on these findings, Dr. Barry began for the first time to consider whether placebo might be an effective intervention for LUTS with a lower risk of side effects than other therapeutic options such as prescription drugs or surgery. As a proponent of shared decision making, he also began to consider whether efficacy or effectiveness data was more appropriate to share with men considering treatment for LUTS.

## A Growing Evidence Base

Dr. Barry’s experience was echoed by many individuals who attended the second event in the RWJF series when they first learned of the emerging data regarding the effectiveness of placebo in the management of a variety of clinical conditions. At the evening program and the working group meeting, presenters described the growing evidence base for the placebo effect.

Over the past few decades a variety of studies have calculated the magnitude of the placebo effect in different clinical conditions. Until recently, most estimates of the magnitude of placebo responses have been based on randomized controlled trials testing for drug effects. The placebo responses in these trials are difficult to interpret because they can include such “extraneous” factors as spontaneous remission, natural waxing and waning of the condition, and the statistical artifact of regression to the mean. Nonetheless, such data provide a good estimate of patient improvement without the benefit of the test medication. More recently, experiments that were designed to investigate placebo effects directly and controlled for such extraneous factors have provided additional clarity. It seems that the placebo effect mainly affects self-reported measures of symptom severity and global ratings of improvement. A double-blind, crossover study of asthma included four arms: albuterol inhaler, sham inhaler, sham acupuncture, and no intervention.<sup>6</sup> Although the objective measure (FEV<sub>1</sub>) demonstrated a difference between the albuterol inhaler and the placebo treatments, on the subjective measure (patients’ reports of improvement) there was no difference between the drug and placebo; and all intervention arms were better than no treatment (50 percent for albuterol inhaler, 46 percent for sham acupuncture, 45 percent for placebo inhaler, 21 percent for no intervention;  $p < 0.001$ ).

When combined, the various components that contribute to the placebo effect have a positive, additive effect on patient reports of improvement. When patients with irritable bowel syndrome (IBS) received sham acupuncture alone, they had significantly improved symptom scores compared with observation alone.<sup>1</sup> Patients who received sham acupuncture within a patient-provider relationship that included warmth, attention, and confidence, reported significant improvement compared with either of the other groups.

A recent series of meta-analyses reviewed randomized controlled trials that studied patients with depression and used unpublished FDA data. The analyses found that as many as half of the trials failed find a significant difference in efficacy between placebo and a drug generally considered and labeled to be effective.<sup>7-9</sup>



Although requiring further replication, the effectiveness of the placebo effect has been demonstrated even when it is administered without deception. In a randomized, controlled trial, patients with IBS received either no treatment or placebo pills that were described as having been shown to “produce significant improvement in IBS symptoms through mind-body self-healing processes.”<sup>10</sup> At 21 days, those who received the open-label placebo reported significantly better symptom scores than those who received no treatment ( $p = 0.002$ ). A significant response to honestly described placebo treatment was also described in the migraine study mentioned previously.<sup>2</sup> A recent large survey suggested that more than 60 percent of patients would be willing to try open-label placebo if recommended by a physician.<sup>11</sup>

## Toward a Greater Understanding of the Placebo Effect

Researchers have long considered the use of placebo group as a means for avoiding the introduction of various types of bias into a controlled study.<sup>12</sup> More recently, researchers have begun to focus less on the inert content of a placebo or sham procedure and more on the clinical context—the constellation of beliefs, symbols, and behaviors that in addition to the sham treatment constitute the placebo intervention.<sup>13</sup>

The “placebo effect” encompasses a wider spectrum of effects than the results associated with the use of a sugar pill in a clinical trial. It comprises all the influences that surround the therapeutic experience, such as expectancy, the patient-provider interaction, trust, empathy, compassion, and the ritual surrounding pill taking. The commonly accepted model for understanding the placebo effect: a subject’s response to placebo reflects the psychosocial context in which it is delivered, while a subject’s response to a drug reflects both the specific active ingredients of the drug *and* the psychosocial context in which it is delivered.<sup>13</sup>

Many experts make a distinction between the placebo response, or the changes in symptoms reported by subjects in a clinical trial who are randomized to receive placebo, and the placebo effect, or the constellation of therapeutic effects seen with a substance or procedure that is not caused by an inherent power of the substance or procedure. Besides the psychosocial impact of the provision of care, the placebo response in a trial can include the natural waxing and waning of a condition and/or the statistical phenomenon of regression to the mean; the placebo effect is the precise psychosocial impact of the context of the clinical encounter alone.

It has become clear that there is not just one placebo effect. Psychological experiments have implicated conscious expectancy, classical conditioning, the patient-clinician encounter, and anxiety reduction as playing a role in the placebo response in different situations.<sup>13</sup> Importantly, researchers also are beginning to delve more deeply into the mechanisms of the placebo effect and have demonstrated a neurobiological basis for clinical improvement induced by placebo. Different neurotransmitters, including endorphins, cannabinoids, and dopamine, have been shown to mediate the placebo effect in different illnesses.<sup>14</sup> Numerous neuroimaging studies of the brain suggest the involvement of prefrontal cognitive areas as well as subcortical and spinal structures in the placebo response.<sup>15</sup> Furthermore, recent evidence suggests that placebo mechanisms can operate outside of conscious awareness.<sup>16</sup>

# Areas of Uncertainty

Over the course of the two-day event, presenters and attendees discussed the many areas of uncertainty that surround the placebo effect. These areas include terminology, the underlying causes of the placebo effect, the potential roles for the use of placebo effects, ethical considerations, framing effects, the relationship of placebo to shared decision making, and consideration in clinical research and clinical practice guidelines.

## Terminology

Currently, the terminology used to describe the placebo effect is inconsistently applied and a source of miscommunication. The development of a standard taxonomy and terminology for the placebo effect is an important first step for advancing the understanding of its potential in clinical management. Clear definitions should be developed for placebo, placebo effect, placebo response, nocebo response (i.e., side effects experienced due to negative (nocebo) suggestion), sham treatment, and active treatment.

## Understanding the underlying causes of the placebo effect

The assumption in the biomedical model is that specific pathophysiologic events lead to the signs and symptoms associated with a condition. However, this assumption does not universally hold. Some patients with biological markers of a disease are asymptomatic, while other patients experience symptoms despite “normal” test results. This discrepancy reflects a lack of understanding about the relationship between biological events, objective alterations that are reflected in disease markers, and the subjective experience of the patient.

It is possible that the placebo effect is especially important when biology and complaints are not closely linked. To take advantage of the potential therapeutic effect of placebo, scientists and clinicians need to better understand the mechanisms of action that underlie the placebo effect—and to what extent if any, these mechanisms are the same as those by which drugs exert their effects.

An essential factor in the placebo effect is the interaction between patient and provider. Certain elements of the interaction, such as empathy, reflective listening, transference, and the “laying on of hands,” appear to be important. The degree of patient engagement or activation and the patient’s expectancy may also be essential factors in the therapeutic effectiveness of placebo. The various components that contribute to the placebo effect and their relative importance, in any particular illness, are currently unclear.

The limitations of the current scientific knowledge of placebo preclude better measurement of its effect. Research into measurement is essential. It is possible that clinically relevant measurement of the placebo effect requires a greater focus on the assessment of *function*. For example, a more sensitive metric for assessing the placebo effect for the treatment of pain might be the ability to perform activities of daily living or achieve restful sleep rather than a symptom score using a visual analog scale.

Additional research also is needed to understand the various contributors to the placebo effect. The patient-provider relationship is an area in need of particular attention, allowing for a better understanding of the role of empathy, ritual, and patient activation in the placebo effect.

## Potential role of placebo effects with medication treatment

Placebo effects seem to re-calibrate symptoms of self-appraisal. These complaints can be part of free-standing symptoms, such as chronic pain, fatigue, depression, anxiety, and functional urinary and bowel symptom, or may accompany diseases with detectable pathophysiology. The therapeutic options for harnessing the placebo effect with medication treatment are not yet well-elucidated. A number of salient questions need to be addressed. For example, to what extent does the active ingredient of placebo involve touch, gaze, warmth, empathy, attentiveness, or time spent with the care provider? Which clinician behaviors and factors in the institutional environment enhance placebo responses? How do hope, trust, intimacy, and uncertainty contribute to or influence placebo effects? How can a better understanding of the placebo response be used to further enhance the effect of treatments with proven efficacy? Prescribing physicians also need to know how the placebo effect interacts with active pharmaceuticals.

## Potential role of placebo treatment

As mentioned previously, preliminary research suggests that open-label, honestly described placebo treatment may be an ethical option to induce placebo responses. Areas needing additional consideration include clarifying the conditions in which placebo has a substantial effect and those in which it does not; patient factors that predict the placebo response; and the effectiveness of patient or care provider behaviors in enhancing the placebo effect. Clinicians, researchers, and patients also need information about the specific clinical scenarios in which placebo treatment may be effective: replacing a drug, as an adjuvant to amplify a drug effect or decrease the required dosage of a drug, in the treatment of side effects of a drug, for a drug holiday, or as a strategy to watch-and-wait before the prescription of active medication.

When considering the potential role of placebo in clinical management, clinicians and patients must assess the balance of harms and benefits of existing treatments. Specifically, a condition such as Parkinson's disease or depression for which some current therapeutic options are associated with substantial risks, might be a better target for the placebo effect than conditions for which many effective therapies exist that carry a relatively low risk of adverse events.

Should a clinician prescribe a drug when it is only marginally better than placebo and is associated with a higher incidence of side effects? What about a drug that is no better than placebo but with no side effects? What parameters should govern such a choice? During the assessment of the relative balance of harms and benefits, clinicians and researchers must consider the difference in risk between the drug and placebo, but must also identify the absolute response rate, and possibly the natural history rate as well.

When assessing the evidence base, it is important to recognize the tension that exists in trials that include placebo. The goal in an efficacy trial is often to show a difference between active treatment and placebo, and thus the tendency is to consider study designs that minimize any therapeutic effects of placebo to maximize the difference in outcomes between the two treatment groups. In contrast, in studies to assess how placebo effects ought to be harnessed in therapy, the goal is to select study designs that will maximize the identification of these effects.

## Ethical considerations

The use of the placebo effect for therapeutic purposes creates a potential for conflict between two ethical interests of the patient: respect and welfare. The ethical principle of respect

recognizes that the heart of the therapeutic alliance is open, honest communication and that deception is never appropriate because it violates the principle of respect for the individual. The principle of welfare recognizes that the care provider is acting with the individual's welfare in mind when he or she behaves in a manner that enhances placebo effects as a therapeutic option.

Questions that arise when considering the ethical implications of placebo include: how can patient expectations of treatment effectiveness be enhanced without crossing the line and providing a deceptively positive prognosis? What should a physician say when patients report that treatments, such as herbs or dietary supplements, are helpful, but the physician believes they are no more effective than placebos? Can a physician ever ethically prescribe treatments that are no better than placebo without disclosing the fact to a patient? Is it ethically acceptable for a physician to recommend an herb that he or she believes only has a placebo effect, telling the patient, "Some people (or in some cases, many people, as in the case of saw palmetto) with your condition have found this herb effective"?

Although there is some evidence that honestly disclosed placebo may have clinically meaningful therapeutic effects, is it acceptable for a physician to prescribe such a treatment before more evidence and information are available? Another potential conflict arises when considering the disclosure to a patient that no active drug is being used. Will the disclosure dash the expectancy that is a contributing factor to the placebo effect? To what extent is conscious expectancy the mechanism underlying placebo effects? What further research is needed to better understand the relationship between expectancy and placebo effects?

## Framing effects

Framing, the manner in which gains and losses are presented or framed (e.g., 10 percent mortality versus 90 percent survival) affects patients' decisions, including treatment preferences and self-reported side-effects.<sup>17-19</sup> It is currently unknown, however, how framing influences the effects of placebo or nocebo effects. Clinicians' awareness of framing effects also creates ethical questions about its use. When is the use of framing deceptive or manipulative? Are there any situations in which it is ethically sound to take advantage of framing effects? For example, is it ethically acceptable to use framing to manipulate a patient's perspective and increase the placebo effect? Or drug effects? Or a patient's ability to recovery from surgery?

## Relationship to shared decision making

Currently the therapeutic potential of placebo is not included in most decision support tools for shared decision making. When placebo is included, it is generally as a comparator for assessing the relative benefits and harms of a drug. Whether decision support tools should present data on efficacy or effectiveness of treatments, or both, is an open question.

Recognition of the placebo effect means that clinicians must now reconsider how best to present data to patients. Given that a patient's awareness of side effects may increase their incidence due to the nocebo effect, clinicians must carefully consider which (and how many) side effects to discuss with patients. Exactly how should care providers describe the frequency and significance of side effects? For example, the list of adverse events reported in a clinical trial is usually extensive and some of the listed events may not be clinically relevant for a particular patient population.

Should clinicians ask for *a priori* permission on the first visit to be permitted to prescribe

placebos in a concealed manner? In an open-label manner? Should physicians prescribe an herb (like saw palmetto mentioned previously) when it is not better than placebo but still has a therapeutic benefit and no apparent side effects? How should factors like the poor quality of many dietary supplements be considered? How should such discussions take place?

Additional study is needed to better understand the ideal balance between increasing the likelihood of side effects with an overly extensive discussion and honestly discussing important risks of which the patient should be aware. As researchers have pointed out, the detailed enumeration of very possible adverse events may create outcomes that are different from what would have happened without this information.<sup>20</sup> A process needs to be developed to help clinicians decide which side effects to discuss and how best to present them fairly in light of framing effects.

Additional study also is needed to determine a threshold for a clinically meaningful effect of a drug or of placebo. For example, under which circumstances would a five percent difference between active treatment and placebo be considered meaningful? What is the degree of difference in response between active treatment and placebo that should be required for drug approval? Should patient education materials present the relative effects of active treatment (i.e., subtract the placebo effectiveness or side effect rate from the drug effect rate) or present the absolute response rates for both placebo and drug?

## Consideration in clinical research and clinical practice guidelines

Clinical guidelines are generally based on expert analysis of systematic reviews of clinical trials. Thus, evidence must be available to create a foundation for clinical policies. Currently, there is an insufficient evidence base for guideline creators to encourage inclusion of placebo effect in practice guidelines. Just as guidelines have begun to incorporate non-trial information (e.g., surveys, interviews and secondary data analyses) recommendations for placebo and non-specific therapeutic behaviors in real-world practice should incorporate a broad range of information.

In addition, the failure of most clinical trials to include a “no intervention” arm (i.e., in addition to active treatment and placebo groups) obscures an accurate assessment of the strength of the placebo effect. For example, if a no intervention arm had been included in Dr. Barry’s LUTS trials, the results could have highlighted the effectiveness of placebo in the study and opened a more expansive debate. Nonetheless, while the reported placebo responses in Dr. Barry’s trial include such factors as spontaneous remission and regression to the mean, this information can still provide, in many cases, rough guidance on the magnitude of placebo responses in clinical practice. Certainly, as mentioned previously, it is a good estimate of the number of patients who improve, for the condition being investigated, without medication.

Clinical practice guidelines commonly present multiple treatment options that have been tested in clinical trials. However, the design of these trials may differ depending on the nature of the treatment. For example, behavioral interventions may be compared against usual care or no treatment, while drugs are often compared against placebo. Often, head-to-head comparisons of different treatment options are lacking. Indirect comparisons of treatments can be biased when the effect of one treatment includes a placebo effect, while for another treatment the placebo effect has been subtracted out.

## Attendees' Responses to the Meeting

The primary goal of the two-part event was to encourage discussion about and consideration of the placebo effect in clinical guidelines, practice, and patient choice. The comments of participants in the working group about their motivations for attending were illustrative:

- "I believe we need to know more about the placebo response."
- "I believe that patients are prescribed a large number of drugs with only marginal effect over placebo."
- "I don't think we've paid enough attention to the sizable placebo effect seen in clinical trials."
- "In preparing for this meeting, I became cognizant of my research team's lack of awareness about placebo."
- "I believe I made a major error in dismissing the placebo response or in not thinking about non-pharmacological interventions."
- "I realize now that it was crazy to ignore the placebo response in the clinical studies I was involved with."

Many participants stated that prior to reviewing pre-meeting reading materials and attendance at the meetings, they were unaware of many aspects of the placebo effect. An important outcome of the event was a new consideration of the placebo effect in each individual's area of focus. Participants discussed ways in which they might view their work differently and potential opportunities for the use of placebo that they now recognized.

The participation of a patient and his spouse added a unique perspective to the working group discussion. As an individual with a chronic condition for which mainstream treatments do not alleviate all symptoms, he shared his view that the priorities of patients and scientists differ in several aspects. First, patients feel greater time urgency for the release of effective drugs than researchers do. Second, the two groups have different level of tolerance for errors: treatments that are effective but falsely deemed to be inefficacious are more problematic for patients, while researchers are more concerned with inaccurately finding drugs to be efficacious when they are not. From the patient's perspective this difference is concerning because it may mean that the development of a potentially effective drug is halted in Phase II trials if there is a large placebo effect that obscures the relative effect of the drug. The patient representative also made it clear that he was whole-heartedly in favor of utilizing placebo effects in his care.

# Recommendations

**The presentations during the evening session and the discussion during the second day's meeting prompted the working group to create a preliminary set of recommendations to further the discussion and advance the current thinking about the therapeutic role of placebo.**

Key suggestions that emerged from the group include:

1. Raise the awareness of clinicians about the placebo effect, including its physiologic underpinnings and the existing evidence base (e.g., through letters to the editor, review articles in clinical journals or additional reporting about placebo responses in drug clinical trial reports).
2. Develop a standard taxonomy for the placebo effect, including terms such as placebo, placebo effect, context, ritual, nocebo, and nocebo effect.
3. To move awareness and use of placebo enhancing behaviors into the mainstream of clinical care, invest in studies to build the evidence base and work with organizations to build the harnessing of placebo effects into standard practice.
4. Conduct mechanistic studies of placebo that include patients (rather than healthy volunteers) and evaluate longer-term outcomes.
5. Fund research to better understand these aspects of the placebo effect:
  - Pathophysiology and the magnitude of the placebo effect
  - The context component of the placebo effect, including ritual, delivery, verbal and nonverbal messages
  - Effectiveness of placebo compared with other treatments
  - Potential usefulness with an active drug (drug holiday or treatment of side effects or to amplify effect of active treatment)
  - How to achieve a more consistent effect
  - Patient factors that predict a greater effect
6. Build placebo into the analytic framework for clinical research (i.e., include both a placebo arm and a no intervention arm in addition to the active treatment arm especially in conditions where drug responses are only marginally greater than placebo).
7. To ensure that the variability of placebo effect is taken into account, encourage stratification by severity of illness in clinical trials.
8. Expand acceptance of the use of subjective measures, especially in light of the heightened focus on improving the patient experience.
9. Encourage clinicians to discuss with patients both the efficacy of drugs relative to placebo and the absolute response rate, or effectiveness of the drugs.
10. Replicate open-label placebo studies.
11. Ensure that measurement of the placebo effect assesses meaningful clinical improvement, whether as functional status metrics, or symptom scores changes.
12. Develop standard outcomes measures and a standard database for collection of results to enable patient-level meta-analysis.



13. Work with AHRQ and National Institutes of Health to ensure that evidence-based practice center (EPC) reports include the responses to questions about placebo use and that data on the placebo response are included in the reports.

While these early recommendations require refinement and expansion, they represent a preliminary blueprint for the action steps that need to be taken to close the gap currently existing in clinical practice related to the consideration and use of placebo.

## Conclusion and Future Steps

In the past, placebo has been largely viewed as a useful control for clinical trials. However, a growing evidence base demonstrates that placebo has a powerful therapeutic effect of its own. This emerging evidence represents an important opportunity to identify and learn to optimize an effective and ubiquitous clinical phenomenon that is currently overlooked in clinical management, clinical guidelines, and patient choice.

Greater understanding is needed to harness the therapeutic power of the placebo effect, identify the factors that facilitate or hinder it, achieve a more consistent effect, and comprehend its effectiveness relative to other treatment options.

Although the current evidence base is not yet solidified sufficiently to make concrete recommendations about the therapeutic use of placebo, policy makers, researchers, and clinicians can take steps to further the investigation of placebo as an effective therapeutic tool.



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## Appendix: Participants in the Working Session

**Michael J. Barry, MD**, President of the Informed Medical Decisions Foundation, medical director of the John D. Stoeckle Center for Primary Care Innovation at Massachusetts General Hospital

**Anne C. Beal, MPH**, Deputy Executive Director and Chief Officer for Engagement, Patient-Centered Outcomes Research Institute (PICORI)

**Josephine P. Briggs, MD**, Director, National Center for Complementary and Alternative Medicine, National Institutes of Health (NCCAM/NIH)

**Perry D. Cohen, PhD**, recognized as an authentic voice advocating for the interests of patients with serious chronic illness

**Joann G. Elmore, MD, MPH**, Professor of Medicine at the University of Washington (UW) School of Medicine and an adjunct professor of epidemiology at the UW School of Public Health

**Martin (“Marty”) J. Gabica, MD**, Chief Medical Officer (CM) at Healthwise, a non-profit organization dedicated to helping people make better health decisions and a board-certified family practice physician

**Sandra Garrelick, MBA**, retired senior marketing and planning executive with extensive experience in complex organizations in the non-profit service sector

**David Jones, PhD, MD**, A. Bernard Ackerman Professor on the Culture of Medicine, jointly appointed on the Faculty of Arts and Sciences and the Faculty of Medicine at Harvard University

**Ted J. Kaptchuk**, Professor of Medicine at Harvard Medical School and director of the Program in Placebo Studies and Therapeutic Encounter at the Beth Israel Deaconess Medical Center, Harvard Medical School

**John M. Kelley, PhD**, Deputy Director of the Program in Placebo Studies and the Therapeutic Encounter, an associate professor of psychology at Endicott College, a faculty member at Harvard Medical School, and a licensed clinical psychologist in the Psychiatry Service at Massachusetts General Hospital

**Franklin G. Miller, PhD**, Senior Faculty, Department of Bioethics, National Institutes of Health (NIH)

**Benjamin Moulton, JD, MPH**, senior health policy and legal advisor for the Informed Medical Decisions Foundation

**Harold Sox, MD**, Professor of Medicine at Dartmouth Medical School and associate director of the Dartmouth Institute for Health Policy and Clinical Practice

**John Williams, MD**, Professor of Medicine, Professor in Psychiatry and Behavioral Medicine, Duke University School of Medicine

**Timothy J. Wilt, MD, MPH**, general internist, health services researcher, and Professor of Medicine at the University of Minnesota and the Minneapolis VA Center for Chronic Disease Outcomes Research