

**Authors:**

Felipe Fregni, MD, PhD  
 Marta Imamura, MD, PhD  
 Hsin Fen Chien, MD, PhD  
 Henry L. Lew, MD, PhD  
 Paulo Boggio, PhD  
 Ted J. Kaptchuk, OMD  
 Marcelo Riberto, MD, PhD  
 Wu Tu Hsing, MD, PhD  
 Linamara Rizzo Battistella, MD, PhD  
 Andrea Furlan, MD, PhD

**Affiliations:**

From the Harvard Medical School (FF, TJK), Boston, Massachusetts; University of Sao Paulo (MI, HFC, MR, WTH, LRB), Sao Paulo, Brazil; Harvard Medical School (HLL), Boston, Massachusetts; Mackenzie Presbyterian University (PB), Sao Paulo, Brazil; and Toronto Rehabilitation Institute and University of Toronto (AF), Toronto, Canada.

**Correspondence:**

All correspondence and requests for reprints should be addressed to Felipe Fregni, MD, PhD, Berenson-Allen Center for Noninvasive Brain Stimulation, 330 Brookline Ave, KS 452, Boston, MA 02215.

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**REVIEW & ANALYSIS**

## Challenges and Recommendations for Placebo Controls in Randomized Trials in Physical and Rehabilitation Medicine

A Report of the International Placebo Symposium Working Group

**ABSTRACT**

Fregni F, Imamura M, Chien HF, Lew HL, Boggio P, Kaptchuk TJ, Riberto M, Hsing WT, Battistella LR, Furlan A: Challenges and recommendations for placebo controls in randomized trials in physical and rehabilitation medicine: A report of the International Placebo Symposium Working Group. *Am J Phys Med Rehabil* 2010;89:160–172.

Compared with other specialties, the field of physical and rehabilitation medicine has not received the deserved recognition from clinicians and researchers in the scientific community. One of the reasons is the lack of sound evidence to support the traditional physical and rehabilitation medicine treatments. The best way to change this disadvantage is through a well conducted clinical research, such as standard placebo- or sham-controlled randomized clinical trials. Therefore, having placebo groups in clinical trials is essential to improve the level of evidence-based practice in physical and rehabilitation medicine that ultimately translates to better clinical care. To address the challenges for the use of placebo in physical and rehabilitation medicine and randomized clinical trials and to create useful recommendations, we convened a working group during the inaugural International Symposium in Placebo (February 2009, in Sao Paulo, Brazil) in which the following topics were discussed: (1) current status of randomized clinical trials in physical and rehabilitation medicine, (2) challenges for the use of placebo in physical and rehabilitation medicine, (3) bioethics, (4) use of placebo in acupuncture trials and for the treatment of low-back pain, (5) mechanisms of placebo, and (6) insights from other specialties. The current article represents the consensus report from the working group.

**Key Words:** Placebo, Physical and Rehabilitation Medicine, Randomized Clinical Trials, Methodology, Clinical Trials Design, Ethics, Acupuncture, Low-Back Pain

**A**lthough physical and rehabilitation medicine (PRM) is an established medical specialty, it has not received the deserved recognition from clinicians and researchers in the scientific community. There are several reasons that might explain this unfavorable scenario, but one that seems to stand out is the lack of high-quality clinical research in PRM because of the inherent difficulty in the specialty to conduct double-blinded placebo-controlled clinical trials. Most of

the studies in PRM are based on clinical observation (naturalistic studies), uncontrolled observational studies, or clinical trials comparing two active interventions. However, these study designs do not provide sufficient proof of efficacy of interventions, which is only achieved in high-quality double-blinded placebo-controlled trials.

The best way to improve the recognition of PRM is by improving clinical research and facilitating the conduct of high-quality clinical trials such as placebo- or sham-controlled randomized clinical trials (RCTs). Therefore, the understanding of placebo use in clinical research and the development of reliable placebos or sham interventions are necessary steps to improve the level of evidence in PRM. The ultimate goal is to improve patient care in PRM.

To understand the challenges for placebo use in RCTs in PRM, we convened a working group of established clinical researchers in PRM and experts in placebo and clinical research methodology on February 12–14, 2009 to discuss the main challenges of placebo use in PRM and to propose potential solutions and recommendations. A summary of the discussion is provided later.

## METHODS

The education committee of the International Society of PRM and the Brazilian Association of Physical Medicine and Rehabilitation were the sponsors of the inaugural International Symposium in Placebo held in Sao Paulo, Brazil, February 12–14, 2009. The local host was Dr. Paulo Boggio from Mackenzie University, and the scientific program was organized by Dr. Felipe Fregni, Dr. Marta Imamura, and Dr. Ted Kaptchuk. The purpose of the symposium was to highlight the main aspects of placebo in clinical research with a special emphasis on PRM. There were a total of 14 presentations given by some members of this working group. In addition, 18 abstracts were submitted and presented at this symposium. Two hundred twenty-six participants attended this event.

The scientific program was structured in two sessions: (1) basic mechanisms and discussion of placebo effect and (2) placebo effect in different specialties. In addition, there was a special panel composed of three PRM researchers (M.I., A.F., M.R.) to discuss the challenges of placebo in PRM.

The current article represents the consensus report from the working group of PRM clinical researchers in addition to experts in placebo and clinical research methodology. Participants from the working group were asked to submit their material to the working group coordinator (F.F.) previously. During the consensus meeting, each participant presented his or her designated topics with input and discussion by all working group

participants. The topics covered different aspects of placebo in PRM, including two sections on a case discussion in acupuncture and low-back pain (LBP) to give the readers practical examples. The meeting lasted 3 hrs and was video recorded. After the meeting, the reports from each participant were compiled by the coordinator using the same format and sections as were used during our working meeting. The final report was reviewed by each member through E-mail interactions.

## Current State of Placebo-Controlled Clinical Trials in PRM

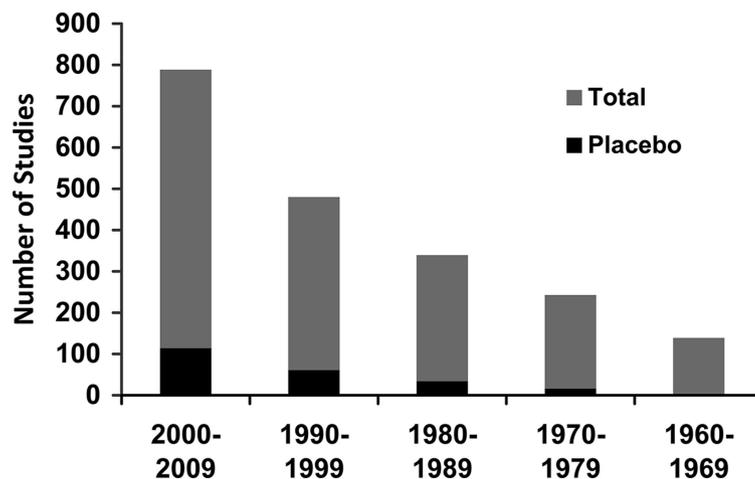
In the recent years, the interest in controlled studies in PRM has increased. Conducting randomized controlled trials has become the goal of clinical researchers involved in PRM, especially when dealing with nonpharmacologic treatments. In fact, the growing interest in controlled trials can be observed in MEDLINE. Figure 1 shows the increase in the number of placebo and sham-controlled studies published since 1964 in rehabilitation, physical medicine, and physical therapy journals. The search strategy is shown in the legend of Figure 1. In the last decade (1999–2008), there were 8680 placebo- or sham-controlled trials in PRM, which indicated an increase of 3743 from the prior decade (1989–1998).

There is also an increasing interest in trials evaluating therapeutic effects of alternative medicine and physical modalities such as acupuncture, electrical stimulation, and application of heat. These topics have had a large number of publications in the field of PRM recently.

The increase in the number of placebo-controlled studies in PRM in the last decade is a result of several factors:

1. The evidence-based medicine movement that started in the early 1990s, in which controlled clinical trials are used as best evidence to support novel interventions to improve the level of quality care.
2. An increased interest in rehabilitation modalities, with emphasis on conditions usually treated by PRM physicians, such as chronic diseases encountered in the aging population (e.g., arthritis and chronic pain).
3. Reimbursement decisions usually dependent on a high level of evidence.

Although there is a clear increase in the number of placebo-controlled studies in PRM, there is still a number of important challenges that are responsible for the delay in the development of high-quality evidence in this specialty. These challenges were discussed in our group meeting and will be presented in this article.



**FIGURE 1** Number of articles when using the following search strategy in Pubmed. Search with the following limits: (1) period (e.g., 2000–2009) and (2) we searched in the five main clinical journals in PRM (“Archives of Physical Medicine and Rehabilitation,” “American Journal of Physical Medicine and Rehabilitation/Association of Academic Physiatrists,” “Physical Therapy,” “Restorative Neurology and Neuroscience,” and “Journal of Rehabilitation Medicine: Official Journal of the UEMS European Board of Physical and Rehabilitation Medicine”). This search yielded the total number of articles in each respective period in these five journals. We then added the word “placebo” for the total number of articles including placebo as a keyword.

### The Need for Sham or Placebo-Controlled Trials in PRM

In PRM, the most commonly used control group includes interventions as simple as nonparticipation (waiting list), usual care, or another intervention. These control interventions are associated with nonspecific physiologic effects that can affect the active intervention, especially when patients and care providers are not blinded to the interventions. Patients’ expectation may also significantly interfere with treatment results,<sup>1</sup> and nocebo effects may also be observed.<sup>2</sup>

Placebo-controlled trials ensure blinding and reduce the risk of potential bias that can also interfere with the observed outcomes. The type of biases that can be minimized by using adequate placebos are as follows.<sup>3</sup>

1. Performance bias is defined as systematic differences between groups in the care that is provided or because of the exposure to factors other than the interventions of interest.
2. Detection bias is defined as systematic differences between groups in how outcomes are determined. This may pose a special challenge because most PRM interventions, by their nature, are associated with the building of relationships among the patient, rehabilitation team members, family members, and care providers.

Although there is a critical need for randomized, placebo-controlled clinical trials in PRM, in some situations, the use of placebo or sham device

might not be practical. For instance, there are situations in which it is not possible to use placebo, such as in a trial testing the effectiveness of lower-limb prosthesis for ambulation after amputation, or use sham orthosis for drop foot; or situations in which it is difficult to sort out the placebo from the real effect, and thus it is problematic to design an adequate placebo intervention such as for hydrotherapy. In the next section, we discuss specific challenges for the use of placebo in PRM clinical trials.

### Challenges of Placebo Use in PRM Clinical Trials

We identified ten important challenges for the use of placebo in PRM clinical trials:

#### Development of Placebo and Sham Devices

Placebos are for drugs as shams are for devices. PRM is a specialty in which most of the treatments are based on devices. Two typical sham treatments in PRM are sham ultrasound<sup>4–6</sup> and “off-transcutaneous electrical nerve stimulation.”<sup>7–15</sup>

The main issue with sham devices is the difficulty to blind subjects effectively because the use of a device is usually associated with a sensation, such as during transcutaneous electrical nerve stimulation. Therefore, subjects with previous experience with that device might be easily unblinded. Even in naïve subjects, active stimulation might induce a larger placebo effect because of the sensations associated with the active treatment.

Interestingly, despite wide use in PRM, the efficacy of therapeutic ultrasound and transcutane-

ous electrical nerve stimulation remains controversial,<sup>4–15</sup> and current evidence does not support their use in routine management because of limited, conflicting, and inconclusive data. On the other hand, there are examples of PRM interventions with proven efficacy over sham devices: radial shockwave therapy<sup>16</sup> and transcranial direct current stimulation.<sup>17–20</sup> One important difference is that for the latter two interventions, the sham method is a reliable one.<sup>21</sup>

There is a need for further engineering development for reliable methods of sham device. An ideal sham device should have the same appearance and induce feelings similar to those of the real device. However, one important point that needs to be considered is whether the feelings associated with a given treatment are also correlates of the active ingredient; for instance, a perfect placebo for acupuncture would induce the qi sensation; however, it is unclear whether inducing the qi sensation regardless of the stimulation point is associated with the physiologic effects of acupuncture. Another example would be designing a perfect placebo for tricyclic antidepressant—in this case, the placebo would ideally also be associated with sleepiness, but then the same question applies: are some of the effects of tricyclic antidepressants associated with sleepiness? Moreover, a reliable sham device should also allow reproducibility of the results in various patient populations.

Finally, because devices have different regulatory requirements (often less restrictive than drugs), development of effective sham methods is not sufficiently supported.

### **Lack of Standards in PRM Therapies**

Several PRM interventions are not standardized or are delivered differently according to each patient or the person administering it (e.g., exercises). There are different types of exercise such as stretching, strengthening, and endurance that can be applied separately or in conjunction. Because many PRM therapies are difficult to be standardized, it is even more difficult to design a “standard” placebo therapy in these situations.

### **Treatment Heterogeneity Resulting from Therapist’s Skill Differences**

A great number of interventions used in PRM depend on the technician’s or clinician’s skills such as the application of acupuncture, injections, and nerve blocks. Therefore, controlling for these interventions becomes difficult with this important source of variability. This makes it even more difficult to design an appropriate placebo in these situations. To control for skills and levels of experience, it would be necessary to conduct multicen-

tric studies with various levels of skills and experiences and perform multivariate analyses to adjust for these variables. In this scenario, a large number of patients would be necessary, increasing the difficulties to conduct such studies.

### **Issues with Adequate Masking**

For a placebo or sham-controlled trial to be valid, it has to ensure adequate blinding: patients, therapists, outcome assessors, and data analysts all must be adequately blinded.<sup>22</sup> However, many interventions in PRM are impossible to blind (e.g., occupational therapy for stroke). In fact, when compared with pharmacologic studies, trials involving nonpharmacologic interventions report less blinding of care providers, patients, and outcome assessors.<sup>23</sup> If blinding is impossible, it does not make sense to design a placebo-controlled trial; however, alternative methods to analyze bias should be then carried out.

Another important issue associated with adequate masking is subjective outcomes. Several conditions in PRM have subjective outcomes such as chronic pain. Usually, subjective outcomes have a higher magnitude of placebo effect,<sup>24</sup> causing the difference between active and sham group to be smaller.

In chronic pain studies, for example, the most commonly used primary outcome is the subjective visual analog scale.<sup>16,17,19,25</sup> In fact, inadequate sham devices (that do not induce the same sensation as the active treatment) might unblind patients, therefore modifying their pain ratings on this subjective scale.

### **Personal Interaction Between Therapist and Patient**

Several PRM interventions involve a close relationship between the patient and the therapist, for example, speech and language therapy after brain injury. Because the placebo effect is directly associated with the degree of such interaction, this factor complicates the design of clinical trials in PRM<sup>26</sup> because it is not possible to isolate this contact completely.

There are other important issues of the relationship between patient and therapist for some interventions such as cognitive behavioral therapy (CBT). For instance, the degree of interaction is important not only to determine the degree of placebo effect but also to induce the real effects. Therefore, motivation is an important part of the active aspects of CBT because this therapy involves relearning strategies. In fact, motivation and preference present an important challenge. For example, randomly assigning exercise or CBT in a RCT does not account for the fact that in practice one

would first determine whether a patient has sufficient motivation and thus whether it makes practical sense to administer a therapy such as CBT; not doing this as for instance in RCT might assign CBT to patients with lack of motivation, and therefore results be biased.<sup>27,28</sup> Therefore, in certain circumstances, the specific and unspecific aspects of the intervention cannot be detangled, decreasing the chances of designing an effective placebo intervention.

### **Personal Beliefs, Previous Experience, and Motivation**

Patients have different expectation levels with nonpharmacologic treatments in PRM. Because expectation plays a critical role for the effects of placebo, the placebo effect might be elevated in some treatments in PRM and therefore difficult to control for, such as in occupational therapy, home exercises, and cognitive-behavioral interventions.<sup>25,29,34</sup>

### **Small Effect Sizes**

Some of the PRM interventions induce small improvements (effect sizes), therefore studies to prove efficacy require large sample sizes, which implies increased costs.

### **Long Follow-Up**

Because many PRM interventions treat chronic conditions, the studies involve long follow-up periods (increasing the costs and complexity of the study). This makes the use of placebo more difficult because of ethical concerns of a long period of exposure to a placebo intervention.

### **Lack of Training to Conduct Clinical Research**

Many PRM practitioners lack appropriate training in clinical research; therefore, the importance and methods of placebo use are sometimes not appreciated.

### **Use of Medical Devices**

PRM is a specialty that largely uses medical devices as compared with other specialties such as infectious diseases or pediatrics. This also has an important impact on placebo use because there is a notion that sham devices would have a higher placebo response than placebo pills.<sup>30</sup> In fact, a sham intervention showed increased response in a sham device *vs.* inert pill trial<sup>31</sup> and in a meta-analysis comparing subcutaneous placebo with oral placebo from acute migraine.<sup>32</sup> A recent meta-analysis on major depression, however, did not find differences between placebo pill and use of a sham device (transcranial magnetic stimulation).<sup>33</sup> A

similar contradictory result was found in an acute-care study that found no difference between parenteral medication and oral medication.<sup>35</sup> Therefore, it is still unclear whether a sham device induces a larger response. But given that it does (or at least a different placebo response), then one challenge is that clinicians should be aware that the number needed to treat in RCTs (that take into account placebo effect and especially when using sham devices) might be different than the number needed to treat in the clinical practice.

### **Ethical Issues for the Use of Placebo in RCTs**

The use of placebo in RCT generates an intense debate and is considered an ethical dilemma. As in any ethical dilemma, benefits in one area can automatically imply shortcomings in another area. A central ethical tension is whether the researcher-clinician should be guided by the ethics of therapeutic medicine or the one underlying research. In this context, the clinical investigator has a different role as compared with a clinician. These two roles need to be differentiated.

In this scenario, an important debate has been around the concept of equipoise. The first principle is that a clinical trial begins with an honest null hypothesis that there is no difference between the two treatments being tested. In fact, defenders of equipoise argue that if a researcher understands that the arms of a trial are not equivalent, then the inferior arm must be excluded or even the entire trial interrupted—it is conceived that all subjects must receive the superior treatment. In 1987, Freedman,<sup>35</sup> in *The New England Journal of Medicine*, proposed the concept of equipoise, arguing that “the requirement is satisfied if there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment.” For instance, although patients and some physicians might believe that acupuncture is effective for fibromyalgia, there is not enough evidence supporting its use; therefore, a trial comparing placebo *vs.* acupuncture for fibromyalgia is considered to have equipoise.

Another important issue is when it is ethically justified to use placebo in a clinical trial. The response might be included in the Declaration of Helsinki. This document states that “The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects. . . . The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current

proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.”

Therefore, it is important that there is a real need to determine the efficacy or safety of a new treatment if this active treatment in the given condition being investigated does not cause any serious or irreversible harm.

In fact, lack of placebo studies might also be associated with ineffective and harmful treatments. The surgical treatment of angina pectoris is a good example of this risk. In the past, internal mammary artery ligation by surgical procedures was considered an effective therapeutic approach relieving the related symptoms. Data supporting this therapeutic procedure were based on uncontrolled trials. Nevertheless, when this method was compared with a sham procedure, no differential effects were observed between groups, and this intervention was discontinued.

In fact, such debate is intense in another specialty, psychiatry. In 2000, Khan et al.<sup>36</sup> published their analysis of the Food and Drug Administration database on antidepressant clinical trials. The use of a placebo in an antidepressant clinical trial usually generates concerns especially associated with suicide risk. In this article, the authors showed, based on RCT of seven new antidepressant drugs, that there was no difference between placebo and experimental groups with regard to rates of suicide and attempted of suicide. They also found a symptom reduction of 40.7% with investigational drugs and 30.9% with placebo. These data raised an intense debate. Leber<sup>37</sup> considered that although these data could not be assumed as a final proof that placebos do not result in risk for the subjects, the spontaneous improvement related to placebo administration is an indicator for the necessity of placebo RCT.

Another important aspect of placebo-controlled trials is that the sample sizes are usually smaller than when an active intervention is used in the control group, therefore the number of subjects exposed to an experimental intervention is reduced. Leon<sup>38</sup> showed that a study comparing an investigational drug with placebo needs a smaller number of subjects, resulting in smaller number of nonresponders compared with the alternative of using an active control.

However, some researchers consider that statistical arguments should not be used as a way to justify ethical issues. Kraemer<sup>39</sup> commented on the

premise that patients do not have full comprehension on the type of medical support they will have when participating in a placebo-controlled study.

The debate becomes more intense when the placebo-controlled group is not an inert placebo but an active one such as surgical procedures or pills that mimic some of the side effects of the pharmacologic therapy under evaluation. Edward et al.<sup>40</sup> discussed this issue considering what they called “three ethical hurdles.” For these authors the “evaluation methods must be the best or only scientific option available to get valid data; acceptable to participants in terms of a utilitarian calculation of risks and benefits; and respectful of the needs of individuals and communities to control their own destinies.”

Another important issue is the cultural aspect when designing placebo-controlled trials. For instance, a placebo-controlled trial of acupuncture might not be accepted in China because it might be an established treatment in Eastern countries, whereas it might not be accepted as an effective treatment in some Western countries. This increases the challenges for placebo use for global clinical trials, especially in PRM where there is a lack of consensus regarding the use of medical devices for several conditions.

Finally, although any research involving human subjects requires the use of an informed consent form and that theoretically patients can decide to participate or not in a given trial based on the knowledge of risks involving participation, it should be noted that in several circumstances patients do not understand the concept of placebo and in addition a level of coercion to participate in a study might be present, especially in PRM patients who often have a close relationship with their physician.

### **Case Study 1: Placebo in Acupuncture Clinical Trials**

Because many PRM physicians are recommending acupuncture treatment, it is important to discuss the challenges and potential solutions for the use of placebo in acupuncture. In fact, results from several RCTs showed that the clinical effect of acupuncture is inconclusive, and one of the reasons is the challenge for the use of placebo in this condition. Here, we list the main issues with placebo use in acupuncture trials.

### **Mechanisms of Action**

Although the neurophysiologic mechanisms of acupuncture are well established in research for experimental pain,<sup>41,42</sup> the exact mechanisms underlying the action of acupuncture in a clinical practice is still unclear, making the development of

effective and reliable sham methods difficult. In fact, we still do not know the relative efficacy of specific acupuncture approaches. Is the dry needling technique equivalent to needling on the real acupuncture point? Do we need to obtain the qi sensation (the sensation after the needling of the specific acupuncture point)? Should we select the point according to standardized traditional Chinese medicine formula, or should we allow selection of points according to the experiences of the practitioner? Does the insertion technique provoke different results? All of these questions exemplify the need of mechanistic studies to develop an effective sham method.

### Different Sham Methods

Clinical trials in acupuncture use different methods of sham because there is still controversy on the best sham method. In addition, some of the methods of sham might induce physiologic effects. For instance, it is possible that sham-controlled acupuncture trials compare two active forms of needling because most of the sham techniques often consist of misplaced needling (superficial or off-point needling), which may have physiologic effects.<sup>43–45</sup> The search for an ideal and physiologic inert acupuncture placebo has involved a variety of different techniques, such as the noninsertive stimulation (using the stage dagger effect) and controls that do not involve needling (mock transcutaneous nerve stimulation).

It seems that these different methods are associated with physiologic effects. A recent study has shown that light touch of the skin by a placebo acupuncture needle (touches the skin without penetrating it) activates mechanoreceptors and slow conducting unmyelinated (C) afferents inducing activity in the insula, thus potentially modulating chronic pain.<sup>46</sup> Therefore, it is possible that this method of placebo acupuncture also has physiologic effects beyond those induced by placebo administration. Similarly, misplaced needling is also associated with significant physiologic effects that are also difficult to untangle from the experience of receiving acupuncture.

The existence of several methods of sham results in an additional methodologic issue because results from different acupuncture trials cannot be easily compared, and therefore conclusions on this technique cannot be easily made.<sup>47,48</sup>

### Increased Expectancy

Patients who seek acupuncture treatment usually have high levels of expectancy. This fact might increase placebo response and therefore decrease the effect sizes in acupuncture trials.

### Therapist's Skills and Interaction

Acupuncture as with other techniques involving devices depends on the acupuncturist's skills and also on the interaction between patient and therapist, therefore making the control more difficult as the active and placebo acupuncture treatment are highly dependent on these variable factors.

Acupuncture is an example of a treatment frequently used in PRM that presents several challenges for the placebo use in RCTs that have critically contributed to the uncertainty regarding the evidence to support this therapeutic method.

### Case Study 2: Placebo Effect in LBP Clinical Trials

LBP was selected for a case study because it is an example of a very prevalent condition with a wide range of possible treatments that, therefore, can generate a discussion on the challenges of placebo research.

Haldeman and Dagenai<sup>49</sup> cite a list of available and commonly used treatment interventions for chronic LBP, which resembles a shopping list in a foreign supermarket because many techniques are unfamiliar for the patients and anyone involved in the management of LBP. In addition, an analysis of 126 randomized trials for LBP by Machado et al.,<sup>50</sup> identified >25 different placebo interventions and concluded that in only 13% of trials was the adequacy of blinding assessed. Furthermore, in 20% of trials, placebo intervention was a potentially genuine treatment (not inert). These results demonstrate that critical challenges for placebo use are common in LBP studies.

To illustrate the most commonly used placebo and sham interventions for the management of LBP, we used the reviews produced by the Cochrane collaboration Back Review Group and cite some of the treatments used and the rate of placebo response. Antidepressants are highly used for the treatment of chronic pain, and their mean placebo response in patients with LBP is 11.7%.<sup>51</sup> In other treatments such as herbal medicines, muscle relaxants, and nonsteroidal anti-inflammatory drugs, the placebo response rate varies from 26% to 41.3%.<sup>52–54</sup> Similarly, the placebo effect in chronic back pain is also elevated for other nonpharmacologic interventions.

For nonpharmacologic treatments, the difficulty for placebo use increases because there is a lack of understanding of their basic mechanisms of action, such as low-level laser therapy for pain. Therefore, it is difficult to design an effective placebo method if the underlying mechanism is not clear. In addition, interventions such as cognitive behavioral therapies or exercises pose additional

difficulty because the placebo arm needs to have the same characteristics as the active arm.

Besides all of these difficulties, LBP is a condition with many subjective outcomes such as pain and functional assessment. It has been shown in a recently meta-analysis that placebo response is significantly higher as compared with nontreatment in subjective (but not objective) outcomes.<sup>24</sup>

In summary, LBP is a condition that the placebo response might markedly change according to the placebo method and expectations of patients especially in conditions in which the main outcome is subjective.

### **Brief Summary of Placebo Mechanisms: Insights for PRM Placebos**

In this section, we will discuss the potential biological mechanisms by which a placebo intervention may cause an effect. These mechanisms are classified into cognitive and neural theory, conditioning, and expectation. This discussion might be helpful for PRM researchers to understand better the placebo effect and therefore design their RCTs appropriately.

To understand placebo effects, it is important to discuss (and differentiate) its two main components: methodologic artifacts (or nonspecific effects) *vs.* specific effects. The methodologic artifacts need to be considered as part of the placebo effects such as the natural history of disease. The following nonspecific effects can be listed: (1) natural history of disease as diseases naturally fluctuate and have cyclical variations, therefore a spontaneous remission is possible; (2) regression to the mean—defined as the statistical phenomenon in which there is a random variability in the measurement, and if the population to be studied has severe symptoms at the start of the trial, it is expected that there will be a regression to the mean in the scores of symptoms; (3) therapist and observer bias—if therapists and observers are not blinded, they can influence the treatment and rating scores; (4) patient biases—if patients are not adequately blinded, they might also influence the results, especially the subjective scores.<sup>55,56</sup>

However, there is a variety of cognitive and neural theory to explain the potential specific, biological effects of placebo. There is a large body of literature showing that changes in the limbic system (associated with emotional and affective processing) might be associated with extensive changes in neural activity and therefore might induce changes in hormonal levels (through modulation of the neuroendocrine axis) and immune system (also through modulation of the sympathetic and parasympathetic systems). Therefore, changes in hope associated with treatment expectations can induce meaningful

changes in neural activity and therefore induce biological changes.<sup>57–59</sup>

A patient's beliefs and expectancies are critically important for the biological effects of placebo and need to be carefully considered in the PRM field, especially because of the intensive interaction among the rehabilitation team, the patients, and their families. Finally, another model that needs to be considered in this context is conditioning (the Pavlovian conditioning models). In fact, several studies have shown that if a repeated stimulus (for instance water and sugar) is linked to a physiologic response, for instance, an injection that can change the immune system, then the water and sugar alone will have by itself an effect in the immune system. This effect is likely a consequence of plastic brain changes induced during the period of conditioning and shares mechanisms similar to the effects induced by learning.

It is already known that not all placebo interventions will have the same effects.<sup>57</sup> Evidence exists that sham devices and procedures have “enhanced” placebo effects compared with placebo pills.<sup>58,59</sup> For example, a RCT prospectively compared the two different placebo controls—a sham device (a validated sham acupuncture needle) and an oral placebo pill—and found that the sham device reduced pain significantly more than an inert pill.<sup>31</sup> Elaborate rituals can produce effects that are greater than simple pill ingestion. Furthermore, the accompanying efforts of participation (for instance—PRM procedures such as laser therapy) are much more evocative and potentially potent than medication. Whether assigned to a genuine or dummy treatment, patients have to make a commitment to travel and therefore do the potentially valuable exercise just to get to the treatment. Transportation often requires the assistance of family and friends who can provide tacit social support. In a trial, these factors, which are accounted as “nonspecific,” are all likely to increase the effect size of the placebo arm and show a difference from the genuine treatment, which is more difficult to detect.

Performing genuine or sham PRM active treatment requires mutual understanding and agreement on completing the procedures. Patients and practitioners often need to negotiate and reach mutual agreement on how to cooperate and work together in a manner far more complex than what is required to take medications. These interactions often require explanations, assurances, opportunities for dialogue, and a high degree of trust. Such genuine patient-physicians encounters, necessary in both the genuine and placebo arms, have demonstrated their ability contribution to positive health outcomes.<sup>60–63</sup> For example, a recent RCT demonstrated that augmenting the patient-practitioner with a patient-centered approach in sham

acupuncture treatment can significantly enhance clinical outcomes compared with sham acupuncture performed in a business-like disease-centered clinical encounter.<sup>64</sup>

### **What Have We Learned from Other Specialties?**

The challenges observed for placebo use in PRM occurs across other specialties. However, different solutions have been proposed and adopted, providing useful insights for placebo trials in PRM.

### **Ethical Issues and Use of Placebo in Psychiatry**

Psychiatry has challenges similar to those for PRM for placebo use. (1) For instance, major depression is similar to chronic pain because both are associated with a large placebo response. (2) They also have to deal with the ethical issue of offering placebo to depressed patients when there is an (evidence-based proven) effective treatment. In this case, the argument for defending placebo-controlled trials in psychiatry is that there is a risk that a trial comparing a new intervention with an established intervention might show no differences in results if the established intervention is not effective either. In this case, the conclusion that a new intervention is as effective as compared with the established intervention is not valid. (3) In addition, there is the issue of assay sensitivity, where a lack of difference between two active interventions might be the result of a poorly executed trial (such as lack of power). A compromised solution is to include patients with mild and moderate depression (to increase sample size) and have a relatively short trial (to decrease the exposure of patients to a less effective therapy). Similarly, in PRM, the same issues should be taken into account when considering testing two active interventions for the treatment of chronic pain, for instance.

### **Testing of Implantable Devices in Neurology**

PRM is a specialty that uses many devices and physical modalities. Exploring the trials that use devices from other specialties might provide useful insights. Since 1997, Parkinson's disease is a condition that has received Food and Drug Administration approval for the treatment with deep brain stimulation. Because of the unethical use of placebo device implantation as a result of the invasiveness of the procedure, one strategy is to implant the device in all the patients and have it turned ON or OFF during different time periods and compare the results. Therefore, a crossover study is an interesting possibility for using an implantable device. The main issue is the carry-over effect. In these cases, treatments that induce long-

lasting effects might not be a candidate for crossover design; alternatively, a longer interval period between conditions will be required.

### **Use of Placebo in Children: Experience with Pediatrics**

PRM is a condition that has also a large proportion of pediatric patients. One interesting aspect is the ethics and difficulties of placebo use in children. As with any other clinical trial, pediatric trials should also involve placebo use as much as possible to ensure the highest trial quality. In addition, because of the mechanisms of disease are different in children and adults, it is important to conduct sound research in children. In fact, children have not benefitted from advances in drug and device development to the same extent as adults. Thus, the same standards should be followed in children as in adults. In a recent article, Flynn et al.<sup>65</sup> discusses the use of placebo in children in antihypertensive trials and proposes the following recommendations for the ethical use of placebo: "(1) The potential subjects have asymptomatic, mild-to-moderate primary hypertension; (2) The potential subjects do not have hypertension-related target organ damage; (3) Placebo treatment will be of short duration (generally <4–8 wks)." Similar principles could be easily translated to PRM interventions in children.

### **Use of Sham Procedures/Surgical Trials: Insights from Surgical Trials**

Because some treatments in PRM might involve the need of surgery or invasive procedures, this issue needs to be visited. The main issue against the use of placebo in surgery is that in a standard, placebo-controlled drug trial, the inert substance used in the placebo group is known to have no adverse effects; however, this is not true for sham surgery. The potential harm in a sham surgery procedure might be ethically unacceptable. However, not performing sham-controlled trials might promote the use of procedures that are not effective. For instance, surgical research with placebo eliminated a common surgical intervention, internal mammary artery ligation, for the treatment of chest pain.<sup>66</sup> In addition, a recent trial on arthroscopy for knee osteoarthritis has shown that outcomes after arthroscopic surgery are not better as compared with placebo surgery.<sup>67</sup> Therefore, alternative procedures such as a small incision for the sham surgery group might be necessary to assess the real effectiveness of interventions associated with the need of surgery. Despite of these issues, the need for placebo-controlled trials using surgical techniques is as important as the test of the clinical pharmacologic procedures.

## General Recommendations to Improve the Quality of Placebo and Sham-Controlled Clinical Trials in PRM

Based on the working group's discussion, it is clear that the use of placebo in PRM is challenging for several reasons, therefore resulting in fewer placebo-controlled RCTs being conducted. This fact in addition to the issues of PRM as a specialty (e.g., less research, lower impact factor journals) led to the use of treatments that do not always have the necessary evidence to support them. We propose 14 recommendations and alternatives to address the challenges for placebo use in PRM and, therefore, encourage whenever possible well designed studies and use of more evidence-based medicine. These recommendations are grouped in five different categories.

### Develop a Better Understanding of Placebos

1. There is a lack of understanding of the mechanisms associated with placebo effects. Therefore, it is critical also to investigate the biological mechanisms of placebo effects to plan better placebo interventions.
2. Patients might respond differently to placebo. Therefore, studies should be conducted to find predictors for placebo response. In fact, some of these studies might be based on secondary analyses of the placebo arm of previous RCTs in the field of PRM.
3. Some placebos might have larger effects than others. It is important, therefore, to learn more about the effect sizes of different placebos before designing a given trial (as we discussed in the case study of LBP).

### Challenges Particular to the Population Seen in PRM

4. PRM is a specialty that has a large number of chronic conditions such as chronic pain and sequela after stroke, brain injury, spinal cord injury, etc. Therefore, for these conditions, a placebo treatment needs to be considered for a longer period of time, and in addition, it is important that the researcher is aware of small effect sizes to detect a meaningful difference because improvement is less dramatic than with acute conditions.
5. Patients in PRM trials might have had previous experiences with the intervention under study (such as receiving acupuncture before participating in a new acupuncture trial) and therefore might have a different expectation regarding treatments that will influence placebo

response. The recommendation of our working group was to use naïve subjects whenever possible. However, this approach might be difficult to follow in some populations, for example, LBP, which is often a chronic condition, and patients are influenced by media, health professionals, and opinions of personal contacts, which introduce beliefs that can either favor or hinder the implementation of a given intervention.

### Challenges Particular to the Type of Interventions Commonly Used in PRM

6. Large placebo effects might be observed because of more interaction between care providers and patients. A potential alternative is that instructions might be given by a computer (such as in a video game) or use of a standard protocol in which investigators would follow a specific protocol. Efforts should be made to try to reduce the variability of interventions both in the real and in the placebo groups. The variability might be as a result of the (1) amount of time spent in each session, (2) number and intensity of sessions, (3) too many providers, (4) different settings (private clinic, academic hospital, inpatient, outpatient, etc.), (5) verbal and nonverbal clues, (6) educational materials or packages of information, and (7) rewards or reimbursements. Therefore, controlling for these factors is recommended to decrease variability.
7. For multicomponent interventions, for example, multidisciplinary rehabilitation treatments, our recommendation is to study the isolated components of rehabilitation; however, this will depend on research question and might not be feasible. When the investigation of the multidisciplinary treatments is needed, some alternatives can be considered: (1) consider a waiting list control group (when placebo and real interventions are similar); (2) consider virtual reality in situations where designing a placebo is difficult and also to avoid provider-patient interaction, and (3) use structural equivalence—a method useful in psychotherapy trials where the experimental and placebo groups have similar degree of therapeutic contact.
8. Development of sham in exercise studies is challenging. Our recommendation is that a better understanding of various mechanisms and types of exercises is necessary to allow the development of a standard sham exercise ther-

apy. This might include studying unique components of exercise at each time, for example, using factorial design.

9. Challenges for the development of sham devices. Our recommendation is to partner with engineers and with industry to develop valid and reliable sham devices.
10. Challenges for the development of sham injection techniques. The interventions using injection raise an additional question as to whether the therapeutic mechanism involves the drug or the procedure: should the control be the same injection with placebo content (corticoid *vs.* saline)<sup>68</sup> or a control procedure (fake injection *vs.* dry needling in a different location). We recommend that study designs should allow the comparisons of two variables (e.g., drug and the procedure). In fact, when injection *vs.* pill administration of the same medication is being tested the adoption of a “double-dummy” procedure—one arm has real injection + placebo pill and the other arm has fake injection + real pill—can be valuable.
11. Use of subjective outcomes. Some conditions in PRM such as chronic pain have subjective outcomes as the main end points. One alternative here is the use of surrogate outcomes if the clinical outcome is a subjective outcome. For instance, ongoing research has attempted to identify brain activity signatures using methods of neuroimaging and electroencephalogram.<sup>69</sup> In addition, models to induce pain might also be valuable as a method to quantify pain in subjects with chronic pain.<sup>70</sup>

### Bioethical Considerations

12. Beliefs regarding treatments vary across different cultures. This is important for global clinical trials. Therefore, it is critical to respect the specific cultural beliefs. Patients need to be asked before they are randomized, and researchers need to be aware of potential biases of including subjects who have a strong belief in favor of one intervention.
13. Patients' rights cannot be jeopardized by the scientific interest. Amdur and Biddle<sup>71</sup> proposed a decision algorithm to evaluate ethical aspects involved in a placebo-controlled RCT. In this algorithm, decision points have the following questions: “Is placebo being used in place of standard therapy? Is standard therapy considered to be effective? Is the toxicity of standard therapy such that patients routinely

refuse this treatment? Could the use of placebo instead of standard treatments cause irreversible health problems or extreme suffering? Is it possible to predict the placebo response rate in this study with a reasonable degree of accuracy? Could this trial benefit future patients to the point that a reasonable person with an average degree of altruism and risk aversiveness would consent to being randomized in this trial?”

14. One important issue when considering the ethics is the concept of equipoise (when there is uncertainty regarding the comparative therapeutic merits of two treatments) that is not usually appreciated by investigators. If a treatment is not proven to be efficacious, then a comparison against placebo is indeed ethical (in addition to the standard treatment if this is the case) and should be the first option.

### Methodologic Considerations

15. There is a critical need to develop an effective method of blinding in trials in PRM especially because some treatments might not be easy to blind. Our recommendation is to assess the effectiveness of blinding during and at the end of the trial; however, the researcher needs to be aware that this procedure might be biased when patients guess correctly because of the therapeutic effects of the intervention.
16. To design proper placebo-controlled RCTs, PRM researchers also need to have a strong foundation in the methodology of clinical research. Therefore, clinical researchers in the field of PRM need to receive appropriate training and education to conduct better clinical trials.

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