Challenges of Differential Placebo Effects in Contemporary Medicine: The Example of Brain Stimulation

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Placebo controls are a fundamental component of evaluating the efficacy of medical treatments. In placebo-controlled randomized trials, the success of a trial depends not only on the effect of the active intervention but also on the difference in effect between the active group and placebo group. If the magnitude of the placebo effect is large, it can make detecting a treatment difference difficult or perhaps even impossible. Thus, it is critical to consider "differential placebo effects," the concept that different types of placebos may yield different magnitudes of placebo effects.

In the context of emerging research on the neurobiology of placebo effects and new medical technologies necessitating elaborate placebo controls, this issue has been thrust into the spotlight. On the surface, differential placebo effects may appear to be simply a nuisance affecting statistical power of clinical trials. However, the core of this issue raises fundamental questions of how we measure efficacy of interventions in medicine. In this Neurology Grand Rounds, we use transcranial magnetic stimulation as an explanatory model and highlight principles generalizable to other treatments in the clinical neurosciences and across medicine. We sequentially review relevant literature while building an argument suggesting that in certain circumstances it may be time to reevaluate conventional interpretation of clinical trial results.

Differential Placebo Effects

Placebo effects can be defined as the response to a diverse set of environmental and psychosocial factors surrounding the administration of an active or inactive treatment.[1] These effects depend on the "external context" (eg, verbal and nonverbal suggestions as well as environmental cues) interacting with the "internal context" (eg, the patient's history with medical treatment, expectations, associations/learned responses, and memories).[2] It is therefore intuitive that some treatment modalities could systematically provide greater placebo effects than others.[3] Attempts to identify and characterize such "enhanced" placebos date back to the early implementations of the randomized controlled trial (RCT). In a landmark 4-arm, double-blind RCT of antihypertensive treatments, intravenous (IV) drug, IV placebo, oral drug, and oral placebo were compared.[4] One of this trial's primary findings was that IV placebo was significantly more effective than oral placebo.

The long and somewhat controversial history of sham-controlled surgical trials has also provided evidence supporting the possibility of enhanced placebos. In such trials, the sham group typically receives surgical preparation, anesthesia, and an initial surgical incision or other invasive procedure (eg, femoral puncture) to access the target organ/structure.[5,6] However, instead of completing the procedure, the access point is closed without removing

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25387

Received Jul 10, 2018, and in revised form Oct 4, 2018. Accepted for publication Nov 25, 2018.

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or altering the target. Marked placebo responses have been demonstrated in many sham-controlled surgical trials. One of the earliest and most noteworthy examples comes from the literature of mammary artery ligation for angina. In a double-blind trial by Cobb and colleagues in 1959,[7] patients with angina received either ligation surgery or a sham operation involving parasternal skin incisions. Striking clinical improvements were reported in patients in the sham group on multiple outcome measures, including angina symptom ratings, use of nitroglycerin, and performance on exercise tolerance testing. Other sham-controlled surgical trials have revealed similar findings. For example, arthroscopic knee surgery for osteoarthritis[8] and degenerative meniscal tear,[9] renal denervation procedures for refractory hypertension,[10] vertebroplasty for osteoporotic compression fractures,[11] and neurosurgical transplantation of embryonic neuronal tissue for Parkinson disease.[12] A variety of theories have been proposed to explain the large placebo responses reported in these trials. Most suggest that elevated placebo effects may stem from the intensive environment and deep-rooted "curative" expectations surrounding surgical procedures, whereas others propose alternate mechanisms, such as potential biological effects from the incision itself.[13]

Two recent, high-profile surgical RCTs have brought the issue of elevated surgical sham responses back under scrutiny. ORBITA, the first double-blind, sham-controlled trial of percutaneous coronary intervention (PCI) for symptomatic angina relief, found unexpectedly large effects of the sham stenting procedure that were not statistically different from PCI.[14] Similarly, CSAW, a trial for shoulder pain, found no significant difference between arthroscopic subacromial decompression and arthroscopy alone (lacking the surgical component of bone/soft-tissue removal).[15] However, despite the impressive placebo responses reported in the previously mentioned studies, to the best of our knowledge, sham surgery procedures have never been directly compared to other types of placebo (eg, inert pill) and thus the argument regarding its "differential" placebo effect is largely inferential.

Prospective studies with the direct intention of investigating differential placebo effects have been scarce. The largest study, a single-blind RCT, aimed at evaluating differences between placebo pills and sham devices. The authors used a model of analgesia for arm pain and found sham acupuncture to have greater effects than inert pill on chronic pain.[16] Other studies have found that levels of perceived innovation[17] and positively augmented patient–practitioner interactions[18] may also enhance placebo responses. Attempts to synthesize the literature of prospective studies have been hampered by small numbers, heterogeneity, and some contradictory findings.[19]

Another approach to assess differential placebo effects has been to retrospectively evaluate placebo groups between RCTs of different treatment modalities for the same indication and compare their placebo responses. Using this technique, a meta-analysis of migraine treatments found significantly larger responses from sham devices/procedures than from inert pills,[20] whereas a meta-analysis of central neuropathic pain reported no significant difference between intervention types.[21] A frequent criticism of many of the previously reported studies is the lack of comparison of the placebo group to "no-treatment" controls. This comparison helps to delineate placebo effects from other nonspecific changes such as regression to the mean, spontaneous changes, elevation bias (higher reported symptom severity at initial/baseline assessment than actually experienced),[22] and the Hawthorne effect (changes in outcomes associated with the act of being studied/observed).[23] Meta-analyses evaluating randomized trials that include both placebo controls and "no-treatment" controls are rare, and the largest one was performed by the Cochrane Library. Their meta-regression analysis showed larger effects of placebo treatments with physical placebo interventions (eg, sham devices).[24]

With the growing use of new device-based treatments across medicine, the need to study these technologies in a blinded fashion has led to the development of more sophisticated types of placebo controls. These placebos, for example, elaborate sham medical devices/procedures, may induce very high placebo effects and therefore considerably magnify the issue of differential placebo effects.[3]

Numerous treatments across medical specialties could be used as a platform for exploring this topic further. In neurology alone, deep brain stimulation,[25] transcranial current stimulation,[26] spinal cord stimulation,[27] and transcranial magnetic stimulation (TMS)[28] all provide relevant examples. We have selected TMS as an optimal model for comprehensive analysis; however, the wide applicability of this line of reasoning needs to be emphasized.

Transcranial Magnetic Stimulation

TMS exemplifies an innovative, rapidly growing field of medicine that is currently trying to understand and interpret differential placebo effects. TMS coils generate brief, rapidly changing magnetic fields that induce electric currents in underlying neural tissue. This process does not require sedation or invasive procedures and is safe and well tolerated if appropriate guidelines and recommendations are followed.[29] Based on the stimulation parameters, repetitive pulses of TMS (rTMS) can either excite or suppress activity in a targeted brain region and modulate activity in its connected neural network. An extensive

literature of animal and human studies support these mechanisms.[30] The neuromodulatory ability of TMS has been translated to provide novel treatment strategies for a variety of neurological and psychiatric disorders.[31] In Europe, multiple TMS devices have gained CE marks (health and safety regulatory certification approval for products within the European Economic Area), and in the USA a number of devices have been cleared by the Food and Drug Administration (FDA) for management of medication-resistant depression, migraine, and presurgical brain mapping. Health care services and medical insurance companies in many countries now cover the cost of TMS for several indications, most notably medication-resistant depression, and the number of specialized private clinics is rapidly increasing.

However, in addition to the neurophysiological or "treatment-specific" effect, the procedure and setting of TMS demonstrate almost all conceivable factors that might enhance placebo effects. Most notably, they include treatment cues from the elaborate TMS device being placed over the head, hands-on procedures to set up/calibrate the device, electromyogram recording and displaying of motor evoked potentials, a room full of sophisticated electrical equipment, prolonged interaction with a TMS technician, physician, and/or scientist, visiting an academic tertiary-care center or a specialized clinic for each treatment, and media attention highlighting the innovation of the treatment. Furthermore, in recent studies, magnetic resonance imaging–based neuronavigation has been used to localize the target brain region. This allows the patient to visualize real-time stimulation of their brain on a nearby display screen. The placebo arm in a TMS clinical trial contains all of the above, with substitution of the active coil for a "sham" coil. Sham TMS techniques attempt to navigate the difficult task of achieving blinding while avoiding delivery of meaningful stimulation to the brain. The current gold standard constitutes a sham coil that mimics TMS's visual and auditory experience but is engineered to shield the brain from the magnetic fields. Some devices also have embedded electrical stimulators to simulate TMS tactile sensations on the scalp.[32]

A recent meta-analysis aimed to quantify the magnitude of placebo responses in sham-controlled trials of TMS for depression.[33] Placebo "effect size" was estimated by comparing pre- versus postintervention depression symptom scores in the placebo (sham TMS) group. They included 61 studies in their analysis and reported a large effect size of 0.8 (Hedge g, $p < 0.01$). Interestingly, their meta-regression showed that placebo response magnitude was positively associated with the year of publication (increasing sham TMS responses over time). This may reflect multiple factors such as growing public/media attention, more sophisticated technological device setups, changes in included patient populations, and more realistic sham coils. TMS's robust placebo responses are not limited to studies of depression and have also been well characterized in other neuropsychiatric fields including schizophrenia,[34] obsessive–compulsive disorder,[35] Parkinson disease,[36] and chronic pain.[37] Other areas of TMS research such as epilepsy[38] and motor learning[39] have reported more modest placebo responses.

Perhaps the most striking example of elevated placebo responses in the TMS field comes from a randomized, double-blind, sham-controlled trial of TMS for patients with chronic migraine.[40] This small, proof-of-principle migraine prevention trial compared 8 weeks of high-frequency rTMS targeted to the left dorsolateral prefrontal cortex (DLPFC) to sham stimulation. Analysis of their primary efficacy endpoint found that the sham group yielded a > 50% average decrease in reported headache days (recorded over 1 month). This placebo response was actually significantly larger than the response of active rTMS and was sustained at both 4- and 8-week evaluations. Clearly, the "treatment-specific" neuromodulatory component of this rTMS protocol failed, and most would retrospectively attribute this to the wrong TMS target site. However, what this study did demonstrate is the remarkable potential power of TMS placebo effects. As an interesting aside, more recent studies of TMS for migraine prevention have revealed that stimulation to occipital cortex may be quite efficacious, and the eNeura TMS device has received FDA approval for this indication.[41,42]

The vast majority of the placebo-focused research in the TMS field to date has centered on issues related to different technical procedures for optimal sham stimulation and blinding.[32] These issues are undoubtedly critical and require careful attention; however, there is a striking paucity of research investigating the notion of differential placebo effects. No prospective studies have evaluated the potential enhanced placebo effect of sham TMS compared to other placebo modalities (such as inert pill) or compared to "no-treatment" control groups. One meta-analysis tried to address this question retrospectively by comparing the placebo pill group from escitalopram medication trials to the sham device group from TMS depression trials.[43] This study found no significant difference in the magnitude of the 2 placebo groups' responses, but the study was hampered by many methodological limitations. The authors outline reasons why the effect of sham TMS was likely underestimated. First, they compared component arms of highly heterogenous trials. The most notable concern in this regard was that patients receiving TMS had treatment-refractory depression and patients receiving escitalopram were treatment-naive. Decay in placebo

response has been suggested to parallel resistance to medical treatments, and this is supported by findings of lower than expected placebo responses in studies recruiting treatment-resistant patients.[43,44] Second, the blinding quality differed between comparison groups. TMS trials were predominately single-blinded, and escitalopram trials were double-blinded. Unsuccessful blinding may alter expectation and confidence in the intervention, which can diminish placebo effects.[45] Finally, it should also be noted that the TMS equipment and environmental cues have changed substantially since the early trials (2002–2008) included in the analysis by Brunoni et al.[43]

Implications of Differential Placebo Effects

The paucity of literature on this topic is surprising given the far-reaching potential implications. The most well-accepted concern of an enhanced placebo effect is the unfavorable impact it may have on statistical power. Accordingly, an RCT investigating a treatment with a large embedded placebo effect will generally need more subjects to prove efficacy than a treatment with a smaller placebo effect.[3,37] This has almost certainly wreaked havoc on translational TMS research and may help explain a common trend in the field: very promising initial open-label, single-arm studies and then mixed results from small (underpowered) RCTs.[28] Very few TMS clinical applications in neurology and psychiatry have been able to maneuver past this stage.

As mentioned previously, the most established therapeutic indication for rTMS is medication-resistant depression. The traditional treatment protocol consists of high-frequency (10–20 Hz) rTMS delivered to the left DLPFC 3 to 5 days per week over 4 to 8 weeks.[28] Despite some mixed results (likely in part related to the issues described above), rTMS for medication-resistant depression has shown efficacy in larger trials, and the FDA has cleared 4 different devices for this indication.[46] Furthermore, multiple studies have gone on to show real-world clinical effectiveness[47] and cost effectiveness.[48] Two companies (Nexstim and Neuronix) have recently completed pivotal, premarket approval studies for 2 new applications of rTMS, motor recovery in stroke rehabilitation[49] and cognitive improvement in Alzheimer disease.[50] These trials have not yet been published, and thus we cannot fully comment on the potential role and impact of enhanced placebo effects. However, press releases from Nexstim's stroke trial described much larger than expected responses from sham stimulation. They reported no separation between active and sham groups, with more than two-thirds of patients responding to both interventions (the size of this effect is described as considerably greater than standard occupational therapy alone, which both groups also received).[51] Stakeholders have launched supplementary studies and are still assessing the proper interpretation of this trial.

Moving beyond questions of power, a bigger and more controversial issue arises from the differential placebo effects paradigm. Let us consider the hypothetical chart[20,52] depicted in Figure 1. In this example, possible sources of treatment efficacy include "treatment-specific" effects, placebo effects, and other nonspecific effects (spontaneous changes, regression to the mean, elevation bias, and the Hawthorne effect). Analyzing these charts, what is the best treatment? Is it Drug A with a small placebo effect and a moderate specific effect, or is it Device B with a large placebo effect and a smaller specific effect? Under conventional RCT evaluation, statistical significance would likely be found for the trial of Drug A but not for Device B. Device B would not be considered efficacious and would be denied approval by certain regulatory bodies. However, if you look at the overall effect, equivalent to the total percentage improvement for the patient, Device B is either just as good or superior. Hence, we have the "efficacy paradox."[52] The implication of this can be further magnified if Drug A has considerably more side effects than Device B or if Device B is the sole candidate treatment for a given disease. In this hypothetical scenario, the only reason for the failure of Device B is because a greater proportion of its overall effect was classified under the "placebo" label. Is this a reasonable conclusion? Arguments can certainly be made either way. However, if we take into account the current understanding of the neurobiology of placebo, this conclusion could be a mistake.

Neurobiology of Placebo Effects

Over the past 20 years, a wide body of neuroimaging, neurophysiological, and neuropharmacological studies has transformed the traditional understanding of "placebo effects."[1] These different lines of research have converged to provide strong evidence that placebos meaningfully and relevantly modulate brain networks and neurotransmitter systems. Opioid, dopamine, cholecystokinin, cannabinoid, cyclo-oxygenase, neuroendocrine, and neuroimmunological pathways have all been implicated in placebo effects.[53,54] Recent studies suggest that the neural mechanisms underlying placebo effects may be the same or similar to those targeted by active pharmaceutical interventions. Placebo analgesia and the opioid system are the most well-understood example. This literature includes (1) neuroimaging studies revealing that placebo-induced analgesia and opioid agonist drug-induced analgesia activate the same brain regions[55,56]; (2) receptor-binding studies that show placebo activates opioid

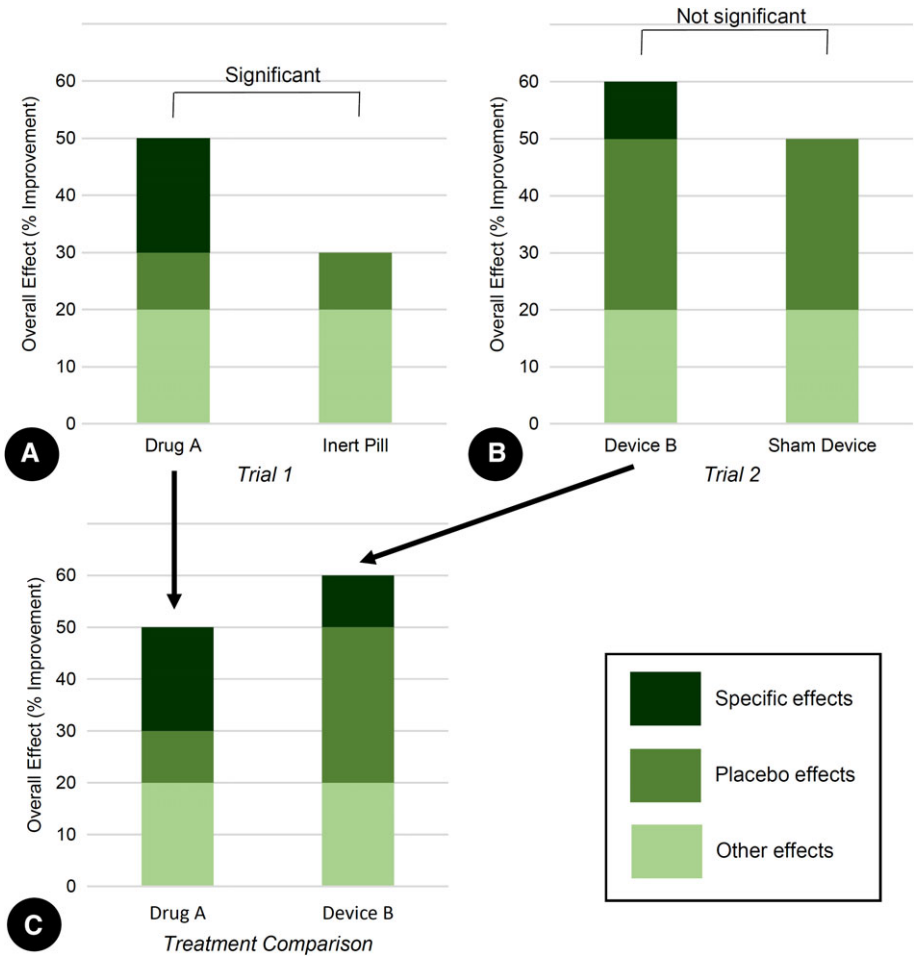

FIGURE 1: Hypothetical comparisons demonstrating the differential placebo effects paradigm. (A) Hypothetical clinical trial 1: Drug A versus inert pill. (B) Hypothetical clinical trial 2: Device B versus sham device. (C) Direct comparison of Drug A versus Device B. Device B has a greater overall effect, but because a larger proportion of its effect is classified under "placebo," it is considered not to be efficacious. To allow for the depicted comparisons, we assume that these hypothetical trials are methodologically identical except for the intervention type. Alternatively, they could be considered randomized substudies within the same 4-arm trial.[9] "Other effects" are assumed to be equal and include spontaneous changes, regression to the mean, and the Hawthorne effect. This chart was adapted from Meissner et al[20] and Walach.[52] [Color figure can be viewed at wileyonlinelibrary.com]

neurotransmitter systems in both humans[57] and animal models[58]; and (3) perhaps the strongest evidence, the demonstration that naloxone, an opioid receptor antagonist, blocks the placebo analgesic effect.[59] The sharing of neural substrates between placebos and drugs has also been demonstrated in other neuropsychiatric conditions such as Parkinson disease[60] and anxiety.[61] An extensive review of these and other examples is provided elsewhere.[53,54]

Another body of literature has investigated what happens when one attempts to experimentally remove placebo effects from active medical treatments. "Open-hidden paradigm" studies, in which participants are not aware that they are receiving a given drug/treatment (eg, IV drug administered by a computer program), have shown that the elimination of expectation and provider interaction leads to a very significant reduction in the effect of the active treatment.[62] Emphasizing this concept, a recent migraine trial showed that placebo treatment mislabeled as active drug (rizatriptan) reduced headache severity as effectively as active drug mislabeled as placebo.[63] Taking this together, it can be argued that what was once primarily considered an annoyance for clinical trialists now presents a legitimate, biologically based treatment opportunity. Strategies to optimally translate placebo effects to clinical practice are a complex and controversial topic that is beyond the scope of this review. Different perspectives on this ongoing debate can be found elsewhere.[1]

An Illustrative Example

Let us now apply this line of reasoning to a relevant and timely clinical example. Chronic pain is common and disabling, has limited effective treatment options, and is costly to health care systems and society.[64] This challenging field is also currently immersed in one of the worst iatrogenic crises to date and is struggling to find new, nonopioid, therapeutic options.[65]

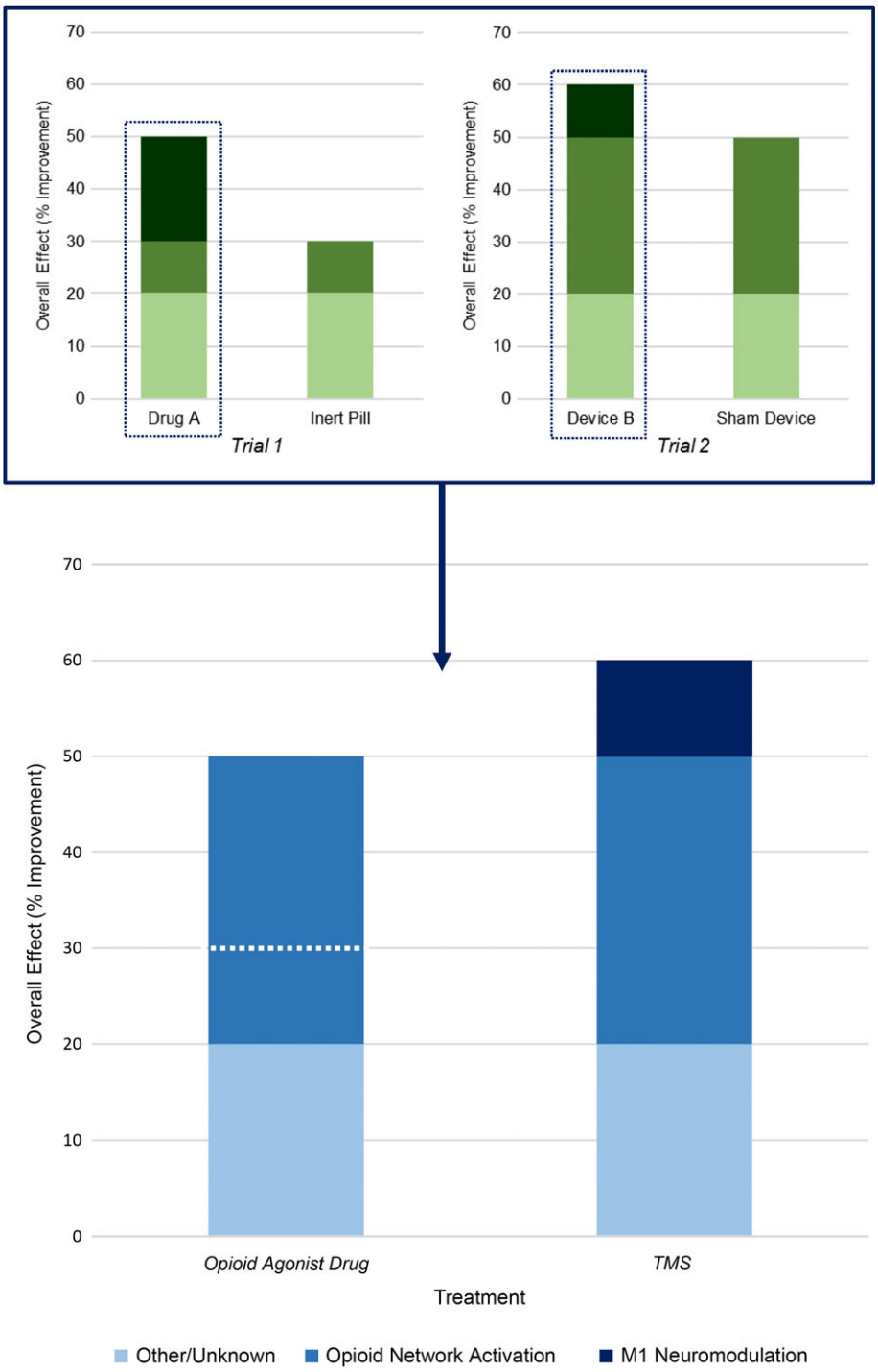

FIGURE 2: Mechanism-based hypothetical example of treatment efficacy for chronic pain. Drug A and Device B are transposed from Figure 1 under a new hypothetical comparison of opioid agonist drug versus transcranial magnetic stimulation (TMS). The effect proportions and magnitudes are kept the same but are relabeled according to presumed mechanism of action. The dotted white line represents the division between opioid activation due to placebo effect and drug effect. M1 = primary motor cortex. [Color figure can be viewed at wileyonlinelibrary.com]

High-frequency rTMS localized to the motor cortex (M1) has been proposed as a novel therapeutic strategy for patients with chronic pain.[37] The M1 target was originally based on reports of analgesic effects after neurosurgical implantation of epidural/subdural electrodes over the motor cortex.[66] More recent work has identified strong network connections between motor cortex and the periaqueductal gray, anterior cingulate cortex, and other critical pain matrix regions.[67] Proposed TMS neurophysiological mechanisms of action include activation of top-down pain inhibition pathways,[68] modulation of thalamocortical circuits,[69] and changes in cortical excitability.[70] In addition to the treatment "specific" effects

described above, rTMS for pain yields a particularly high placebo response.[28] This is not surprising, as the factors related to enhanced placebo devices are combined with a patient population known to be high placebo responders.[21,37]

Over 30 randomized studies of rTMS for chronic pain have been conducted. Most trials have yielded positive results, and it is listed as level A evidence by a recent consensus statement of TMS experts offering evidence-based guidelines.[28] However, mixed findings in a number of studies and considerable heterogeneity in trial designs have resulted in other more guarded recommendations.[71] TMS for chronic pain management is currently approved for use in Europe, but devices for this indication have yet to meet FDA regulatory standards for efficacy.

Let us analyze this example of chronic pain under the efficacy paradox. Aligned with the previous template (see Fig 1), let us assume that TMS for pain, like Device B, has large placebo effects contributing to its overall analgesic effect. The mechanism of this placebo effect is activating opioid receptors in pain-processing regions of the central nervous system. Similarly, let us consider an opioid agonist drug such as morphine or oxycodone. Let us assume that the opioid pills have a smaller placebo effect and a larger pharmacologic or "specific" effect. The mechanism of this pharmacologic effect is activating opioid receptors in pain-processing regions of the central nervous system. Arguably, the same biological responses are being arbitrarily classified under different labels. If we modify the labels to reflect mechanism (Fig 2), the interpretation that opioid agonist pills are efficacious, and that the hypothetical TMS device is not, poses a conundrum that needs further discussion and critical reflection.

Conclusions

First and foremost, this analysis highlights the critical need for prospective, placebo versus placebo studies (eg, one kind of placebo vs another kind of placebo) in fields using device/-procedure-based technologies such as noninvasive brain stimulation. The efforts to retrospectively meta-analyze existing RCT data on this topic should be commended, but the heterogeneity and inconsistent findings underscore the need for prospective research of differential placebo effects. In addition, research manipulating factors embedded in the therapeutic context of these "enhanced" placebos, independent of placebo type/modality, may provide valuable information regarding what other components may be contributing to the elevated responses. These data could then be used to better control such placebo versus placebo modality studies. Furthermore, these lines of prospective, comparative placebo research are critical not only to better understand differential placebo effects but also to corroborate causal effects of placebos that have been demonstrated through other study designs.[72] Our analysis primarily focused on TMS as an explanatory model, but the principles and implications can and should be extrapolated to other medical technologies and surgical treatments that also necessitate elaborate sham device-s/procedures. We also focused on the topic of placebo effects and did not discuss other issues such as nocebo effects, the potential effects of negative psychosocial context surrounding a treatment.[73] It is important to note that nocebo effects could also systematically vary between different treatment modalities, and this is a topic that requires further study.

Second, we have emphasized that in select circumstances, we either need to think carefully and justify current interpretations of RCTs or be open to new interpretations. Changing the evaluation schema for a subset of RCTs (eg, those involving enhanced placebo effects in certain fields of medicine) would be difficult to implement and likely to be poorly accepted by stakeholders. However, it should be noted that clinical trialists have used very similar principles to modify conventional RCT design via the use of placebo run-in periods prior to the RCT.[74,75] One of the primary aims of the placebo run-in is to identify and exclude high placebo responders due to concerns that elevated placebo effects may negatively impact the interpretation of the trial and its results. We are not arguing in favor of this somewhat contentious protocol but using it as an example to show precedent for trial design modifications based on interpreting enhanced placebo effects. Alternatively, a more feasible option may be promoting a shift to study designs that avoid placebo comparisons. This would include RCTs with active comparators, RCTs with active comparators and placebos, or the use of real-world data for comparative analyses between different active interventions. We are aware that these methods have their own shortcomings that would need to be weighed against the current argument.

Although some may consider this line of reasoning to be a radical departure, this analysis does not present dramatically new ideas. Instead, it highlights concepts that have been gradually building across different segments of medicine and neuroscience, and offers a critical examination of the status quo. As our scientific understandings evolve, so should our practices. The research uncovering the neurobiology of placebo and differential placebo effects epitomizes such evolution. To be complacent with current practices because they are familiar and firmly ingrained is a folly that has held back many previous generations of medicine. Conducting placebo-focused research to better understand these issues is not trivial and has many obstacles. The study designs are complex, ethical considerations are challenging to navigate, and funding opportunities are limited. We advocate for more resources and stream-lined research pathways to help remove such obstacles and allow for proper assessment of these critical questions.

Acknowledgment

MJB is primarily supported by a Sidney R. Baer, Jr. Foundation fellowship. TJK is partly supported by NIH/NCCIH grants: R01AT008573 and R33AT009306. APL is partly supported by the Sidney R. Baer, Jr. Foundation, and Harvard Catalyst | The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758). No funding source had any role in the design, sourcing, and writing of this review, nor in the decision to submit it for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health, or the Sidney R. Baer, Jr Foundation.

Author Contributions

Manuscript design: all authors. Review of literature: M.J.B. Drafting of the manuscript: all authors. Critical revision of the manuscript: T.J.K., A.P.-L.

Potential Conflicts of Interest

A.P.-L. reports personal fees from Neuroelectrics, Starlab, Cognito, Neosync, and NovaVision outside the submitted work, and has been issued patents on TMS–electroencephalography and TMS–functional magnetic resonance imaging. The other authors have nothing to report.

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