

The Fallacy of the Placebo-controlled Clinical Trials: Are Positive Outcomes the Result of “Indirect” Treatment Effects?

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Abstract

This paper argues that placebo effects have a larger influence on clinical trial outcomes than purported treatment effects, raising questions about the size of effects currently attributed to clinical treatments. Placebo-controlled clinical trials usually do not include an “active” placebo and thus the clinical outcome could be due to the placebo responses to nontherapeutic side effects of the treatment. For this paper, an active placebo includes substances or procedures that permit attribution of a physiological effect such as a B-vitamin that safely causes flushing, or a very low, subtherapeutic dose of a medication, as well as a biofeedback training procedure that safely trains physiological responses other than the target response. The paper also discusses the positive outcome of a sham treatment procedure (e.g., not actually doing the proposed treatment) in contrast to the nocebo effect (e.g., a worse or negative outcome associated with unintended effects of the treatment procedure). This paper emphasizes exercising caution when interpreting results from clinical trials using pharmaceutical or surgical treatments. The paper discusses possible mechanisms underlying the acceptance of treatment procedures which later have been shown to be ineffective or harmful, and highlights the importance of incorporating active placebo procedures to address any covert treatment side effects induced by placebo response. Finally, the authors suggest that clinical trials of bio/neurofeedback treatments carefully consider the important and consequential influences of placebos when designing studies or interpreting the results of trial outcomes.

Keywords: placebo; nocebo; active placebo; clinical trials; depression

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When research studies report that randomized placebo-controlled clinical trials are proof that pharmaceutical, surgical, or other bio/neurofeedback treatments are effective, the positive outcomes need to be questioned. For example, the positive findings, even in placebo-controlled trials, may be due to the indirect or “nondirected” placebo responses attributable to treatment side effects that include: the postsurgical discomfort which signals to the patient that the procedure was successful, or a dry mouth and constipation that were caused by the

antidepressant medication, which signals to the person that the trial medication or procedure-related medication is working (Bell, Rear, Cunningham, Dawnay, & Yellon, 2014; Stewart-Williams & Podd, 2004). It is possible that the placebo response to treatment side effects (e.g., physical discomfort, dry mouth, or constipation) explains why some medical and psychopharmacology studies are not replicable (Leichsenring et al, 2017; Shader, 2017). Most placebo-controlled studies only control for the placebo effect with a “passive” or inert placebo

group versus an “active” placebo control group (Shader, 2017). This paper provides an overview of the concepts of placebo and nocebo, explores the impact placebo and nocebo, discusses the importance of an active placebo, and suggests questions to ask about the benefits of procedures which could be more attributed to placebo rather than to treatment effects.

What Is a Placebo?

The term *placebo* originates from the Latin for “I shall please” and *nocebo* for “I shall harm” (Bok, 2013). A placebo outcome is associated with the belief that a therapeutic technique or procedure will be beneficial (Haanstra et al., 2015; Moerman & Jonas, 2002). Rather than a simple definition such as “a placebo is a sugar pill,” there is a more nuanced definition referring to the “placebo and nocebo processes” where beliefs are formed about the extent to which any benefits or harms are attributable to or are the result of a treatment procedure (Sellaro et al., 2015).

Typically, statements about placebo begin something like: “A placebo is defined as a sham medication, treatment, or procedure inducing, promulgating, or resulting in positive effects caused by nonspecific treatment ingredients.” To generalize, a placebo is a medication, treatment, or procedure that supports a placebo belief or learned expectancy leading to a physical, behavioral, or psychological effect called a placebo effect. Placebo effects are illustrated in the following two examples:

(1) Treatment of headaches. Eight hundred thirty-five women who regularly used analgesics for headache were randomly assigned to one of four groups (Branthwaite & Cooper, 1981). One group received aspirin labeled with a widely advertised brand name (“one of the most

popular” analgesics in the United Kingdom that had been “widely available for many years and supported by extensive advertising”). The other groups received the same aspirin in a plain package, placebo marked with the same widely advertised brand name, or unmarked placebo.

The results of the Branthwaite and Cooper (1981) study showed that the branded aspirin worked better than unbranded aspirin, which worked better than branded placebo, which worked better than unbranded placebo. Namely, among 435 headaches reported by branded placebo users, 64% were reported as improved 1 hour after pill administration compared with only 45% of the 410 headaches reported as improved among the unbranded placebo users.

(2) Treatment for pain reduction. When pain patients are administered pain medication via a needle injection by the nurse versus an automated infusion where the patient does not know that the medication is given, they experience doubling of the pain relief, presumably because the nurse influenced their belief that the treatment would have beneficial effects by reducing pain (Benedetti, 2007; Colloca & Benedetti, 2005).

In summary, Benedetti (2007) and Colloca and Benedetti (2005) each found the more dramatic the placebo procedure, the more confident the purported practitioner, and the more prevailing the cultural beliefs of the patient and practitioner that “help is on the way,” the more likely it will be that the patient will benefit. A dramatized example of how the placebo response can be optimized is shown in the Derren Brown BBC video *Fear and Faith Placebo* (nlptechiques, 2013).

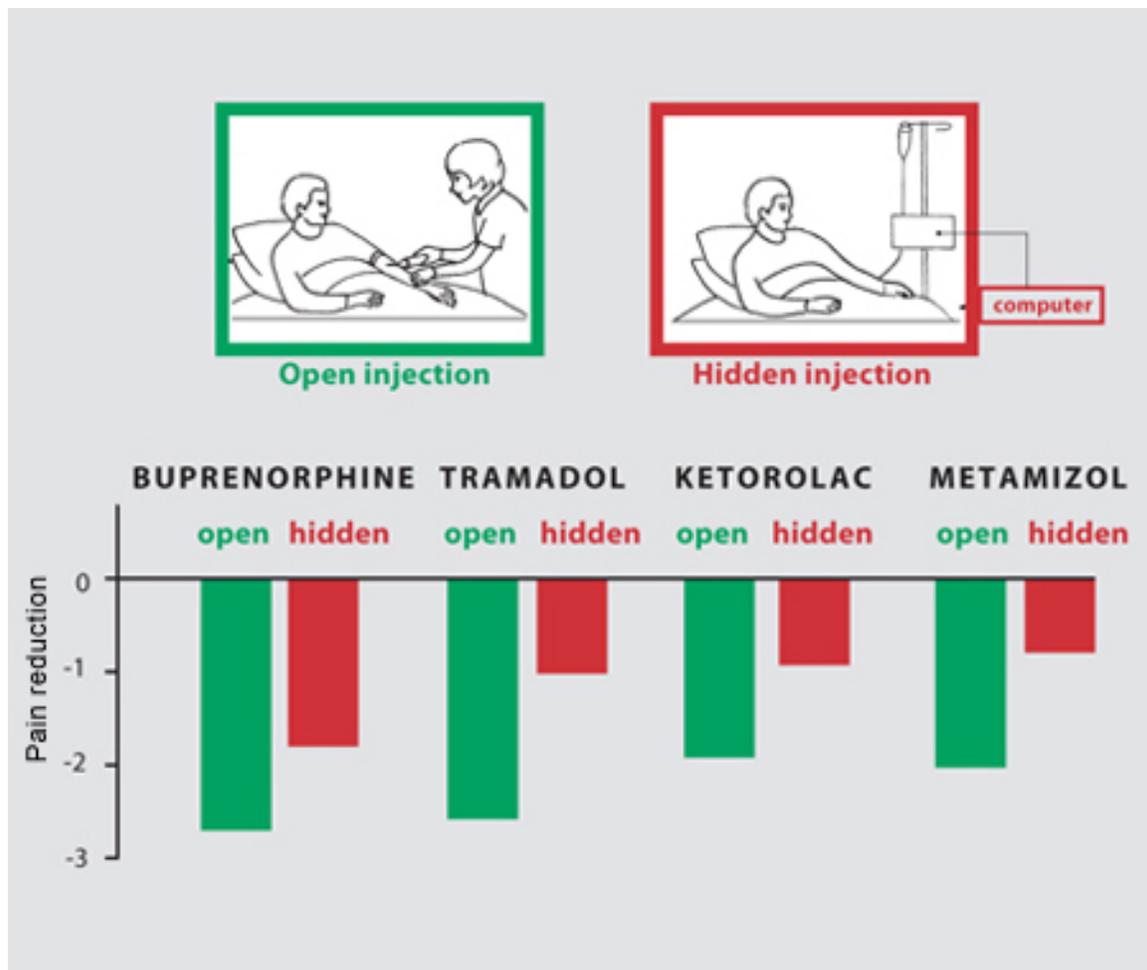


Figure 1. An open injection is compared to a hidden injection of one of four painkillers. An open injection is performed by a doctor in full view of the patient, whereas a hidden injection is carried out by a computer with the patient completely unaware that a medication is being administered. In all cases, a hidden injection is less effective than an open one. (Benedetti, 2007; Colloca & Benedetti, 2005).

What Is a Nocebo?

A nocebo refers to a noxious effect resulting in a nonhealing process of the body. A nocebo effect, treatment, or procedure induces negative expectations and beliefs that the treatment or procedure will be harmful. A nocebo treatment or procedure leads to the perception that the treatment or procedure will have a negative outcome in a way that actively influences the results of exposure to the treatment or procedure. As a result of the nocebo beliefs, the symptoms become worse (Colloca & Finniss, 2012). A common example of a nocebo effect is associated “white coat hypertension” when blood pressure increases after seeing the physician’s white coat and believes that something unpleasant may occur during their treatment (Planès, Villier & Mallaret, 2016). The nocebo response occurs when the person gets worse

because they now believe that a treatment could be harmful. For instance, when students are given instructions that placing a small electric, possibly undetectable current through their head will have no permanent harm but could result in a minor headache, more than two thirds of the students experience a headache, even though no actual electric current was passed through their head (Schweiger & Parducci, 1981). The symptoms were caused by the nocebo effect, the belief or expectancy (nocebo response) associated with the procedure of placing electrodes on their head.

Similarly, preoperative anxiety is correlated with increased postsurgical pain and discomfort (Vaughn, Wichowski, & Bosworth, 2007). Thus, one role of the healthcare professional is to use positive, reassuring communication to reduce the

preoperative anxiety. For example, when anesthesiologists before surgery simply describe all the possible problems that could occur, without providing a context that the problems are unlikely, some patients have more postoperative complications compared to when anesthesiologists share that they are required by law to describe the possible complications; however, they expect this specific situation to work out well (Cohen, 2014; Rosendahl, Koranyi, Jacob, Zech, & Hansen, 2016; Ruan & Kaye, 2016). Healing is promoted when patients feel safe; the task of the health provider is to support an experience of safety and trust.

Anecdotally, numerous clients have reported experiencing nocebo effects when they share with their physician that they are receiving treatments using traditional Chinese herbs and acupuncture, or bio/neurofeedback. Their doctor may imply verbally or nonverbally, “you are wasting your time and money.” Nocebo communications are much more powerful than placebo communications, and nocebo suggestion has been called Western medicine’s “voodoo curse” (Brabant, 2016; Dispenza, 2014; Lucas & Booth, 2014). The negative (nocebo) or positive (placebo) phrasing of patient communication influences treatment or procedure outcomes. For example, placebo benefits will more likely occur when the practitioner states or implies: “If you do the treatment (e.g., surgery, medication, bio/neurofeedback therapy), then there is hope that you will get better.” On the other hand, nocebo effects will more likely occur when the practitioner states or implies: “If you do not do the treatment then you will stay the same, get significantly worse, or possibly even die.” Careful consideration must go into the phrasing of patient communications in order to avoid unwanted nocebo consequences.

Nocebo communications may also be the result of a practitioner fear of litigation such as being sued for malpractice (Johnston, Wester & Sartwelle, 2016). For example, a patient with end-stage cancer may be encouraged to continue the standard medical procedures even though continuing those treatments is unlikely to prolong life: The continuation of treatment implies that there is hope even though the treatment may not provide a known benefit and may in fact lead to complications and an earlier death compared to stopping treatment.

If the patient dies, the medical staff as well as family and friends may then say, “We did everything we could have done.” On the other hand, if a practitioner encourages the patient to choose an alternative medication, treatment, or procedure

which is not the current “standard of care” and then the patient dies, the medical community, family, and friends may say, “The practitioner was a quack and caused the death.” This unspoken fear may prevent practitioners from suggesting alternative treatments. The same fear may also prevent patients from participating in a placebo-controlled study for fear that a placebo administration and not the “real” (i.e., legally safe) treatment will be linked to poor outcome or even a death (Johnston, Wester, & Sartwelle, 2016).

Cautionary Tales

The following are but a few of the many treatments that were initially widely accepted as effective, only to be proven harmful or ineffective in subsequent investigations:

- **Bloodletting.** A bloodletting treatment for various illnesses which was logically consistent with the humoral theory of medicine in the 18th and 19th century may have contributed to the death of numerous patients (Greenstone, 2010).
- **Intensive psychological debriefing** (e.g., emotional “flooding”). A flooding treatment after trauma event was recommended as the treatment to reduce PTSD; however, flooding increased PTSD (Bisson, Jenkins, Alexander, & Bannister, 1997; Mayou, Ehlers, & Hobbs, 2000).
- **Thalidomide.** A medical remedy for sleeplessness and morning sickness for pregnant women lead to an epidemic of congenital abnormalities (Carey et al., 2017; McBride, 1961).
- **Anti-anxiety medication.** An anxiolytic treatment for panic attacks unfortunately increased panic attacks during medication withdrawal when compared to a placebo which had no withdrawal effects (Ballenger et al., 1988; Brown et al., 2016; Johnson, Federici, & Shekhar, 2014; Pecknold, Swinson, Kuch, & Lewis, 1988; Salzman & Shader, 2015).
- **Hormone replacement therapy (HRT).** A treatment for menopausal women to reduce menopausal symptoms seemed to reduce the risk of breast cancer; however, instead HRT was shown to increase the risk of breast cancer (Zbuk & Anand, 2012).
- **Vineberg procedure.** A procedure (Vineberg & Miller, 1951) in which the internal mammary artery was ligated by surgery for the treatment of angina pectoralis. Cobb, Thomas, Dillard,

Merendino, and Bruce (1959) showed that a double-blind (placebo-controlled) sham/mock surgery was equally effective as a real surgery; thus, the Vineberg procedure was abandoned (Beecher, 1961).

- **Arthroscopic knee surgery.** A surgery of the knee for people with osteoarthritis that uses a biomechanical approach to remove microscopic or macroscopic fragments of calcium phosphate crystals associated with synovitis (Felson & Buckwalter, 2002); however, there are no benefits in long-term follow-up for patients receiving surgery as compared to physical therapy (Brignardello-Petersen et al., 2017; Kirkley et al., 2008; Monk et al., 2017). More importantly, when the arthroscopic surgery outcomes were compared with a sham/mock surgery, there was no difference in outcome (Moseley et al., 2002).
- **Reducing dietary fat.** Despite “fat causes heart disease; therefore, eat a low-fat diet,” recent studies have shown that low-fat diets were often very high in simple carbohydrates and much more harmful to the patients (Taubes, 2016).

Future treatment procedures may capitalize on the beneficial effects of placebo responses observed during placebo-controlled trials. A few examples include:

- **Bypass surgery.** Ornish et al. (1990; 1998), van Dixhoorn and White (2005), and others have shown that lifestyle changes appear more effective than traditional coronary surgery treatments (Pischke, Scherwitz, Weidner, & Ornish, 2009). The only way to test whether bypass surgery treatments are effective is to test against a sham/mock surgery group which for ethical reasons has not yet been done.
- **Annual mammogram screening.** Autier, Boniol, Gavin, and Vatten (2011) and Nelson et al. (2009) studied healthy women receiving routine mammography which may have unintentionally caused an excessive number of treatment and surgical interventions due to excessive x-ray exposure. Possibly screening of healthy women is not predictive of reduced incidence of breast cancers and may be less related to reducing breast cancer death rates when compared to other factors. In countries where screening did not occur until much later breast cancer deaths also

decreased as compared to countries that started screening early (Autier et al., 2011; Nelson et al., 2009).

- **Treatment of depression.** An antidepressant medication for mild to moderate depression may be less effective compared to a treatment of exercise and behavior therapy which appear as, if not more, effective (Babyak et al., 2000; Hallgren et al., 2016).

Pharmaceutical Marketing Practices and Placebo Effects

Many of the benefits claimed by pharmaceutical companies for successfully treating depression, insomnia, or anxiety may be due to the placebo response evoked by changes in body sensations (e.g., “a flushing experience means the treatment or procedure is working”) that are attributed to the “effectiveness” of the medication or medical treatment procedures. For example, selective serotonin reuptake inhibitors (SSRI) antidepressant medications such as Paxil or Prozac have side effects within hours compared to therapeutic effects that reportedly take at least one or two weeks to have an effect. Patients may report almost immediate benefits from Prozac, as reported by the many published research studies; however, as a cynical observation, many of those studies are funded by pharmaceutical companies. It is not clear that the therapeutic benefits are due to Prozac’s purported direct mechanism of action or rather due to indirect effects associated with priming a belief that Prozac will be an effective medication (Kirsch & Sapirstein, 1998; Mayberg et al., 2002; Mora, Nestoriuc, & Rief, 2011). A similar example occurs with the purported benefits of Zoloft, an antidepressant, that may be due solely to the placebo response associated with medication side effects which according to the Drugwatch website typically “decrease after the first or second week of use and include: nausea, diarrhea, weight loss or gain, increased sweating, dizziness, sleepiness or insomnia, tremor, dry mouth, headache, restlessness, suicidal thoughts, and sexual dysfunction” (Llamas, 2017).

When independent researchers (e.g., not funded by pharmaceutical companies) reanalyzed research data from published or unpublished studies, they often found that a treatment medication was no more effective than placebo for the treatment of mild and moderate depression, both within the first week or two of administration, as well as at long-term follow-up (Doering, Rief, & Petrie, 2014; Kirsch, 2014; Kirsch & Sapirstein, 1998; Mayberg et al.,

2002). Even though antidepressant medications such as Prozac may be no more effective than a placebo treatment, medications such as Prozac allow the pharmaceutical industry to post global sales in 2013 of \$23.8 billion dollars for mental health medications, with tens of millions of pill prescriptions for antidepressant medications annually (Lindsley, 2015).

When pharmaceutical companies fully report both positive and negative results of medication studies, the positive data becomes much less favorable when the negative side effects from medications are included. For example, SmithKline Beecham's Study 329 data was reanalyzed by Le Noury et al. (2015) to compare the safety of paroxetine and imipramine which are SSRIs with placebo in the treatment of adolescents with unipolar major depression. The results showed that there was no significant difference in outcome between the medications and the placebos. Sadly, there were clinically significant increases in harms, including suicidal ideation, suicidal behavior, and other serious adverse events in the paroxetine group as well as cardiovascular problems in the imipramine group. In 2012, GlaxoSmithKline pleaded guilty and paid a \$3 billion fine to resolve fraud allegations and failure to fully report safety data (U.S. Department of Justice, 2012).

How Come the Medical Procedures were Initially Accepted?

Medical interventions and procedures make rational sense, and any initial positive outcome is enhanced by "confirmation bias" when we "detect, attend to, and recall circumstances that confirm prior beliefs" (Kassin, Dror, & Kukucka, 2013; Schwarz & Büchel, 2015). Simply stated, when patients, researchers, and clinicians observe any—even minimal—positive physical, behavioral, or psychological effects of a treatment or procedure, it confirms their clinical bias that the treatment procedures were a success. The patient "improved" in the expected way. Eventually the treatment procedure becomes accepted and adopted by others.

Later when the results are "confirmed" by randomized, placebo-controlled trials, the procedures gain even more credibility. The patients' positive benefits are given as proof that the particular procedures "as described" was instrumental to cause the associated positive benefits. However, association is not causation (Bollen & Diamantopoulos, 2017; Bollen & Pearl, 2013). When clinical trials use inert placebo, the treatment will perform relatively better than when

compared to an active placebo (Howick, 2017; Howick et al., 2013; Roose, Rutherford, Wall & Thase, 2016). Other factors that impact the reporting of predominantly positive findings are that:

- Scientific journals are biased to publish positive findings and tend not to publish negative findings (Every-Palmer et al., 2014; Franco et al., 2014).
- Researchers tend to publish positive findings; since, they may not receive follow-up grants if they report negative findings (Ioannidis, 2005).
- Lack of long-term follow-up and assessment of negative side effects of procedures are absent.
- Undue industry pressure and funding influence the outcome and publication of the research (Friedman & Friedman, 2016; Stamatakis, Weiler, & Ioannidis, 2013).
- Profit incentive to continue the practices (financial loss aversion) since the privatized medical industry's major goal is increasing shareholder value.

Once a procedure is believed to be effective, it is very challenging to stop the practice from becoming standardized even when later the positive outcomes are shown to be attributable more to a placebo response. For example, arthroscopic surgery for degenerative knee problems continues to be practiced at a cost of 3 billion dollars a year. Obvious questions are raised: If a positive outcome is mostly attributable to a placebo response, what is the harm, and why continue the medical or surgical procedure? Is it ethical to try new procedures once the patient believes the initial procedure is effective because a "positive outcome" occurred? Some answers may be found by exploring components of the placebo response.

Components of the Placebo Response

Before accepting whether any benefits are the result of the planned procedure, clinicians need to assess the following components of a placebo response and then document:

- The causally "direct" overt effect of the medication, surgery, or other treatment procedure such as the direct effects of both planned placebo (positive, encouraging) instructions, procedures, or substances used as a control.
- The causally "indirect" covert effects of the medication, surgery, or other treatment

procedure such as the unplanned effects the treatment procedures have on patients.

- The causally direct or indirect, overt or covert placebo effects attributable to the “side effects” of surgery; medication (e.g., discomfort, dry mouth, or even sitting still for an hour during biofeedback training) which evokes somatic changes that the person experiences and then attributes the outcome to the intervention.
- The overt or covert nocebo communication effects (e.g., “voodoo” instruction/communication) about what would happen when the participant does not partake in the recommended treatment procedure.

The Importance of Active Placebo

It is impossible to separate direct and indirect, overt and covert components unless the study design includes an active placebo procedure. An active placebo is a procedure that induces psychophysiological effects, yet offers no obvious, causally direct therapeutic benefit. For example, Pollan (2015) primed student volunteers with a communication that if they experience a “skin flushing” then they may be experiencing the effects of a hallucinogenic substance, with the result that many reported a “psychedelic trip” even when they only received niacin (e.g., vitamin B3). Similarly, Lee (2015) primed student athletes with a communication that if they experience increased heart rate then they may have received an athletic performance-enhancing substance, with the result that many had observable athletic performance

improvements when they only received a mild dose of caffeine. Another example was shown when study participants had improvements in “attentional performance” even though EEG biofeedback sensors were positioned over irrelevant anatomical locations (Bjørkedal, 2016; Jensen, Bielefeldt, & Hróbjartsson, 2017; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2014).

During surgical procedures, an active placebo control would be a sham/mock surgery in which the patient would undergo the same medical procedure (e.g., external surgery incision) without continuing some internal surgical procedure (Jonas et al., 2015). In numerous cases of accepted surgery, such as the Vineberg procedure (Vineburg & Miller, 1951) for angina, or arthroscopic knee surgery for treating osteoarthritis, the clinical benefits of a sham/mock surgery were just as successful as the actual surgery. Similar studies suggest the clinical benefits were solely (or primarily) due directly to the placebo response (Beecher, 1961; Cobb et al., 1959; Moseley et al., 2002).

The Hidden Placebo in Study Designs

Many research studies employ a placebo control, however what is less typical is a double-blind study using an active placebo (Enck, Bingel, Schedlowski, & Rief, 2013). Unfortunately, a typical placebo-controlled study design is problematic for identifying the direct and indirect (covert) placebo effects that occur within the study as shown in Figure 1.

Randomized double blind controlled study with passive placebo

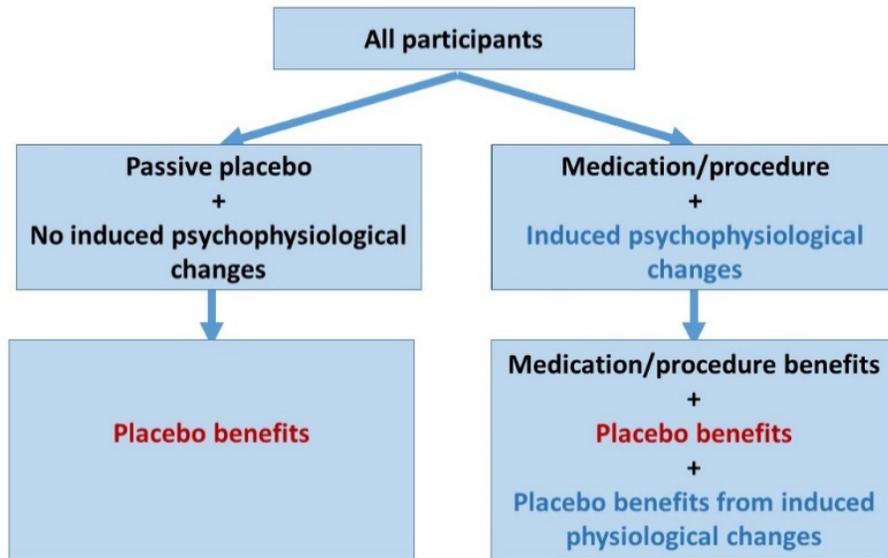


Figure 1. Normal (passive) placebo control group controls and experimental group. What is not assessed are placebo benefits induced by the medication/treatment induced side effects.

With a passive placebo, there is no way to know if the observed benefits are from the medication/medical procedure or from the placebo/self-healing response triggered by the medication/medical procedure. The only way to know if the treatment is

actually beneficial is to use an active placebo instead of a passive placebo. The active placebo triggers observed and felt body changes which do not affect the actual illness. A study design using an active placebo arm is shown in Figure 2.

Randomized double blind controlled study with active placebo

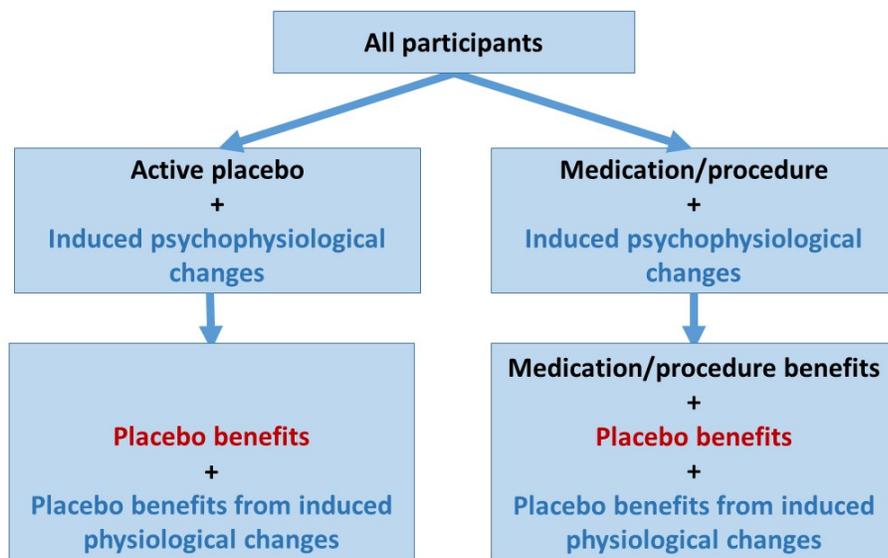


Figure 2. Active placebo control group controls for the normal placebo benefits plus those placebo benefits induced by the medication/treatment-induced side effects.

The implications of an active placebo may suggest that numerous treatments may not be as successful as claimed and may be one of the major factors why so many medical and psychological studies cannot be replicated.

Questions to Ask Before Agreeing on the Procedure or Medication

A quick way to ask whether a medication or medical treatment benefit is the result of placebo components is with the following questions:

(1) Are there successful self-care or behavioral approaches that have demonstrated success? When successful treatments are reported, then questions are raised whether pharmaceutical or surgical outcomes are also attributable to the result of placebo effects. On the other hand, if there are no successful self-care approaches, then the benefits may be more due to the therapeutic effect of a surgical procedure or medication.

(2) Has the procedure been compared to an active placebo control? If not, then it is possible that the results could be attributed to a placebo response.

What are the long-term benefits and complication rates of the medication, treatment, or procedure? When benefits are low and risks of the procedure are high, explore the risks associated with “watchful waiting” (Colloca, Pine, Ernst, Miller, & Grillon, 2016; Thomas, Williams, Sharma, Chaudry, & Bellamy, 2014).

Finally, interventions reflect the biases of the clinicians; therefore, more objective approaches to determining the fitness and appropriateness of the intervention may take trial-and-error over many variations of the interventions. To quote or paraphrase the work of Taleb (2012) from his book *Antifragile: Things That Gain from Disorder*:

- Over millions of years through natural selection, whatever increased reproductive fitness predominates; thus, it is unlikely we can do better than natural selection with technology.
- Nature produces ongoing experiments to improve reproductive fitness. As Taleb (2012) points out:

It was an insult to Mother Nature to override her programmed reactions unless we have a good reason to do so, backed by proper empirical testing to

show that we humans can do better; the burden of evidence falls on us humans.

- How can we improve health with some simple procedure or medication when nature has experimented for millions of years? It is unlikely that we can do anything to improve fitness.
- Nature had to have tinkered through selection in inverse proportion to the rarity of the condition.
- Of the hundred and twenty thousand medications available today, none make a person better. For example, steroid substances may enhance athletic performance; however, they can reduce sperm production, increase aggression, heart attacks, or strokes, and may result in gynecomastia.
- If the patient is near healthy, then Mother Nature should be the doctor (e.g., eating well, avoiding stress, and getting lots of good rest should cure colds).
- If the patient is close to death, all speculative treatments should be encouraged—no holds barred.

Summary

All observed outcomes result from a combination of overt and covert, direct and indirect, specific and nonspecific effects of a medication, treatment, or procedure, including placebo components.

Because medications, treatments, or procedures may have both placebo and nocebo components, those medications, treatments, or procedures should only be recommended when they significantly improve the health of the patient more than an active placebo treatment group and not merely a passive placebo group. Unfortunately, most clinical studies that include pharmaceuticals or surgery do not test their medication or surgery against an active placebo. Sadly, the FDA does not require a standard of double-blind, active placebo controls for studies, which may work to support “Big Pharma” to maximize profits.

Fortunately, the design of active placebo-controlled studies is very possible for anyone interested in comparing the effectiveness of medications, treatments, and procedures in various settings, from hospitals and clinics to university classrooms and individual homes.

Finally, the benefits of the treatment must significantly outweigh any risks of negative treatment side effects. Short-term treatment benefits need to be balanced by any long-term benefits. Unfortunately, short-term benefits may lead to significant, long-term harm such as in the use of some medications (e.g., sleep medications, opioid pain killers) that result in chronic dependency and which lead to a significant increase in morbidity and mortality of many kinds. Using active placebo procedures have far less damaging side effects compared to many pharmaceutical interventions. Furthermore, bio/neurofeedback procedures are built on operant conditioning principles, which facilitate active learning techniques that have few, short-lived side effects compared to many long-lived pharmaceutical side effects (Luctkar-Flude, Groll, & Tyerman, 2017; Rogel et al., 2015).

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