The Placebo Problem

Michael Kuss and Scott Millard
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For hundreds of years, the medical community has known that the mere act of receiving treatment, even if it’s just a sugar pill, can improve a patient’s symptoms. Therefore, in order to ensure that the effects of an experimental treatment are real, most randomized controlled trials (RCTs) include a placebo arm.

Placebos are most often pharmacologically inactive pills that mimic the physical characteristics of the study drug, but they can also take the form of inert medical devices, sham surgeries, and fake acupuncture. The placebo effect is broader than just patient improvement in response to this inactive treatment; it encompasses the patient’s response to the entire therapeutic context in which treatment is administered.

Details Matter
There is actually not one single placebo effect – but many – all of which come together to produce symptom improvement through mind-brain responses to treatment context. Psychosocial factors such as expecting to get better, rituals of care, active engagement in treatment, and even the mere act of taking a pill can all contribute to the placebo response. Research has also shown that how the placebo is administered is just as important as what is administered. The type of placebo, the color and dosing regimen of pills, and how caring the physician acts can all influence the magnitude of the response.

Although the placebo effect was once thought to be an irrelevant and illegitimate nuisance, it is now a field of research in its own right. Multiple brain systems and neurotransmitters underlie the many components of the placebo effect, and a growing body of literature has shown that it improves health in a number of very real ways. The placebo effect doesn’t cure – it won’t shrink a tumor or heal a broken bone – but it can relieve chemotherapy-induced nausea and diminish chronic pain. It can also produce changes in physiological functions such as heart rate, blood pressure, lung function, and gastric motility, and can even lead to improved survival rates in some diseases. In general, the placebo response is most effective at relieving pain and improving depression, anxiety, and fatigue – all conditions in which symptoms are self-reported and psychological distress plays a significant role.

Placebo ... Uh Oh
In an RCT, the true effects of the experimental treatment are those that are above and beyond the placebo response. But there is an inherent problem in this design: the bigger the placebo response, the harder it is to show that an experimental treatment is effective. Ultimately, these reduced drug-placebo differences result in a higher likelihood of a negative trial outcome despite drug effectiveness. Such late-stage trial failures come at a great financial cost to pharmaceutical companies and can lead to an erroneous abandonment of viable drugs.

Indeed, a large placebo response has been the downfall of a number of major clinical trials with solid preclinical and prior-clinical evidence of efficacy. In an analysis of 52 antidepressant trials that examined the relationship
between placebo response magnitude and trial outcome, trials with a low placebo response fared much better than those with a high placebo response. In high placebo-response trials, only 20 percent of treatment arms achieved significance, compared to 75 percent in low placebo-response trials.

The magnitude of the placebo response has also been deemed the biggest contributor to trial outcome in neuropathic pain, and a high placebo response is thought to be partially to blame for the fact that more than nine out of 10 late-stage trials of treatments for neuropathic and cancer pain have failed over the last decade.

Even more alarming is the fact that the placebo response is growing over time, especially in analgesic, antipsychotic, and antidepressant trials. Strangely, this increasing effect seems to be specific to the U.S., at least for trials of neuropathic pain.

In this eBook, we examine issues surrounding the placebo response and its rise in more detail. Section One explores how and why the placebo effect is growing over time, and concludes with a brief history of the placebo. Section Two turns to the underlying psychological, neurobiological, and genetic mechanisms responsible for the placebo response. Section Three examines how the placebo response can be accurately measured in studies, its relationship to drug effects, and a few disease-related factors that contribute to it. Section Four discusses the latest research on strategies to reduce the placebo response, and the many factors that can influence its magnitude. Section Five covers a few other placebo-related topics: the placebo’s opposite – the nocebo effect – where the brain’s response to treatment context negatively impacts health; the placebo response in pediatric populations; and ends with some ethical considerations of placebo use.

FURTHER READING


Kemp AS, Schooler NR, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophr Bull 2010;36(3):504-509.


Analgesic and psychiatric drug development is facing an enormous problem: rising placebo responses in randomized controlled trials (RCTs) threaten the ability of pharmaceutical companies to successfully identify novel effective drugs. Even some older drugs like Prozac aren’t surpassing placebo anymore.

**UP, UP, UP**

While trials of other drug classes may also be similarly affected, the rising placebo effect has been well documented for three classes of drugs – analgesics, antidepressants, and antipsychotics – all of whom share a reliance on subjective, patient-reported outcome measures. The increasing placebo response among antidepressant and antipsychotic trials has been noted since at least the early 2000s, while a similar trend in analgesia has come to light more recently.

Several analyses of antidepressant trials have found that on average roughly one-third of adult patients in the placebo group exhibit a response (compared to half in the drug group), and this proportion is even greater in pediatric and adolescent trials. Between 1981 and 2000, the proportion of adult participants responding to placebo in antidepressant trials has grown by approximately seven percent per decade.

Multiple analyses also demonstrate that antipsychotic trials in schizophrenia are experiencing a similar effect. Compared to baseline, improvements in several measures of symptom severity after six weeks have been found across time. For example, the placebo group’s average Positive and Negative Syndrome Scale (PANSS) score of schizophrenia symptoms, the most common metric used in clinical trials of the illness, improved by 10 points between 1991 and 2006.

A 2015 meta-analysis that examined 84 neuropathic pain RCTs conducted between 1990 and 2013 found that placebo responses in this therapeutic area have also increased dramatically, while drug responses have stayed the same. The end result is a greatly diminished drug advantage over placebo across time. While drugs produced nearly 30 percent more pain relief than placebos in 1996, by 2013 this margin of difference had decreased to a meager nine percent.

Kemp AS, Schoeler NR, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophr Bull 2010;36(3):504-509.
SECTION ONE: PLACEBO PROBLEM OVERVIEW

AN AMERICAN PROBLEM?

Surprisingly, the increase in placebo response observed in neuropathic pain was true only of trials conducted in the U.S.; placebo response rates in Europe and Asia remained similar across the 24 years examined in the meta-analysis. This is consistent with some (but not all) analyses of antipsychotic trials, which have also found worsening placebo responses in the U.S. but not elsewhere.

For both antidepressants and antipsychotics, a number of trial design factors such as an increased number of drug groups and larger sample size have been associated with the increasing placebo response. Two U.S.-specific trial characteristics seem to be driving the increased placebo effect in neuropathic analgesics: size and length. Across time in the U.S., but not Europe or Asia, trials have become bigger, longer, and comprised of more study sites. In 1990, the average neuropathic pain trial enrolled fewer than 50 people and was four weeks long. By 2013, these statistics had jumped to more than 700 participants and a 12-week trial duration.

Increasing sample size and trial duration also predict a higher placebo response in analyses of osteoarthritis pain as well as chronic low back pain trials, although these studies did not assess the effect of geography. Interestingly, however, trial duration is associated with a lower placebo response in antipsychotic trials, underscoring the complexity of the placebo problem and its underlying causes.

REASONS FOR THE RISE

A number of reasons for the association of certain trial characteristics with the increasing placebo response have been proposed. A greater number of drug arms – and therefore a reduced probability of receiving placebo – likely increases patient expectancy of receiving an active drug, which in turn boosts the placebo response. Larger sample sizes, with the increased clinical support staff and other added resources they necessitate, may feel more official and legitimate to trial participants, and therefore also contribute to increased patient expectancy of pain relief.

Two possible mechanisms could account for the finding that placebo effect increases as trial length does. First, as patients experience some initial placebo analgesia, a positive feedback loop drives subsequent pain relief. Second, longer trials allow for more exposure to placebo response-boosting aspects of the treatment experience – for example, increased contact with clinicians, better education about disease management, and more social support.

Another possible explanation for the U.S.-specific increase in placebo response is that the U.S. is only one of two countries worldwide that allows direct-to-consumer (DTC) pharmaceutical advertising. The use of DTC television, print, and online ads has sky rocketed over the past several decades – American television viewers now watch an average of nine drug ads per day – leading to the hypothesis that this influx of information about powerful drug responses has increased patient expectations of pain reduction.

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The term “placebo” first took hold in an unlikely place: funerals. Placebo, Latin for “I shall please” first came into use in the 14th century as the name for a professional mourner, an individual who was paid to stand in for a family member of the deceased and “sing placebos,” a term for the chanting of the phrase “Placebo Domino in regione vivorum” (which translates to “I will please the Lord in the land of the living”).

Thus, the term placebo came to mean something that was pleasing and satisfying. Over time, placebo singers began to have a derogatory connotation, likely due to their low social status, and the term placebo also came to be synonymous with a sycophant, like Geoffrey Chaucer’s character Placebo in Canterbury Tales.

The first placebo-controlled medical experiment was conducted in 1784 by Benjamin Franklin and Antoine Lavoisier, who used placebos to discount Franz Mesmer’s theory of mesmerism, which claimed that an invisible natural force called “animal magnetism” could produce strange bodily sensations that culminated in healing. Franklin and Lavoisier’s experiment involved the exposure of participants to both regular objects, such as trees, they were told had been “magnetized” (the term for objects that had been treated by Mesmer to elicit healing powers), as well as trees that had been authentically but secretly “magnetized.” Participants experienced effects in the former case but not the latter, leading the team to conclude that the effects were due to imagination.

According to a historical overview of placebo use in medicine, placebo was first defined in a medical dictionary the following year as “a commonplace method or medicine.” By 1811, it was defined as “an epithet given to any medicine adapted more to please than to benefit the patient.”

However, it was Henry Beecher who first popularized the concept of the placebo effect and demonstrated its importance in modern medicine. In a now-famous 1955 JAMA article entitled “The Powerful Placebo,” Beecher presented the results of 15 placebo-controlled trials and reported that the average placebo improvement was substantial – about 35 percent. In hindsight, the vast majority of these studies did not include a no-treatment group, making it impossible to say whether the observed effects were due to the placebo effect itself or the natural course of disease (see Chapter 9 for more information on disease-related contributors to the placebo response). Nevertheless, it was Beecher’s seminal paper that cemented the placebo response as a legitimate medical phenomenon.
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Solutions to the placebo problem require an understanding of the underlying mechanisms. Broadly, research on contributors to the placebo response falls into three categories: psychological, neurobiological, and genetic. Section Two examines this research, much of which focuses on placebo analgesia. In this chapter, we’ll explore the psychological mechanisms, taking a look at the theoretical constructs and empirical findings that contribute to the placebo response.

THIS, THAT, OR BOTH?

Historically, the best accepted psychological theory underlining the placebo response has been patient expectancy, where a patient’s belief that he or she will get better drives symptom improvement. This belief may be pre-existing as a result of the patient’s past experiences, or based on information from the current therapeutic environment gleaned prior to or during placebo administration.

Classical conditioning, too, has long been implicated in the placebo response, and is often viewed as an alternative to patient expectancy. According to the conditioning theory, a prior association between the therapeutic environment and the active drug produces a memory that causes the patient to respond to the environment as if it were the drug. Pavlov and his famous dogs provided one of the earliest demonstrations of this effect in 1927. He paired morphine, known to induce restlessness in dogs, with a bell, then later showed that the sound of the bell alone could recreate the animals’ restlessness.

More recently, a unified theory that marries the dual role of expectancy and conditioning, and which characterizes the placebo response more broadly as a learned phenomenon, has been presented. In this model, a combination of verbal, conditioned, and social observational cues trigger patient expectancy of symptom improvement that in turn drives central nervous system responses.

SPOKEN AND UNSPOKEN

The majority of research on the role of learned cues in the placebo effect has focused on placebo analgesia. Verbal cues, such as an explicit statement made by trial staff that a placebo is actually a potent analgesic, are always consciously perceived by the patient. In contrast, the patient may or may not be aware of the contextual elements of the therapeutic environment – for example, the clinician in a white coat or the specific characteristics of the treatment room – to which he or she becomes conditioned. However, research shows that while verbal and conditioned cues can each induce placebo relief from pain, itch, nausea, and fatigue on their own, pairing them together elicits the largest response.

Verbal and conditioned cues involve first-hand experiences; however, placebo analgesia can also be learned through social observation. For example, having study participants merely watch a video of a person reporting less pain following a placebo is enough to induce an effect in the observers. In addition, new research is underway to examine the contributions of other psychological variables, such as motivation, empathy, anxiety, and attention, to the placebo response.
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SECTION TWO: UNDERLYING MECHANISMS

As with many other aspects of placebo research, the majority of research on underlying neurobiological mechanisms has focused on placebo analgesia. In fact, roughly 40 positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies over the last 15 years have shed light on the specific central nervous system underpinnings of pain improvement in response to placebo.

REduced nocIception

These functional neuroimaging studies have implicated a number of brain areas in placebo analgesia. Placebo treatment reduces activity in a number of “classical” pain-related brain regions that receive input from spinal nociceptive pathways. Regions displaying diminished activity include primary and secondary somatosensory cortices, thalamus, insula, and anterior cingulate cortex (ACC). These reductions are evident not only during the anticipation and later reporting of pain, but also during the administration of the painful stimulus itself. A spinal cord fMRI study showed that pain-related activity in the dorsal horn is also reduced by placebo, suggesting that the reduction in nociception-related activity is not limited to the brain.

The descending pain modulatory system, a network of brain regions that modulates analgesia through top-down control, has also been heavily implicated in placebo analgesia. Neuroimaging studies have demonstrated increased functional coupling of several brain areas in this network, including dorsolateral prefrontal cortex (DLPFC), ACC, and periaqueductal grey (PAG), during placebo analgesia. Placebo-induced increases in PAG activity are correlated with the strength of the pain relief provided.

It is important to note that many of these pain-related brain regions are also involved in mediating other placebo-related processes such as perception, decision-making, and emotion. For example, the DLPFC is thought to maintain and update the expectancies that are an important component of placebo analgesia. It is therefore difficult to definitively say which aspects of the placebo response these brain changes sub-serve. In addition, some brain areas such as the ACC and PAG show opposite effects across studies and with respect to the timing of the imaging relative to the noxious stimulus, findings that underscore the complexity of the placebo response and the challenges of studying it.

ENDogenous opioids ...

A wealth of pharmacological and neuroimaging studies has characterized the role of the endogenous opioid system in placebo analgesia. The first experimental evidence of opioid involvement occurred nearly 40 years ago. In a landmark 1978 study that has since been replicated numerous times, placebo analgesia was used to treat postoperative dental pain, and this effect was reversed by administration of the opioid antagonist naloxone. Endogenous opioids also mediate other effects of analgesia outside of the pain reduction itself, such as a slowing of respiration and heart rate, as these symptoms can also be blocked with naloxone.

Molecular imaging studies suggest that a specific receptor, the mu opioid receptor, mediates many of these effects. For example, placebo analgesia is associated with increased mu opioid receptor activity in a number of brain areas including ACC and PAG, and the strength of this activity is directly related to the size of the placebo effect. The increased PAG activity in response to placebo analgesia can also be blocked by naloxone. Opioid mechanisms of placebo analgesia have been linked to learning-related placebo responses, and are thought to underlie both expectancy and conditioned mechanisms.
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... AND BEYOND

Although many studies on the chemical mediators of placebo analgesia have focused on the endogenous opioid system, other neurotransmitter systems have also been implicated. PET studies of dopamine neurotransmission demonstrate that placebo analgesia is associated with dopaminergic release in the basal ganglia, particularly in the nucleus accumbens. This higher dopamine release is associated with greater analgesia, expectation of relief, and perceived effectiveness of the placebo. In fact, dopamine release accounted for a quarter of the variance in placebo analgesia in one study.

More recently, the endocannabinoid system, previously linked to analgesia, reward, and reinforcement, has also been implicated in placebo analgesia. Placebo analgesia was observed following tourniquet pain when participants were preconditioned with a nonsteroidal anti-inflammatory drug, and this effect was reversed after administration of a cannabinoid 1 receptor antagonist. The antagonist had no effect on placebo analgesia preconditioned with morphine, indicating that endocannabinoids function separately from endogenous opioids in mediating placebo effects.

MANY EFFECTS = MANY MECHANISMS

Mirroring the trend in the literature, we’ve focused on the neurobiology of placebo analgesia. We now turn briefly to the findings from the relatively sparse literature examining placebo effects in two other conditions: Parkinson’s disease (PD) and depression.

In PD, the placebo effect can improve specific symptoms such as rigidity as well as decrease overall disability, in some cases in as many as 40 percent of patients. In a PET study, PD patients who responded to placebo showed increased dopamine release in the striatum (a key area of dopamine loss in the disease) compared to non-responders, a finding that was correlated with patients’ therapeutic expectations.

In a PET study of depression, brain activity changes in placebo responders – cortical increases and limbic-paralimbic decreases – mimicked those of subjects receiving a selective serotonin reuptake inhibitor (SSRI). Interestingly, despite similar clinical improvement between the two groups, SSRI responders displayed additional activity changes in subcortical and limbic regions not present in placebo responders.

While more research on this topic is needed, in general it seems that, unsurprisingly, the varied placebo responses observed in different diseases work through disease-specific mechanisms. It will be interesting to see if this trend holds true in other conditions such as anxiety and multiple sclerosis that also have high placebo responses.

FURTHER READING


Studies examining genetic variants associated with high or low placebo responses – the “placebome” – are relatively recent, but represent an important line of research that can yield insights into both the placebo’s underlying mechanisms and also potentially identify populations that display especially high or low responses. While we’re not there yet, the idea of increasing randomized controlled trial efficiency by screening for and excluding high placebo responders is certainly an attractive one.

To date, placebome studies have been plagued by small sample sizes, and no comprehensive genome-wide association studies have yet been performed; nevertheless, the existing literature has yielded some exciting clues. If you read Chapter 5, which covered the neurobiological mechanisms underlying the placebo response, the key players in this story will be familiar. Existing placebo-associated variants are located primarily in genes that regulate the levels of dopamine, endogenous opioids, and endocannabinoids in the brain.

DOPAMINE

The rs4680 single nucleotide polymorphism (SNP) in the catechol-O-methyltransferase (COMT) gene, which encodes an enzyme that breaks down dopamine and other catecholamines, has some of the best evidence for involvement in the placebo response. It’s also one of the most widely-studied dopamine polymorphisms. The substitution of a valine (val) amino acid for a methionine (met) one in rs4680 reduces the activity of the enzyme by as much as fourfold in homozygous (met/met) individuals, and is associated with increased dopamine in the prefrontal cortex. The minor met/met allele is quite common, found in about one-quarter of Caucasian populations.

In a trial of irritable bowel syndrome (IBS) patients, met/met carriers displayed the highest placebo response, val/met carriers had intermediate levels, and val/val carriers had the lowest. An examination of placebo response in acute pain in healthy individuals found similar results: met/met individuals experienced the greatest placebo analgesia.

In addition to rs4680, other COMT SNPs, as well as SNPs in other dopamine-related genes, have been linked to the magnitude of placebo response. For example, an allele associated with low activity of another dopamine catabolizing enzyme, monoamine oxidase A (MAO-A), was linked with improved placebo response in several trials of depression.

OPIOIDS AND ENDOCANNABINOIDS

It seems a common theme is emerging: individuals with higher dopamine levels have larger placebo responses across a variety of patient populations, including healthy controls. The evidence for genetic variation in endogenous opioid and endocannabinoid systems modulating placebo response, on the other hand, is thus far considerably sparser.

In one study, homozygous carriers of a mu opioid receptor (OPMR1) gene variant associated with reduced receptor function had less placebo-induced activation of dopamine signaling in the nucleus accumbens than carriers with normal receptor function. In terms of endocannabinoids, the gene encoding the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) has been linked to placebo-response magnitudes. Homozygous carriers of the allele previously associated with higher endocannabinoid levels in response to pain displayed higher levels of placebo analgesia than homozygous carriers of the other allele.

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By comparing the difference in response between the placebo and no treatment group, researchers can assess the true placebo response, while ruling out these extrinsic factors. For ethical reasons, few clinical trials designed to test a novel drug or other treatment utilize a no treatment group—in fact, no treatment arms are never included in clinical trials we conduct—and mainly consist of one or more active treatment arms compared to a placebo arm. Therefore, it is challenging to obtain rigorous estimates of the magnitude of the placebo response in most clinical trials. Meta-analyses of the placebo arms of multiple clinical trials can shed some light, but they are subject to a number of limitations and caveats.

Another trial design that can potentially be used to study placebo responses is a cross-over design, in which each subject serves as his or her own control and participates in both the active treatment and placebo groups at different phases of the trial. However, the utility of this design in placebo research is limited due to confounding learning effects—prior exposure to the drug or placebo affects subsequent placebo or drug responses, respectively. As we learned in Chapter 4, learning and past experiences are major components of the psychological mechanisms that underlie the placebo response.

**CONDITIONING PARADIGMS**

Classical conditioning also plays a significant role in the generation of the placebo response. Two common conditioning paradigms are used in placebo research to maximize the placebo response in order to study the underlying brain activity or pharmacological contributors that we discussed in Chapter 5.

In a response-conditioning design, verbal instructions are used to condition subjects. For example, two topical creams are applied to participants: one they are told is an effective analgesic and one they are told has no pain-relieving properties. Subjects are then given a painful stimulus at the site where the control cream was applied and a less intense stimulus where the “analgesic” was applied, but told both stimuli are equivalent. In the third phase of the experiment, an equally painful stimulus is applied to both sites. The placebo response is measured as the difference in pain levels between the two sites. This response conditioning design is the most common one used in neuroimaging studies.

In a pharmacological conditioning design, subjects are conditioned with a drug. In half of participants, an active drug is paired with verbal and nonverbal cues over several
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days; the other half of subjects receive the same cues but without the drug. The cues are then presented alone and the placebo response is measured by the difference between the drug-paired and non-paired conditions. Many studies that have measured the role that various neurotransmitter systems such as endogenous opioids and endocannabinoids play in the placebo response have done so by adding an additional phase to the pharmacological conditioning design in which subjects are given drugs that inhibit or potentiate these systems. The blockade or enhancement, respectively, of the conditioning becomes evidence that these systems are involved.

In Chapter 8, we’ll look at how drug and placebo effects interact. Is the response of the drug group in a trial simply the pharmacological action of the drug plus the placebo response (the additivity hypothesis), or is the relationship between the two more complicated? We’ll examine whether the additivity hypothesis, first proposed in 1955, still holds up, and discuss the implications for the interpretation of clinical trial data.

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The placebo response is broad. It goes far beyond the effects of merely consuming a sugar pill; it is the patient’s response to the entire therapeutic context in which that treatment is administered. In a placebo-controlled trial, because the drug group also receives treatment in this same therapeutic context, the drug group’s overall response includes the placebo response. The pharmacological effect of the drug – what we really want to know – is then calculated as the overall drug response minus the placebo response.

**ADDITIVE OR INTERACTIVE?**

This method of calculating the true effect of a drug is predicated on one fundamental assumption: that the drug effect and placebo response are additive. That is, that the response in the drug group equals the sum of the placebo response and the drug’s pharmacological effect. Said another way, it assumes that the placebo response is the same in the placebo group as in the drug group. It also predicts that the pharmacological effect of the drug isn’t affected by whether or not the patient thinks he or she has received the drug.

This so-called additivity hypothesis has been guiding clinical trial interpretation for decades, yet it’s never been directly tested. In fact, over the last 10 years a growing body of evidence, though far from conclusive, suggests that perhaps drug-placebo interactions aren’t so simple.

Meta-analyses of placebo-controlled trials have shown that some factors that are associated with a higher response in the placebo group, such as lower symptom severity at the start of the trial, are not associated with the response of the drug group. This suggests that different mechanisms underlie the placebo response in the placebo and drug arms.

Neurobiological evidence also calls the additive model into question. Made possible using computer-controlled drug infusion pumps, studies using an open-hidden design, where one group of participants is aware they are receiving a drug (open group) and another group has no idea (hidden group), have demonstrated that hidden administration of a drug substantially reduces or even completely negates its pharmacological effect. Thus, patient expectancy likely plays a role in a drug’s pharmacological effect. Neuroimaging data also suggest that placebo effects during open-drug treatment are different from those in the placebo group.

Taken together, this body of research suggests that the additive hypothesis may not apply, at least not in all trials. An interactive model of the drug-placebo relationship that produces unequal placebo responses in the drug and placebo treatment groups has also been proposed, but not yet directly tested. According to this hypothesis, drug-specific and nonspecific (placebo) effects in the drug treatment group interact to yield a total treatment response that is different than the simple sum of the placebo group response plus the pharmacological effect of the drug.

**LOOKING FORWARD**

With the additive model of the drug-placebo relationship called into question, where do we go from here? One conclusion is that current clinical trial designs are misleading with respect to the true pharmacological effects of drugs and are not the best way to assess the efficacy of novel compounds. To say this realization would have a dramatic effect on the pharmaceutical industry is an understatement; fortunately, this is a premature conclusion. However, these findings do suggest that it would be prudent to devote more research to the topic, as well as explore alternative trial designs that could better incorporate non-additive, drug-placebo interactions.
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There are many trial-related details that can influence the magnitude of the placebo response, which we’ll cover in detail in Chapter 12. But there are also two extrinsic, trial-independent factors that also contribute to a subject’s improvement in the absence of a pharmacologically active treatment: the natural tendency of diseases to get better over time and “regression to the mean,” a statistical phenomenon in which outliers in a dataset tend to move toward the mean value over time.

**HEADED TOWARD BETTER**

Many illnesses, including pain and depression, tend to improve over time. Coupled with the fact that subjects have a tendency to enroll in a clinical trial when their symptoms are more severe and therefore bothersome, it is not surprising that a substantial proportion of subjects get better over time without any treatment. This spontaneous improvement is thus part of the response seen in all clinical trial groups. One analysis of antidepressant trials that utilized a “wait list” control group to track natural improvement over time found that participants in this group experienced about 40 percent of the symptom improvement of those in the placebo group.

OUTLIERS MOVE IN

A second extrinsic factor that can influence the placebo response is regression to the mean. When repeated measures are made on a subject over time, random error results in variability. Many of the values are higher or lower than the mean. If the initial measurement is not close to the mean, subsequent measurements are likely to be closer to the mean than the original. So, if in the initial measurement a person’s symptoms were worse than their true mean, they appear to improve as the trial progresses. When this happens on a group level, there appears to be more improvement in the group than there really is. However, there is no corresponding worsening toward the mean to offset this effect, because trials have minimum symptom severity cutoffs. Therefore, subjects whose initial value showed that they were less sick than reality are excluded from the trial.

Unlike the trial-related details we’ll discuss in Chapter 12, these extrinsic, disease-related factors are largely outside of our control. No-treatment and waitlist groups are potential ways to tease apart the relative contributions of these extrinsic factors compared to other placebo contributors in research on the placebo effect. However, these groups aren’t practical or really even necessary in placebo-controlled clinical trials evaluating novel therapeutics, since the placebo response incorporates the effects of these factors.

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Section Four will discuss specific solutions to minimize the placebo response, first focusing on the strategy of excluding placebo responders and alternative study designs in this chapter, before Chapter 11 turns to training strategies for trial participants and staff that can lead to lower placebo responses. Section Four ends with a discussion of the many factors that can influence the magnitude of the response in more detail.

EXCLUDING PLACEBO RESPONDERS

One potential option to counteract the rising placebo response in psychiatry and analgesia trials, and improve drug-placebo differences (also known as assay sensitivity) in all clinical trials, is to identify and subsequently exclude high-placebo responders. A large body of literature has identified factors that are associated with a smaller or greater magnitude of placebo response, but the vast majority of those identified are trial related and not due to any particular traits of an individual. We discussed these factors in Chapter 9. The 1950s saw a flurry of attempts to characterize the personality of the placebo responder, with little success at identifying personality traits that held up to replication. The few attempts that have been made since have also come up empty-handed.

Another possibility that has garnered widespread interest is to perform a placebo run-in prior to the start of the trial and subsequently exclude any high responders. While this has been tried a number of times in psychiatry drug trials, several meta-analyses have found that excluding subjects who show a high response during the placebo run-in does not lower response in the placebo group or increase the effect sizes in the drug groups. A potential explanation for the latter finding is that placebo non-responders are also drug non-responders.

Conversely, another proposed placebo reduction approach is to strengthen drug effects. This could be achieved by identifying and selecting for drug responders, although this approach is subject to the same limitation of the exclusion of placebo responders noted above. It also raises concerns of introducing bias by only testing a drug in a specific subpopulation of individuals, which could lead to regulatory approval for only a limited indication.

One strategy that is becoming increasingly popular is the exclusion of participants with high variability in baseline pain reports, which has been associated with a high placebo but not drug response in several clinical trials. A related strategy is to use sensory training to improve the accuracy of pain reporting. We’ll discuss the recent evidence in favor of this approach in Chapter 11.

NOVEL STUDY DESIGNS

An alternative placebo reduction strategy to the placebo run-in, and one that has received much attention, is the sequential parallel comparison design (SPCD). First proposed in 2003, the SPCD is a two-phase design: in the first phase, subjects are randomized to receive placebo or active treatment; in the second phase, placebo
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Another option is to eliminate the placebo group entirely, and instead compare novel drugs to other approved ones or other standard-of-care options. However, meta-analyses in both depression and schizophrenia have shown that this approach actually heightens the placebo effect, presumably because of increased patient expectancy since all participants receive a drug.

FUTURE STRATEGIES

Perhaps research on the placebome – the genes associated with stronger or weaker placebo responses (see Chapter 6) – will lead to knowledge of specific genetic variants, or a group of variants, that predict a high placebo response. Excluding individuals with these variants from clinical trials could reduce the magnitude of the placebo response.

Greater placebo responses are found in trials that utilize patient-reported outcomes rather than physician-reported ones. Therefore, another placebo reduction strategy is to move away from patient-reported outcomes. In psychiatry and analgesia trials, this would necessitate the identification of biomarkers of mood symptoms and pain, both active areas of research.

FURTHER READING

Baer L and Ivanova A. When should the sequential parallel comparison design be used in clinical trials. Clin Invest 2013;3(9):823-833.


Chapter 10 reviewed several potential strategies to reduce the placebo effect, focusing on excluding high placebo responders and alternative trial designs. In this chapter, we’ll turn to the evidence that training programs for both patients and trial staff can decrease the placebo response and improve assay sensitivity.

SENSORY TRAINING
As we discussed in the last chapter, higher baseline variability in pain ratings is associated with a greater placebo but not drug response, and eliminating subjects with high variability is one strategy to reduce the placebo response. A second option is to train patients to become more accurate at reporting their pain so that they exhibit less of a placebo response. In a poster presented at the 2016 World Congress on Pain (IASP), researchers described pilot data from a recent clinical trial evaluating their Accurate Pain Reporting (APR) protocol in 51 subjects with painful diabetic neuropathy who received either the known analgesic pregabalin or placebo.

The APR involves stimulation of a subject’s thumbnail bed at varying intensities, recording their perceived pain levels, and then providing feedback on the accuracy of their pain reporting based on stimulation intensity. In the first stage of the trial, subjects were randomized to receive APR or no APR in a parallel, unblinded fashion. Subjects showed measurable improvements in the ability to accurately and reliably report their pain across the four training sessions. In the second evaluation phase of the trial, subjects then received pregabalin or placebo in a randomized, double-blind crossover design. Pregabalin was not superior to placebo in the overall cohort, but subjects who received the APR had larger pregabalin effect sizes, which trended toward statistical significance, than the untrained group, and this was due to a decreased placebo response rather than an increased drug response. Variability in pain reporting was also reduced in the APR group. Although this trial was quite small, the results are nevertheless intriguing and warrant further study.

DECREASING EXPECTANCY
Several studies have examined the effect of manipulating patient expectancy on the magnitude of the placebo response. One trial of Maxalt in patients with episodic migraine found that manipulating pill labels could influence the placebo response. Placebo response was greatest in pills labeled “Maxalt,” intermediate in pills labeled “placebo or Maxalt,” and lowest in pills labeled “placebo.”
Another study assessed the effects of more in-depth patient expectancy manipulation on placebo response in asthma. Four groups of patients were used: patients received either montelukast or placebo, and high or low expectation messaging. The messaging consisted of three components: a scripted message, a computer presentation, and drug capsule appearance. The high expectation messaging was composed of an oral script and a computer program that touted the benefits of montelukast and expressed a high probability of symptom improvement, as well as blue capsules labeled with brand name of the drug. Low expectation messaging, on the other hand, included uncertainty about whether montelukast would be effective and did not describe the drug’s benefits, as well as capsules that were white and labeled with the generic name of the drug. Consistent with greater patient expectancy producing elevated placebo effects, the high expectation group showed higher placebo responses with patient-reported outcomes about asthma symptom severity and control, but not on objective measures of lung function.

Placebo response reduction (PRR) training is a related strategy that aims to modify both patient and clinician expectancy in an effort to reduce the placebo response. To date, it’s been used in at least 19 clinical trials. It focuses on neutralizing expectations of benefit in both trial staff and patients. PRR training includes staff preparation and quizzes to assess retention of the information, as well as a workbook with a quiz for subjects that emphasizes the uncertainty of benefits derived from clinical trials.

An analysis presented at the 2017 American Pain Society annual meeting compared placebo response in patients with chronic low back pain from a single trial that utilized PRR to 28 trials that did not employ any placebo response reduction strategies. While this type of comparison is subject to many limitations which must be considered, the analysis did find that while 38 percent of subjects in the placebo groups in the non-PRR trials had a greater than 30 percent improvement in pain, while only 19 percent of subjects in the PRR training trial did.

Taken together, these results highlight the importance of future research on the placebo-reducing benefits of these sensory and psychoeducational training approaches. In the next chapter we'll take a closer look at some of the individual trial-related factors such as pill color and doctor-patient interactions that can be used to manipulate expectancy, many of which have already been exploited in the studies presented here.

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In the last two chapters, we discussed several specific strategies to reduce the placebo response. One effort that is becoming increasingly popular is the manipulation of expectancy. Patient and clinician expectancy of improvement is a major contributor to the placebo response (for more details, see Chapter 4), and decreasing expectations is an effective placebo response reduction strategy. Today we turn to the long list of specific trial-related factors such as pill color and placebo type that can be used to manipulate expectancy, many of which are quite subtle and have already been exploited in the strategies we discussed in the last two chapters.

PILL DETAILS

A number of pill characteristics influence the magnitude of the placebo response: bigger pills are more effective than smaller ones, capsules are more effective than tablets, and having a name printed on the pill also boosts its perceived efficacy. The dosing schedule, too, plays a role: placebos given more often elicit a bigger response than ones with a single administration.

Of all the pill characteristics, however, color seems to be the most important. In general, colored pills work better than white ones, and brightly colored pills even seem to be superior to those that have a dull color. But the specific color can also impact patient expectancy, both in terms of the drug’s perceived action and its perceived effectiveness. Red, yellow, and orange pills are judged as more likely to be stimulants, while subjects feel blue and green pills are more likely to be tranquilizers. In addition, drugs seem to work best when their color matches the goal. So, a white burn cream works better than a red one.

The color of a drug’s packaging, too, can also modulate patient expectancy. Darker shades of packaging, such as brown and red, are rated as indicating the drug is for a more severe illness, and will have a more potent effect, than drugs in lighter packaging such as green and yellow. Red packages are also most associated with being treatments for the heart and pain; yellow, with treatments for the skin and heart; and green, with pain and liver. Blue and grey packages are also associated with the treatment of pain.

Different colors have different implications in different cultures, so perhaps it’s not surprising that the interpretation of pill color differs across cultures. In one study, Caucasians viewed white capsules as analgesics, while African Americans viewed them as stimulants. The reverse was true for black capsules: Caucasians saw them as stimulants; African Americans thought they were analgesics. Culture can also affect the way many other trial details are perceived, so it’s worth being mindful of the culture(s) of potential participants in the early stages of trial design.

MODE MATTERS

The exact type of placebo seems to matter a lot, too. In general, sham acupuncture seems to be more effective than oral placebos. For example, a systematic review of placebo treatments in 79 migraine prophylaxis trials found that 38 percent of people receiving sham acupuncture experienced a greater than 50 percent reduction in subsequent migraines, yet only 22 percent of those receiving a placebo pill experienced an effect. The finding that sham acupuncture works better than oral placebos has also been replicated in other medical conditions. One study also demonstrated that a placebo laser treatment generated greater somatic sensations among participants than a placebo irritant solution.
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CLINICIAN ATTITUDES AND MANNERISMS

A number of characteristics of a trial’s medical practitioners also influence the magnitude of the placebo response. The clinician’s reputation is one important contributor. In addition, tone of voice, body language, eye contact, and other subtle cues can all influence the patient’s perception of the amount of attention, interest, and the overall level of concern the clinician is showing. Participants who feel like they are being cared for are more likely to exhibit a greater placebo response than those who rate their clinician as uncaring.

And, of course, what is said to the patient matters a lot. A verbal suggestion that the treatment will make the patient feel better increases his or her expectation of improvement, which in turn leads to a greater placebo response. In contrast, referring to the likelihood of improvement as possible rather than probable, can limit the placebo response.

Elements of the treatment context that make participants feel like they are being given a “medical treatment” – such as being in a medical setting like a doctor’s office, seeing the doctor’s white coat and other symbols of medicine, and feeling the needle stick – can also lead to an increased placebo response, though here again is an area where a patient’s culture can influence the meaning they ascribe to these details.

Finally, factors that make a patient think they are in a treatment group compared to a placebo group also affect the magnitude of the placebo response. For example, as the number of treatment arms increases, the placebo response increases because participants assume they have a greater chance of receiving the experimental treatment over the placebo and are therefore getting better. In fact, in one study of Parkinson’s disease that compared transplantation of embryonic dopamine neurons to sham surgery, the patient’s perceived treatment group, and not their actual group, was the biggest predictor of improvement.

When it comes to controlling patient expectancy as a tool to limit the placebo response, it’s clear that details matter. That’s why it’s important to choose a CRO with experience in navigating these difficult waters.

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Section Five covers an assortment of placebo-related topics. After focusing exclusively on the placebo effect up until this point, we’re now going to take a quick detour in this chapter, turning to the placebo’s opposite, the nocebo response. We’ll then turn to the placebo response in pediatric patients, before concluding with a discussion of ethical issues surrounding placebo use.

The placebo response is when trial participants improve when administered an inert substance; in a nocebo response, their symptoms get worse. More broadly, just as the placebo effect is the brain’s response to the positive psychosocial context in which treatment occurs, the nocebo effect is the brain’s response to negative psychosocial context. A classic example of the nocebo effect, first described in the 1960s, is when trial participants who are told the drug they will receive has side effects later report stronger and/or more frequent adverse effects than participants not given any information about potential side effects.

Unlike the placebo response, the nocebo response has been much less well studied, in part due to ethical concerns. While the term “placebo” originates from the Latin phrase for “I shall please,” “nocebo” arises from the Latin for “I shall harm.” A nocebo response is, by definition, one that induces a negative experience, so detailed examinations of the nocebo response are few and far between.

Nevertheless, the nocebo response does seem to have a big impact on clinical trials. A meta-analysis of fibromyalgia and painful diabetic neuropathy trials calculated that the nocebo effect accounted for 72 percent of patient drop-outs in the drug groups, while a meta-analysis of the nocebo effect in pain trials found overall nocebo effect sizes to be moderate to large, highly variable, and similar in magnitude to placebo responses. This study also noted that, again similar to the placebo response, larger nocebo effect sizes occurred in trials that used a combination of verbal suggestion and conditioning compared to trial that used verbal suggestion alone.
BELIEVING BAD

As in the placebo response, expectation seems to play a large role in driving the nocebo effect. A trial participant is told there is a possibility of adverse effects, causing him or her to expect these effects, which then leads to the belief coming true. In a meta-analysis of clinical trials of an antidepressant versus placebo, adverse events were most often reported in Phase II clinical trials, followed by Phase III trials. Phase IV trials had the fewest adverse events, suggesting that the nocebo response decreases as a treatment comes to be viewed as less experimental and uncertain.

Additional evidence that expectation plays a role in the nocebo response comes from a systematic review that found that the factors which predicted a greater nocebo response included higher perceived doses, verbal suggestion that the treatment would produce symptoms, and greater expectations about symptoms.

Interestingly, a sense of control over treatment also appears to contribute to the nocebo response. A study in which healthy volunteers could either choose between two equivalent beta blockers or be randomly assigned to one of the two found that the nocebo response was greater in the group that did not have a choice in their treatment.

BAD ON THE BRAIN

The neurochemical contributors to the nocebo response seem to overlap, at least partially, with those that play a role in the placebo response, although they exert opposite effects. As we discussed in Chapter 5, placebo analgesia has been associated with increases in opioid and dopamine neurotransmission. One study of placebo analgesia found that the small number of nocebo responders showed decreased dopamine and opioid neurotransmission in the same brain areas that showed increases in these neurotransmitters in placebo analgesia.

The neuropeptide cholecystokinin (CCK) has also been linked to the nocebo response in pain. Verbal suggestions of worsening pain seem to increase anxiety about the impending increase in pain, which in turn activates the CCK system, leading to increased pain neurotransmission. In support of this theory, both anxiolytics (benzodiazepines) and a CCK antagonist can block nocebo-induced hyperalgesia.

FURTHER READING


Throughout this eBook, we’ve focused exclusively on the placebo response in adults. Now, we turn to another population: kids. Not surprisingly, due to ethical issues, very few studies have examined placebo effects in pediatric populations. One 2013 literature review calculated that of the roughly 2000 PubMed citations that investigated the placebo effect, only about 2.5 percent discussed it in the context of children and adolescents. Nevertheless, pediatric placebo responses have been observed in a number of conditions, including asthma, atopic dermatitis, autism, depression, epilepsy, hypertension, and migraine.

GREATER MAGNITUDE
On the whole, the randomized controlled trial literature indicates that placebo response rates are higher in children and adolescents than adults, but that drug responses do not differ by age. Younger children seem to exhibit greater placebo responses than older kids. For example, in a meta-analysis of pediatric major depressive disorder, kids less than 12 years old had a placebo response rate of 54 percent, while those older than 12 responded to placebo 45 percent of the time. For comparison, similar studies of adults suggest the placebo response rate is roughly 34 percent. This negative correlation between placebo response and age is also present in other illnesses, including epilepsy, migraine, attention deficit hyperactivity disorder (ADHD), anxiety, obsessive compulsive disorder (OCD), and painful functional gastrointestinal disorders.

Taken to its logical conclusion, if placebo responses are greater in kids than adults, yet drug responses are similar, then extending information about drug efficacy gained from adult studies to pediatric populations may be problematic. Specifically, it may lead to an overestimation of drug efficacy in children.

However, the one study that has actually experimentally tested the relationship between placebo response magnitude and age, by using an experimental model of placebo analgesia in both children and adults, reported no difference in placebo response between the two groups. In the study, participants received two identical creams on their forearm. They were informed that one cream would provide pain relief and told the other was a control. During the conditioning phase, the painful stimulation at the site of the “analgesic” was lower than the stimulation at the “control” site. The next day, identical stimulus intensities were used to test for placebo analgesic effects. The researchers found no difference in the magnitude of placebo analgesia experienced by adults and children, a result at odds with the rest of the literature. Clearly, more research is needed to definitively determine the true association between placebo response and age.

SIMILAR MECHANISMS
As we discussed in Chapter 4, the two main psychological mechanisms that are responsible for the placebo response are expectancy and conditioning. It has been hypothesized that these same mechanisms also play a role in pediatric
populations. The few studies that have directly examined the role of expectancy in placebo response in kids have found that it does indeed play a role.

For example, in one study, 49 children between the ages of six and nine were randomly assigned to an “analgesia expectation” group, which was told that an applied placebo lotion could reduce pain, and a “control expectation” group, which was told the lotion was necessary to measure pain but wouldn’t affect pain levels. Both groups then received a heat pain paradigm on their forearms. The kids who were told the lotion could relieve pain experienced increased heat pain threshold and tolerance compared to those whose expectancy was not manipulated.

Case studies and observational studies of infants and children suggest, albeit indirectly, that, just as in adults, conditioning also plays a role in pediatric placebo responses. For example, infants who have received repeated heel lancing without anesthetic for blood glucose monitoring showed higher pain levels during subsequent procedures than infants receiving the procedure for the first time, indicating that prior experiences can influence pain levels.

Interestingly, the experiment described above that found no difference in the magnitude of placebo responses between kids and adults did find that experience during the conditioning procedure had a larger effect on the magnitude of the placebo response in children than adults, suggesting that conditioning may play a greater role in the pediatric placebo response.

A third possible mechanism that may be at work in pediatric placebo responses is a phenomenon known as “placebo by proxy” where parent beliefs can affect outcomes. Numerous studies have shown that parent beliefs and stress levels can exert measurable effects in their children. Principally, placebo by proxy can be explained in two ways. The first is characterized by a shift in parental perception. Parents expect children to get better and therefore perceive that they are getting better. This is especially relevant in trials that use parent-reported outcomes. In the second case, a behavioral change in the parent, such as acting less worried after treatment is administered, changes the behavior of the child, who then experiences less pain.

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We conclude our eBook by taking a brief look at three ethical issues that surround the use of placebos in clinical trials. A complete discussion of these issues is well beyond the scope of a single eBook, so be sure to check out the Further Reading section at the end of the chapter for articles that can provide a deeper understanding.

WHEN IS IT ETHICAL TO USE PLACEBOS IN CLINICAL TRIALS?
First, we turn to the most obvious ethical issue surrounding placebo-controlled trials – under what circumstances is the use of placebos morally correct? According to the World Medical Association’s Declaration of Helsinki, which addresses ethical issues surrounding the use of human subjects in research, placebo use is acceptable when there is no proven acceptable treatment for the condition, when “for compelling and scientifically sound methodological reasons” it’s necessary to determine the experimental treatment’s efficacy or safety, and when patients who receive placebo “will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.” However, determining which methodological reasons and risks of harm fall under this description is difficult at best.

CAN OPEN-LABEL PLACEBOS SIDESTEP THE ISSUE OF DECEPTION?
Historically, deception has been considered a major component of placebos, and one of the main ethical problems of placebo use. However, perhaps surprisingly, a small body of literature suggests that placebos are still effective even when patients know they are receiving a placebo.

A few such open-label placebo trials have been conducted in the last decade. In the most well-known study, 80 patients with IBS were randomized to receive either no treatment or an open-label placebo, which they were told was a non-active placebo pill that has been shown reduce IBS symptoms. Participants who received the open-label placebo had significantly greater symptom improvement than those who received no treatment. Although more research is certainly needed, these results raise the possibility that deception is not integral to the placebo effect, and therefore not needed.

IS TRULY INFORMED CONSENT THE BEST OPTION?
In clinical trials, participants are informed of the possible side effects that may result from the experimental treatment. But, the mere suggestion that these negative outcomes could occur may lead to a greater incidence of them, a phenomenon known as the nocebo effect. In other words, the side effects become a self-fulfilling prophecy. As we saw in Chapter 13, the nocebo effect can not only increase symptoms but also lead to patient distress. It can also lead to medication nonadherence, participant dropouts, and the need for additional medications to treat the added symptoms. Traditionally, a full disclosure of potential side effects is considered the most ethical course of action, but, at least in some cases, should we consider only disclosing the most critical information about possible adverse events in order to avoid undue patient distress?

CONCLUSION
Placebos have played a major role in medicine for hundreds of years. More recently, the placebo effect has become a field of research in its own right, and it is now known that placebos can lead to substantial improvements in health. While much is known about the psychological, neurobiological, and genetic mechanisms responsible for its effects, many unanswered questions remain and more research is needed.

One especially crucial area of future research concerns the rising placebo response that has been plaguing analgesic and psychiatric drug development. As the magnitude of the placebo response has grown over time, it has become progressively harder to show that an experimental treatment is effective, threatening the ability of pharmaceutical companies to successfully identify novel effective drugs. This eBook has examined a variety of topics about the placebo response and it’s rise over time. Several strategies to combat the growing placebo response in RCTs of antidepressants, antipsychotics, and analgesics have been proposed in the literature and are currently being tested.
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