

PLACEBO

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Abstract

A placebo is a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient. Sometimes patients given a placebo treatment will have a perceived or actual improvement in a medical condition, a phenomenon commonly called the placebo effect.

In one common placebo procedure, however, a patient is given an inert pill, told that it may improve his/her condition, but not told that it is in fact inert. Such an intervention may cause the patient to believe the treatment will change his/her condition; and this belief may produce a subjective perception of a therapeutic effect, causing the patient to feel their condition has improved — or an actual improvement in their condition. This phenomenon is known as the placebo effect.

Keywords: Placebo, diseases, Clinical significance, side effects

Introduction

In medical research, placebos are given as control treatments and depend on the use of measured deception. Common placebos include inert tablets, sham surgery, and other procedures based on false information.[1] However, placebos can also have a surprisingly positive effect on a patient who knows that the given treatment is without any active drug, as compared with a control group who knowingly did not get a placebo.

Placebos are widely used in medical research and medicine, and the placebo effect is a pervasive phenomenon in fact, it is part of the response to any active medical intervention. Archie Cochrane suggested in 1972 "It is important to distinguish the very respectable, conscious use of placebos. The effect of placebos has been shown by randomized controlled trials to be very large. Their use in the correct place is to be encouraged.

The placebo effect points to the importance of perception and the brain's role in physical health. However, the use of placebos as treatment in clinical medicine (as opposed to laboratory research) is ethically problematic as it introduces deception and dishonesty into the doctor-patient relationship. The United Kingdom Parliamentary Committee on Science and Technology has stated that: "prescribing placebos... usually relies on some degree of patient deception" and "prescribing pure placebos is bad medicine. Their effect is unreliable and unpredictable and cannot form the sole basis of any treatment on the NHS." [2]

Since the publication of Henry K. Beecher's *The Powerful Placebo* in 1955, the phenomenon has been considered to have clinically important effects. This view was notably challenged when, in 2001, a systematic review of clinical trials concluded that there was no evidence of clinically important effects, except perhaps in the treatment of pain and continuous subjective outcomes. The article received a flurry of criticism, but the authors later published a Cochrane review with similar conclusions (updated as of 2010). Most studies have attributed the difference from baseline till the end of the trial to a placebo effect, but the reviewers examined studies which had both placebo and untreated groups in order to distinguish the placebo effect from the natural progression of the disease. However these conclusions have been criticized because of the great variety of diseases—more than 40—in this metastudy. The effect of placebo is very different in different diseases. By pooling quite different diseases the results can be leveled out.[3]

Definitions, effects, and ethics

A placebo has been defined as "a substance or procedure... that is objectively without specific activity for the condition being treated". Under this definition, a wide variety of things can be placebos and exhibit a placebo

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effect. Pharmacological substances administered through any means can act as placebos, including pills, creams, inhalants, and injections. Medical devices such as ultrasound can act as placebos. Sham surgery, sham electrodes implanted in the brain,[1] and sham acupuncture, either with sham needles or on fake acupuncture points, have all exhibited placebo effects. Bedding not treated to reduce allergies has been used as a placebo to control for treated bedding. The physician has even been called a placebo a study found that patient recovery can be increased by words that suggest the patient "would be better in a few days", and if the patient is given treatment, that "the treatment would certainly make him better" rather than negative words such as "I am not sure that the treatment I am going to give you will have an effect". The placebo effect may be a component of pharmacological therapies: Pain killing and anxiety reducing drugs that are infused secretly without an individual's knowledge are

less effective than when a patient knows they are receiving them. Likewise, the effects of stimulation from implanted electrodes in the brains of those with advanced Parkinson's disease are greater when they are aware they are receiving this stimulation.[22] Sometimes administering or prescribing a placebo merges into fake medicine.[4]

The placebo effect has sometimes been defined as a physiological effect caused by the placebo, but Moerman and Jonas have pointed out that this seems illogical, as a placebo is an inert substance that does not directly cause anything. Instead they introduced the word "meaning response" for the meaning that the brain associates with the placebo, which causes a physiological placebo effect. They propose that the placebo, which may be unethical, could be avoided entirely if doctors comfort and encourage their patients' health.[5] Ernst and Resch also attempted to distinguish between the "true" and "perceived" placebo effect, as they argued that some of the effects attributed to the placebo effect could be due to other factors.[6]

The placebo effect has been controversial throughout history. Notable medical organizations have endorsed it, but in 1903 Richard Cabot concluded that it should be avoided because it is deceptive. Newman points out the "placebo paradox", – it may be unethical to use a placebo, but also unethical "not to use something that heals". He suggests to solve this dilemma by appropriating the meaning response in medicine, that is make use of the placebo effect, as long as the "one administering... is honest, open, and believes in its potential healing power". Another possible resolution of the ethical dilemma might come from the "honest placebo" effect found in a 2010 study[6] carried out by researchers in the Program in Placebo Studies at the Harvard Medical School, where patients with irritable bowel syndrome experienced a significant beneficial effect even though they were told the pills they were taking were placebos, as compared to a control group who received no pills.

History

The word 'placebo', Latin for "I will please", dates back to a Latin translation of the Bible by Jerome. It was first used in a medicinal context in the 18th century. In 1785 it was defined as a "commonplace method or medicine" and in 1811 it was defined as "any medicine adapted more to please than to benefit the patient", sometimes with a derogatory implication but not with the implication of no effect. Placebos were widespread in medicine until the 20th century, and they were sometimes endorsed as necessary deceptions. In 1903 Richard Cabot said that he was brought up to use placebos, but he ultimately concluded by saying that "I have not yet found any case in which a lie does not do more harm than good". In 1961 Henry K. Beecher found that surgeons he categorized as enthusiasts relieved their patients' chest pain and heart problems more than skeptic surgeons. In 1961 Walter Kennedy introduced the word *nocebo*. Beginning in the 1960s, the placebo effect became widely recognized and placebo controlled trials became the norm in the approval of new medications. Later, researchers became interested in understanding the placebo effect, rather than just controlling for its effects, and in 2011, a Program in Placebo Studies was established at the Harvard Medical School.[8]

Mechanism of the effect

The phenomenon of a patient's perceived medical improvement following treatment with an inert substance is called the placebo effect. The placebo effect is highly variable in its magnitude and reliability and is typically

strongest in measures of subjective symptoms (e.g., pain) and typically weak-to-nonexistent in objective measures of health points (e.g., blood pressure, infection clearance).

A 2001 meta-analysis of clinical trials with placebo groups and no-treatment groups found no evidence for a placebo effect on objectively measured outcomes and possible small benefits in studies with continuous subjective outcomes (particularly pain).] A 2004 follow-up analysis found similar results and increased evidence of bias in smaller trials that calls into question the apparent placebo effect on subjective outcomes. [9]

Because the placebo response is simply the patient response that cannot be attributed to an investigational intervention, there are multiple possible components of a measured placebo effect. These components having varying relevance depending on study design and the types of observations. While there is some evidence that placebo interventions can alter levels of hormones and endogenous opioids, other prominent components include expectancy effects, regression to the mean, and flawed research methodologies. [10]

Expectancy and conditioning

The placebo effect is related to the perceptions and expectations of the patient; if the substance is viewed as helpful, it can heal, but, if it is viewed as harmful, it can cause negative effects, which is known as the nocebo effect. In 1985, Irving Kirsch hypothesized that placebo effects are produced by the self-fulfilling effects of response expectancies, in which the belief that one will feel different leads a person to actually feel different. According to this theory, the belief that one has received an active treatment can produce the subjective changes thought to be produced by the real treatment. Placebos can act similarly through classical conditioning, wherein a placebo and an actual stimulus are used simultaneously until the placebo is associated with the effect from the actual stimulus. Both conditioning and expectations play a role in placebo effect, and make different kinds of contribution. Conditioning has a longer-lasting effect, and can affect earlier stages of information processing. The expectancy effect can be enhanced through factors such as the enthusiasm of the doctor, differences in size and color of placebo pills, or the use of other interventions such as injections. In one study, the response to a placebo increased from 44% to 62% when the doctor treated them with "warmth, attention, and confidence." Expectancy effects have been found to occur with a range of substances. Those that think that a treatment will work display a stronger placebo effect than those that do not, as evidenced by a study of acupuncture. [11]

Because the placebo effect is based upon expectations and conditioning, the effect disappears if the patient is told that their expectations are unrealistic, or that the placebo intervention is ineffective. A conditioned pain reduction can be totally removed when its existence is explained. It has also been reported of subjects given placebos in a trial of anti-depressants, that "Once the trial was over and the patients who had been given placebos were told as much, they quickly deteriorated." [12]

A placebo described as a muscle relaxant will cause muscle relaxation and, if described as the opposite, muscle tension. A placebo presented as a stimulant will have this effect on heart rhythm, and blood pressure, but, when administered as a depressant, the opposite effect. The perceived consumption of caffeine has been reported to cause similar effects even when decaffeinated coffee is consumed, although a 2003 study found only limited support for this. Placebos represented as alcohol can cause intoxication and sensorimotor impairment. Perceived ergogenic aids can increase endurance, [54] speed [55] and weight-lifting ability, leading to the question of whether placebos should be allowed in sport competition. Placebos can help smokers quit. Perceived allergens that are not truly allergenic can cause allergies. [59] Interventions such as psychotherapy can have placebo effects. The effect has been observed in the transplantation of human embryonic neurons into the brains of those with advanced Parkinson's disease. [13]

Because placebos are dependent upon perception and expectation, various factors that change the perception can increase the magnitude of the placebo response. For example, studies have found that the color and size of the placebo pill makes a difference, with "hot-colored" pills working better as stimulants while "cool-colored" pills work better as depressants. Capsules rather than tablets seem to be more effective, and size can make a difference. One researcher has found that big pills increase the effect while another has argued that the effect is

dependent upon cultural background. More pills, branding, past experience, and high price increase the effect of placebo pills. Injection and acupuncture have larger effect than pills. Proper adherence to placebos is associated with decreased mortality.[14]

Motivation may contribute to the placebo effect. The active goals of an individual changes his/her somatic experience by altering the detection and interpretation of expectation-congruent symptoms, and by changing the behavioral strategies a person pursues. Motivation may link to the meaning through which people experience illness and treatment. Such meaning is derived from the culture in which they live and which informs them about the nature of illness and how it responds to treatment. Research into the placebo treatment of gastric and duodenal ulcers shows that this varies widely with society. The placebo effect in treating gastric ulcers is low in Brazil, higher in northern Europe (Denmark, Netherlands), and extremely high in Germany. However, the placebo effect in treating hypertension is lower in Germany than elsewhere. Social observation can induce a placebo effect such when a person sees another having reduced pain following what they believe is a pain reducing procedure.

The placebo effect can work selectively, under the influence of various psychological factors. If a placebo cream is applied on one hand with the expectation that it is an analgesic, it will reduce pain only in that hand and not elsewhere on the body. If a person is given a placebo under one name, and they respond, they will respond in the same way on a later occasion to that placebo under that name but not if under another. [15]

Placebo effect and the brain

Functional imaging upon placebo analgesia shows that it links to the activation, and increased functional correlation between this activation, in the anterior cingulate, prefrontal, orbitofrontal and insular cortices, nucleus accumbens, amygdala, the brainstemperiaqueductal gray matter, and the spinal cord.

These changes can act upon the brain's early stages of information processing: Research using evoked brain potentials upon painful laser pulses, for example, finds placebo effects upon the N2–P2, a biphasic negative–positive complex response, the N2 peak of which is at about 230 ms, and the P2 one at about 380 ms. They occur not only during placebo analgesia but after receiving the analgesic placebo (the areas are different here, and involve the medial prefrontal cortex, posterior parietal cortex and inferior parietal lobule).

Different areas in the higher brain have different functions. The prefrontal involvement could be related to recalling the placebo and maintaining its cognitive presence in a "self-reinforcing feedback loop" (during pain an individual recalls having taken the placebo and reduced pain reinforces its status as an analgesic). The rostral anterior cingulate cortex (rACC) and its subcortical connectivity could be related to the expectation of potential pain stimuli. The higher brain works by regulating subcortical processes. High placebo responses link with enhanced dopamine and mu-opioid activity in the circuitry for reward responses and motivated behavior of the nucleus accumbens, and, on the converse, anti-analgesic nocebos responses were associated with deactivation in this part of the brain of dopamine and opioid release. (It has been known that placebo analgesia depends upon the release in the brain of endogenous opioids since 1978. Such analgesic placebos activation changes processing lower down in the brain by enhancing the descending inhibition through the periaqueductal gray on spinal nociceptive reflexes, while the expectations of anti-analgesic nocebos acts in the opposite way to block this.

The brain is also involved in less-studied ways upon nonanalgesic placebo effects:

- Parkinson's disease: Placebo relief is associated with the release of dopamine in the brain.
- Depression: Placebos reducing depression affect many of the same areas that are activated by antidepressants with the addition of the prefrontal cortex
- Caffeine: Placebo-caffeinated coffee causes an increase in bilateral dopamine release in the thalamus.
- Glucose: The expectation of an intravenous injection of glucose increases the release of dopamine in the basal ganglia of men (but not women).

- Methylphenidate: The expectation of intravenous injection of this drug in inexperienced drug users increased the release of dopamine in the ventral cingulate gyrus and nucleus accumbens, with this effect being largest in those with no prior experience of the drug.

Present functional imaging upon placebo analgesia has been summarized as showing that the placebo response is "mediated by "top-down" processes dependent on frontal cortical areas that generate and maintain cognitive expectancies. Dopaminergic reward pathways may underlie these expectancies".[95] "Diseases lacking major 'top-down' or cortically based regulation may be less prone to placebo-related improvement".[16]

Brain and body

The brain has control over the body processes affected by placebos. Pain, motor fatigue, and fever are directly organized by the brain. Other processes usually regulated by the body such as the immune system are also controlled indirectly through the sympathetic and parasympathetic nervous system.

Research upon conditioning in animals shows the brain can learn control over them.

In conditioning, a neutral stimulus saccharin is paired in a drink with an agent that produces an unconditioned response. For example, that agent might be cyclophosphamide that causes immunosuppression. After learning this pairing, the taste of saccharin by itself through neural top-down control created immunosuppression, as a new conditioned response.[97] Such conditioning has been found to affect a diverse variety of not just basic physiological processes in the immune system but ones such as serum iron levels, oxidative DNA damage levels, and insulin secretion. This work was originally done on rats, however the same conditioning of basic physiological processes can also occur in humans. Recent reviews have argued the placebo effect is due to top-down control by the brain for immunity and pain. Pacheco-López and colleagues have raised the possibility of "neocortical-sympathetic-immune axis providing neuroanatomical substrates that might explain the link between placebo/conditioned and placebo/expectation responses."

A recent fMRI study has shown that a placebo can reduce pain-related neural activity in the spinal cord, indicating that placebo effects can extend beyond the brain.[17]

Evolved health regulation

Evolutionary medicine identifies many symptoms such as fever, pain, and sickness behavior as evolved responses to protect or enhance the recovery from infection and injury. Fever, for example, is an evolved self-treatment that removes bacteria or viruses through raised body temperature. These evolved responses, however, also have a cost that depending upon circumstances can outweigh their benefit (due to this, for example, there is a reduction in fever during malnutrition or late pregnancy). According to the health management system theory proposed by Nicholas Humphrey, the brain has been selected to ensure that evolved responses are deployed only when the cost benefit is biologically advantageous. To do this, the brain factors in a variety of information sources, including the likelihood derived from beliefs that the body will get well without deploying its costly evolved responses. One such source of information is the knowledge the body is receiving care and treatment. The placebo effect in this perspective arises when false information about medications misleads the health management system about the likelihood of getting well so that it selects not to deploy an evolved self-treatment. [18]

Clinical utility

Duration

Placebo effects can last for a long time: over 8 weeks for panic disorder, 6 months for angina pectoris, and two and half years for rheumatoid arthritis.[104] Placebo effects after verbal suggestion for mild pain can be robust and still exist after being repeated ten times even if they have no actual pharmacological pain killing action.[19]

Clinical significance

Hróbjartsson and Peter Gøtzsche published a study in 2001 and a follow-up study in 2004 questioning the nature of the placebo effect. The studies were performed as two meta-analyses. They found that in studies with a binary outcome, meaning patients were classified as improved or not improved, the placebo group had no statistically significant improvement over the no-treatment group. Likewise, there was no significant placebo effect in studies in which objective outcomes (such as blood pressure) were measured by an independent observer. The placebo effect could be documented only in studies in which the outcomes (improvement or failure to improve) were reported by the subjects themselves. The authors concluded that the placebo effect does not have "powerful clinical effects," (objective effects) and that patient-reported improvements (subjective effects) in pain were small and could not be clearly distinguished from reporting bias. Other researchers (Wampold et al.) re-analysed the same data from the 2001 meta-analysis and concluded that the placebo effects for objective symptom measures are comparable to placebo effects for subjective ones and that the placebo effect can exceed the effect of the active treatment by 20% for disorders amenable to the placebo effect, a conclusion which Hróbjartsson & Gøtzsche described as "powerful spin". Another group of researchers noted the dramatically different conclusions between these two sets of authors despite nearly identical meta-analytic results, and suggested that placebo effects are indeed significant but small in magnitude.

Hróbjartsson and Gøtzsche's conclusion has been criticised on several grounds. Their meta-analysis covered studies into a highly mixed group of conditions. It has been reported that for measurements in peripheral organs the placebo effect seems to be more effective in achieving improvements in physical parameters (such as decreasing hypertension, improving FEV1 in asthma sufferers, or decreasing prostatic hyperplasia or anal fissure) than in improving biochemical parameters (such as cholesterol or cortisol) in various conditions such as venous leg ulcers, Crohn's disease, urinary tract infection, and chronic heart failure.[109] Placebos also do not work as strongly in clinical trials because the subjects do not know whether they might be getting a real treatment or a sham one. Where studies are made of placebos in which people think they are receiving actual treatment (rather than merely its possibility) the placebo effect has been observed. Other writers have argued that the placebo effect can be reliably demonstrated under appropriate conditions.

In another update by Hróbjartsson & Gøtzsche, published as a 2010 Cochrane systematic review which confirms and modifies their previous work, over 200 trials investigating 60 clinical conditions were included. Placebo interventions were again not found to have important clinical effects in general but may influence patient-reported outcomes in some situations, especially pain and nausea, although it was "difficult to distinguish patient-reported effects of placebo from response bias". The pooled relative risk they calculated for placebo was 0.93 (effect of only 7%) but significant. Effects were also found for phobia and asthma but were uncertain due to high risk of bias. In other conditions involving three or more trials, there was no statistically significant effect for smoking, dementia, depression, obesity, hypertension, insomnia and anxiety, although confidence intervals were wide. Several clinical (physical placebos, patient-involved outcomes, falsely informing patients there was no placebo) and methodological (small sample size, explicit aim of studying the placebo effect) factors were associated with higher effects of placebo. Despite low effects in general and the risk of bias, the authors acknowledged that large effects of placebo interventions may occur in certain situations. [20]

Negative effects

Similar to the placebo effect, inert substances have the potential to cause negative effects via the "nocebo effect". In this effect, giving an inert substance has negative consequences.

Another negative consequence is that placebos can cause side-effects associated with real treatment. One example of this is with those that have already taken an opiate, can then show respiratory depression when given it again in the form of a placebo.

Withdrawal symptoms can also occur after placebo treatment. This was found, for example, after the discontinuation of the Women's Health Initiative study of hormone replacement therapy for menopause. Women had been on placebo for an average of 5.7 years. Moderate or severe withdrawal symptoms were reported by 40.5% of those on placebo compared to 63.3% of those on hormone replacement. [21]

Doctor-patient relationship

A study of Danish general practitioners found that 48% had prescribed a placebo at least 10 times in the past year. The most frequently prescribed placebos were antibiotics for viral infections, and vitamins for fatigue. Specialists and hospital-based physicians reported much lower rates of placebo use. A 2004 study in the British Medical Journal of physicians in Israel found that 60% used placebos in their medical practice, most commonly to "fend off" requests for unjustified medications or to calm a patient. The accompanying editorial concluded, "We cannot afford to dispense with any treatment that works, even if we are not certain how it does." Other researches have argued that open provision of placebos for treating ADHD in children can be effective in maintaining ADHD children on lower stimulant doses in the short term. [22]

Critics of the practice responded that it is unethical to prescribe treatments that do not work, and that telling a patient (as opposed to a research test subject) that a placebo is a real medication is deceptive and harms the doctor-patient relationship in the long run. Critics also argued that using placebos can delay the proper diagnosis and treatment of serious medical conditions.

The following impracticalities exist with placebos: (See the BMJ posted responses to Spiegel's editorial rapid response online section.

- Roughly only 30% of the population seems susceptible to placebo effects, and it is not possible to determine ahead of time whether a placebo will work or not. (However the placebo effect is zero in studies of blood poisoning and up to 80% in studies of wound on the duodenum).
- Patients rightfully want immediate relief or improvement from their illness or symptoms. A non-placebo can often provide that, while a placebo might not.
- Legitimate doctors and pharmacists could open themselves up to charges of fraud since sugar pills would cost pennies or cents for a bottle, but the price for a "real" medication would have to be charged to avoid making the patient suspicious.

About 25% of physicians in both the Danish and Israeli studies used placebos as a diagnostic tool to determine if a patient's symptoms were real, or if the patient was malingering. Both the critics and defenders of the medical use of placebos agreed that this was unethical. The British Medical Journal editorial said, "That a patient gets pain relief from a placebo does not imply that the pain is not real or organic in origin...the use of the placebo for 'diagnosis' of whether or not pain is real is misguided." [23]

The placebo administration may prove to be a useful treatment in some specific cases where recommended drugs cannot be used. For example, burn patients who are experiencing respiratory problems cannot often be prescribed opioid (morphine) or opioid derivatives (pethidine), as these can cause further respiratory depression. In such cases placebo injections (normal saline, etc.) are of use in providing real pain relief to burn patients if those not in delirium are told they are being given a powerful dose of painkiller.

Referring specifically to homeopathy, the House of Commons of the United Kingdom Science and Technology

Committee has stated:

In the Committee's view, homeopathy is a placebo treatment and the Government should have a policy on prescribing placebos. The Government is reluctant to address the appropriateness and ethics of prescribing placebos to patients, which usually relies on some degree of patient deception. Prescribing of placebos is not consistent with informed patient choice-which the Government claims is very important-as it means patients do

not have all the information needed to make choice meaningful. Beyond ethical issues and the integrity of the doctor-patient relationship, prescribing pure placebos is bad medicine. Their effect is unreliable and unpredictable and cannot form the sole basis of any treatment on the NHS.

A survey in the United States of more than 10,000 physicians came to the result that while 24% of physicians would prescribe a treatment that is a placebo simply because the patient wanted treatment, 58% would not, and for the remaining 18%, it would depend on the circumstances. [24]

The individual

Who is affected

Placebos do not work for everyone. Henry K. Beecher, in a paper in 1955, suggested placebo effects occurred in about 35% of people. However, the response rate is wide, ranging from 0% up to nearly everyone. In a dental postoperative pain model, placebo analgesia occurred in 39%. In research upon ischemic arm pain, placebo analgesia was found in 27%. The placebo analgesia rate for cutaneous healing of left hand skin was 56%.

Though not everyone responds to a placebo, neither does everyone respond to an active drug. The percentage of patients who reported relief following placebo (39%) is similar to the percentage following 4 mg (36%) and 6 mg (50%) of hidden morphine. [25]

Individual differences

In the 1950s, there was considerable research to find whether there was a specific personality to those that responded to placebos. The findings could not be replicated and it is now thought to have no effect.

The desire for relief from pain, "goal motivation", and how far pain is expected to be relieved increases placebo analgesia. Another factor increasing the effectiveness of placebos is the degree to which a person attends to their symptoms, "somatic focus". Individual variation in response to analgesic placebos has been linked to regional neurochemical differences in the internal affective state of the individuals experiencing pain. [26]

Those with Alzheimer's disease lose the capacity to be influenced by placebos, and this is attributed to the loss of their prefrontal cortex dependent capacity to have expectations. [129]

Children seem to have greater response than adults to placebos. [27]

Genes

In social anxiety disorder (SAD) an inherited variant of the gene for tryptophan hydroxylase 2 (enzyme that synthesizes the neurotransmitter serotonin) is linked to reduced amygdala activity and greater susceptibility to the placebo effect. The authors note "additional work is necessary to elucidate the generalizability of the findings".

In a 2012 study, variations on the COMT (catechol-O-methyltransferase) gene related to dopamine release are found to be critical in the placebo effect among the patients with irritable bowel syndrome participating in the trial, a research group in Harvard Medical School reported. Patients with a variation of met/met, for having two copies of the methionine allele were shown to be more likely to respond to the placebo treatment, while the variation of val/val, for their two copies of valine allele responded the least. The response of patients with one copy each of methionine and valine fell in the middle. Release of dopamine in patients with the met/met variations is thought to link to reward and 'confirmation bias' which enhance the sense that the treatment is working. The role of the COMT gene variations are expected to be more prominent in studies where patients report more subjective conditions such as pain and fatigue rather than objective physiological measurements. [28]

Symptoms and conditions

The placebo effect occurs more strongly in some conditions than others. Dylan Evans has suggested that placebos work most strongly upon conditions such as pain, swelling, stomach ulcers, depression, and anxiety that have been linked with activation of the acute-phase response.

Pain

Placebo analgesia is more likely to work the more severe the pain. One study found that for postoperative pain following the extraction of the third molar, saline injected while telling the patient it was a powerful painkiller was as potent as a 6–8 mg dose of morphine.

Most research reports average reduction for a group of people, but this can be lower (some people do not respond). In one study using injection of capsaicin below the skin found that this reduced group average pain compared to no placebo by ~46% to ~57%. Another measure is the ability to endure pain. In one study, placebos increased this on average by about 3.5 minutes compared to just under 14 minutes without it. The average strength of placebos upon pain on a visual analog scale is 2 out of 10 units. Individuals who respond to placebos may show even greater effects up to 5 out of 10 units. [29]

Depression

In 1998, a meta-analysis of published antidepressant trials found that 75% of the effectiveness of antidepressant medication is due to the placebo effect and other non-specific effects, rather than the treatment itself. Later, meta-analyses including data from unpublished trials found that the overall difference between drug and placebo is not clinically significant except in cases of very extreme depression. Another meta-analysis found that 79% of depressed patients receiving placebo remained well (for 12 weeks after an initial 6–8 weeks of successful therapy) compared to 93% of those receiving antidepressants. A meta-analysis in 2002 found a 30% reduction in suicide and attempted suicide in the placebo groups compared to a 40% reduction in the treated groups.

A 2002 article in The Washington Post titled "Against Depression, a Sugar Pill Is Hard to Beat" summarized research as follows:

In the majority of trials conducted by drug companies in recent decades, sugar pills have done as well as -- or better than -- antidepressants. Companies have had to conduct numerous trials to get two that show a positive result, which is the Food and Drug Administration's minimum for approval. The makers of Prozac had to run five trials to obtain two that were positive, and the makers of Paxil and Zoloft had to run even more. [30]

Gastric and duodenal ulcers

A meta-study of 31 placebo-controlled trials of the gastric acid secretion inhibitor drug cimetidine in the treatment of gastric or duodenal ulcers found that placebo treatments, in many cases, were as effective as active drugs: of the 1692 patients treated in the 31 trials, 76% of the 916 treated with the drug were "healed", and 48% of the 776 treated with placebo were "healed". These results were confirmed by the direct post-treatment endoscopy. It was also found that German placebos were "stronger" than others; and that, overall, different physicians evoked quite different placebo responses in the same clinical trial. Moreover, in many of these trials the gap between the active drugs and the placebo controls was "not because [the trials' constituents] had high drug effectiveness, but because they had low placebo effectiveness".

In some trials, placebos were effective in 90% of the cases, whereas in others the placebos were effective in only 10% of the cases. It was argued that "what is demonstrated in [these] studies is not enhanced healing in drug groups but reduced healing in placebo groups". It was also noted the results of two studies (one conducted in Germany, the other in Denmark), which examined "ulcerrelapse in healed patients" showed that the rate of relapse amongst those "healed" by the active drug treatment was five times that of those "healed" by the placebo treatment. [31]

Chronic fatigue syndrome

It was previously assumed that placebo response rates in patients with chronic fatigue syndrome (CFS) are unusually high, "at least 30% to 50%", because of the subjective reporting of symptoms and the fluctuating nature of the condition. According to a meta-analysis and contrary to conventional wisdom, the pooled response rate in the placebo group was 19.6%, even lower than in some other medical conditions. The authors offer possible explanations for this result: CFS is widely understood to be difficult to treat, which could reduce expectations of improvement. In context of evidence showing placebos do not have powerful clinical effects when compared to no treatment, a low rate of spontaneous remission in CFS could contribute to reduced improvement rates in the placebo group. Intervention type also contributed to the heterogeneity of the response. Low patient and provider expectations regarding psychological treatment may explain particularly low placebo responses to psychiatric treatments. [32]

List of medical conditions

The effect of placebo treatments (an inert pill unless otherwise noted) has been studied for the following medical conditions. Many of these citations concern research showing that active treatments are effective, but that placebo effects exist as well.[33]

- ADHD: adult, child
- Amalgam fillings: attributed symptoms (inert "chelation" therapy)
- Anxiety disorders
- Asthma (water aerosol inhalant)
- Asthma
- Autism: language and behavior problems
- Crohn's disease
- Depression (light treatment; low red light placebo)
- Depression
- Dyspepsia and Epilepsy
- Erectile dysfunction
- Food allergy: ability to eat ill - making foods
- Gastric and duodenal ulcers
- Headache
- Heart failure, congestive
- Herpes simplex
- Hypertension: mild and moderate
- Irritable bowel syndrome
- Migraine prophylaxis
- Multiple sclerosis
- Nausea: gastric activity
- Nausea: chemotherapy
- Nausea and vomiting : postoperative (sham acupuncture)
- Pain
- Panic disorders
- Parkinson's disease
- Pathological gambling
- Premenstrual dysphoric disorder.
- Psoriatic arthritis
- Reflux esophagitis
- Restless leg syndrome
- Rheumatic diseases
- Sexual dysfunction:women
- Social phobia
- Third molar extraction swelling (sham ultrasound)
- Ulcerative colitis
- Vulvar vestibulitis

Effects on research

Placebo-controlled studies

The placebo effect makes it more difficult to evaluate new treatments. Apparent benefits of a new treatment (usually a drug but not necessarily so) may not derive from the treatment but from the placebo effect. This is particularly likely, given that new therapies seem to have greater placebo effects. Clinical trials control for this effect by including a group of subjects that receives a sham treatment. The subjects in such trials are blinded as to whether they receive the treatment or a placebo. Clinical trials are often double-blinded so that the researchers also do not know which test subjects are receiving the active or placebo treatment.

The placebo effect in such clinical trials is weaker than in normal therapy since the subjects are not sure whether the treatment they are receiving is active.

Knowingly giving a person a placebo when there is an effective treatment available is a bioethically complex issue. While placebo-controlled trials might provide information about the effectiveness of a treatment, it denies some patients what could be the best available (if unproven) treatment. Informed consent is usually required for a study to be considered ethical, including the disclosure that some test subjects will receive placebo treatments.

The ethics of placebo-controlled studies have been debated in the revision process of the Declaration of Helsinki. Of particular concern has been the difference between trials comparing inert placebos with experimental treatments, versus comparing the best available treatment with an experimental treatment; and differences between trials in the sponsor's developed countries versus the trial's targeted developing countries.

A further issue of concern to pharmaceutical companies is that the effectiveness of placebos has increased over time,[194] thus making it more difficult to demonstrate the effectiveness of new drugs. The reason for the increased effectiveness is disputed.[34]

Nocebo

In the opposite effect, a patient who disbelieves in a treatment may experience a worsening of symptoms. This effect, now called by analogy nocebo (nocebo = "I shall harm") can be measured in the same way as the placebo effect, e.g., when members of a control group receiving an inert substance report a worsening of symptoms. The recipients of the inert substance may nullify the placebo effect intended by simply having a negative attitude towards the effectiveness of the substance prescribed, which often leads to a nocebo effect, which is not caused by the substance, but due to other factors, such as the patient's mentality towards his or her ability to get well, or even purely coincidental worsening of symptoms. [35]

Placebo ingredients

Placebos used in clinical trials have sometimes had unintended consequences. A report in the *Annals of Internal Medicine* that looked at details from 150 clinical trials found that certain placebos used in the trials affected the results. For example, one study on cholesterol-lowering drugs used olive oil and corn oil in the placebo pills. However, according to the report, this "may lead to an understatement of drug benefit: The monounsaturated and polyunsaturated fatty acids of these 'placebos,' and their antioxidant and anti-inflammatory effects, can reduce lipid levels and heart disease." Another example researchers reported in the study was a clinical trial of a new therapy for cancer patients suffering from anorexia. The placebo that was used included lactose. However, since cancer patients typically face a higher risk of lactose intolerance, the placebo pill might actually have caused unintended side-effects that made the experimental drug look better in comparison. [36]

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