

The Psychological and Neurological Effectiveness of Placebo Treatment

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Abstract

Placebo effect is an alternative medical approach that doctors utilize in treating health issues. For years, people thought that placebo pills were inert drugs or medically illegitimate measures that have psychological effects on the patient, therefore alleviating the patient's pain. However, in recent years, with the advent of technology, more studies are involving neurological aspects to the already-proven psychological aspects of the placebo effect. Yet there is still some opposition and much to be proven better on this topic. What is very important is that although there is opposition, there is growing recognition that the placebo effect may actually involve changes in brain chemistry, and that the placebo effect might be a fundamental part of good medical care that will one day be universally embraced by doctors and patients as well.

Acronyms:

CBP	Chronic Back Pain
CCK	Cholecystokinin
CR	Conditioned Response
CS	Conditioned Stimulus/Stimuli
NSAID	Nonsteroidal Anti-Inflammatory Drug
PAG	Periaqueductal Gray
UCR	Unconditioned Response
UCS	Unconditioned Stimulus/Stimuli

Introduction

Since the 18th century, people have believed that placebo pills were inert drugs or medically unqualified measures that have psychological effects on the patient, therefore easing the patient's pain (Beecher 1955). Hence, the term placebo is a Latin derivative for "I shall please" (Moerman 2002). Furthermore, in recent years, many studies are associating neurological aspects to the psychological effects of the placebo effect.

Today there is a range of treatment that people categorize as placebo - as basic as administering a Band-Aid on a wound to inserting needles into a patient receiving acupuncture. Because such procedures do not contain much medical efficiency, their pain-reducing results are termed 'placebo effect.' If these practices do not involve elements or substances that are responsible for altering a health condition then what is it about these techniques that can make one pain free? Because placebo analgesia has proven to be one of the most successful models in the research of the placebo effect, this review will explain the long-known psychological influences of the placebo analgesia, as well as the newer and unconcluded neurological influences of the placebo analgesia.

Several psychological mechanisms contribute to the appearance, enhancement or duration of the placebo effects. Firstly, Pavlov's classical conditioning is a major contributor towards the placebo effect, whereby a patient is trained to respond positively towards a placebo stimulus. Expectations also play a big role - the patient's anticipation of clinical improvement is partially responsible for the onset of the placebo effect. The overall experience that the patient experiences influences the patient's expectations; doctor-patient relationship, the trial site, the appearance of the pill, and the way the treatment is given are all experience related factors that impact one's expectations.

How can it be that just by one merely having belief one can experience less or no pain? The neural mechanisms whereby placebo conditioning leads to placebo analgesia remain unclear. Scientists are attempting to find better explanations for the placebo effect by attributing it to neurological mechanisms of the body. Ascending pain signals travel through one's spinal cord, then to the thalamus, and then to the sensory-processing regions of one's cerebral cortex. In order for one not to experience pain due to a pain provoking stimulus, there would have to be changes in the sensory network of the brain or in the spinal cord. Recently, researchers are associating opiate analgesics to the placebo effect. They are attempting to prove that placebo treatment engages opioid systems which block pain in the spinal cord. However, studies also show that there in fact is non-opioid related analgesia. Nonetheless, the explanations remain unclear. From the research done, it is evident that the placebo effect has psychological aspects and that there is a difference in brain activity due to placebo treatment which is seemingly responsible for placebo analgesia. Nonetheless, future research is required in order to pinpoint the definite neural activity responsible for the pain reduction.

Methods

In an effort to answer the question asked above, many published articles, clinical trials, and research papers have been examined. Primarily, Touro College's library database as well as Google Scholar were used to search for pertinent material. Original research papers that were referenced were also studied. An

attempt was made to determine if the placebo effect, as a result of the placebo treatment, is psychologically and or neurologically fact or fiction.

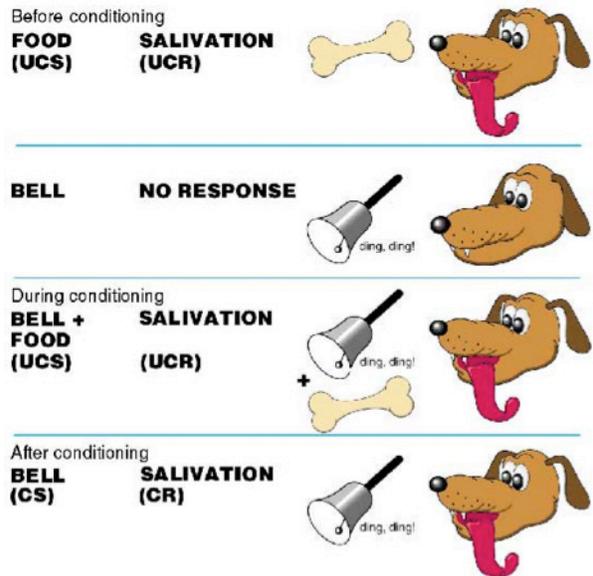
Discussion

Psychological Aspects: Learning and Classical Conditioning

People who suffer from pain, like a headache, and who usually ingest aspirin, learn to associate the color, taste, and shape of the pill with pain-decrease. After recurring associations, if such people are given a placebo pill, such as a sugar pill resembling aspirin, they will feel less pain. Other stimuli, such as medical personnel features, hospitals, and therapeutic equipment can also be associated with clinical improvements and therefore act as conditioned stimuli that impact healing effects (Benedetti, et. al. 2010). A 1960s' experiment found that a scopolamine injection, a medication used to treat motion sickness and other types of nausea, affected motor changes in a rat. Furthermore, identical motor changes also transpired after a placebo injection made of saline solution was administered after the scopolamine injection (Herrnstein 1962). Corresponding occurrences exist in humans too. Notably, if a placebo pill or procedure is given after two preceding administrations of an effective painkiller or practice, the placebo analgesic response is much larger (Amanzio, Benedetti, 1999). That effect emphasizes that the placebo effect is definitely a learning phenomenon.

Like other profound scientific developments, classical conditioning was discovered accidentally. In the 1890s, Russian physiologist Ivan Pavlov was observing dogs salivate in response to being fed. He then noticed that the dogs began salivating whenever he arrived in the room they were in, while he did not always have food with him (McLeod 2007). From this incident, Pavlov believed that some responses are innate, they don't need to be learned. In example, dogs do not learn to salivate whenever they see food as this reflex is inherent. In psychological terms, an unconditioned stimulus leads to an unconditioned response. Furthermore, over time the dogs began salivating as soon as they saw anything that they associated with their food. Therefore, they would salivate in the presence of a lab assistant even when he did not come with food (Windholz 1995). In psychological terms, the phenomenon is due because when an unconditioned stimulus is paired with a neutral stimulus, the latter becomes a conditioned stimulus that propels a conditioned response comparable to the unconditioned response. Pavlov furthered his research by experimenting with a bell; the dog was conditioned to salivate when a bell rang as he associated it with the food.

Numerous clinical trials attribute the positive placebo treatment effects to Pavlov's classical conditioning. Just as a dog salivated in response to a food-associated person or object, people



can experience a reduction in pain due to a painkiller-associated placebo procedure or drug. Indeed, a 1970s' experiment proves that placebo effects are in large due to classical conditioning; saccharin, a flavored drinking solution, was paired with cyclophosphamide, an immunosuppressive drug, and given to rats. After, the rats were immunized with sheep red blood cells. On the seventh day, the rats that had been again exposed to saccharin at the time of antigenic stimulation had a lower concentration of hemagglutinating antibodies in comparison with non-conditioned animals given saccharin, conditioned animals that were not re-exposed to saccharin, and a placebo group. Hence, the experiment proves that after associative learning, simply a liquid has the ability to mimic the effects of an active drug and thus legitimizes the placebo effect (Ader, Cohen 1975).

In response to people who argue that such conditioning is not possible to exist amongst human beings, an analogous trial provides substantial evidence that behavioral conditioning of immunosuppression is in fact promising in humans. Recurrent associations between cyclosporine A - an immunosuppressant drug - and a flavored drink incited conditioned immunosuppression in healthy male volunteers. However, more than one associative learning trial was necessary in order to bring about the fascinating results (Goebel, et al 2002).

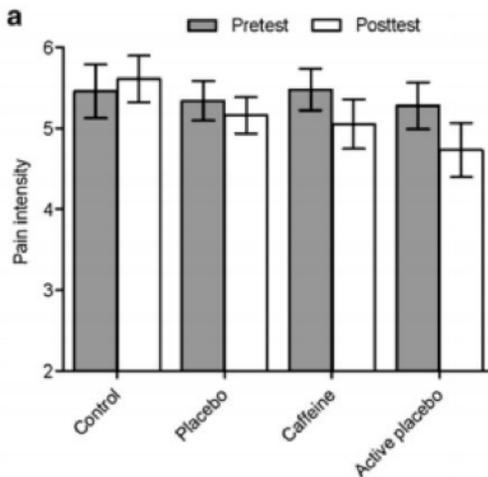
Psychological Aspects: Expectancy

While Pavlovian conditioning serves as an unconscious influence towards placebo effects, expectancy serves as a conscious one. The expectancy theory hypothesizes that one's expectations impact ones future experience (Kirsch 1999). Therefore, if one expects clinical improvement, his chances of improving are that much greater. This theory is evident in the following 2010

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double-blind clinical trial: A painful laser stimulus was delivered individually to twenty healthy participants before and after each was given a 0 or 4 mg/kg cup of caffeine. Some participants were told that their drink contained a painkiller, while the others were told their drink was a placebo solution. After measuring the reported pain and expectancy levels, it was clear that the information that a painkiller was given enhanced the analgesic effect of caffeine compared to caffeine given with no drug information (Bjorkedal, Flaten 2011). Moreover, those that were in the active placebo condition group - were told they were given a painkiller and they received caffeine - overall reported less pain than the subjects in the caffeine condition group - were not told they were given painkiller and they received caffeine. This reiterates the expectancy theory, as the first group was given two qualities (caffeine and drug information) that made them expect an improvement, while the latter group was only given one (caffeine). The expectancy of pain relief modulated the

Figure 2



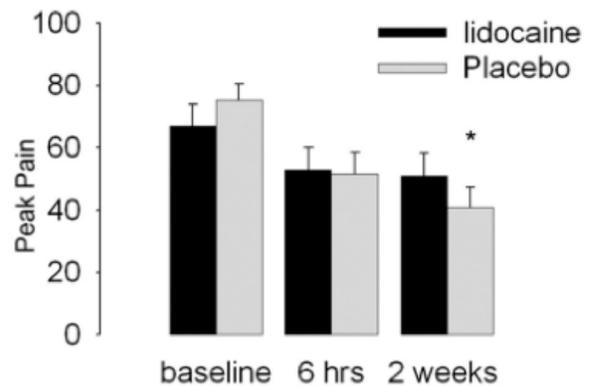
Subjects reported larger reductions in pain after 4mg/kg caffeine (caffeine, active placebo) compared to after 0mg caffeine (control, placebo). (Bjorkedal, Flaten 2011)

decreased pain experienced by the subjects (fig. 2).

From the above trial, it is evident that verbal gestures enhance expectancy in patients. Additionally, the overall experience that the patient experiences influences his/her expectancy of clinical improvement and consequently his/her clinical results. The doctor-patient relationship, the trial site, the appearance of the pill, and the way the treatment is given are all included in one's experience and can enhance the placebo effect. In another study, the effectiveness of 5% Lidocaine patches was compared with the effectiveness of placebo patches in treating chronic back pain. In the randomized double-blind study, 15 patients received 5% Lidocaine patches and 15 received placebo patches. Functional MRI was used to ascertain brain activity for

variations of spontaneous pain, at the starting time and at two more points thereafter (6 hours and 2 weeks). As reported, there was no noteworthy difference between the two groups in their pain intensity and in pain related brain activity. And both groups reported more than a 50% pain decrease. Moreover, when compared with an untreated chronic-back-pain-group at similar intervals, the patch treated CBP group experienced a considerably bigger decrease in back pain (Hashmi et al, 2012).

Figure 3



Variation of CBP pain with treatment type and treatment duration. Treatment duration, but not type, significantly decreased CBP pain. (Hashmi et al).

These findings support the expectancy theory, as the patients who experienced a more encouraging experience by being given a patch consequently felt less pain later on (fig. 3).

Another method to reinforce one's expectation of clinical improvement, is to educate the individual about the so-called painkiller one is going to ingest. A random group of fifty university students agreed to either undergo placebo treatment under the appearance of a new analgesic painkiller capsule or to be put in the control group which did not receive placebo treatment. While some participants were handed educational handouts explaining the analgesic effect, others were not. The subjects then received electrically-induced pain at varied intensities, and those that ingested the realistic looking drug capsules reported analgesia. Furthermore, participants who also read the handouts regarding analgesia reported an even higher decrease in pain (Tang, Colagiuri 2013). This experiment highlights that the appearance of the pill and the knowledge of analgesia both contribute towards the patients expectancy and thus towards his or her placebo analgesia.

Psychological Aspects: Conditioning vs. Expectancy Theory

After much research, it is evident that both the conditioning and expectancy theories are driving forces of placebo effects.

However, can they coexist, and is one more potent than the other? In response to the former, both psychological mechanisms can surely coincide. For example, a patient who receives a sugar pill on its own after repetitively receiving the pill together with other analgesic drugs will imply both mechanisms; the sugar pill has become the conditioned stimulus to invoke analgesia, and the fact that the patient received medicine prompts him to expect a recovery.

Regarding which mechanism is more vital, Stewart-Williams and Podd (2004) reviewed many clinical trials and concluded similarly to what many others have suggested: each mechanism plays a different part in the production of placebo effects. When a doctor verbally encourages a patient, when an inert pill or procedure resembles a legitimate pill or procedure, and when other such characteristics mentioned previously exist when a patient receives a placebo, he/she learns to expect an improvement, which is a conscious belief. When one's conscious is involved, he can experience subjective and or physiological placebo effects. On the other hand, when placebos represent CS, the patient can either unconsciously believe in a placebo effect or the patient can consciously expect improvements in his situation. The conscious expectations and the non-conscious learning yields subjective and physiological (objective) placebo effects. Whilst expectancy learning is always a conscious action, conditioning can be conscious or not - depending on whether expectancy coincides with the conditioning. Nonetheless, each form of learning can produce subjective as well as physiological outcomes.

Others describe the correlation between expectations and conditioning differently. A study concluded that placebo responses are facilitated by expectation when conscious physiological processes - for example, pain - exist, notwithstanding, a conditioning procedure may simultaneously be implemented (Benedetti et. al, 2003). Sixty participants were divided into five groups and induced with pain in their forearms once per day for five days. Such ischemic pain increases over time rapidly, and the pain becomes excruciating after approximately 13 minutes. After the painful stimulus was implied, each participant stopped a timer when the pain became unbearable, and thus the average pain tolerance level for each group was recorded. As each group was treated differently throughout the five days, the results of each group greatly varied. Some were told analgesia suggestions or hyperalgesia suggestion, some experienced conditioning via ketorolac anti inflammatory analgesic, and some received a combination. Evidently, verbally induced analgesia expectations raised the pain tolerance; whereas, suggestions of hyperalgesia eradicated pain tolerance. This testifies that not only are positive words empowering, negativity is impactful too. Moreover, this highlights the detrimental effects of unencouraging words

in the medical scene. When analgesia suggestions and conditioning were both implemented, the tolerance level rose higher. Yet, when conditioning and hyperalgesia suggestions coincided, the expectations outweighed the preconditioning effects of ketorolac, as the subjects's overall pain tolerance decreased. The study proves that analgesic placebo responses seem to be primarily mediated by expectations, such as verbally induced expectations.

The study of the placebo phenomenon has important implications on non-placebo procedures. The equivalent psychological factors that mediate the placebo effect are likely to be effective when an individual is given an active substance or undergoes an active procedure. Accordingly, a better understanding of the psychological mechanisms essential to the placebo effect is relevant in order to contribute these psychological factors to non-placebo treatments as well. For example, by increasing patients' positive expectancies for the effects of an active drug or procedure, it is conceivable that the drug or procedure will yield stronger drug effects without the use of stronger doses. There are numerous ways that physicians can achieve this: They can inform patients about others for whom the treatment proved successful, and doctors should update patients on the clinical research that portrays the treatment as worthwhile. Additionally, physicians should make people aware of the minor side effects related with the treatment. Then, when people come across any such symptoms in themselves (irrespective of whether these symptoms are a result of the active drug), they are likely to assume that the drug is working well. This will possibly boost their expectations for a positive effect, which will thereafter enhance the placebo element of the active treatment. Using these strategies, physicians can probably achieve stronger drug results without administering alternative stronger drugs or greater doses. This would be a safer solution for the patient, as he or she will not be exposed to unnecessary strong medication, and this will also decrease the costs of medical care. (Podd, Stewart-Williams 2004)

Neurological Aspects

Placebos have no innate power to elicit given results. Yet, they can produce the effects which are anticipated or sought. Placebo pills and procedures do not act on the brain to bring about placebo effects; however, placebos can stimulate expectations and CR which impact pain-reducing neural systems. What is responsible for the relation between the psychological mechanisms and placebo analgesia?

Neurological Aspects: Opioids

The neurology of placebo was discovered when researchers found that placebo analgesia is facilitated by endogenous opioids. They were prompted to make this hypothesis after they observed that naloxone, the opioid antagonist, can oppose the

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effects of placebo analgesia (Levine et. al, 1978). Since then, further studies have emphasized that finding. Researchers examined the mechanisms fundamental to the activation of endogenous opioids in placebo analgesia (Benedetti, Amanzio 1999). Once a day, for five days, ischemic arm pain was induced into 229 participants. The subjects were divided into twelve groups, each treated differently. Each group received a combination of two or more of these

treatments throughout the five-day-experiment duration: the opioid agonist morphine hydrochloride, the non-opioid ketorolac (nonsteroidal anti-inflammatory drug; NSAID) tromethamine, no treatment, an open injection of saline, or open or hidden opioid antagonist naloxone. The order of each group's treatment was made so that the treatment can serve as drug conditioning, expectation cues, or both. When morphine was administered, and when saline was openly injected and was believed to be a morphine-like (expectation and or drug conditioning), participants experienced less pain. Any participant who received naloxone after morphine (ketorolac was not administered), whether open or hidden and whether used as an expectation cue or not, experienced no difference in pain. When ketorolac was issued, there was pain relief. Moreover, when saline was issued, it mimicked the ketorolac effects. What was even more fascinating about the results was that when naloxone was issued after ketorolac, pain was partially diminished. This proves that naloxone only somewhat blocks analgesic effects; therefore, there must be non-opioid factors in addition to opioid factors influencing placebo analgesia. The results of the experiment prove that the opioid system is surely involved in placebo analgesia, yet there are also other aspects sometimes involved.

There is a lack of evidence proving how non-opioid pathways serve in placebo analgesia. However, just as ketorolac is a NSAID, placebos that mimic ketorolac or other NSAIDs' activity, probably behave like such drugs. They act at peripheral and also central places in the spinal cord, hindering the cyclo-oxygenase enzyme that is essential for the transformation of arachidonic acid into prostaglandins and thus preventing a painful experience.

Because studies prove the anti-opioid accomplishments of the neuropeptide cholecystokinin (CCK), further studies were done and demonstrated that the blockade of CCK receptors makes the placebo analgesic response possible, thus suggesting that the CCK role in placebo analgesia is quite impeding and that the opioid system is important in order for placebo analgesia to occur. This finding imparts that by irritating the anti-opioid action of CCK at the time of a placebo practice, the endogenous opioid systems can be activated. (Benedetti, Amanzio 1997) In

a more recent study, forty participants were divided into four groups in order for the effects of CCK type-2 receptors to be examined (Benedetti et. al, 2010). Each participant was induced with ischemic arm pain like in previously mentioned experiments, and each group was treated differently. The results portrayed that activation of CCK type-2 receptors, which was achieved by means of administering the agonist pentagastrin, abolished placebo analgesia even after morphine-conditioning (placebo treatment) occurred. Evidently, CCK resembles naloxone. Furthermore, this study suggests that the equilibrium between CCK elements and opioids is critical in placebo treatment. So, when patients do not respond as predicted to placebo treatments, possibly CCK type-2 receptor hyperactivity exists in the patient's body-makeup.

What exactly is the endogenous opioid system? In general, the endogenous opioid system is an inborn pain-relieving method. It consists of dispersed neurons that produce three opioids: beta-endorphin, the met- and leu-enkephalins, and the dynorphins. These opioids behave like neurotransmitters and neuromodulators at three main categories of receptors - mu (μ), Delta (δ), and kappa (κ). Once attached to the receptors, they send signals which in turn block pain, slow down breathing, and have an overall calming effect; therefore, the patient experiences analgesia.

In order to more fully comprehend how opioids modulate the conduction of pain, one needs to understand the pathway by which pain is transmitted - beginning from its origin until its place of interpretation and perception in the brain. There are two types of first order neurons in which pain is transmitted along: In terms of nociceptive pain transmission, acute pain is transmitted mainly by A-delta afferent sensory nerve fibers, while chronic pain is transmitted mainly by unmyelinated C sensory afferent nerve fibers until it reaches the spinal cord. Because these nerve fibers are unmyelinated, chronic pain is transmitted slower than acute pain. Nociceptors, free nerve endings which are found in numerous visceral and somatic tissues all over the body, are stimulated by different sorts of noxious (harmful) stimuli - such as chemical, thermal, and mechanical - and once stimulated there is a release of leukotrienes, bradykinin, histamine, prostaglandins, potassium ions, and substance P. These substances activate the nociceptors which results in the generation of an action potential down the first order neurons and heading towards the spinal cord. When the fibers arrive at the dorsal gray horn of the spinal cord, they release neurotransmitters - glutamate, substance P, and calcitonin gene related peptide - and thus synapse with second order nerve fibers. The released neurotransmitters incite the depolarization of the second order neuron which crosses over to the opposite side of the spinal cord, entering the contralateral spinothalamic tract and from there ascends up the spinal cord and ultimately into the brain.

Here, pain is modified via descending pathways and this results in an individual experiencing pain.

Now, how do opioids hinder the descending pathways so that an individual does not perceive pain? Opioid agonists bind to μ -opioid receptors within the midbrain of the brainstem, on inhibitory interneurons. The opioid agonist action at these neurons results in a lessening in the inhibitory effects on the nerve fibers exiting the periaqueductal gray (PAG). Hence, they lead to disinhibition of the descending nerves from the PAG. In turn, there is an increase in their motion and in their communication to the raphe nuclei. Moreover, there will be a disinhibition of neurons in the raphe nuclei. There will be a general stimulation of the descending nerve fibers which are descending through the lateral funiculus in the spinal cord, and they eventually reach the dorsal horn of the spinal cord. As this is the site in which the original pain stimulus enters the spinal cord in its ascent to the brain, here the nerve fibers influence the activity of the initial pain stimulus.

Opioids impede afferent sensory nerve fibers, as well, that are ascending the spinal cord traveling towards the brain. Opioids directly attach to presynaptic mu-opioid receptors and thus cause an inhibition of pain transmission through the first order afferent sensory nerve fibers which enter the spinal cord. This leads to a lessening in the discharge of substance P that is required for the stimulation of second order neurons. Furthermore, opioids can directly attach to postsynaptic mu-opioid receptors on different ascending nerve fibers, and this adds to the diminished communication to the ventral posterolateral nucleus and consequently to the cerebral cortex. Additionally, opioids can indirectly inhibit second order ascending neurons in the spinal cord; they modify the ejection of substance P and serotonin from the stimulated descending nerve fibers from the raphe nuclei which control endorphin containing neurons inside the dorsal horn. The outcome of the impacts of opioids on the nerves found in the dorsal horn is the pain transmission inhibition.

As one's body does not produce enough natural opioids to alleviate excruciating or prolonged pain, opioid drugs are manufactured. Comparable to their endogenous complements, opioid drugs - opiates - act at the same receptor sites, producing analgesia as well. This wonder is possible, as the drugs mimic the endogenous opioids' chemical makeup. For this reason, patients who experience much pain are prescribed with painkillers - as they are opiates which mediate analgesia. When a placebo is administered, the goal is that the endogenous opioid system is activated as a result of the psychological influence on the patient's mind - the individual is convinced he or she received an opiate, so his body responds respectively.

Ethics of Placebo Treatment

As the physiology caused by placebo treatment is not conclusive, the placebo effect is not universally recommended. In fact, many view placebo treatment as immoral. According to Nikola Biller-Andorno (2004) of University of Goettingen, Germany, placebo treatment is only permissible when used for therapeutic reasons and when no better proven alternative exists. Additionally, the patient cannot be deceived, rather the doctor must acknowledge the patient's empowerment and autonomy. If the physician fails to abide by these standards, rather than practicing ethically he is practicing blunderingly. Because of such guidelines, it is difficult to practice placebo treatment on sick patients. Therefore, researchers are forced to set up trials in order to examine placebo effects.

Ethnic

After much research, it is noticeable that the placebo effect has become more effective. DiSalvo elaborated about the placebo effect in a 2015 edition of the Forbes magazine. He wrote that after reviewing a study of 84 clinical trials which were carried out between the years 1990 and 2013, he concluded that the placebo effect is getting stronger. However, he adds that this is only true of trials in the United States. Possibly because America is more advanced than many countries, the ability to conduct placebo treatments is more feasible. More importantly, he adds that America is the only country aside from New Zealand that allows drug companies to sell their products directly to consumers. This is blatant when one watches TV and sees the numerous drug commercials. The advertising in itself can contribute towards the placebo effect by creating expectation cues.

Conclusion

After examining the articles and experiments regarding placebo treatments and effects, it is apparent that while placebo treatment definitely has psychological influence on patients, the neurological influence is unclear. Many are skeptical of placebo effect all together. They argue that possibly the percentage of patients that report improvement would regardless have improvement - that is to say, often pain reduces over time so even without a placebo treatment one can be somewhat relieved from pain. However, in many trials, there are 'natural history' groups which are used to compare their pain tolerance to the placebo treated group's pain tolerance. And these studies have proven that the placebo treated group's pain tolerance was better than the non-placebo treated group's tolerance. This topic is fascinating as it proves the power of the mind over matter. Placebo management can trigger mechanisms that are equivalent to those triggered by drugs, which points out a parallel between psychological and pharmaceutical effects. With further research, placebo effect may become completely acceptable and instead of administering drugs which often have harmful side

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effects or which are sometimes rejected by patients, placebo treatments will serve as alternatives.

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