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To what extent are placebos an effective method of treatment for pain?

Contents

Abstract

THE ACTION OF PLACEBOS UPON MU OPIOD RECEPTORS BEING BLOCKED BY INDIGENOUS OPIODS SUCH AS ENDORPHINS CAUSES THE PLACEBO RESPONSE KNOWN AS PLACEBO ANALGESIA. LOOKING INTO WHETHER THIS IS AN EFFECTIVE METHOD OF TREATMENT OF PAIN IN A CLINICAL ENVIRONMENT RAISES MANY CONCERNS. THIS INCLUDES WHETHER IT WOULD BE ETHICAL AND ALSO WHETHER THERE IS A HIGH EFFICACY RATE FOR THE SPECIFIC TREATMENT OF THAT CONDITION. ON THE WHOLE THE TREATMENT IS VERY UNPREDICTABLE IN SOME CASES. THEREFORE IT SHOULD IDEALLY ONLY BE USED IN CASES WHERE ALL OTHER TREATMENTS METHODS HAVE BEEN EXHAUSTED AND THE PLACEBO IS A LAST RESORT.

Introduction – What is the placebo effect?

A placebo response is 'any and all measured effects other than a physiological response to the treatment itself,'[1] as defined during clinical trials.

This is to say the placebo effect is all the perceived physical and mental responses of the body after a treatment has been administered. Treatments that can initiate placebo responses include inert substances such as sugar pills, sham surgeries/therapies and even the active treatments used within the healthcare profession. However the effects of active treatments are not counted as part of the placebo effect. It is dubbed as the "mind over matter" effect, meaning the mind is responsible for any changes and not the substance or treatment given.

Misconceptions

Since the placebo effect is phenomenon that has attracted a lot of attention, with that it has also generated many misconceptions amongst the general public and scientific community. For instance, there is no single 'placebo effect' to talk of, but there are multiple effects initiated by placebos within the body. A lot of people believe that prescriptions of placebos will directly cure the ailment; however the response affects the symptoms being experienced. Another misconception is that patients receiving placebos must not be aware that they are receiving an inactive or ineffective treatment or they will not be fooled into believing they are making a recovery. Patients can in fact be told they are receiving a placebo, and still experience an alleviation of symptoms if they receive an explanation as to how to the placebo effect takes place, however this method can reduce success rates, but removes the ethical concern of deceiving a patient. Also, there is a belief that the placebo effect cannot occur in small children and animals, however due to observer bias, the person interpreting the results of the treatment in children and animals may perceive an improvement meaning there was a placebo response since it is subject to the beholder. Clearing these misconceptions enables a clear understanding of the placebo response, to be able to make a judgement on whether it is in fact an effective and viable method of treatment.

What conditions are affected by placebos?

Placebos can affect an array of conditions, both by aiding recovery or even inducing more negative effects (known as the nocebo effect). The effect occurs in varying strengths depending upon the condition. Some psychological conditions such as pain, depression and anxiety especially have been known to produce very strong placebo responses due to the areas of the brain which are activated. Some of the many conditions for which the placebo effects have been studied and proven to exist for include:

- Asthma
- Autism
- Bipolar Mania
- Binge Eating Disorder
- Depression

- Epilepsy
- Food Allergies
- Hypertension
- Irritable Bowel Syndrome
- Nausea
- Pain
- Pathological gambling
- Rheumatic diseases

There are many more conditions for which placebo responses occur, all with varying degrees of success. Although the effect is not seen in all people, it undeniably occurs in some, therefore proving its existence. While placebos responses can exist in cases of cancer, they are very uncommon, which may be influenced by many factors.

Factors influencing the placebo effect

Simply prescribing a placebo for a condition, without explaining what the treatment is supposed to do, will lead to a very weak or even no placebo response. The effect is dependent on many factors and therefore there are different types of placebos effects that are thought to occur.

- Something such as a visit to the doctors can trigger the **expectancy of improvement** of a condition leading patients to feel better, as the mind is put into a psychological state focusing on wellbeing. This is one of the basic principles behind the placebo effect, whereby belief leads to what is thought to be recovery as some of the symptoms are eased. This explains why when doctors explain the mechanisms of a treatment and how it will help, that a greater number of patients experience a positive effect.
- The **fallacy of treatments**, or how effective it looks, can affect how intense a placebo response is. An injection would produce a greater response compared to a pill as the patient would think they are receiving a stronger treatment and believe their condition will improve rapidly.
- Sometimes when a placebo has been prescribed to a patient many illness will improve of their own accord over time. As the **condition naturally eases**, people assume it to be due to placebo and experience positive feedback, fuelling the recovery process.
- If a person has previous experience of a drug working in his favour, if the drug is re-prescribed, but replaced with an inert placebo, the mind is prepared for recovery and the patient readily experiences improvements. This type of placebo effect is a 'learned response after **personal experience** (and) is called the *conditioning effect.*'[2]
- In other cases, the placebo effect may be explained by other factors that aided recovery, such as changes in lifestyle by partaking in regular exercise and eating a balanced diet while taking the treatment.

This highlights that there are many factors that must be considered when using placebos as a method of treatment and it can be difficult to achieve them all.

Nocebo Effect

The positive placebo effect can also work in reverse, known as the nocebo effect, causing negative side effects to appear or a worsening in symptoms. Simply being made aware of the possible side effects that can occur as a result of a treatment, can cause expectancy and lead to them surfacing during the recovery period. Patients who disbelieve that a treatment will work and have a negative attitude towards it can experience a worsening of their symptoms, because of their mentality or simply a

coincidental worsening of symptoms.[3] The factors influencing the placebo effect also apply to the nocebo. For example, the more strong/dangerous a pill looks, the more likely the patient is expecting the side effects mentioned to appear. Also if a patient has had a negative response to a treatment in the past, they will be wary of it and experience the conditioning effect.

How the placebo effect works neurologically to combat pain?

The placebo effect is a psychological phenomenon, which is linked to brain stimulation and activation of certain areas of the brain. It has long been hypothesised that the areas of the brain which are activated can cause a release of natural painkillers to alleviate symptoms. Also stimulation of certain areas of the brain with a placebo acts as a distraction and draw attention away from pain sensing regions, causing a reduction in the amount of pain felt by a patient.

What is pain?

To understand how a placebo can work against pain in the body, the concept of pain must be clarified. Pain is a subjective experience, which means to be able to measure the amount present; it depends upon comparison of pain levels felt by a test subject. Somebody involved in placebo analgesia research would be exposed to a source of pain and then be given a placebo. Upon re-exposure to the same source at the same intensity, the subject would be able to form a comparison of whether there was a decrease/increase in the amount of pain that they experience. This method can show that people are able to withstand the same intensity of pain and yet report a decrease in pain experienced when given a placebo, proving that pain is only as painful as you think it is.

Pain is picked up by sensory neurones and its severity is determined by nociceptors (pain receptors). An impulse is carried up to the spinal cord, where reflexes can kick in without conscious choice of the brain. In the case where the impulse has travelled through the spine and into the brain, it is interpreted by different areas of the brain. Dependant on what part of the brain is stimulated, responses can include emotions being evoked and tears being released.

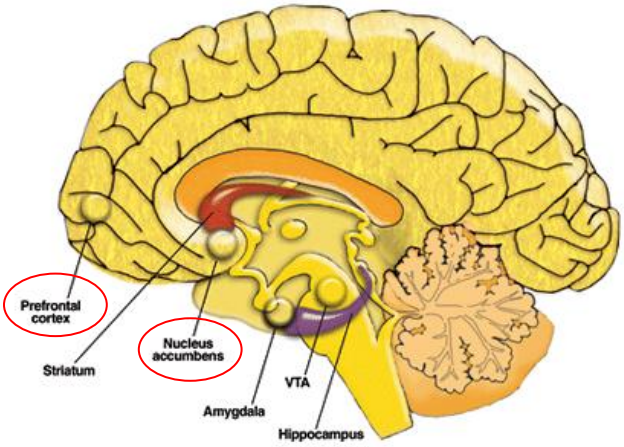
Painkillers are the most conventional method of blocking pain, as the drugs act upon the central nervous system by blocking synapses in nerves to stop impulses reaching the brain. They also inhibit receptors that are involved in pain sensory. As in many cases where drug treatments have been reported to not be working, placebos can also produce a similar effect, making them a useful alternative.

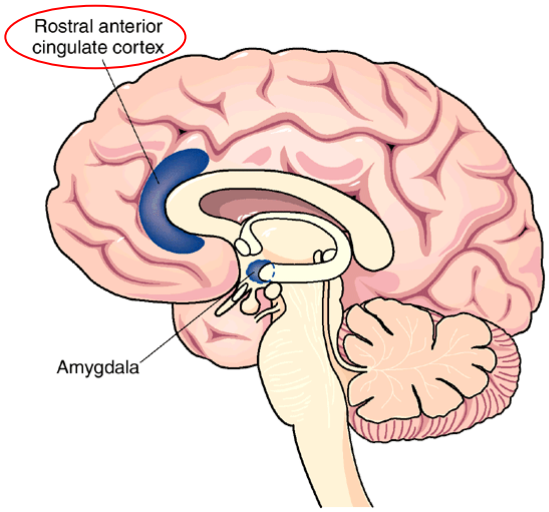
Pain is one of the body's natural defences and it is a warning system for when the body is being harmed, preventing and protecting from injuries. There have been cases where people are born with mutations in their SCN9A gene, which blocks pathways to certain types of pain. A reduced sensitivity to extreme temperatures is most commonly experienced and can lead to the sufferers of the mutation to get burnt without realising.[4] In essence, pain is an essential function of the human body and when it is hindered, it is a hazard that can lead to harm. However when the body is constantly at its pain threshold in those who suffer from chronic pain, it can negatively affect the person's quality of life to a point where they are unable to cope with simple daily life tasks. This means that pain can be very dominating in the lives

of some and drastic measures may need to be taken to relieve it, which is an argument for why placebos may need to be used.

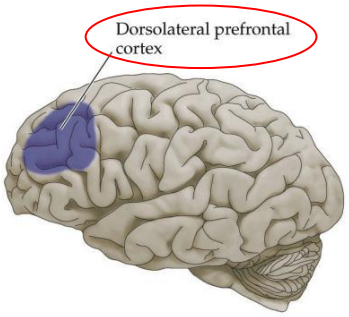
How placebo analgesia takes place in the brain?

Brain imaging (fMRI) from the Zubieta study showed that 'activation of μ-opioid receptor-mediated neurotransmission was observed in both higher-order and sub-cortical brain regions, which included the pregenual and subgenual rostral anterior cingulate, the dorsolateral prefrontal cortex, the insular cortex, and the nucleus accumbens.' The activation of the receptors in these areas of the brain reduced pain sensory and pain intensity experienced.[5]





Opioids are psychoactive chemicals that bind to the opioid receptors that are located in the body. One of the world's oldest known drugs includes the opium poppy, which was used as a painkiller. The body is known to have its own endogenous opioids, most commonly endorphins. [6] Endorphins therefore display similar effects to opiates such as analgesia and a feeling of well-being. The μ-opioid receptors have a high affinity for β-Endorphins which cause the receptors in the areas of the brain circled in the diagrams above to be activated, producing an analgesic effect.



Clinical Trial Procedures

Clinical trials are the extensive testing period of pharmaceuticals, therapies, surgeries, medical devices, and nutritional changes before they are released onto the market. Producers of the new treatment need to be sure it is effective and safe for the general public to consume with minimal side effects. The primary principal of these trials is to learn, rather than treat patients[7] who have signed up to the trial, although every care is taken to ensure the safety of the participant. The new treatments are tested for efficacy and safety against existing treatments or placebos.

Placebo controlled trials

In cases where placebos are used as the control, there are blind studies in which subjects are chosen to take a treatment. Some of the group are given an actual treatment and others are given an inert placebo, but the test subjects do not know what they are taking to keep the trial fair. This allows the testers to see all effects that are account for by placebo responses in the placebo controlled group that do not depend on the treatment. It is then possible to determine whether the treatment was effective. These are known as blinded placebo trials.

Another type of placebo trial is the double blinded placebo trials. This is where both patients and doctors prescribing placebos do not know whether the treatment is a placebo. This cancels out the effects of the doctor's disbelief in the inactive treatment which can transfer to the patient and deter a placebo response as the patient can pick up the doctors mentality towards the treatment. Also on the reverse side, the fact that the doctor knows he has prescribed a placebo, he may perceive an improvement in the patient if he is looking for it from the theory of the concept.

Ethical concerns with placebos for pain

The use of placebos to treat pain has long been an area subjected to great debate. The underlying ethical question surrounding placebo analgesia is exactly who can really decide whether the placebo should be prescribed, as there are many varying opinions. Is it up to a doctor to choose what is best for the patient by means of deception even if the efficacy of a placebo is proven?

There are many things to consider when a placebo is being prescribed to treat pain. One such consideration would be the amount of pain the individual is in, because if the patient is in chronic pain then the administration of a placebo may be justifiable, but not without consequences. If the patient is building a tolerance to the drugs used to control pain, placebos can be turned to as a last resort to try and improve the condition of the patient, as a last desperate measure to help.

Also, a person who has sought the aid of healthcare professionals expects/has the right to a treatment that is based on scientific evidence and administered under truthfully and sincerely without abusing the trust that a patient has in the healthcare worker. Concealed use of placebos holds the risk of being accused for malpractice and violation of informed consent legal requirements.[8]

As time has gone on, medical practices have evolved in such a way that patients are much more involved in the decision making of the treatments they are to receive; patients can even go as far as to refuse any and all medical treatment so long as they are in a fit mental state to make decisions on behalf of themselves concerning their health. The full disclosure of what treatment is being given to the patient is a requirement and failure to mention the treatment is pharmacologically inactive can lead to lawsuits being pursued.

Case studies from National Ethics Teleconference[9]

Case Study 1

A patient who learned that his prescribed pain medication – Obecalp – was really placebo spelled backwards. The patient was angry that his physician deceived him, and his relationship with his physician broke down completely.[9]

From the first case study it is clear that the patient felt strongly about the deception involved in his treatment leading to the deterioration of his trust in the healthcare professional responsible and possibly the healthcare system itself, highlighting that placebos that have been prescribed under deception are highly unethical, regardless of whether they have a positive outcome. In the case that the placebo did in fact work, the patient would question whether his pain was in fact real and whether any of the genuine pain medication being prescribed actually works. This sets a negative and disbelieving mind-frame towards healthcare which could lead to a nocebo effect in treatment for later illnesses. Also since placebos only aid symptoms, they may be able to relieve pain, but this can be dangerous as the pain may have been an indicator of an underlying problem. If the pain has been dismissed, this leaves the root of the disease untreated which can be very harmful.

There are many downfalls to the use of placebos, however this does not rule them out as a method of treatment. They can be given to patients in a deception free manner, where the patient is told they are receiving an inactive treatment. This can still work if there is an explanation provided of how the placebo effect works, although this can reduce efficacy of treatment. This allows the patient to choose whether they want this as a method of treatment or would rather have an alternative active treatment. Clinical placebo analgesia should always be given as a last resort, after exhaustive testing has been undertaken to show there is no underlying cause of the pain, and no other effective treatment for it.

Case Study 2

Take Michael, a 45-year-old male experiencing chronic back pain that is limiting his ability to work. A neurological evaluation did not reveal any serious abnormalities. He has had physical therapy, chiropractic manipulations, acupuncture, and a range of narcotic and anti-inflammatory treatments. Michael was referred to the pain clinic. After carefully examining Michael and reviewing his records, Dr. Davis told him about a medicine that he generally reserves for complex pain. Although there may be some side effects he encouraged the patient to try it because he believed it could work. The prescribed substance was a placebo.

Three weeks following his initial visit, Michael noted improvement in his pain, but subsequently learned by searching WebMD that his medication was a sugar pill commonly prescribed as a placebo. Feeling confused and betrayed, Michael never returned to see Dr. Davis.[9]

The central ethical conflict for the use of placebos is whether the truth-telling outweighs the benefits a patient may receive under deception. It is a grey area, with mixed views on whether a doctor should have dispensed inactive medication as this is deceiving the patient even when the treatment has positive outcomes, as demonstrated in the second case study.

The scenario above shows that even when all other therapies had been exhausted in trying to alleviate Michael's pain, his doctor resorted to a placebo. Even though the therapy had worked, he clearly felt he couldn't trust the doctor as he never returned to him. Each person will have a different reaction to finding out they were lied to depending on their situation, including how much pain they were in and how desperate they are to have it relieved.

Case Study 3

During the interview I conducted on a sufferer of chronic pain, I found that Ms Lynam would be grateful to have the pain she is experiencing in everyday life reduced, but it would raise a lot of questions if the treatment worked. For example, she said it could lead to her questioning her mental state and whether the pain was all a product of her imagination or if it was not a bad as she thought it to be for all that time. Besides the stressful nature of questioning herself, she would be concerned with the motives of the doctor. She would wonder whether the doctor took her seriously or thought she was over exaggerating her condition. However if it didn't work, she told me she would feel a variety of emotions branching out from her anger. Mostly the fact that the doctor's treatment suggests he didn't take her reports of pain seriously, thinking she could be tricked into feeling better, which would be very unsympathetic to her condition, adding insult to her injury.[10]

Should placebos be used for analgesic effects in clinical care

The American Society for Pain Management Nursing (ASPMN) took a stance where they believe placebos should not be prescribed during clinical care, but only in clinical trials.[8] The main concern is the deception involved and the negative repercussion that arise as a result. However, after consideration of the efficacy for the placebo on the certain type of pain, and the case of the individual, there is no reason why placebos cannot be used as an aid to recovery, when dispensed in a deception-free manner.

Effectiveness of placebos

The effectiveness of placebos varies greatly between studies and it is said to occur within the range of nobody to nearly everybody. The wide gap can be explained by the fact that the placebo effect is multi-factorial. This means consideration has to be taken when dispensing placebos as you need the most up to date rates of success, to determine whether the placebo treatment would work and whether it should take place.

- ‘During a study for headaches, 120 out of 199 patients receiving the placebo obtained relief.’
- ‘In postoperative patients, 14% had pain reduction using a placebo.’ [11]

Success rates have a wide spread when used in medical research, however if a placebo was to be used in a clinical setting, the efficacy statistics would need to be available for the practitioner, as not all placebos responses are as strong as each other.

In terms of the effectiveness of placebos on conditions rather than symptoms the success rates are very low. 2% of people saw a direct impact on tumour development[12] although this placebo response can be assumed to be a result of other factors, such as natural recovery, rather than the placebo treatment itself, as they only have an impact on symptoms.

As the effectiveness of placebos is not a set figure it is very much up to a practitioner to decide whether a placebo would be a suitable method of treatment. This could also depend on the mentality of the patient and if they have a good expectancy of recovery.

It is not uncommon to see success rates that outperform drugs when tested in clinical trials which can cause great inconvenience to pharmaceutical companies who would have been spending lots of time and money on working towards pharmacological substances.

<u>What this means for pharmaceutical companies</u>

In recent years, many of the large firms investing money into the research and development of new medical breakthroughs are experiencing bitter disappointment in their testing stages when the drugs that have been created are performing on par or even below the effects a placebo would have. This means the new drug would have to be dropped from production. This is because when tested against placebos, the drugs produce the same response so developers cannot be sure the new drug is responsible for curing the condition via a pharmacological response or whether the drug is just producing a placebo response.

Drugs that are in the second and third phases of clinical trialling and undergo development cuts are usually tested against placebos in these stages. The main cause for dropping the production of the drug is due to poor drug responses when compared against placebos. Over the period of 2001 to 2006 the drug company Merck saw a 20 percent increase in new product cuts when drugs were first tested against placebos in the second phase. The more extensive phase three trial showed a rise by 11 percent, mainly because of poor response of the drug compared to placebos over the period.[13] This shows that the drug firms are experiencing increased difficulty as the placebo response seems to be getting stronger. One explanation for this may be the fact that many more people in society are now aware of the placebo effect, making them more susceptible to recovery during clinical trials as they are aware of how the process works. This makes the placebo effect a more useful tool in treatment as a wider range of people are aware of it, believing that it will work.

Conclusion

If the set factors such as expectant of recovery, desire for recovery and conditioning effects are in place, then other variables can be adjusted to maximise the success of placebo treatment. These variables could include any measures that can be taken to increase a patient's expectation of recovery. This is when it is most likely for a successful placebo response occur, highlighting how delicate the conditions required are.

In the case of the treatment of pain, it can be tricky to decide at what point a doctor may consider introducing a placebo. This depends on how all other possible treatments have worked and if there is no success the placebo can be used as a last resort.

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