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THE PSYCHOSOCIAL FACTORS OF COVID-19 VACCINE EFFICACY

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ABSTRACT

Disturbances in which emotional maladjustment leads to dysfunction in some organ system can lead to illness. Positive emotional adjustment towards a therapy can bring about positive outcomes without recourse to the known potency of the administered substance. The contrary is also the case where negative emotional adjustment towards a therapy can bring about negative clinical outcomes. These effects are referred to as the placebo and nocebo effects respectively. Placebos have the appearance of being real but lack the capacity to perform as expected when applied in situations. Nocebos on the other hand are known for having a tendency to cause harm especially based on expectation from societal cues. Some of the successes attributed to Covid-19 vaccines are ascribed to the expectation that the vaccines will work while many adverse events and death have been associated with coerced vaccinations in the face of vaccine hesitancy. This review highlights the evidence showing that some people do feel or get better after taking Covid-19 vaccines, while some other people display unexpected or severe adverse effect after the same therapy mostly due to their mental or emotional disposition.

KEYWORDS: Covid-19 Vaccine, Nocebo, Placebo Response, Placebo Responders, Placebo Effect.

INTRODUCTION

Placebo and nocebo effects are actually the body's responses to a general expectancy through absorbing some cues, including physical and psychological ones.[1-3] A placebo can be defined as an inert treatment which can be used to simulate administration of a real medical treatment. A placebo can be something like a sugar pill or an injection made with saline solution.[4] It doesn't have medicinal effects, but people may perceive that it does because they believe they have received the active treatment. A placebo is usually given as a dummy. It is mostly used in clinical trials to test the effectiveness of treatments in drug studies.[5] For instance, people in one group get the actual drug, while the others receive an inactive substance. The participants in the clinical trial don't know if they receive the real thing or the placebo. This way, the researchers can measure if the drug works by comparing how both groups react. If they both have the same reaction the drug is deemed not to work. In drug testing and medical research, a placebo can be made to resemble an active medication or therapy so that it functions as a control; this is to prevent the recipient or others from knowing whether a treatment is active or inactive, as expectations about efficacy can influence results.[6] In a placebo-controlled clinical trial any change in the control group is known as the placebo response, and the difference between this and the result of no treatment is the placebo effect.[7] Placebos have been shown to improve patient-reported outcomes such as pain and nausea.[8] Highlighting the importance of the nocebo response associated with current vaccination against Covid-19 is appropriate as there are many countries, like Nigeria and Sub Sahara African countries, where the vaccine has been made available; but there is an overwhelming majority who refuse to be vaccinated, mostly because they are not convinced about the vaccine's safety, its ability to protect against severe infection and the advocacy for community immunity in the face of lower mortality than endemic diseases.

Placebo effects

It is important to keep in mind that a placebo and the placebo effect are different things. While the term 'placebo' refers to the chemically inactive substance itself, the term 'placebo effect' refers to perceived medical benefits of the administration of an inert substance.[9] The placebo effect refers to the phenomenon in which patients feel better after receiving a placebo. In other words, the mere thought that a treatment has been received causes a beneficial physical response.[10] The placebo effect is more than positive thinking and creates a stronger connection between the brain and body and how they work together. They have been shown to be most effective for conditions like pain management, stress-related

insomnia, and cancer treatment side effects like fatigue and nausea.[8] In a study conducted by Jon Levine, postoperative patients received either a secret dose of 6-8 mg of morphine, or an overt dose of a substance described as a powerful medicine used to relieve pain (but were actually saline solution). The results were remarkable: patients in both groups reported the same degree of pain relief.[11]

Characteristics of Placebo and Nocebo effects

Placebo effects usually have the following characteristics: (1) they rarely cure the illness but may provide relief of some patients' subjective symptoms, such as pain, (2) placebo and nocebo effects widely vary in patients with different diseases and in patients with the same disease treated with different medicines,[12] (3) the adverse consequences of placebo effects is the nocebo effect. Up to 26% of patients randomly assigned to placebos in randomised clinical trials (RCT) are estimated to discontinue the use of placebos because these patients have perceived adverse effects,[13] Actually, the psychosocial factors that induce nocebo effects can also cause adverse medication effects,[4] Placebo effects are beyond the reach of medical intervention or treatment, the patients' cognitive level on the treatment and/or the physician–patient relationship can enhance the effectiveness of medical treatment. An interesting study demonstrated that the patients who took the real drug rizatriptan but labelled as 'placebo' had no different outcomes from those taking placebos labelled with 'rizatriptan'. But when patients took the real drug rizatriptan correctly labelled as 'rizatriptan', the effect of this drug increased by about 50%,[14] Another study also obtained similar results in which the effects of open versus hidden administration of morphine for postoperative pain, beta-blockers for cardiovascular function, sub thalamic stimulation for Parkinson's disease and diazepam for anxiety were compared. The open treatment was found to induce significantly greater improvement than that of the hidden one,[15] In the view of Miller and Colloca, the placebo effect is a learnt response generated by expectancies via the central nervous system.[16] When a patient has an active or placebo treatment, the different cues may cause the patient to remember the previously experienced sensations and thereby develop expectancy.[17] Different cues can converge into a single conceptual model to generate key expectancies, which is a more general state that relates to consciousness or sub consciousness according to the specific process involved. To understand both placebo and nocebo effects, although they have different psychobiological mechanisms, the universal conceptual model is considered to be the same as the anticipations determined by prior experience.[18] Placebos

are not limited to inert agents but many active treatments may also have the similar effects of placebo. In the same vein, nocebo effects can be generated by any substance.

Mechanism of the placebo effect

How placebos work is thought to involve complex neurobiological reaction that includes everything from increases in neurotransmitters, like endorphins and dopamine, to greater activity in certain brain regions linked to moods, emotional reactions, and self-awareness. There are several theories that attempt to explain the mechanism of the placebo effect: the expectancy theory, classical conditioning accounts, and context effects.[19,20] The proposed framework based on integrative framework theory by Colloca and Miller has been widely accepted.[17] The integrative framework theory emphasises that cues of a different nature (verbal, contextual, social) may be integrated to generate key treatment expectancies, which can influence the effects of active or placebo treatment.[17] The number of different physiological, psychological and biological factors across different diseases seen to mediate placebo effects include:

Hormone response

Researchers have been able to demonstrate the placebo effect in action using brain scans focused on the mid-frontal gyrus, which runs along the frontal lobes just above the eyes, and showing that areas which contain many opiate receptors were activated in both the placebo and treatment groups.[21,22] In this study functional magnetic resonance imaging was used to scan the brains of people with chronic pain from knee osteoarthritis. Then everyone was given a placebo and had another brain scan. The researchers noticed that those who felt pain relief had greater activity in the middle frontal gyrus brain region, which makes up about one-third of the frontal lobe.[22] One possible explanation is that expectation on taking the placebo activated the reward pathways in the brain, in turn stimulating the release of the brain's own natural painkillers; endorphins, which are chemically similar to opiate painkillers like morphine.[21] Like morphine, these endorphins bind to opioid receptors and cause pain relief. This effect can be partially made ineffective by naloxone, a narcotic antagonist that blocks both natural endorphins and opioid drugs, which was developed for patients who overdose on opiates, such as morphine or heroine. By acting on and blocking key opioid receptors in the central nervous system, naloxone also partially prevents placebo responses.[21] This signifies that the placebo effect can be biochemically modulated.

Conditioning

Other possible explanations include classical conditioning, when there is an association between two stimuli resulting in a learned response. In some cases, a placebo can be paired with an actual treatment until it evokes the desired effect.[23] For example, being regularly given the same arthritis pill to relieve stiff, sore joints, one may begin to associate that pill with pain relief. On being given a placebo that looks similar to the arthritis pill, the patients may still believe it provides pain relief because they've been conditioned to do so.

Expectation

Expectations, or what we believe we will experience, have been found to play a significant role in the placebo effect.[24] People who are highly motivated and expect the treatment to work may be more likely to experience a placebo effect. Verbal, behavioural, and social cues can contribute to a person's expectations of whether the medication will have an effect. Some results support the hypothesis that structured manipulation of physician's verbal and non-verbal performance, designed to build rapport and increase faith in treatment, is feasible and may have a significant beneficial effect on the size of the response to placebo analgesia. They also demonstrate that subjects, who are not susceptible to placebo, are also not susceptible to performance style.[25]

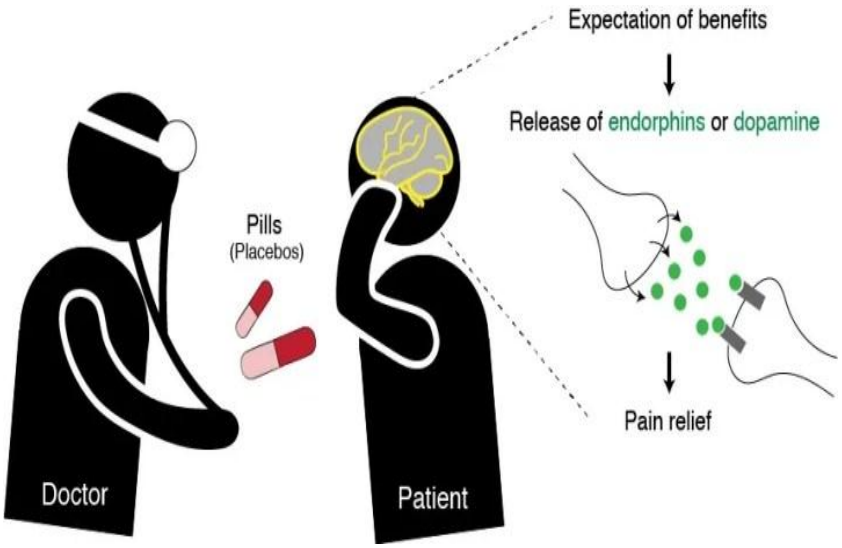

Figure 1: The expectation of benefit associated with a placebo causes measureable changes in neurobiological signalling pathways, resulting in pain relief.[22]

Genetics

Genes may also influence how people respond to placebo treatments. Some people are genetically predisposed to respond more to placebos. One study found that people with a

gene variant that codes for higher levels of the brain chemical dopamine are more prone to the placebo effect than those with the low dopamine version. People with the high-dopamine version of this gene also tend to have higher levels of pain perception and reward-seeking.[26] Genetic signatures that alter the opioid and dopamine signalling pathways are predictive of whether a patient is more or less likely to experience a strong placebo effect. For example, patients with opioid receptors that are less active are less likely to be placebo responders. On the other hand, patients with reduced dopamine metabolism, and therefore higher dopamine levels in the brain, are more likely to experience a strong placebo effect.[26]

Effect

While placebos can affect how a person feels, studies suggest that they do not have a significant impact on underlying illnesses. A major review of more than 150 clinical trials involving placebos found that placebos had no major clinical effects on illnesses. Instead, the placebo effect had a small influence on patient-reported outcomes, particularly of perceptions of nausea and pain.[2] However, another review conducted nearly 10 years later found that in similar populations, both placebos and treatments had similar effects. The authors concluded that placebos, when used appropriately, could potentially benefit patients as part of a therapeutic plan.[27]

Clinical application of placebo effects

Depression: The placebo effect has been found to impact people with major depression disorder. In one study, participants who weren't currently taking any other medication were given placebo pills labelled as either fast-acting antidepressants or placebo for one week. After the week, the researchers used a computerized radiographic technique to examine the metabolic activity in the brain (PET scans) and told the participants they were receiving an injection to improve mood. Participants who took the placebo labelled as an antidepressant as well as the injection reported decreased depression symptoms and increased brain activity in areas of the brain linked to emotion and stress regulation.[28]

Pain management: A small 2014 study tested the placebo effect on 66 people with occasional migraine, who were asked to take an assigned pill—either a placebo or rizatriptan, which is a known migraine medication—and rate their pain intensity level. Some people were told the pill was a placebo, some were told it was rizatriptan, and others were told it could be either. Researchers found that the expectations set by the pill labelling influenced the participants'

responses. Even when rizatriptan was labelled as a placebo, participants gave it the same rating as a placebo that was labelled rizatriptan.[29]

Symptom relief: The placebo effect has also been studied on cancer survivors who experience cancer-related fatigue. Participants received three weeks of treatment, either their regular treatment or a pill labelled as a placebo. The study found that the placebo (despite being labelled as such) was reported to improve symptoms while taking the medication and three weeks after discontinuation.[30]

Biochemical basis for the placebo effect

Through integrating the behavioural, neurobiological and genetic findings on the placebo effect, the dopamine, opioid, endocannabinoid and serotonin signalling pathways are used as the primary means for identifying molecular biological components through analysis of the genetic variants.[20] High-throughput analysis technologies have produced a large number of gene and protein–protein interaction data that have stimulated studies on the biochemical bases for placebo effects.

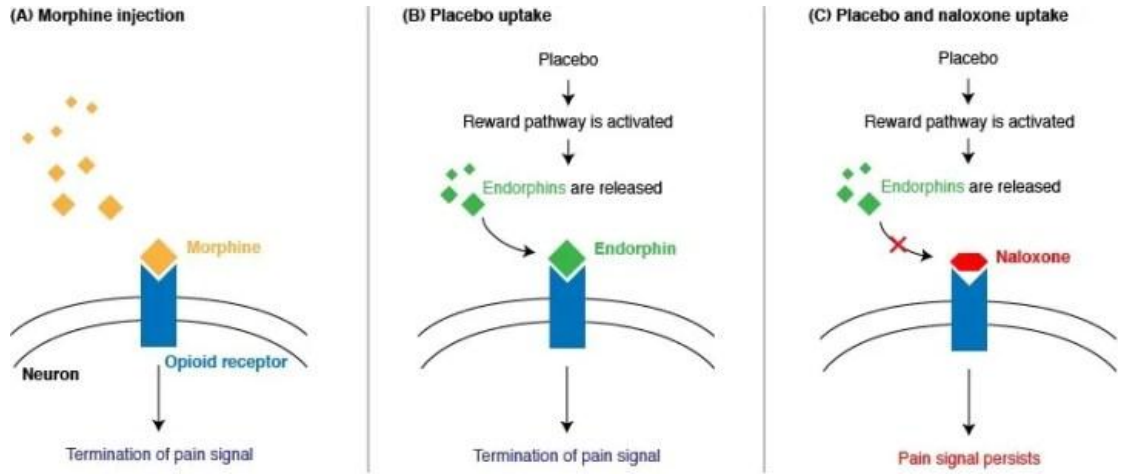

Figure 2: (A) Morphine causes pain relief by binding to opioid receptors in the brain. (B) The reward pathways activated by placebos cause the release of endorphins, which bind to opioid receptors. (C) Naloxone blocks opioid receptors, preventing the binding of endorphins, thereby partially blocking the placebo effect.[21 and 22]

An increasing number of studies have demonstrated that the neurotransmitter and neurological pathways can mediate placebo effects, and have provided candidate genes for further studies. The fact that a placebo was found to induce the pain suppression system of the body, which can be blocked by an opioid receptor antagonist[31,32] demonstrated that the

opioid signalling pathways may be involved in a placebo analgesic effect. Further physiological experiments have demonstrated that the endocannabinoid signalling pathway is also implicated in the placebo analgesia.[33] Based on the finding of analgesic effects of opioid receptor signalling, expectancy of reward is postulated as a key general contributor to the placebo effect. In a pain model, anticipation of the placebo effect stimulated the activation of opioid and dopamine receptor in brain, and higher placebo effects have been found to correspond to higher levels of dopamine receptor activation. Additionally, both dopaminergic and opioid signalling were found to be reduced in individuals with nocebo effects.[32] Furthermore, the serotonin signalling pathway has major roles in depression which causes a much higher rate of placebo effects in randomised clinical trials.[34] Placebo treatment in depression has been shown to cause changes in brain function.

Activation of some brain regions induced by expectation of analgesia is related to endogenous opioid transmission and analgesia. Positron emission tomography studies have recently shown that the placebo effect in Parkinson's disease, pain, and depression is related to the activation of the limbic circuitry.[35] The observation that placebo administration induces the release of dopamine in the ventral striatum of patients with Parkinson's disease suggests a link between the placebo effect and reward mechanisms. In addition to Parkinson's disease, the placebo-reward model may also apply to other disorders. However, the relative contribution of the different neurotransmitters and neuropeptides that are known to be involved in modulating the activity of the limbic system may be disease-specific. Thus, while the placebo-induced clinical benefit observed in Parkinson's disease would mostly reflect the release of dopamine in the dorsal striatum, the activation of opioid and serotonin pathways could be particularly implicated in mediating placebo responses encountered in pain and depression, respectively.[35]

The placebo effect on COVID-19 Vaccine

The fact that the human mind is so powerful that it somehow convinces the human body that an inert medication given in a procedure is equivalent to the proper medication affects the response to Covid-19 vaccination.[36] The placebo effect seen to have a role curing pain and depression is also thought to have a role in curing the symptoms of the coronavirus (COVID-19) disease. It is thus possible that placebo effect may have healing effect on the body of COVID-19 patients. This conclusion has been made by considering the related experiments and researches of placebo effect. The influences of the placebo effect on Covid treatment

have been highlighted in an online survey to find an approximation of the placebo effect on Covid-19 patient.[36]

The nocebo effect on Covid-19 vaccination

Individuals can experience more symptoms or side effects as a response unrelated to the potency of the substance, the response mentioned as the nocebo effect.[37] The nocebo effect is like the evil twin of the placebo effect — for example, it heightens pain if a person anticipates that something will hurt. Most of the side effects that people experience after a Covid-19 vaccination can be blamed on the nocebo effect. Widespread dissemination of concerns about an adverse reaction to a medicine leads to an increase in the number of reports of the adverse reaction. For example, in 2013, British media highlighted the adverse effects, including muscle pains, of statins following an article in the British Medical Journal. An estimated 200,000 patients stopped taking statins within six months of the story being published, many due to adverse reactions.[38] There was also an increase in the number of adverse reaction reports of rhabdomyolysis with statins during this time. This incident has since been attributed to the nocebo effect.[39] Certainly expectation contributes significantly to both placebo and nocebo responses in clinical trials. This expectation is itself multidimensional, as there are different types of expectation, including hope and need, which must be considered.[40]

It is not surprising if expectations of adverse reaction are seen to trigger response to covid-19 vaccines.[41] Among participants who received an actual Covid-19 vaccine, 76% of systemic adverse effects after the first vaccination were attributable to the nocebo response rather than the vaccine itself.[42] In this study investigators assumed that all the effects that lead to unpleasant symptoms after placebo treatment are also evident when recipients get the real vaccine. They found that 35% of placebo recipients reported systemic adverse effects like headache or fatigue. This number is three-quarters as high as the number of vaccine recipients with such symptoms (46% reported systemic adverse events and 35 is 76% of 46). This means three-quarters of the systemic symptoms vaccine recipients experience are not due to the vaccine itself but would have also occurred if they had received a placebo. This is the nocebo response. For second doses of vaccines, reported adverse effects went up from 46% to 61%, while AEs for placebo recipients decreased from 35% to 32%.

There are a number of factors that can contribute to a person experiencing a nocebo effect. This includes a person's expectation that they will have an adverse reaction because they'd heard about another case in which one occurred to the first vaccination and anticipate the second dose or booster will cause the same.[17] It can also include people who may have had an adverse reaction with similar treatments; no trust in the healthcare provider, worrisome information highlighting possible side effects, mistaken beliefs, pessimistic expectations, misattribution of symptoms and social messaging.[41,42] All these factors can contribute to the high incidence of nocebo responses to various treatments but fear and misinformation have been seen as major reasons for vaccine hesitancy.

A January 2022 systematic review and meta-analysis concluded that nocebo responses accounted for 72% of adverse effects after the first Covid-19 Vaccine dose and 52% after the second dose.[43] More than a third of participants in Covid-19 vaccine clinical trials who received a placebo reported adverse events such as headache and fatigue and contributed to the nocebo effect, potentially rendering 76% of all adverse events reports after the first dose not true adverse events.[43] The authors identified 3 studies of Covid-19 vaccines-two mRNA based and one adenovirus type- involving approximately 45,000 subjects. They compared the rates of solicited adverse events in patients' assigned placebo and active vaccination.[43] The key findings were high rates of commonly encountered adverse events in both placebo and active arms of the trials. Fatigue was reported by 21–29% of patients in the placebo arms and 38–42% in the active treatment arms. For headache the proportions were 24–27% and 33–39% for placebo and active arms respectively, and for muscle aches and pains 10–14% and 18–33% respectively. Injection site reactions were also common (12–17%) in placebo and 48–84% following active vaccination. Other adverse events were reported less frequently but also in both placebo and active treatment arms. Whilst a significant number of people included in this study reported experiencing unpleasant side effects after receiving the COVID-19 vaccine despite only receiving a placebo, the authors attributed the nocebo reaction as the cause of most of these symptoms.[43]

COVID-19 vaccine side effects

Getting vaccinated against COVID-19 infection reduces the risk of severe disease, hospitalization, and death for which vaccines are designed to give immunity without the danger of getting the disease. This notwithstanding, it is common to experience some mild-to-moderate side effects when receiving vaccinations in general.[44] The vaccines are detected

as antigens and the immune system instructs the body to react in certain ways: it increases blood flow so more immune cells can circulate, and raises body temperature in order to kill the virus. Mild-to-moderate side effects, like a low-grade fever or muscle aches, are normal and not a cause for alarm as they are signs that the body's immune system is responding to the vaccine and is gearing up to fight the virus. Such side effects usually go away without intervention after a few days.[44]

Most COVID-19 vaccine side effects are usually nonexistent to mild and severe side effects are quite rare.[45-47] While reports of severe vaccine side effects have drawn a lot of attention, the majority of people are said to have either no or minimal side effects from COVID-19 vaccines. Interferences in physiological aspects of blood clotting have been reported in a handful of people with blockages of blood vessels or internal bleeding in the brain, while allergic reaction or anaphylaxis was reported in only 0.3 percent of participants after partial vaccination and 0.2 percent of participants after full vaccination.[48] Myocarditis and pericarditis have been reported, especially in adolescents and young adult males, within several days after COVID-19 vaccination.[48] Evidence suggests that prior information about the side effects of Covid-19 vaccines may cause people to misattribute common daily background sensations as arising from the vaccine or cause anxiety and worry that make people hyper alert to bodily feelings about adverse events.[49-51] Both placebo and nocebo effects are believed to be mental or emotional rather than physiological in origin, but they can induce measurable changes in the body.[52]

CONCLUSION

Both Nocebo and placebo effects highlight the importance of the environment in which treatment is received, and indicate that patients can benefit from trust and language used; to boost expectations. While evidence suggests that disclosing information about potential adverse effects of an intervention can cause people to misattribute common ailments to the vaccine, or make people hyper-alert to how they are feeling, it is ethical to do so. Thus, it is suggested that better public information about placebo and nocebo responses may improve Covid-19 vaccine uptake by reducing the concerns that make some people hesitant.

Conflict of interest

There is absolutely no conflict of interest between the authors and we do not intend to use this review as an avenue for any litigation but for the advancement of knowledge. Also, the research was fully funded by personal efforts of the authors.

Author's contribution

This work was carried out in collaboration among all authors. M.O. Nwokike designed the study and wrote the first draft of the manuscript. M.O. Nwokike and S.I. Ghasi managed the literature searches. S. I. Ghasi proofread the manuscript. All authors read and approved the final manuscript.

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To God be the Glory.

REFERENCES

1. Rutherford BR, Mori S, Sneed JR, et al. Contribution of spontaneous improvement to placebo response in depression: a meta-analytic review. J Psychiatr Res, 2012; 46: 697–702. 10.1016/j.jpsychires.2012.02.008.
2. Colloca L. The placebo effect in pain therapies. Annu Rev Pharmacol Toxicol, 2019; 59: 191-211.
3. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA, 2002; 287: 622-627.
4. Jütte R. The early history of the placebo. Complement Ther Med, 2013; 21: 94–7. 10.1016/j.ctim.2012.06.002
5. De Craen AJM, Kaptchuk TJ, Tijssen JGP, et al. Placebos and placebo effects in medicine: historical overview. J R Soc Med, 1999; 92: 511–5. 10.1177/014107689909201005
6. Dictionary.com. Retrieved, 2022; 23.
7. Chaplin S. "The placebo response: an important part of treatment". Prescriber, 2006; 17(5): 16–22. Doi: 10.1002/psb.344. S2CID 72626022.
8. Hróbjartsson A, Gøtzsche PC. Hróbjartsson A (ed.). "Placebo interventions for all clinical conditions" (PDF). The Cochrane Database of Systematic Reviews, 2010; 106(1): CD003974. doi:10.1002/14651858.CD003974.pub3.
9. Enck P, Bingel U, Schedlowski M, Rief W: The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov, 2013; 12: 191–204.
10. Benedetti F: Placebo Effects. Understanding the Mechanisms in Health and Disease, New York, Oxford University Press, 2015; 2.

11. Levine JD, Gordon NC, Fields HL. "The mechanism of placebo analgesia". Lancet, 1978; 2(8091): 54–7. doi:10.1016/s0140-6736(78)92762 9. PMID 8059. S2CID 454 03755.
12. Wang R-S, Hall KT, Giulianini F, et al. Network analysis of the genomic basis of the placebo effect. JCI Insight, 2017; 2 10.1172/jci.insight.93911.
13. Kaptchuk TJ, Miller FG. Placebo effects in medicine. New England Journal of Medicine, 2015; 373: 8–9. 10.1056/NEJMp1504023.
14. Láinez MJA. Rizatriptan in the treatment of migraine. Neuropsychiatr Dis Treat, 2006; 2: 247–59. 10.2147/nedt.2006.2.3.247
15. Benedetti F, Carlino E, Pollo A. How placebos change the patient's brain. Neuropsychopharmacology, 2011; 36: 339–54. 10.1038/npp.2010.81.
16. Miller FG, Colloca L. Semiotics and the placebo effect. Perspect Biol Med, 2010; 53: 509–16. 10.1353/pbm.2010.0004
17. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. Philosophical Transactions of the Royal Society B: Biological Sciences, 2011; 366: 1859–69. 10.1098/rstb.2010.0398.
18. Turi Z, Bjørkedal E, Gunkel L, et al. Evidence for cognitive placebo and nocebo effects in healthy individuals. Sci Rep, 2018; 8: 17443 10.1038/s41598-018-35124-w.
19. Blasi ZD, Harkness E, Ernst E, et al. Influence of context effects on health outcomes: a systematic review. Lancet, 2001; 357: 757–62. 10.1016/S0140-6736(00)04169-6] and the meaning response.
20. Colagiuri B, Schenk LA, Kessler MD, et al. The placebo effect: from concepts to genes. Neuroscience, 2015; 307: 171–90. 10.1016/j.neuroscience.2015.08.017.
21. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron, 2009; 63(4): 533-543. doi:10.1016/j.neuron.2009.07.014.
22. Harvard Health Publishing December, 2021; 13. https://www.health.harvard.edu/ Accessed Feb.22 2022.
23. Bąbel P. Classical conditioning as a distinct mechanism of placebo effects. Front Psychiatry, 2019; 10: 449. doi:10.3389/fpsyt.2019.00449.
24. Brown WA. Expectation, the placebo effect and the response to treatment. R I Med J, 2013; 98(5): 19-21.
25. Efrat Czerniak, Anat Biegon, Amitai Ziv, Orit Karnieli-Miller, Mark Weiser, Uri Alon and Atay Citron. Manipulating the Placebo Response in Experimental Pain by Altering

Doctor's Performance Style. http://journal.frontiersin.org/article/10.3389/fpsyg.2016.00874/full

26. Hall KT, Lembo AJ, Kirsch I, et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One, 2012; 7(10): e48135. doi:10.1371/journal.pone.0048135
27. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev, 2004; (3): CD003974. doi:10.1002/14651858.CD003974.pub2.
28. Peciña M, Bohnert ASB, Sikora M, et al. Association between placebo-activated neural systems and antidepressant responses: Neurochemistry of placebo effects in major depression. JAMA Psychiatry, 2015; 72(11): 1087. doi:10.1001/jamapsychiatry.2015.1335
29. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Science Translational Medicine, 2014; 6(218): 218ra5-218ra5. doi:10.1126/scitranslmed.3006175
30. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: A randomized-controlled clinical trial. Sci Rep, 2018; 8(1): 2784. doi:10.1038/s41598-018-20993-y
31. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron, 2009; 63: 533–43. 10.1016/j.neuron.2009.07.014.
32. Sobczak M, Sałaga M, Storr MA, et al., Physiology, signaling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future perspectives. J Gastroenterol, 2014; 49: 24–45. 10.1007/s00535-013-0753-x
33. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci, 2018; 19.
34. Kraus C, Castrén E, Kasper S, et al. Serotonin and neuroplasticity – links between molecular, functional and structural pathophysiology in depression. Neuroscience & Biobehavioral Reviews, 2017; 77: 317–26. 10.1016/j.neubiorev.2017.03.007.
35. Raúl de la Fuente-Fernández , A Jon Stoessl. The biochemical bases of the placebo effect. Sci Eng Ethics, 2004; 10(1): 143-50. doi: 10.1007/s11948-004-0071-z.
36. Mishra, K.. The Placebo Effect on COVID Patients: When the Mind Cures the Body. Journal of Pharmaceutical Research International, 2021; 33(20A): 85-93. Article in English | Web of Science | ID: covidwho-1314955.
37. https://abcnews.go.com/author/Dr._Aubrie_Ford

38. Abrahamson JD, Rosenberg HG, Jewel N, et al. should people at low risk of cardiovascular disease take a statin? *British Medical Journal*, 2013; 347: f6123. DOI: https://doi.org/10.1136/bmj.f6123
39. Brasil R. Nocebo: the placebo effect's evil twin. The Pharmaceutical Journal, 2018; 300(7911): 05. DOI: 10.1211/PJ.2018.20204524.
40. Lorber W, Mazzoni G, Kirsch I. Illness by suggestion: expectancy, modeling, and gender in the production of psychosomatic symptoms. Ann Behav Med, 2007; 33: 112-116.
41. Lees-Haley PR, Brown RS. Biases in perception and reporting following a perceived toxic exposure. Percept Mot Skills, 1992; 75: 531-544.
42. Haas, Julia W.; Bender, Friederike L.; Ballou, Sarah; Kelley, John M.; Wilhelm, Marcel; Miller, Franklin G.; Rief, Winfried; Kaptchuk, Ted J. "Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials: A Systematic Review and Meta-analysis". JAMA Network Open, 5 (1): e2143955. doi:10.1001/jamanetworkopen.2021.43955. ISSN 2574-3805. PMC 8767431. PMID 35040967.
43. Amanzio M., Mitsikostas M., Mitsikostas D.D. et al. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: a systematic review. Lancet Reg Health Eur, 2022; 12: 100253
44. https://www.facebook.com/WHO/videos/525963241713633
45. Jackson LA, Anderson EJ, Rouphael NG et al. An mRNA Vaccine against SARS-CoV-2. NEJM, 2020. DOI: 10.1056/NEJMoa2022483.
46. Food and Drug Administration (FDA). FDA Review of Efficacy and Safety of Moderna COVID-19 Vaccine EUA. https://www.fda.gov/media/144585/download.external icon,
47. Walsh EE, Frenck RW, Falsey AR et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. NEJM, 2020. DOI: 1056/NEJMoa2027906external icon.
48. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/explainers
49. Colloca L, Finniss D: Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA, 2012; 307: 567–568.
50. Greville-Harris M, Dieppe P: Bad is more powerful than good: the nocebo response in medical consultations. Am J Med, 2015; 128: 126–129.
51. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, Vase L: The magnitude of nocebo effects in pain: a meta-analysis. Pain, 2014; 155: 1426–1434.

52. Barber, Theodore Xenophon. "Death by suggestion. A critical note". Psychosomatic Medicine, 1961; 23: 153–5.