A Review of the Placebo Effect: Psychological and Biological Factors

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Abstract

The placebo effect, wherein an inert treatment yields real therapeutic outcomes, underscores the powerful role of psychological and biological factors in health outcomes. This literature review explores the mechanisms underlying the placebo effect, focusing on its psychological drivers such as expectation, suggestion, conditioning, and doctor-patient interactions, as well as its biological basis involving neurotransmitters like dopamine and endorphins. The placebo effect is particularly prominent in neurodegenerative diseases like Parkinson's, where patient expectations can trigger neurochemical responses, such as dopamine release, that improve symptoms. Additionally, endorphins play a crucial role in placebo-induced pain relief. The interaction of psychological and biological factors further shapes the therapeutic outcomes of placebo treatments. Ethical considerations, especially regarding informed consent and deception, are discussed in the context of clinical practice. Future research should expand on the role of genetics, personality traits, and other factors influencing placebo responses, as well as the potential for personalized medicine. This paper highlights the importance of a holistic approach to understanding the placebo effect to maximize patient benefit and enhance clinical outcomes.

Introduction

The placebo effect, where an inactive treatment leads to real improvements in a patient's condition, has long been recognized in clinical medicine and psychology (Wager, 2005). Understanding the mechanisms behind this effect is crucial, as it highlights the powerful role of expectation, conditioning, and patient-doctor interactions in treatment outcomes. This paper aims to review the placebo effect by examining both psychological and biological factors that contribute to its effects. Additionally, this paper will explore its clinical implications, with examples from published studies on how it can be used to enhance treatment outcomes in neurodegenerative diseases like Parkinson's.

Parkinson's disease is a progressive brain disorder that affects movement and is caused by the loss of dopamine-producing cells in the brain (Bloem et al., 2021). While treatments like medication and deep brain stimulation (DBS) can help manage symptoms, there is no cure for Parkinson’s. Interestingly, research shows that the placebo effect can improve symptoms in patients with Parkinson’s (Bloem et al., 2021; de la Fuente-Fernández, 2004; Fuente-Fernández et al., 2001; Lidstone et al., 2010). Simply believing they are receiving treatment can trigger the release of dopamine, which helps with movement and mood. This suggests that the placebo effect could be used to boost the effectiveness of existing treatments.

Origin and History of the Placebo Effect

The word "placebo" first entered medical language in the late 18th century. It was believed that Scottish physician William Cullen coined the term in 1772, but it was actually English doctor Alexander Sutherland who first used it in a medical context (Benedetti et al., 2022). During this period, doctors often prescribed placebos—whether pure (like sugar pills) or impure (using treatments meant for other conditions)—to alleviate patients. Early observations noted that patient expectations significantly influenced the effectiveness of these treatments (Jütte, 2013).

While the concept of placebos has evolved, these early experiences laid the foundation for understanding that the mind plays a vital role in physical health. Placebos are now understood to trigger real physiological changes, driven by both conscious and unconscious psychological processes. This paper will explore how these effects are influenced by various factors, including doctor-patient interactions, personality traits, and neurobiological mechanisms.

Psychological Factors Influencing the Placebo Response

Expectation and Suggestion

Expectation is a powerful psychological driver of the placebo effect. When patients believe a treatment will work, they are more likely to experience relief (Wager & Atlas, 2015). Verbal suggestions from healthcare providers often shape these expectations, as seen in studies where patients report reduced pain after being told to expect relief (Fuente-Fernández et al., 2001; Jütte, 2013; Schneider, 2007; Wager & Atlas, 2015). For example, one study demonstrated that verbal suggestions could induce placebo and nocebo effects. Specifically, an increase in negative verbal suggestions regarding the stimuli led to higher pain and itch levels, while a decrease in suggestions resulted in diminished discomfort (Van Laarhoven et al., 2011). Another study showed that both placebo and nocebo responses could be effectively triggered by verbal cues, highlighting the role of expectations in shaping pain perception (Benedetti et al., 2003). Individuals do not always form expectations consciously, but implicit factors such as the context of the treatment environment or prior experiences, can also shape them. Both conscious and unconscious expectations influence the effectiveness of placebo treatments (Schneider, 2007). One study found that verbally induced expectations can alter pain and motor performance (Benedetti et al., 2003). For instance, in patients with Parkinson's, verbal suggestions of motor improvement or worsening completely counteracted the effects of a conditioning procedure, indicating that placebo responses are driven by expectations for conscious processes like motor performance and by conditioning for unconscious functions such as hormonal secretion (Benedetti et al., 2003).

Conditioning

Classical conditioning is another key mechanism underlying the placebo effect. By repeatedly pairing a neutral stimulus (e.g., a pill) with an active treatment (e.g., a painkiller), patients can learn to associate the neutral stimulus with therapeutic effects. This has been demonstrated in pain management studies, where patients continue to experience pain relief even when the active treatment is no longer administered (Geuter et al., 2017). For example, in a sample of 90 healthy female volunteers, each was randomly assigned to one of three groups (hidden

conditioning, open conditioning, and control) and received electrical stimuli paired with either a painful or nonpainful association (Bąbel et al., 2018). Interestingly, significant analgesia was observed only in the hidden conditioning group, where no explicit suggestions were provided, highlighting the role of unconscious learning processes in placebo effects (Bąbel et al., 2018). While conditioning often reinforces expectations, placebo effects can occur even without conditioning, suggesting that the mechanisms at play are complex (Schneider, 2007).

Doctor-Patient Interaction

The relationship between the patient and the doctor is crucial in shaping the placebo response. Trust, empathy, and effective communication can positively influence a patient's expectations and overall experience. Empathy, in particular, has been shown to affect patients' psychobiology, leading to improved outcomes by amplifying the placebo effect. Trust and effective communication help reduce anxiety and foster a sense of safety, which can enhance treatment outcomes by shaping a patient's belief in the effectiveness of the therapy. The interaction between the patient and doctors is part of a biopsychosocial process, where each influences the other's behavior and biology (Adler, 2007). This makes the patient-doctor relationship a form of treatment in itself.

Personality Traits

Individual personality traits, such as optimism, suggestibility, and anxiety, can also affect the placebo response. Patients who are more suggestible or optimistic are more likely to experience positive effects from placebos (Wager & Atlas, 2015). In contrast, an individual's anxiety level can negatively influence the placebo effect by heightening pain perception and reducing the effectiveness of the treatment. Research has shown that anxiety and expectations both play critical roles in modulating placebo-induced pain relief, with reduced anxiety levels often correlating with increased analgesic effects (Wager, 2005). Personality Systems Interaction (PSI) theory, developed by Kuhl (2000), offers a framework for understanding how different personality systems interact to influence the placebo effect, ranging from basic emotional processes to higher-level self-regulation (Schneider, 2007). Assessing an individual's PSI profile is a multifaceted process that involves both self-report measures and objective behavioral assessments. By examining how a person manages goals, emotions, and responses to their environment, clinicians and researchers can gain insights into their unique PSI profile. This understanding can help predict how they might respond to interventions, including the placebo effect (Kuhl, 2000).

Biological Factors Affecting the Placebo Response

Neurotransmitters and Brain Structure

Dopamine and endorphins are important neurotransmitters that help regulate mood, reward, and pain in the brain. Dopamine is often referred to as the "feel-good" chemical because it plays a key role in the brain's reward system, influencing motivation, pleasure, and motor control (Wise, 2004). It is particularly important in conditions like Parkinson's disease, where the loss of dopamine-producing cells leads to movement problems (Lidstone et al., 2010). Endorphins, on

the other hand, are the body's natural painkillers (Ali et al., 2021). They are released in response to stress or discomfort, helping reduce pain and enhance well-being.

The release of these neurotransmitters plays a crucial role in mediating the placebo response. For instance, dopamine is often released in response to placebo treatments in patients with Parkinson's disease, while endorphins are involved in placebo-related pain relief. Neuroimaging studies have shown increased dopamine activity in the nucleus accumbens during placebo-induced pain relief (Wager & Atlas, 2015). For example, in 35 patients with mild to moderate Parkinson's Disease undergoing treatment, PET imaging showed significant dopamine release in the nucleus accumbens when patients reported high probabilities of receiving the active medication (Lidstone et al., 2010). Similarly, the endogenous opioid system, involving the release of endorphins, has been implicated in placebo analgesia, particularly in pain management (Benedetti et al., 2022).

Placebo Effects in Parkinson's Disease

The placebo effect is well-documented in Parkinson's disease, where it is observed across various treatments, including drug therapy, deep brain stimulation (DBS), and dopamine tissue transplantation (Fuente-Fernández et al., 2001). One notable study found that patients who believed they received a dopamine neuron transplant reported improvements in quality of life, regardless of whether they had the actual transplant or a sham surgery (McRae et al., 2004). Similarly, in a study of DBS, 39% of the treatment's effect was attributed to the placebo response, demonstrating the significant role of patient expectations in therapeutic outcomes (de la Fuente-Fernández, 2004).

Endorphins and Pain Relief

Endorphins can bind to μ-opioid receptors and mimic the effects of painkillers. A study used molecular imaging to investigate how the placebo effect reduced pain by examining μ-opioid receptor activity in the brain (Zubieta et al., 2005). The study found that placebo treatment activated the brain's opioid system, leading to reduced pain intensity and emotional distress, highlighting the neurobiological basis of placebo-induced analgesia. The release of these natural pain-relieving chemicals can mimic the effects of painkillers, providing relief even when no active medication was given (Zubieta et al., 2005). While the hypothesis that endorphins mediate placebo-induced pain relief has gained traction in recent years, more research is needed to fully understand the mechanisms involved. Although endorphins have not been directly proven to cause the placebo effect, their involvement raises curiosity about the neurobiological complexities underlying this phenomenon.

Genetic Influences

Genetics also play a role in determining susceptibility to placebo effects. For example, the Catechol-O-methyltransferase (COMT) gene, which is involved in dopamine metabolism, has been linked to placebo responses in patients with irritable bowel syndrome (IBS), which is a common gastrointestinal disorder characterized by chronic abdominal pain, bloating, and changes in bowel habits, such as diarrhea or constipation. Studies suggest that individuals with certain COMT gene variants, particularly those with higher dopamine levels, are more likely to

experience strong placebo responses (Hall et al., 2012). While several studies have reported a COMT association with Parkinson's and Alzheimer's diseases, additional research is needed to understand whether these associations play a role in the effectiveness of the placebo effect in these patients (Hall et al., 2019).

The Interaction of Psychological and Biological Factors

Psychological factors like expectation can influence biological processes during placebo responses. For example, cognitive appraisals (belief in treatment effectiveness) can directly affect dopamine release within the brain's reward system (Geuter et al., 2017). The amygdala, a key structure in processing emotions such as fear and reward, plays a crucial role in this process. It interacts with the prefrontal cortex (PFC), which is responsible for regulating thought and behavior, allowing the brain to weigh emotional responses against expectations. This interaction shapes the placebo effect by helping the brain evaluate and anticipate the outcome of a treatment.

The amygdala and PFC work together to influence psychophysiological processes, such as pain reduction and stress management, by integrating emotional and cognitive inputs (Banks et al., 2007). As a result, placebo effects emerge from this dynamic interaction, where beliefs and emotions influence health outcomes through both psychological and biological mechanisms (Benedetti et al., 2022).

Ethical Implications for Clinical Practice

The ethical considerations of using placebos in clinical practice, particularly in pain management, are complex. While placebo treatments can offer significant benefits in terms of symptom relief, they raise ethical concerns regarding informed consent and the potential for deception. Strategies for ethically leveraging placebo effects focus on maximizing patient benefit while maintaining trust and transparency in the therapeutic process (Wager & Atlas, 2015).

Placebo responses in neurodegenerative diseases like Alzheimer's are significant, with clinical trials showing placebo effects in cognitive function and disease progression. This highlights the potential for leveraging placebo effects in the management of symptoms in such conditions (Benedetti et al., 2022).

Limitations and Future Directions

New placebo-controlled trials are needed to more accurately understand and measure the placebo effect. Advanced brain imaging techniques, like fMRI and PET scans, are providing deeper insights into how placebos affect brain activity (Benedetti et al., 2022). Identifying markers that predict how well someone will respond to a placebo could lead to more personalized and effective treatments, while also avoiding unnecessary ones (Wager & Atlas, 2015).

While this paper provides a comprehensive review of the psychological and biological mechanisms behind the placebo effect, it has limitations in its scope. For one, the focus on specific neurotransmitters like dopamine and endorphins and brain structures like the amygdala

and prefrontal cortex, does not fully address the complex interplay of other systems involved in the placebo response, such as the immune and autonomic nervous systems. Additionally, the role of individual differences, such as those in genetics and personality traits, though touched upon, warrants further exploration. Factors like cultural influences, environmental context, and the placebo effect's variability across different medical conditions were also not deeply explored here.

Future research should aim to broaden the understanding of these diverse elements, examining how lifestyle factors, mental health, and social dynamics impact placebo responses. Furthermore, while neuroimaging studies offer valuable insights, they remain expensive and limited to controlled environments, which may not fully capture real-world therapeutic settings. Expanding research into these areas could lead to a more holistic understanding of the placebo effect and its potential applications in personalized medicine.

Conclusion

The placebo effect is a complex phenomenon influenced by both psychological and biological factors. The close connection between the mind and body in creating placebo responses highlights the need for a comprehensive approach to understanding and utilizing placebo effects in medical practice. As our understanding deepens, there is potential for harnessing the placebo effect to improve patient outcomes ethically and effectively, especially for patients with Parkinson's disease and other neurodegenerative conditions.

References

Adler, H. M. (2007). Toward a Biopsychosocial Understanding of the Patient–Physician Relationship: An Emerging Dialogue. *Journal of General Internal Medicine*, *22*(2), 280–285. https://doi.org/10.1007/s11606-006-0037-8

Ali, A. H., Ahmed, H. S., Jawad, A. S., & Mustafa, M. A. (2021). Endorphin: Function and mechanism of action. *Science Archives*, *02*(01), 09–13. https://doi.org/10.47587/SA.2021.2102

Bąbel, P., Adamczyk, W., Świder, K., Bajcar, E. A., Kicman, P., & Lisińska, N. (2018). How Classical Conditioning Shapes Placebo Analgesia: Hidden versus Open Conditioning. *Pain Medicine*, *19*(6), 1156–1169. https://doi.org/10.1093/pm/pnx177

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala–frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–312. https://doi.org/10.1093/scan/nsm029

Benedetti, F., Frisaldi, E., & Shaibani, A. (2022). Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annual Review of Pharmacology and Toxicology*, *62*(1), 323–340. https://doi.org/10.1146/annurev-pharmtox-052120-104536

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious Expectation and Unconscious Conditioning in Analgesic, Motor, and Hormonal Placebo/Nocebo Responses. *Journal of Neuroscience*, *23*(10), 4315–4323. https://doi.org/10.1523/JNEUROSCI.23-10-04315.2003

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet*, *397*(10291), 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X

de la Fuente-Fernández, R. (2004). Uncovering the hidden placebo effect in deep-brain stimulation for Parkinson's disease. *Parkinsonism & Related Disorders*, *10*(3), 125–127. https://doi.org/10.1016/j.parkreldis.2003.10.003

Fuente-Fernández, R., Ruth, T., Sossi, V., Schulzer, M., Calne, D., & Stoessl, A. J. (2001). Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease. *Science*, *293*, 1164–1166. https://doi.org/10.1126/science.1060937

Geuter, S., Koban, L., & Wager, T. D. (2017). The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology. *Annual Review of Neuroscience*, *40*(1), 167–188. https://doi.org/10.1146/annurev-neuro-072116-031132

Hall, K. T., Lembo, A. J., Kirsch, I., Ziogas, D. C., Douaiher, J., Jensen, K. B., Conboy, L. A., Kelley, J. M., Kokkotou, E., & Kaptchuk, T. J. (2012). Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome. *PLoS ONE*, *7*(10), e48135. https://doi.org/10.1371/journal.pone.0048135

Hall, K. T., Loscalzo, J., & Kaptchuk, T. J. (2019). Systems Pharmacogenomics – Gene, Disease, Drug and Placebo Interactions: A Case Study in COMT. *Pharmacogenomics*, *20*(7), 529–551. https://doi.org/10.2217/pgs-2019-0001

Jütte, R. (2013). The early history of the placebo. *Complementary Therapies in Medicine*, *21*(2), 94–97. https://doi.org/10.1016/j.ctim.2012.06.002

Kuhl, J. (2000). Chapter 5 - A Functional-Design Approach to Motivation and Self-Regulation: The Dynamics of Personality Systems Interactions. In M. Boekaerts, P. R. Pintrich, & M. Zeidner (Eds.), *Handbook of Self-Regulation* (pp. 111–169). Academic Press. https://doi.org/10.1016/B978-012109890-2/50034-2

Lidstone, S. C., Schulzer, M., Dinelle, K., Mak, E., Sossi, V., Ruth, T. J., de la Fuente-Fernández, R., Phillips, A. G., & Stoessl, A. J. (2010). Effects of Expectation on Placebo-Induced Dopamine Release in Parkinson Disease. *Archives of General Psychiatry*, *67*(8), 857–865. https://doi.org/10.1001/archgenpsychiatry.2010.88

McRae, C., Cherin, E., Yamazaki, T. G., Diem, G., Vo, A. H., Russell, D., Ellgring, J. H., Fahn, S., Greene, P., Dillon, S., Winfield, H., Bjugstad, K. B., & Freed, C. R. (2004). Effects of Perceived Treatment on Quality of Life and Medical Outcomesin a Double-blind Placebo Surgery Trial. *Archives of General Psychiatry*, *61*(4), 412–420. https://doi.org/10.1001/archpsyc.61.4.412

Schneider, R. (2007). The Psychology of the Placebo Effect: Exploring Meaning from a Functional Account. *The Journal of Mind and Behavior*, *28*(1), 1–17.

Van Laarhoven, A. I. M., Vogelaar, M. L., Wilder-Smith, O. H., Van Riel, P. L. C. M., Van De Kerkhof, P. C. M., Kraaimaat, F. W., & Evers, A. W. M. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain*, *152*(7), 1486–1494. https://doi.org/10.1016/j.pain.2011.01.043

Wager, T. D. (2005). Expectations and anxiety as mediators of placebo effects in pain. *Pain*, *115*(3), 225–226. https://doi.org/10.1016/j.pain.2005.03.018

Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: Connecting context, learning and health. *Nature Reviews Neuroscience*, *16*(7), 403–418. https://doi.org/10.1038/nrn3976

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, *5*(6), 483–494. https://doi.org/10.1038/nrn1406

Zubieta, J.-K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., Nichols, T. E., & Stohler, C. S. (2005). Placebo Effects Mediated by Endogenous Opioid Activity on

μ-Opioid Receptors. *Journal of Neuroscience*, *25*(34), 7754–7762. https://doi.org/10.1523/JNEUROSCI.0439-05.2005