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PANACEA Learning Materials

Module 1: Concepts and History

Module information

This module aims to elucidate the multifaceted nature of the placebo and nocebo phenomena by defining and exploring the various concepts and interpretations of these terms. Moreover, a thorough historical overview of their development and use in clinical practice will be provided.

1.1 Overview

This module explores the complex concepts of placebo and nocebo, which are central to understanding the psychosocial mechanisms that influence health outcomes. The module discusses how the placebo concept has evolved, highlighting the importance of broadening its definition beyond inert substances. It also differentiates between placebo and nocebo effects and responses.

The module further delves into the concepts of placebo and nocebo mechanisms, which involve psychological and neurobiological processes that trigger these effects. Placebo interventions in clinical and research contexts are discussed, with an emphasis on the therapeutic use of placebo to improve patient outcomes.

Lastly, the historical background of placebos is examined, from their ancient use to their role in clinical trials and modern medicine. The module highlights key milestones in placebo research, and the development of the nocebo effect as a counterpart to placebo. The understanding of these phenomena is framed within evolutionary and psychological contexts, offering a comprehensive view of their clinical implications.

1.2 Placebo and nocebo concepts

Introduction

Placebo, often in the form of a pill, is commonly understood by non-experts as an inert treatment, or a sham intervention, lacking any active ingredient with a direct influence on the disease-specific or relevant pathophysiology (Kaptchuk et al., 2020). It is important to highlight that what is a placebo for one condition does not

need to be one for another. A sugar pill is not a placebo for a diabetic, for instance. However, it is important to recognize that the concept of a placebo extends beyond this definition. Contemporary scientific evidence, as highlighted, emphasizes the need to broaden our understanding of placebos beyond their inert nature.

The scientific literature (see Bagnis et al., 2025, PANACEA Scoping Review) and clinical practice (O'Keeffe et al., accepted; Linde et al., 2018) indicate a lack of a full consensus in the definition of the term "placebo." While there are work groups that have made significant efforts in clarifying these concepts (e.g., Evers et al., 2018; Mitsikostas et al. 2020), it is still necessary to differentiate the phenomenon into distinct categories to ensure precise understanding and application (see PANACEA Glossary).

It is important to underly that while the placebo phenomenon has been well-studied, the nocebo phenomenon, though equally significant, remains less understood.

The following categorization acknowledges the multifaceted nature of the term and underscores the importance of considering its various dimensions for a more nuanced understanding.

Placebo and Nocebo Effect

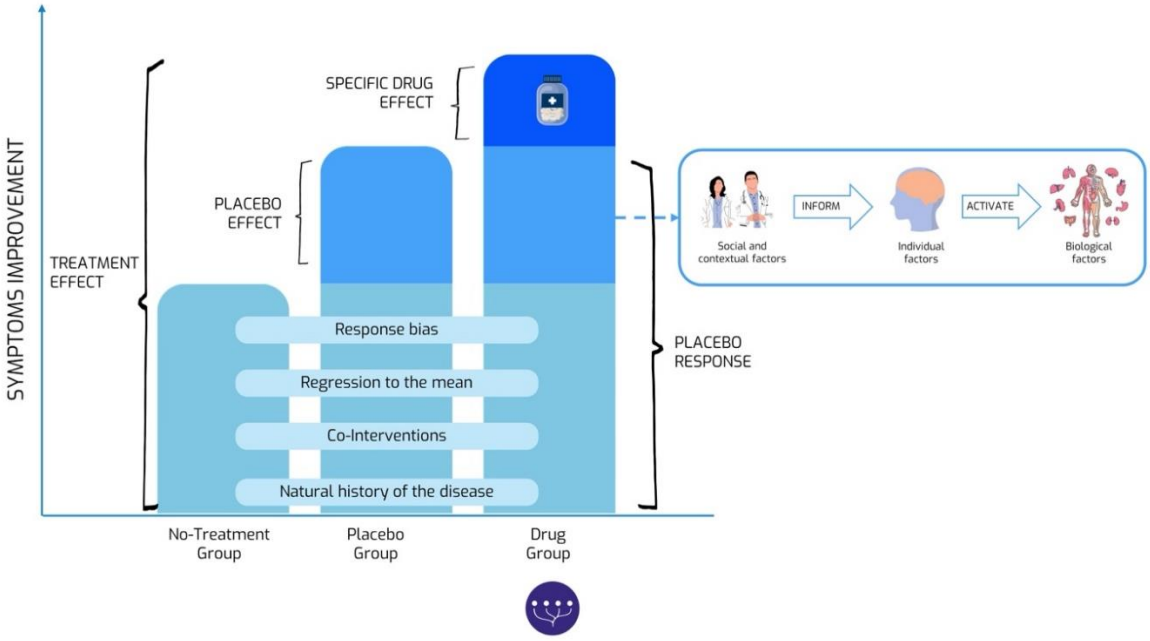
Placebo and nocebo effects are, respectively, positive and negative health changes that occur specifically due to mechanisms activated by the psychosocial context surrounding the patient and stemming from expectations influenced by learning from direct experience, verbal suggestion, or observing others.

Placebo and Nocebo Response

Placebo and nocebo responses are a broader concept including, respectively, any positive and negative health changes occurring after the administration of an inert or active treatment. This includes placebo and nocebo effects, but also other non-specific factors, such as the natural course of disease. In essence, the placebo or nocebo *response* concerns a wider array of influences, and within that, the placebo or nocebo *effect* can be pinpointed as a distinctive phenomenon evoked by specific mechanisms (Fig 1.1).

Figure 1.1

Placebo response and effect



Note. The placebo/nocebo *effect* refers to the positive or negative changes in symptoms that occur specifically due to placebo mechanisms. The placebo/nocebo *response* includes all the positive or negative health changes occurring after administration of a placebo; it includes placebo effects, but also other non-specific factors, such as the natural course of disease.

Placebo and Nocebo Mechanisms

Placebo and nocebo mechanisms are the psychological and neurobiological processes by which the psychosocial context may evoke placebo or nocebo effects.

A *mechanism* can be defined as the specific components and processes that work together to produce a phenomenon (Illari & Williamson, 2010). A *placebo/nocebo mechanism* therefore refers to the psychological or biological processes that cause observable placebo and nocebo effects (Schedlowski et al., 2015). These mechanisms (see Module 2) can occur on multiple and interconnected levels, including physiological (e.g., neurotransmitters), cognitive (e.g., learning and expectancy), and social (e.g., the doctor-patient relationship). See Box 1.1. for example. It is important to note that, at least at the psychological level, the same processes are responsible for both placebo and nocebo effects. However, this overlap does not necessarily extend to the physiological level, where different physiological mechanisms may be involved. For instance, the activation of endogenous opioids and dopamine has been found to play a significant role in the

placebo effect, whereas the deactivation of these same systems is often associated with the nocebo effect (Benedetti, 2014; Scott et al., 2008).

Box 1.1. Expectation-induced placebo analgesia and nocebo hyperalgesia

In a study about how expectations affect pain, people were told they would receive a pain-reducing, or *analgesic*, cream (lidocaine) on one part of their arm and a pain-increasing, or *hyperalgesic*, cream (capsaicin) on another part. In fact, both areas received the same inert cream. Experimenters then applied mild heat pain to the area where participants thought they had the pain-reducing cream and intense heat pain to where they thought they had the pain-increasing cream. Later, the same cream was applied again, and both areas were exposed to the same, moderate level of heat pain. Even though the heat intensity was the same for both areas, people reported less pain in the area where they thought they had the pain-reducing cream and more pain where they thought they had the pain-increasing cream. This shows that what people expect of a treatment can affect how they experience it, and this can lead to placebo analgesia or nocebo hyperalgesia (Tu et al., 2021).

It is crucial for a health care professional to distinguish nocebo effects from iatrogenic effects, as both have different underlying mechanisms and implications for patient care. Iatrogenic effects are adverse outcomes or unintended negative consequences directly caused by medical treatment or intervention. These effects result from the actions of healthcare providers or the treatment itself, rather than from the patient's expectations or beliefs. They stem from the medical treatment, procedure, or diagnostic process. Iatrogenic effects can range from mild to severe and may arise from drug interactions, surgical complications, medical errors, or other aspects of medical care. For example, a patient might develop an infection at the site of a surgical incision or experience harmful drug interaction due to a combination of prescribed medications.

In contrast, nocebo effects arise from various nonpharmacological factors such as patient expectations, previous negative experiences with medications, instructions provided by healthcare providers, and psychosocial influences like media reports and socially transmitted beliefs (Barsky et al.). Media reports and socially transmitted information, such as exaggerated portrayals of COVID-19 severity or unfounded concerns about vaccine safety, can amplify nocebo effects and significantly influence patient health outcomes (Mattarozzi et al., 2023).

Placebo Intervention

Placebo intervention is a broader term that encompasses all factors that can activate a placebo effect in healthcare. This includes tangible placebo interventions

(involving physical substances or procedures that may not have therapeutic effects but mimic real treatment, such as pure and impure placebos) and contextual placebo interventions (relating to environmental and interpersonal factors, such as the patient-provider relationship and communication style) that influence a patient's perception and response to treatment.

Given the ethical concerns accompanying the induction of nocebo effects and the fact that an intervention in clinical practice is historically associated with a symptom's relief, it is unusual to refer to an intervention as a *nocebo intervention*. However, a placebo intervention may result in a placebo response/effect or a nocebo response/effect or both, in function of the positive or negative expectations about the treatment respectively. Much less is known about nocebo effects than about placebo effects, mainly due to the ethical concerns of willfully aiming to produce unpleasant symptoms in patients or research participants.

It is important to emphasize that a placebo intervention can vary significantly depending on the context in which it is applied and its intended objective. In clinical practice, placebo interventions may be used to enhance patient outcomes by leveraging the patient's positive expectations and the therapeutic environment (see Module 5). However, in research contexts, the application of placebo interventions is more nuanced. Within clinical trials, a placebo is often used as a control to verify the efficacy of a new therapy. In this setting, the placebo serves as an experimental paradigm, involving a sham treatment that is compared against the active treatment to determine the latter's true effects (see Module 4). Additionally, placebo interventions play a crucial role in basic research on the placebo phenomenon itself, where they are used to explore and understand the underlying mechanisms and factors that contribute to placebo effects. Thus, the context—whether it be clinical practice or research—greatly influences both the nature of the placebo intervention and its intended purpose.

1.3. Placebo and nocebo in a historical context

Introduction

Placebos are as old as medicine itself. Using inactive remedies as treatments dates back to ancient civilizations, where healers would use sham treatments to take advantage of the power of belief in the healing process (Czerniak & Davidson, 2012). Thus, historically, the relationship between doctor and patient has been central to easing suffering. Indeed, in the early history of medicine, the doctor-patient relationship "… *comprised all that the doctor [really] had to offer the patient*" (Houston, 1938, p. 1417).

From an evolutionary standpoint, based on Darwinian principles, the placebo response and effect in clinical improvements can be explained by our ancestors not having access to modern medicine. Instead, they had to rely on diverse adaptive mechanisms, particularly mental processes, to navigate health challenges. These mental processes evolved to help humans influence their own health, with environmental experiences and social factors playing a crucial role in activating these mental processes. This theory suggests that the mental processes underlying the placebo effect are evolutionary adaptations that helped our ancestors survive without modern drugs through self-regulation, thus improving health outcomes (Evans, 2002; Humphrey, 2002; Trimmer et al., 2013).

The word "placebo" originates from the Latin verb "placere," meaning, "to please" (Shapiro, 1968). The Scottish physician, William Cullen is widely regarded as the first person to have used the word "placebo" in a medical context. In a lecture from 1772, Cullen revealed that he had given mustard powder to a patient he considered incurable, believing the remedy to be ineffective. Cullen stated that sometimes "… *it is necessary to give a medicine and [this is] what I call a placebo*" (Cullen, 1772, cited in Jütte, 2013, p. 95). Thus, placebos can be viewed as a means for physicians to offer comfort and reassurance to patients when conventional treatments prove inadequate.

As is suggested by the excerpt from Cullen's lecture, most support for the efficacy of medical treatments used to come from doctors' own experiences. Today, the most common meaning known by people of the term placebo refers to an inert pill used as a methodological paradigm in Randomized Controlled Trials (RCTs). RCTs represent an important gold standard of clinical research. Placebos are an integral part of those trials, serving as comparisons to help researchers assess the true

effectiveness of medical treatments by disentangling specific treatment effects from non-specific ones.

One of the earliest placebo trials was conducted in 1863 by the American physician Austin Flint. Flint tested the effectiveness of available treatments for articular rheumatism by giving a subset of patients an herbal extract. Flint found no differences in outcomes between the existing treatments and his herbal extract, and thus concluded that existing medications for articular rheumatism did not influence the natural course of the disease. In doing so, Flint effectively produced the earliest example of an inactive treatment being used as a control in medical research (De Craen et al., 1999, p. 512). In 1980, the U.S. Food and Drug Administration required that evidence for any drug's effectiveness be proven through double-blind placebo trials (Wampold et al., 2007, p. 380). Thus, the necessity for placebo controls in clinical trials was made official.

In pharmacology, *specific* drug effects refer to the effects of a drug that are directly related to its specific pharmacological action. *Non-specific* drug effects, on the other hand, are effects that are not directly related to the mechanism of action of the drug itself but are caused by other factors related to the drug's administration. These factors are often psychological and social in nature, and can include, for example, attention from a medical professional and the anticipation of symptom relief. Therefore, in the context of medical treatments, many of these non-specific drug effects are in fact placebo effects.

Studying the placebo itself

Around the same time, researchers became interested in understanding not just the potential of placebos as clinical research tools, but also the underlying mechanisms of placebos.

In 1955, Beecher conducted a comprehensive review of clinical trials and observed that a significant portion of patients experienced symptom relief even when administered inert treatments, such as sugar pills or saline injections. He famously concluded that about one-third of patients responded positively to placebos, highlighting the potent influence of psychological factors in shaping health outcomes.

In 1957, independent works by Gliedman et al. and Kurland suggested classical conditioning as a mechanism for placebo effects, marking a significant turning point in placebo research. These studies proposed that conditioned responses, influenced

by prior experiences and expectations, played a pivotal role in shaping the efficacy of placebos. By highlighting the importance of learned associations between treatments and symptom relief, these pioneering investigations provided key insights into the psychological underpinnings of the placebo effect, paving the way for further exploration into its mechanisms and clinical implications.

In 1978, the American neuroscientist Jon Levine and his colleagues investigated a potential biological mechanism of placebo effects. The scientists showed that placebo pain relief, or *analgesia*, following dental surgery, could be blocked by the opioid antagonist naloxone (Levine et al., 1978). This was the first evidence that endogenous opioids play a role in placebo analgesia. Aligned with this, the placebo phenomenon has been mostly investigated in the field of pain (Colloca, 2019).

Nocebo

The empirical study of placebo phenomena has also shed light on the negative side of the placebo phenomenon: the "nocebo effect" (Latin for "I shall harm"). In direct contrast to placebo effects, nocebo effects are *negative* health changes occurring after administering an inactive treatment dependent on a patient's *negative* expectations of the treatment (Evers et al., 2018). In pharmacology, nocebo effects are likely responsible for the side effects experienced by patients in everyday clinical settings that are not attributable to a drug's specific mechanism of action.

In 1961, American physician and pharmacologist Walter Kennedy observed that patients were experiencing negative symptoms, which could not be explained by the properties of the treatments they were receiving (Kennedy, 1961, cited in Wartolowska et al., 2023, p. 1). Kennedy described this phenomenon as the negative side of the placebo phenomenon. He coined the term "nocebo," after the Latin verb "nocere," meaning, "to hurt" (Kennedy, 1961).

A few years later, Kissel and Barrucand (1964) elaborated on Kennedy's findings and showed that 80% of patients who were given sugar water but were told it was an emetic (a medicine that induces vomiting) subsequently vomited (Kissel & Barrucand, 1964, cited in Hahn, 1997, p. 607).

However, it was not until 1997 that Robert Hahn argued that Kennedy had been discussing *placebo side effects* rather than nocebo effects, and that Kissel and Barrucand had not actually differentiated between placebo side effects and nocebo effects. Hahn defined placebo side effects as negative health outcomes resulting

from an inert treatment, despite the expectation of a positive effect. He emphasized the critical role of negative expectations in nocebo effects, arguing that genuine nocebo effects occur only when patients have negative expectations about the treatment they receive.

From an evolutionary standpoint, the nocebo effect can be understood through the lens of the Signaling Theory of Symptoms (STS). The STS proposes that certain aspects of an immune response, such as pain, swelling, or nausea, not only play a role in defense and healing but also serve as signals indicating the need for care and treatment. These symptoms act as communicative signals to potential helpers, prompting them to provide care (Steinkopf, 2015).

However, this explanation only accounts for symptoms caused by nocebo effects that can be consciously experienced. Other theories also exist. For instance, learned immune responses, such as those seen in allergies, are often considered nocebo effects, and are frequently explained as evolutionary mechanisms for conserving resources: recognizing a harmful substance more quickly results in a less costly immune response (Evans, 2003; cited in Steinkopf, 2015, p. 2). Thus, the nocebo effect may partly originate from different evolutionary strategies aimed at optimizing survival and managing resources.

So far, we have learned that placebos are of interest in three different areas: 1) as a therapeutic tool in clinical practice; 2) as a control condition in clinical studies, to determine the effectiveness of active treatments; and 3) as an experimental tool to study the placebo effect itself, including its underlying mechanisms.

1.4. Conclusion

The multifaceted nature of placebo effects underscores their ubiquity in medical practice, where they often elicit therapeutic responses even in the absence of active treatment. While placebo control groups remain the gold standard in clinical trials, the lack of a universally accepted definition of a placebo and limited understanding of its mechanisms pose challenges. However, recognizing that placebo mechanisms can be triggered independently or in conjunction with active treatments highlights their significant role in shaping health outcomes. Leveraging this knowledge, clinicians can harness expectancy-related effects to enhance treatment efficacy and optimize patient care. Thus, ongoing research into placebo phenomena and underlying processes holds promise for improving treatment effects and advancing healthcare practices.

In conclusion, the history of placebos underlines the importance of the relationship between the environment and the individual, especially the context of care and the doctor and patient relationship. From ancient times to today, placebos have been central to medicine. They are a useful tool in the clinic and in research and help to further our understanding of how the mind and body work together to both ease and increase suffering.

References

Ahn, H.-N., & Wampold, B. E. (2001). Where Oh Where Are the Specific Ingredients? A Meta-Analysis of Component Studies in Counseling and Psychotherapy. *Journal of Counseling Psychology*, *48*(3), 251–257. https://doi.org/10.1037/0022-0167.48.3.251

Bagnis, A., Meeuwis, S. H., Haas, J. W., O'Keeffe, M., Bajcar, E. A., Babel, P., Evers, A. W. M., Glogan, E., Oleszczyk, M., Portoles, A., Vlaeyen, J. W. S., Mattarozzi, K., & PANACEA Consortium (2025). A scoping review of placebo and nocebo responses and effects: insights for clinical trials and practice. *Health psychology review*, *19*(2), 409–447. https://doi.org/10.1080/17437199.2025.2471792

Barsky, A. J., Saintfort, R., Rogers, M. P., & Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *Jama, 287*(5), 622-627. 10.1001/jama.287.5.622

Beecher, H. K. (1955). The powerful placebo. *Journal of the American Medical Association*, *159*(17), 1602-1606. 10.1001/jama.1955.02960340022006 https://jamanetwork.com/journals/jama/article-abstract/303530

Bell, E. C., Marcus, D. K., & Goodlad, J. K. (2013). Are the parts as good as the whole? A meta-analysis of component treatment studies. *Journal of Consulting and Clinical Psychology*, *81*(4), 722–736. https://doi.org/10.1037/a0033004

Benedetti, F. (2014). Drugs and placebos: What's the difference?: Understanding the molecular basis of the placebo effect could help clinicians to better use it in clinical practice. *EMBO Reports*, *15*(4), 329–332. https://doi.org/10.1002/embr.201338399

Colloca, L. (2019). The Placebo Effect in Pain Therapies. *Annual Review of Pharmacology and Toxicology*, *59*, 191–211. https://doi.org/10.1146/annurev-pharmtox-010818-021542

Colloca, L. (2024). The Nocebo Effect. *Annual Review of Pharmacology and Toxicology*, *Epub ahead of print*. https://doi.org/10.1146/annurev-pharmtox-022723-112425

Cullen, W. (1772). Clinical lectures. *Edinburgh*.

Czerniak, E., & Davidson, M. (2012). Placebo, a historical perspective. *European Neuropsychopharmacology*, *22*(11), 770–774. https://doi.org/10.1016/j.euroneuro.2012.04.003

De Craen, A. J. M., Kaptchuk, T. J., Tijssen, J. G. P., & Kleijnen, J. (1999). Placebos and placebo effects in medicine: historical overview. *Journal of The Royal Society of Medicine*, *92*, 51–52. https://doi.org/10.1177/014107689909201005

Enck, P., & Zipfel, S. (2019). Placebo effects in psychotherapy: A framework. *Frontiers in Psychiatry*, *10*(JUN). https://doi.org/10.3389/fpsyt.2019.00456

Evans, D. (2002). Pain, evolution, and the placebo response. *Behavioral and Brain Sciences, 25*(4), 459-460.

Evans, D. (2003). Placebo: The belief effect. London, England: HarperCollins.

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Flückiger, C., Del Re, A. C., Wampold, B. E., Symonds, D., & Horvath, A. O. (2012). How central is the alliance in psychotherapy? A multilevel longitudinal meta-analysis. *Journal of Counseling Psychology*, *59*(1), 10–17. https://doi.org/10.1037/a0025749

Gliedman, L. H., Gantt, W. H., & Teitelbaum, H. A. (1957). Some implications of conditional reflex studies for placebo research. *American Journal of Psychiatry*, *113*(12), 1103-1107. https://doi.org/10.1176/ajp.113.12.1103

Hahn, R. A. (1997). The nocebo phenomenon: concept, evidence, and implications for public health. *Prev Med*, Sep-Oct;26(5 Pt 1):607-11. 10.1006/pmed.1996.0124

Hölsken, S., Schedlowski, M., Hadamitzky, M., & Heiss-Lückermann, L. (2023). Learned immune responses: How associations affect immunity, in Colloca, L., et al. (eds). Placebo Effects Through the Lens of Translational Research. Oxford Academic, New York. https://doi.org/10.1093/med/9780197645444.003.0011

Houston, W. (1938). The Doctor Himself as a Therapeutic Agent. *Annals of Internal Medicine*, *11*(8), 1416–1425. https://doi.org/https://doi.org/10.7326/0003-4819-11-8-1416

Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews*, *2010*(1). https://doi.org/10.1002/14651858.CD003974.pub3

Humphrey, N. (2002). Great expectations: The evolutionary psychology of faith healing and the placebo effect. In Psychology at the Turn of the Millennium, Volume 2 (pp. 241-259). Psychology Press. https://www.taylorfrancis.com/chapters/edit/10.4324/9780203989432-35/great-expectations-evolutionary-psychology-faith-healing-placebo-e%EF%AC%80ect-nicholas-humphrey

Illari, P. M., & Williamson, J. (2012). What is a mechanism? Thinking about mechanisms across the sciences. *European Journal for Philosophy of Science, 2*, 119-135. https://doi.org/10.1007/s13194-011-0038-2

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

Kaptchuk, T. J. (1998). Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine. *Bulletin of the History of Medicine*, *72*(3), 389–433. https://doi.org/https://doi.org/10.1353/bhm.1998.0159

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE*, *5*(12). https://doi.org/10.1371/journal.pone.0015591

Kaptchuk, T. J., Hemond, C. C., & Miller, F. G. (2020). Placebos in chronic pain: Evidence, theory, ethics, and use in clinical practice. *The BMJ*, *370*. https://doi.org/10.1136/bmj.m1668

Kennedy, W. P. (1961). The nocebo reaction. *Medicina Experimentalis International Journal of Experimental Medicine*, *95*, 203–205.

Kirsch, I., Wampold, B., & Kelley, J. M. (2016). Controlling for the placebo effect in psychotherapy: Noble quest or tilting at windmills? *Psychology of Consciousness: Theory, Research, and Practice*, *3*(2), 121–131. https://doi.org/10.1037/cns0000065

Kissel, P., Barrucand, D., & Barrucand, D. (1964). *Placebos et effet placebo en médecine*. Masson.

Krupnick, J. L., Sotsky, S. M., Elkin, I., Simmens, S., Moyer, J., Watkins, J., & Pilkonis, P. A. (2006). The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: Findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Focus, 64*(2), 532-277. https://doi.org/10.1176/foc.4.2.269

Kurland, A. A. (1957). The drug placebo–its psychodynamic and conditional reflex action. *Behavioral Science*, *2*(2), 101-110. https://doi.org/10.1002/bs.3830020203

Levine, J. D., Gordon, N. C., & Howard, L. F. (1978). The Mechanism of Placebo Analgesia. *The Lancet*, *312*(8091), 654–657. https://doi.org/https://doi.org/10.1016/S0140-6736(78)92762-9

Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PloS one, 13*(8), e0202211. https://doi.org/10.1371/journal.pone.0202211

Mattarozzi, K., Bagnis, A., Kłosowska, J., Bąbel, P., Cremonini, V., De Palma, A., ... & Russo, P. M. (2023). No (cebo) Vax: COVID-19 Vaccine Beliefs Are Important Determinants of Both Occurrence and Perceived Severity of Common Vaccines' Adverse Effects. *Psychological Science, 34*(5), 603-615. https://doi.org/10.1177/09567976231163875

Meyer, B., Pilkonis, P. A., Krupnick, J. L., Egan, M. K., Simmens, S. J., & Sotsky, S. M. (2002). Treatment expectancies, patient alliance, and outcome: Further analyses from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Journal of Consulting and Clinical Psychology*, *70*(4), 1051–1055. https://doi.org/10.1037/0022-006X.70.4.1051

Miller, F. G., & Colloca, L. (2009). The legitimacy of placebo treatments in clinical practice: Evidence and ethics. *American Journal of Bioethics*, *9*(12), 39–47. https://doi.org/10.1080/15265160903316263

Mitsikostas, D. D., Blease, C., Carlino, E., Colloca, L., Geers, A. L., Howick, J., ... & European Headache Federation. (2020). European Headache Federation recommendations for placebo and nocebo terminology. *The journal of headache and pain, 21*, 1-7. https://doi.org/10.1186/s10194-020-01178-3

Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. In *Pharmacological Reviews* (Vol. 67, Issue 3, pp. 697–730). American Society for Pharmacology and Experimental Therapy. https://doi.org/10.1124/pr.114.009423

Scott DJ, Stohler CS, Egnatuk CM, Wang H,Koeppe RA, Zubieta JK (2008). Placebo andnocebo effects are defined by opposite opioidand dopaminergic responses. Arch Gen Psychi-atry 65: 220 – 231 10.1001/archgenpsychiatry.2007.34 link: https://jamanetwork.com/journals/jamapsychiatry/article-abstract/482600

Shapiro, A. K. (1968). Semantics of the placebo. *The Psychiatric Quarterly*, *42*(4), 653–695. https://doi.org/10.1007/BF01564309

Steinkopf, L. (2015). The signaling theory of symptoms: an evolutionary explanation of the placebo effect. *Evolutionary Psychology, 13*(3), 1474704915600559. https://doi.org/10.1177/1474704915600559

Trimmer, P. C., Marshall, J. A., Fromhage, L., McNamara, J. M., & Houston, A. I. (2013). Understanding the placebo effect from an evolutionary perspective. *Evolution and human behavior, 34*(1), 8-15. https://doi.org/10.1016/j.evolhumbehav.2012.07.004

Tu, Y., Wilson, G., Camprodon, J., Dougherty, D. D., Vangel, M., Benedetti, F., Kaptchuk, T. J., Gollub, R. L., & Kong, J. (2021). Manipulating placebo analgesia and nocebo hyperalgesia by changing brain excitability. *PNAS*, *118*(19). https://doi.org/10.1073/pnas.2101273118

Wampold, B. E., Imel, Z. E., & Minami, T. (2007). The story of placebo effects in medicine: Evidence in context. In *Journal of Clinical Psychology* (Vol. 63, Issue 4, pp. 379–390). https://doi.org/10.1002/jclp.20354

Wartolowska, K., Colloca, L., & Amanzio, M. (2023). The nocebo effect and its consequences for clinical trials and clinical practice. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.1111324

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PANACEA Learning Materials

Module 2: Placebo and nocebo mechanisms

Module information

In this Module, we will describe the mechanisms underlying placebo and nocebo effects/responses. We will begin by discussing expectations as one of the primary cognitive determinants: what are they and why are they so fundamental to placebo and nocebo effects? We will then learn how expectations are formed via different types of learning. We will also discuss the impacts of emotions on placebo and nocebo effects. Finally, we will end by looking at what happens in the body that manifests as observable placebo and nocebo effects.

2.1 Overview

As we learned in the first Module, a *mechanism* can be defined as the specific components and processes that work together to produce a phenomenon (Illari & Williamson, 2012). A placebo mechanism therefore refers to the psychological or biological processes that evoke observable placebo effects (Schedlowski et al., 2015). These mechanisms can comprise multiple and interconnected levels, including physiological (e.g., neurotransmitters), cognitive (e.g., learning and expectations), and social (e.g., doctor-patient relationship). For example, a patient's positive expectations about treatment may trigger the release of neurotransmitters, resulting in placebo effects (Benedetti, 2014).

Similarly, a nocebo mechanism refers to the physiological, cognitive, and social processes that underlie observable nocebo effects (Schedlowski et al., 2015). In contrast to placebo effects, nocebo effects are driven by a patient's negative experiences and expectations (Colloca, 2024). For example, negative expectations about a treatment may trigger the release of neurotransmitters that adversely alter treatment outcomes resulting in nocebo effects. These can include reduced drug efficacy or the activation of side effects (Benedetti, 2014).

This Module delves into the various ways in which learning, through expectation, both conscious and unconscious, shapes placebo and nocebo effects, and how these psychological mechanisms can influence health outcomes. It begins with an

exploration of how expectations, driven by learning, lead to symptom relief or worsening. The concept of predictive processing is introduced, explaining how our brain anticipates future experiences and how these expectations can trigger placebo or nocebo effects. Next, the Module covers classical and operant conditioning, demonstrating how learned associations and reinforcement shape patients' responses to treatments. It then transitions to observational learning, emphasizing how observing others' experiences with treatments can influence one's own health outcomes, particularly in the healthcare context. Verbal suggestions and instructions are also discussed, highlighting their role in both laboratory settings and real-world clinical environments.

The Module emphasizes how healthcare providers can intervene in the processes underlying these phenomena by using verbal cues to shape patient expectations and responses to treatments. The influence of emotions on placebo and nocebo phenomena is also examined, focusing on how emotional states can either enhance or diminish treatment effects. The reciprocal relationship between placebo interventions and emotional responses is explored, shedding light on how emotional regulation can influence health outcomes. Finally, the Module addresses basic physiological processes, such as neurological, immunological, and endocrine responses, illustrating how these systems are engaged by placebo and nocebo effects.

2.2. Learning leads to expectations

Introduction

Research has demonstrated that an individual's learning from experiences—whether directly through treatments (classical and operant conditioning) or indirectly through verbal instructions (instructed learning) or social observation (observational learning), or the interaction between these different types of learning—plays a crucial role in shaping both placebo effects and responses (Colagiuri et al., 2015; Finniss et al., 2010). One fundamental concept that emerges is that expectations, varying in levels of awareness, emanate from this learning process. Recent studies underscore the essential role of expectations in placebo effects, emphasizing how these anticipations, molded through diverse learning pathways, significantly influence responses to treatments and interventions.

Expectations refer to the mental representations individuals hold about the likelihood of future events or outcomes. These expectations are shaped by past experiences, beliefs, knowledge, and contextual cues. Extensive evidence-based literature underscores the profound impact of expectations on perception, behavior, decision-making, and overall cognitive processes (Haanstra et al., 2012; Szpunar, 2010; Roese and Sherman, 2023). Expectations about a treatment are central to placebo and nocebo responses and effects (Kirsch, 1985). Meta-analyses, which combine data from the placebo arms of multiple randomized controlled trials (RCTs), have shown that placebo responses can account for up to nearly 70% of the effectiveness of treatments for pain and depression (Moore et al., 2014; Rief et al., 2009). This demonstrates how the mere anticipation of symptom relief can alleviate symptoms, by means of the activation of placebo mechanisms. Similarly, the mere anticipation of side effects in the placebo groups of clinical trials can result in symptoms that mirror the side effects of the active treatment by means of the activation of nocebo mechanisms (Amanzio et al., 2009; Rief et al., 2006).

Expecting relief increases placebo effects

Expectations of treatment increase the strength of placebo effects, thus enhancing the effectiveness of the treatment (Papakostas & Fava, 2009; Rutherford et al., 2009).

Some of the most convincing evidence supporting the effect of expectations on treatment outcomes comes from studies on hidden/open treatment administration, which investigate the impact of knowing that one is receiving a treatment and its effect (see Module 5). In these studies, one group is aware they are receiving an active treatment, such as a painkiller, while in the other group, the same treatment is administered without informing the patient, for instance, through an automatic infusion machine. Typically, these studies show that treatments are less effective when patients do not know they are receiving them (Benedetti, Maggi, et al., 2003; Pollo et al., 2001), highlighting that awareness and expectation of receiving a treatment and its effect is crucial for its efficacy.

Predictive processing: how do expectations result in symptom relief or worsening?

The human brain is constantly processing a huge amount of information coming from the senses, and thus needs to organize it into a reliable representation of the psyche, body and the external world. Traditionally, the biomedical model of disease

has viewed this perception as a bottom-up process, where the brain passively receives information from the senses, resulting in perceptions that directly reflect the external world (Van den Bergh et al., 2017). However, this view does not explain how an inert treatment can relieve symptoms. The biomedical model moreover tends to limit itself to biological explanations of symptoms and fails to explain how social or psychological factors may impact symptoms. Other models, such as the biopsychosocial model of illness, described by Engel in 1977, do include these domains (Engel, 1977. In: Borrel-Carrió, Suchman & Epstein, 2004). While not particularly focused on placebo effects, the biopsychosocial model stresses the importance of patient's subjective experience. It also underlines the impact that social processes can have on symptom perception, including the relationship between clinicians and patients. Theoretical frameworks for placebo effects, such as the response expectancy theory (Kirsch, 1985; Kirsch, 1999) and mentalistic theory (Byerly, 1976) explain that treatment cues from the (social) environment can result in expectancies, which can generate placebo effects. However, while these models do describe that expectancy and inert treatments *can* relieve symptoms, they fail to explain *how* this happens, or by which process inert treatments can affect symptom perception.

A relatively recent approach uses a Bayesian model to address this question (Ongaro & Kaptchuk, 2019). The Bayesian model stands as a fundamental concept in understanding the placebo effect, underscoring the critical role of expectations in shaping both placebo and nocebo responses. According to this approach, perceptions are shaped by current incoming information from the senses combining with the brain's predictions, which are based on past experiences and individual differences, such as personality traits, attitudes, motivation (Clark, 2013). As one of the possible models, the Bayesian framework suggests that prior beliefs and incoming information are integrated to update expectations, thereby influencing the magnitude and direction of the placebo or nocebo effect. Expectations are key in modulating these effects, demonstrating how cognitive processes interact with physiological responses to influence treatment outcomes.

The brain continuously makes predictions about the environment and the body, drawing on past experiences, and these predictions are updated as the brain receives new sensory information (Clark, 2013). When the incoming sensory input does not match the brain's predictions, the resulting "prediction error" causes the brain to adjust its predictions. This process combines sensory information ascending

from the body (i.e. "bottom-up" sensory processes) with descending predictions from the brain (i.e. "top-down" processes). Therefore, our perception of the world does not fully correspond to its actual state but is "the brain's best guess of it" (p. 1, Ongaro & Kaptchuk, 2019). The more ingrained the brain's predictions, the harder it is for new information to change them. Conversely, very unambiguous and emotionally salient information generating surprise is more able to change these predictions (O'Reilly et al., 2012).

According to this perspective, we feel bodily symptoms, such as pain, because the brain predicts it, based on incoming sensory data and past experiences (Van den Bergh et al., 2017). Generally, the brain assumes that the body is in a good balance, but if it gets clear signals to the contrary, such as pain from an injury, it revises its predictions. Because these signals are unambiguous and surprising, the brain interprets them as accurate, and thus, they result in the perception of pain (Van den Bergh et al., 2017). This is why in acute pain, the correlation between the physical condition and the pain we feel is often strong (Van den Bergh et al., 2017).

However, in the case of chronic illness, such as chronic pain, the perception of symptoms has become more heavily reliant on the brain's predictions, which can be influenced by a variety of factors, such as past trauma. This could explain the sometimes low correlation between physical pathology and the experience of symptoms in such conditions (Van den Bergh et al., 2017).

Within this framework, all symptoms are the result of predictive processing. Therefore, it is not necessarily helpful or accurate to classify symptoms as medically "explained" or "unexplained". Instead, symptoms should be seen as existing on a continuum, varying only in how closely they are connected to physical pathologies (Van den Bergh et al., 2017).

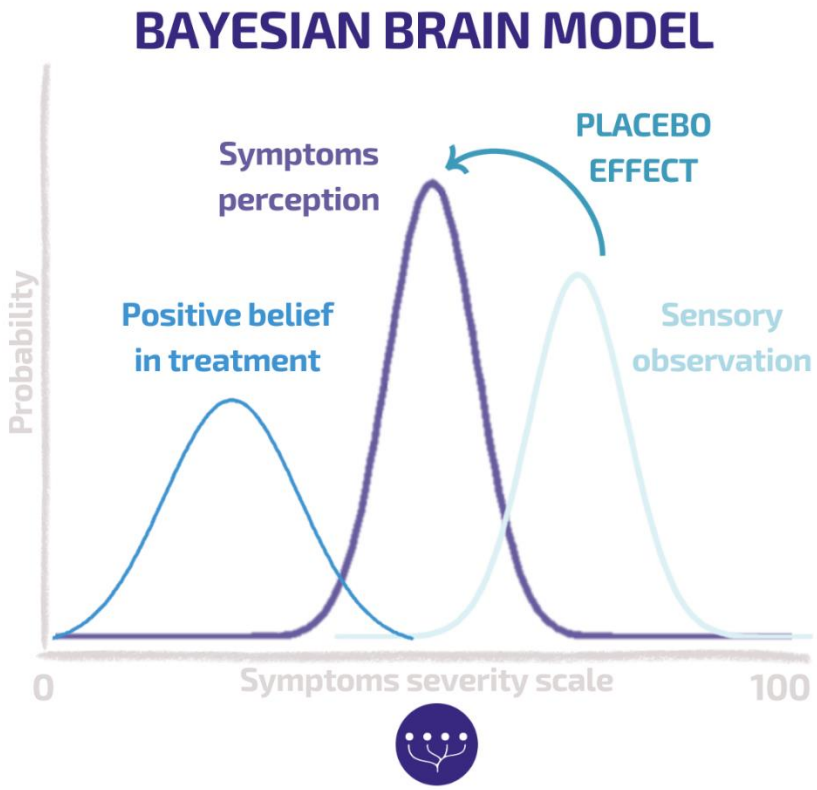
Predictive processing and placebo and nocebo effects

In terms of placebo effects, the explanation is similar. From this perspective, experiencing symptom relief is not directly connected to physical recovery, but results from the brain predicting that certain changes in the body are signs of healing (Büchel et al., 2014). The updating of predictions in this event is made more efficient by external cues suggesting that relief is on the way. Such information helps the brain to interpret signs of recovery as more than just "noise," and to

incorporate them into its predictions of the state of the body. For example, sensory information about receiving a treatment (e.g., visual, gustatory or olfactory cues) may predispose the brain to interpret even small changes in the body as signs of healing, and to experience symptom relief (Fig. 2.1).

Figure 2.1

Bayesian brain model



Note. The figure illustrates an example where the subject has a positive belief in the treatment, expecting to feel pain at a level of 30 on a rating scale of 0-100. The actual sensory observation indicates a much higher pain level, around 70. Due to the placebo effect induced by the positive belief in treatment, the subject experiences pain at an intermediate level of approximately 50.

A similar process can also be used to explain nocebo effects, but in this case, updating predictions of symptom exacerbation is made more efficient by external cues suggesting that exacerbation (Hechler et al., 2016).

Thus, it is evident that treatment expectations significantly impact the effectiveness of treatments. But how are these expectations formed in the first place? Typically, they develop through learning, which can include personal experiences, verbal suggestions, and observing others. Emotional and contextual factors also play a role in shaping these expectations. Next, we will explore exactly how this happens.

2.3. Learning by classical and operant conditioning

Introduction

Classical conditioning is a key psychological process where an organism learns to associate two stimuli, leading to a learned response. A classic example is Pavlov's experiment with dogs, where the sound of a bell, previously neutral, eventually triggered salivation after being paired with food. This phenomenon explains how certain environmental cues, like the appearance of medicine, can become linked with its effects, producing placebo responses even when no active ingredients are present. Additionally, operant conditioning, which involves learning from the consequences of behavior, also plays a role in shaping placebo and nocebo effects. In operant conditioning, behaviors that lead to positive outcomes are reinforced and more likely to be repeated. In the context of healthcare, patients who have had positive experiences with treatments may develop expectations that enhance their response to similar interventions in the future. Together, classical and operant conditioning shed light on how learning processes can shape physiological and psychological responses to both active and inert treatments, influencing clinical outcomes in important ways.

Classical conditioning

Classical conditioning is a process where an organism learns to associate two stimuli or events with each other. That is, when one thing happens, the organism learns to expect another thing to happen, and the organism anticipates the response. The most famous example is Pavlov's experiments with dogs. He found that dogs would salivate when they heard the sound of a bell, which had previously been paired with food. In classical conditioning terms, the dogs learned to associate the bell (an initially neutral stimulus) with food (an unconditioned stimulus, i.e. something that naturally triggers a physiological response; in this case, something that makes dogs salivate). After receiving food a few times following the sound of the bell, the dogs started to salivate just from hearing the bell, even when no food

was given. Thus, the dogs learned that the bell sound meant food was coming, and this resulted in a physiological response to the bell on its own that was similar to the natural response to food. The bell thus became a conditioned stimulus, meaning it could evoke physiological responses on its own (Figure 2.2).

This phenomenon can also be applied to other situations, such as taking medicine. The way medicine looks, feels, and tastes, as well as any stimuli related to the context of the therapy, can become associated with the physiological changes that the active ingredient of those medicines evokes. Thus, through repetition, the stimuli and events associated with taking a medicine can become conditioned stimuli that evoke the effects of the medicine, even when no active ingredient is present.

Therefore, in the context of placebos, to observe placebo effects on the physiological level, the body often first needs to directly experience an active treatment (Benedetti, Pollo, et al., 2003; Colloca & Miller, 2011).

An inert treatment or a part of the treatment context can become a conditioned stimulus by being repeatedly paired with an active treatment that elicits a therapeutic effect. Classical conditioning is often used to explain how physiological placebo effects are produced. In these studies, injections of inert solutions, or simply the insertion of a needle, produced responses similar to those produced by a previously administered drug.

For instance, in the study of Benedetti and colleagues (2003), people were given sumatriptan - a medicine that causes the body to release growth hormone. Placebo administration after sumatriptan preconditioning mimicked the effects of the sumatriptan itself. When sumatriptan was replaced with placebo, the body still released growth hormone. The reaction was dependent on earlier experience with the active treatment generating pharmacological conditioning (Hadamitzky et al., 2020; Tekampe et al., 2018; Tekampe et al., 2017).

Classical conditioning can operate without the need for conscious expectations or individual awareness. However, in some cases, the experiences gained through classical conditioning can create conscious expectancies. These response expectancies often lead to corresponding subjective experiences, which are substantiated by changes in behavior and physiological function (Kirsh, 1985).

For example, Colloca and Benedetti (2006) found that placebo analgesia works better if people have previously had effective pain treatments. In their study, the

researchers made participants believe that a sham analgesic treatment was effective by secretly lowering the intensity of painful electrical stimuli that participants were receiving. Later, when these participants were exposed to electrical stimuli that were all equally intense, they felt less pain when they believed they were receiving the analgesic treatment, compared to when they thought they were not. Another group underwent the same manipulation, but in the reversed order; they first received pain stimuli of equal intensities applied with or without a placebo, and only after that experienced the secretly reduced pain intensities. The group that received effective treatment showed a placebo effect even 4-7 days later. However, in the group that initially had negative experiences with a placebo, inducing placebo analgesia was not possible (Colloca & Benedetti, 2006).

Nocebo hyperalgesia can also be conditioned using a similar manipulation where the severity of pain stimuli is secretly increased rather than decreased. This method of conditioning leads to increased perceptions of pain when people are exposed to moderately intense pain stimuli (Bąbel et al., 2017; Bajcar et al., 2020; Bräscher et al., 2017). These adverse conditioned responses are not confined to pain. For instance, environmental cues can trigger anticipatory nausea and vomiting in individuals undergoing cancer chemotherapy (Colagiuri & Zachariae, 2010; Colloca & Miller, 2011).

Operant conditioning

Another learning process, namely the operant conditioning, has been proposed as a mechanism explaining placebo and nocebo effects. According to Skinner's theory, operant conditioning involves learning about the consequences of our actions, which in turn influences our future behaviors. In operant conditioning, behaviors that lead to the satisfaction of a need or reward are more likely to be repeated (Figure 2.2).

For example, if a person finds that eating when they are hungry leads to a feeling of satisfaction, they are more likely to eat when they are hungry in the future. In the medical field, if a patient takes a drug that suppresses a symptom, the relief experienced reinforces the behavior, making it more likely the patient will continue taking the drug when symptoms arise.

Within the context of the placebo phenomenon, this reinforcement process influences both the effect of the active drug because of the synergic placebo effect and potentially an effect following an inert treatment. If taking a placebo has

previously led to symptom relief, the behavior is reinforced, thereby increasing the likelihood that taking the inert treatment will activate a placebo effect in the future (Babel, 2020).

In a study by Adamczyk and colleagues (2019), participants were verbally rewarded for reporting low pain and punished for reporting high pain in the presence of placebo. They were also rewarded for reporting high pain and punished for reporting low pain in the absence of placebo. Then, when the rewards and punishments were stopped, participants continued to report lower pain when pain stimuli were applied with a placebo, and higher pain when placebo was absent (Adamczyk et al., 2019).

What this means for the health care context

Together, these results underscore the significant impact that an individual's treatment history can have on the success of subsequent treatments. Patients who have experienced positive outcomes from a medication are more likely to respond positively to similar medications in the future or benefit from placebo treatments. Conversely, if prior treatments were ineffective or had negative outcomes, patients might exhibit a diminished response to similar medications or placebos, or even experience nocebo effects. Therefore, it is crucial for healthcare professionals to consider patients' personal perceptions and experiences with medical treatments when providing care. The implications extend to both the behavior of medical staff and the effectiveness of placebo interventions. Attentive and empathetic behavior from medical personnel can significantly enhance the effectiveness of placebos. However, if medical staff ignore a patient taking a placebo or the placebo proves ineffective, the likelihood of the patient using placebos in the future decreases (Bąbel, 2020). The degree of relief a patient experiences from a placebo can also reinforce whether they will use placebos again in the future.

Figure 2.2

Classical vs Operant Conditioning

2.4. Learning by observation

Introduction

Experiencing an event firsthand is a powerful way of learning, but individuals can also gain knowledge by observing others, without directly participating. Albert Bandura's theory of observational learning, or social learning theory, suggests that people can learn new behaviors by watching others, particularly when they see those others being rewarded or punished for their actions. This process is significant in the context of placebo and nocebo effects, as observing someone else's experience with a treatment can shape one's own expectations and responses. For instance, seeing someone benefit from a placebo treatment may lead an observer to expect similar positive outcomes, while witnessing someone suffering adverse

effects can trigger negative expectations and nocebo effects. Healthcare providers need to be aware of how observational learning can influence patient outcomes and consider it when designing treatment strategies.

Observational learning

Experiencing an event firsthand is a potent form of learning. Yet, people can also gain knowledge by observing others, without the need for direct personal experience. Albert Bandura's theory of observational learning, or social learning theory, posits that individuals can learn new behaviors by watching others, particularly when they observe rewards or punishments that others receive. In this vein, both placebo and nocebo effects can emerge through the process of observational learning. By observing someone else experiencing a positive effect from a treatment, a person may develop a similar positive expectation and experience beneficial effects themselves. Conversely, witnessing someone experiencing adverse effects can lead to negative expectations and nocebo effects.

Colloca and Benedetti (2009) investigated how seeing someone else experience placebo analgesia influences one's own response to a placebo. In their study, healthy participants observed another person in the lab receiving painful electrical stimuli. This person pretended to feel less pain from the electrical stimuli during a placebo treatment. Later, when the participants themselves were subjected to the painful stimuli at the same moderate intensity, they reported experiencing pain relief during the same sham intervention (Colloca & Benedetti, 2009).

Similarly, in a study by Vögtle and colleagues (2013), participants watched a video of someone exhibiting increased pain reactions to a pressure pain stimulus following the application of a cream. After this, participants themselves reported experiencing increased pain in the arm that received the same inert cream, compared to the arm that did not receive the cream. However, the pressure pain applied to both arms was equally intense. These findings imply that simply observing someone else's experience can lead people to anticipate similar outcomes for themselves, leading to placebo analgesia or nocebo hyperalgesia (Vögtle et al., 2013).

In a recent meta-analysis conducted by Meeuwis et al. (2023), researchers delved into the impact of observational learning on both placebo-induced pain reduction and nocebo-induced heightened pain sensitivity. Twenty-one studies were included in the systematic review, 17 of which were suitable for meta-analysis (18

experiments; n = 764 healthy individuals) This research yielded valuable insights into how observing others' experiences can shape our perception of pain. The analysis revealed that observational learning exerted a moderate effect on pain ratings and a substantial effect on pain expectancy, with the magnitude of these effects varying across studies depending on methodological differences. Interestingly, the mode of observation, whether in-person or via videotape, emerged as a significant factor influencing these effects. In-person observation of a model resulted in large but ultimately nonsignificant effects on pain, whereas observation of a videotaped model led to smaller yet significant effects. Prior research suggests that video observation provides less information, potentially leading to smaller effects compared to in-person observation. This meta-analysis found greater variance in studies using in-person models, with some showing large effects and others moderate, leading to overall non significance. This indicates that in-person observation can be more powerful but harder to achieve consistently. Moreover, fewer studies used in-person models, so these findings may evolve with more data. The type of placebo (e.g., an inert treatment or intervention) used did not significantly influence the observed effects. Whether the placebos were medically connoted (e.g., inert cream or sham toxin) or abstract cues (e.g., colored dots), both exhibited significant modulation of pain experience through observational learning. Moreover, individuals with heightened levels of empathic concern were found to be particularly susceptible to the influence of observational learning.

Although the data are inconclusive, it seems that the mode of observation (in-person vs. via videotape) may be considered as one of the factors influencing the effectiveness of this type of learning in shaping placebo effects.

Other factors that can influence observationally induced placebo effects include the characteristics of the model, such as their sex, and the role of 'pain indicators,' which encompass both verbal and non-verbal information provided by the model (Świder, & Bąbel, 2013). These elements can affect the observer's expectations and the magnitude of the placebo effect they experience, highlighting the complexity and variability of observational learning in the context of placebo responses and effects.

What this means for the health care context

In healthcare settings, medical procedures, such as injections, sometimes take place where other patients can observe them. These patients may go through similar procedures themselves in the future and witnessing someone else's experience can

positively or negatively influence people's responses to treatments. Healthcare providers should be mindful of the potential negative consequences that witnessing painful treatments could have (Meeuwis, et al., 2023). Conversely, healthcare professionals may be able to leverage the positive health effects of a patient observing successful treatments (Bajcar & Bąbel, 2018). See Module 5 and 6 for more details.

2.5. Learning by verbal suggestion/instruction

Introduction

In the context of placebo and nocebo effects, verbal suggestion means telling someone what to expect from a treatment, usually through oral communication. For example, if a doctor tells a patient that a treatment usually reduces pain, this can lead to a placebo effect. On the other hand, if a doctor mentions that a treatment has side effects, it can lead to nocebo effects. The way a healthcare provider speaks about a treatment, how confident they sound, and even the specific words they use can change what a patient expects and how they react to a treatment.

The open-hidden paradigm highlights the significant impact of verbal suggestions on therapeutic outcomes. In this model, treatments administered openly, with patients thoroughly informed about the effects and objectives, consistently yield better results compared to hidden administrations (Price et al., 2008). This underscores the importance of therapeutic interaction and the context in which treatment is provided (Finniss et al., 2010). By fully informing patients and making the treatment process visible, healthcare providers can enhance patient engagement, trust, and treatment efficacy (see Module 5 and Module 6).

Next, we will give some examples of how verbal suggestion can lead to positive and negative expectations in laboratory with healthy participants and clinical settings with patients, and what this means for clinical practice.

Verbal suggestions in the lab setting

Colloca et al. (2008) investigated the distinct roles of verbal suggestions and learning in the development of nocebo and placebo responses. They found that stimuli linked to a green light, combined with verbal suggestions of worsening, whether pre-conditioned or not, were able to transform both low and high non-

painful tactile stimuli into painful ones. This demonstrates that verbal suggestions of nocebo treatment can induce allodynic effects, where non-painful tactile sensations are perceived as painful. Similarly, it has been shown the effect of verbal suggestions on placebo effect. For example, a study by Meeuwis et al. (2018) demonstrated that open-label positive verbal suggestions alone can generate outcome expectations and decrease the level of itch experienced.

Positive or negative verbal information can also enhance or reverse the effectiveness of active treatments. Aslaksen and colleagues (2015) found that the pain-relieving effect of an active analgesic cream could turn into increased pain (nocebo hyperalgesia) when participants were told it had pain increasing effects. Conversely, positive information about the cream amplified its pain-relieving effects (Aslaksen et al., 2015).

These findings illustrate that the efficacy of placebo and active pain treatments can be significantly influenced by the information provided to research participants, whether positive or negative.

Verbal suggestions in clinical settings

Similar findings have been observed outside the lab, in medical settings. For instance, in a study by Pollo and colleagues (2001), patients who had undergone thoracotomy (a surgical procedure where an incision is made in the chest) were administered the opioid painkiller buprenorphine upon request for three days, alongside a placebo treatment of inactive intravenous saline solution.

The patients were categorized into three groups, each receiving different explanations about the saline solution. The first group received no information about the saline solution (natural history group). The second group was informed that saline could be either a potent painkiller or a placebo (double-blind group). The third group was told that saline was a potent painkiller (deceived group).

The study measured the placebo effect by tracking how much buprenorphine each group requested over the three days. Both the double-blind and deceived groups asked for less buprenorphine compared to the natural history group, with the fully deceived group requesting it the least, indicating the lowest need for painkillers (Pollo et al., 2001). Importantly, the level of experienced pain relief was similar across all groups. This suggests that the way patients are informed about their

treatment can lead to changes in their medication intake, in this case, resulting in decreased use of painkillers.

Finally, a review of 85 studies investigating the impact of expectations on various clinical conditions showed that enhancing treatment expectations via the information given to patients in medical settings had significant benefits (Crow et al., 1999). The review demonstrated that preparing patients for medical procedures by explaining treatment processes lead to reduced anxiety and reduced use of analgesics. Furthermore, when practitioners demonstrated confidence in a treatment, it fostered positive outcomes, such as lower anxiety, pain, and distress. In contrast, practitioners expressing doubt about a treatment or focusing on potential side effects increased patient-reported symptoms. This investigation showed that expectations induced by health care professionals directly influence patient outcomes in the clinic.

What this means for the health care context

The studies discussed here highlight how verbal suggestions from healthcare providers can influence patient outcomes via placebo and nocebo effects. Positive or negative expectations shaped by these communications can enhance or diminish treatment efficacy, underscoring the critical role that healthcare professionals can play when they present treatments to patients. This topic will be discussed in more detail in Module 5 and 6.

2.6. Emotions

Introduction

While placebo and nocebo effects have predominantly been studied in the context of expectations and learning, it is crucial to recognize that these effects are not solely driven by cognitive processes; emotional factors also significantly contribute by either triggering or modulating the placebo/nocebo effects or response.

Next, we will delve into how emotions can significantly impact both the placebo and nocebo phenomena, and conversely, how these effects can influence emotions. Understanding the interplay between emotions and placebo/nocebo responses sheds light on the complex mechanisms at play in shaping our health outcomes.

How emotions influence placebo and nocebo phenomena

Emotions can influence how we process information (Takahashi & Earl, 2020; Tyng et al., 2017). See Box 2.1 for more details.

Box 2.1. The Role of Emotion in Learning and Memory (Tyng et al., 2017)

Learning

- Positive emotions: can enhance learning by increasing self-motivation, engagement, and satisfaction with materials, leading to better academic performance (Um et al., 2012).
- Negative emotions (e.g., confusion): can improve learning by increasing focus and promoting deeper cognitive processing, leading to better test performance (D'Mello et al., 2014).
- Stress:
    - Mild and acute stress: facilitates learning and cognitive performance.
    - Chronic stress: impairs learning and memory by overactivating stress pathways (Vogel and Schwabe, 2016; Joëls et al., 2004).
- Curiosity: motivational state driven by emotional responses to novel stimuli, enhancing learning and exploration (Oudeyer et al., 2016).

Memory

- Salient stimuli: can enhance memory by capturing attention and increasing the likelihood of encoding into long-term memory (Vuilleumier et al., 2005).
- "Pop-out" effect: emotional information stands out, demanding greater attention and facilitating memory retention (Öhman et al., 2001).
- Motivational states: direct attention toward important emotional information, improving memory encoding and retrieval.
- Emotional states: Enhance memory retrieval, especially for emotionally charged events, by improving focus and increasing the chances of recalling significant information.

Learning and memory processes are closely linked to expectations, as emotions and attention play a key role in shaping information processing. When we encounter something emotionally significant, our attentional resources are drawn to it, leading to deeper encoding in memory. This information, in turn, can influence our future expectations. These expectations, in turn, influence how we perceive and respond to new experiences, including medical treatments. Positive expectations, often formed

through prior learning and emotional experiences, can lead to placebo effects, while negative expectations, shaped by past discomfort or fear, can result in nocebo effects. Therefore, what we learn and remember from past experiences heavily influences the expectations we have, which directly impact how we respond to treatments.

Research has examined how experimentally induced emotions influence placebo and nocebo effects. In two experiments, Geers and colleagues (2019a, 2019b) used videos to induce either positive or neutral moods in participants. After the positive or neutral mood induction, participants were subjected to a nocebo manipulation through verbal suggestion of hyperalgesia. In one study, participants were told that an inert cream would increase pain during a cold-water hand immersion task. In the other, participants underwent a sham intervention, which they were told might cause headaches.

In both studies, participants given the neutral mood induction experienced increased pain in response to the nocebo manipulation, whereas participants who underwent the positive mood induction did not experience nocebo effects, despite similar warnings of increased pain (Geers et al., 2019a; Geers et al., 2019b). Thus, simply inducing positive emotions may prevent nocebo effects. This is also an ethically sound approach, because it does not involve the need for healthcare professionals to downplay the risks associated with a treatment.

However, it should be noted that emotions alone do not necessarily influence placebo and nocebo effects. For instance, a study by Elsenbruch and colleagues (2019) revealed that reducing stress and physiological arousal through relaxation exercises did not lead to placebo analgesia on its own. The emergence of placebo analgesia required both the relaxation exercise and the expectation of analgesia. This interaction was observed only in participants who underwent the relaxation exercise, indicating that the combination of positive expectations and a relaxed state facilitated placebo analgesia. In this research, saline was the placebo, and verbal suggestion was employed to elicit the expectancy of analgesia. Hence, this study suggests that inducing a positive state, such as relaxation, not only can prevent nocebo hyperalgesia but also contributes to placebo analgesia.

How placebos interventions influence emotions

Substantial evidence suggests that placebo interventions (i.e. inert treatments) increase positive emotions and diminish negative ones. Experimental placebo manipulations can reduce anxiety and worry, improve mood, and impact physiological markers of stress, such as heart rate. For example, Aslaksen and Flaten (2008) found that participants who received a placebo with the information it was a potent painkiller, showed reduced heart rate variability – a physiological marker of stress – and elevated mood, compared to participants in a no-treatment control group. These benefits were associated with lower levels of self-reported stress, which in turn predicted significant placebo pain relief during experimental heat pain (Aslaksen & Flaten, 2008).

In contrast, nocebo manipulations can increase fear, worry, worsen mood, and increase both self-reported and physiological indicators of anxiety. A study by Colagiuri and Quinn (2018) showed that participants who underwent classical conditioning of nocebo hyperalgesia – where the intensity of pain stimuli were secretly increased – reported increased anxiety. This was also reflected in heightened skin conductance responses – another physiological marker of stress (Colagiuri & Quinn, 2018). Together, these results show that placebo and nocebo manipulations can influence emotions on psychological and physiological levels.

What this means for the healthcare context

Considering that placebos can influence emotions, which can subsequently impact treatment responses, inert treatment could be used in the clinic to reduce negative emotions and other symptoms. This could be done using impure placebos (i.e., treatments with active ingredients but are used in a context where their active properties are not relevant to the condition being treated) on their own for less critical conditions or to enhance the effectiveness of active treatments. However, research on whether this is a truly effective option is still lacking (Coleshill et al., 2018). Furthermore, since emotions influence placebo and nocebo effects, and thereby potentially the success of active treatments, it is important to consider the emotional states of patients in the clinic. Furthermore, it may also be necessary to not only consider patients' emotional states but to also *induce* positive emotions, for instance, through a positive patient-healthcare provider relationship (see Module 5, and 6).

2.7. Basic physiological processes

Introduction

The neurobiological processes underlying placebo and nocebo effects involve complex interactions between the brain, immune system, and endocrine system, each playing a crucial role in shaping treatment outcomes. Neurological processes, for example, show how expectations of relief can modulate brain regions responsible for pain perception, with placebo analgesia offering insight into the top-down regulation of pain. The communication between the brain and immune system further illustrates how placebo effects can influence immune responses through conditioning, while nocebo effects can exacerbate immune functions. Similarly, hormonal processes demonstrate how placebo treatments can induce changes in hormone levels, such as insulin and growth hormone, reinforcing the mind-body connection. These mechanisms highlight the importance of understanding how psychological factors influence physiological responses, offering valuable implications for the development of personalized treatment strategies that optimize patient outcomes and reduce the impact of nocebo effects.

Neurological

Placebo analgesia

Placebo effects have been studied most extensively in the area of pain. Placebo analgesia has therefore been used as the main model to describe the neurobiological mechanisms of placebo/nocebo effects. The first evidence of biological mechanisms underlying placebo analgesia came from the study of Levine and colleagues, discussed in Module 1, where post-surgical patients who were given the opioid antagonist naloxone experienced more pain than those given a placebo, indicating that naloxone blocked the effects of placebo analgesia. This was taken as evidence that placebo analgesia engages the endogenous opioid system, thus imitating the mechanism of action of opioids (Levine et al., 1978).

Pain is caused by the activation of pain receptors, called nociceptors, which are specialized to detect current or potential damage to body tissues. When activated, these receptors send signals through nerve fibers into the spinal cord and then to various parts of the brain (i.e., the bottom-up component of the perceptual process of pain). This process results in the experience of pain. Research using functional magnetic resonance imaging (fMRI) has shown that the brain areas activated by pain include the anterior cingulate cortex (ACC), thalamus, somatosensory cortex, and

insula. These brain areas receive information from nociceptive nerves and contain nociceptive brain cells (Wager et al., 2013).

Similarly, fMRI studies comparing placebo interventions to no treatment show that placebos can diminish responses to pain in similar regions (Wager et al., 2004). However, these reductions in pain-associated brain regions during placebo analgesia are not consistently accompanied by changes in the neurological pain signature (Zunhammer et al., 2018) – a reliable pattern of brain activity in response to pain that includes areas the abovementioned brain areas but also other areas. Instead, placebo interventions seem to selectively increase activation in different brain areas, including the dorsolateral prefrontal cortex, rostral ACC, and amygdala (Atlas & Wager, 2014). This implies that placebos may primarily engage higher-order brain regions involved in emotional and cognitive processing rather than directly influencing nociception (i.e., the top-down component of the perceptual process of pain).

Meta-analyses of neuroimaging data have confirmed the involvement of certain brain regions in placebo effects during painful stimulation. Specifically, reductions in activation have been consistently observed in regions associated with pain processing, such as the dorsal anterior cingulate, thalamus, and insula (Amanzio et al., 2013; Atlas & Wager, 2014; Zunhammer et al., 2021). Moreover, compared to control conditions, placebo effects are associated with consistent reductions in activation in areas linked to affect and valuation, such as the amygdala and striatum (Atlas & Wager, 2014). Interestingly, increases in activation have been noted in various brain regions, including the prefrontal cortex (encompassing dorsolateral, ventromedial, and orbitofrontal cortices), the midbrain surrounding the periaqueductal grey, and the anterior cingulate (Amanzio et al., 2013; Atlas & Wager, 2014; Romanella et al., 2023; Zunhammer et al., 2021).

Nocebo hyperalgesia

Subsequent research by Bingel and colleagues (2011) showed that nocebo pain exacerbation, or hyperalgesia, is linked to reduced activity in the subgenual part of the ACC, suggesting that negative treatment expectations might influence pain through a pathway similar to positive expectations, but in an opposite way (Bingel et al., 2011). Furthermore, the same study showed that only nocebo hyperalgesia, but not placebo analgesia, was associated with activity in the hippocampus - a region associated with pain intensification due to heightened anxiety (Ploghaus et al., 2001).

In line with this, anxiety appears to affect pain through the activation of endogenous cholecystokinin (CCK; (Benedetti et al., 2006)). CCK is an anxiogenic neurotransmitter, which can counteract opioid analgesia, suggesting that nocebo hyperalgesia might work by indirectly influencing the opioid system by inhibiting it with CCK (Frisaldi et al., 2015).

The activity in the posterior insula is involved in the processing of both interoceptive and affective information and has been implicated in the experience of pain and negative emotions, suggesting that this area is pivotal for nocebo hyperalgesia processing as well (Fu et al., 2021). Consistently, together with the parietal operculum, changes in posterior insula activity match changes in pain intensity perception (Segerdahl et al., 2015) and mediate the effects of negative expectations on perception of pain in the future (Rodriguez-Raecke et al., 2010).
Finally, the prefrontal cortex, particularly the dorsal anterior cingulate cortex (dACC), plays a crucial role in in negative affect and pain processing, suggesting a correlation between increased activation of dACC and nocebo hyperalgesia processing (Fu et al., 2021).

Together, these results suggest a top-down (brain-to-body) modulation of pain, where expectation of pain relief or increase can activate higher-order cortical regions, which influence endogenous neurotransmitter pathways further down the line.

Brain mechanisms of placebo/nocebo effects in other health conditions

Placebos can induce neurobiological effects, similar to those triggered by active medications, in health conditions other than pain. In Parkinson's disease, placebos can induce the release of dopamine in the brain, mimicking the effect of active Parkinson's medications (Murray & Stoessl, 2013). For example, a systematic review by Quattrone and collaborators (2018) showed that the magnitude of placebo effects, modulated by an expectancy of improvement, is related to the release of dopamine within the ventral striatum. Specifically, the greater likelihood of improvement corresponds to an increased release of endogenous dopamine in the ventral striatum. In depression, placebos activate brain areas associated with expectations and emotions, including the prefrontal-, anterior cingulate-, and motor cortices (Huneke et al., 2022; Murray and Stoessl, 2013). Interestingly, this neural pattern is similar to that seen in placebo analgesia, as discussed above.

In social anxiety, placebos have been found to change the connectivity between emotion-related brain regions, such as the amygdala, prefrontal cortex, and ACC, in a similar manner to selective serotonin reuptake inhibitors (Faria et al., 2014); one of the most used classes of anxiety medications.

In the nocebo effects in itch, negative expectations were associated with changes in connectivity between the insula and brainstem (van de Sand et al., 2018). Similarly, experimentally induced shortness of breath, together with negative verbal information, reduced activity in the ACC and increased activity in the brainstem (Vlemincx et al., 2021). These findings suggest a similar expectation-induced top-down modulation of itch and breathlessness as previously found in pain.

Together, these findings underscore the role of treatment expectations in modulating brain activity and alleviating symptoms across a spectrum of conditions, mirroring the effects of active medications.

Immunological

The nervous and immune systems communicate with each other. For example, stress influences the immune system, whereas immune responses can affect mood and behavior (Dhabhar et al., 2012; Herkenham & Kigar, 2017).

This bidirectional communication between the brain and body takes place via two types of pathways: efferent and afferent. Efferent pathways send signals from the brain either to "calm" the body via the vagus nerve and other components of the parasympathetic nervous system, or to "activate" the body via the sympathetic nervous system. Afferent pathways send signals from the body to the brain also using – among others - the vagus nerve. Furthermore, chemical signals, such as cytokines "inform" the brain about the status of the immune system (Bonaz et al., 2017; Quan, 2014).

Brain-immune communication facilitates the placebo effects in immune reactions. The immune response to contextual cues is a placebo effect itself, not a response to a placebo effect. As discussed previously, most of the time, classical conditioning is needed for placebo effects to occur on an immunological level (Albring et al., 2012; Schedlowski & Pacheco-López, 2010). Evidence for classically conditioned immunosuppression comes from studies employing specific conditioning paradigms, where a novel taste or scent is paired with an immunomodulating drug. When the taste is experienced again, even in the absence of the active drug, changes

occur in immune parameters that mimic those produced by the drug (Hadamitzky et al., 2013). The majority of evidence for conditioned immunosuppression stems from animal research. For instance, in murine models, the immunosuppressive drug cyclosporin A (as unconditioned stimulus) has often been combined with a taste (conditioned stimulus; saccharin solution). After classical conditioning, the exposure to the taste of saccharin can evoke significant immunosuppressive responses, including the reduction of cytokine release (e.g., interleukin 2; Hadamitzky et al., 2020). Cytokines are proteins that play a large role in immune regulation and the initiation and regulation of inflammatory responses (Zhang & An, 2009).

Similar classical conditioning paradigms have been investigated in humans and tested for their potential to affect medical conditions (Hadamitzky et al., 2020; Tekampe et al., 2017). For example, Kirchhof and colleagues (2018) found evidence of conditioned immunosuppression in 30 kidney transplant patients. On the first day of the study, patients were given the immunosuppressants cyclosporine A or tacrolimus to prevent organ rejection. During the subsequent three testing days, patients received cyclosporine A or tacrolimus alongside a novel gustatory stimulus. On the final two days of the study, the gustatory stimulus was paired with either the immunosuppressant or a placebo. The results showed that when the gustatory stimulus and placebo were administered, there was a significant, conditioned reduction in the proliferative capacity of T lymphocyte activity. These results indicate that the learned immunosuppressive, evoked by the taste stimulus, can enhance the efficacy of the drug without altering the dosage.

Nocebo immunomodulation can be evident as well. In one study, participants with seasonal allergies underwent classical conditioning, where a specific scent was paired with nasal administration of a seasonal grass allergen. One week later, participants were exposed to the scent paired with a placebo instead. This group exhibited increased nasal histamine levels compared to a control group that only ever received a placebo paired with the scent, thus demonstrating conditioned nocebo effects in allergic reactions (Barrett et al., 2000). Similarly, a study in healthy volunteers demonstrated that, after combining epinephrine (unconditioned stimulus) with a taste stimulus (CS; sweet drink), observed that, upon tasting the sweet drink alone, immune reactions were stimulated: natural killer (NK) cells activity increased significantly (Buske-Kirschbaum et al., 1992).

Despite these advances in our understanding of placebo and nocebo effects in immune responses. Nonetheless, these studies show that immune responses can be modulated through expectation.

Endocrine

Hormonal placebo and nocebo effects are also mostly evoked and studied using similar taste or scent conditioning paradigms. Cortisol and insulin release are the most widely investigated responses in the placebo endocrine literature.

Stockhorst and colleagues (2004, 2011) demonstrated increased insulin levels in response to a placebo. The researchers paired intravenous (2004) and intranasal (2011) insulin with a scent on the first days of testing. On the final day of testing, the scent was paired with a placebo, and insulin levels increased in the conditioning group, compared to a group who had only ever received placebo with the scent stimulus (Stockhorst et al., 2004, 2011). Nevertheless, this finding does not seem to be consistently replicated, as other studies failed to condition insulin (e.g., Skvortsova et al., 2023).

Stockhorst and colleagues (2004) also reported significant increases in growth hormone levels through this same classical conditioning paradigm. Similar effects were found in the study of Benedetti and colleagues (2003), where participants who had previously received an injection of sumatriptan showed a placebo-induced increase in growth hormone levels when given a placebo injection (Benedetti, Pollo, et al., 2003). In this case, the injection procedure, instead of a scent or taste, was the stimulus that evoked the conditioned placebo effect.

These studies provide evidence for the potential of placebo interventions to influence endocrine responses. Despite this promising evidence, not all studies have been able to find endocrine placebo effects (Overduin et al., 1997) and overall, the evidence appears mixed. Thus, more research is needed to explore placebo and nocebo effects of endocrine responses.

What this means for the healthcare context

Expanding on these concepts outlined above, the implications for clinical practice stemming from in-depth studies on the psycho-physiological mechanisms of placebo and nocebo effects are highly promising. While some findings may vary across studies, the overall insights gained point towards innovative future

therapeutic approaches that could yield substantial benefits for patients. Understanding how psychological and physiological factors interact to influence treatment outcomes opens possibilities for tailored interventions that leverage and mitigate nocebo responses. By incorporating this knowledge into clinical practice, healthcare professionals can develop more effective and personalized treatment strategies that optimize patient care and well-being. The groundwork laid by these studies offers exciting prospects for the evolution of therapies that capitalize on the mind-body connection to enhance overall patient outcomes.

2.8 Conclusion

In conclusion, this Module has provided a comprehensive exploration of the mechanisms underlying placebo and nocebo effects. We began by delving into the concept of expectations, highlighting their crucial role in these phenomena. By examining how expectations are shaped through various learning processes (i.e., classical and operant conditioning, observational learning, and learning by verbal suggestions/instructions), we gained insight into the psychological foundations of placebo and nocebo responses. Additionally, we discussed the significant influence of emotions, elucidating how they can modulate these effects. Finally, we explored the physiological processes that translate these psychological factors into observable outcomes in the body. Through this multifaceted approach, we have gained a deeper understanding of the intricate interplay between mind and body in placebo and nocebo effects.

References

Adamczyk, W. M., Wiercioch-Kuzianik, K., Bajcar, E. A., & Bąbel, P. (2019). Rewarded placebo analgesia: A new mechanism of placebo effects based on operant conditioning. *European Journal of Pain*, *23*(5), 923–935. https://doi.org/10.1002/ejp.1360

Albring, A., Wendt, L., Benson, S., Witzke, O., Kribben, A., Engler, H., & Schedlowski, M. (2012). Placebo Effects on the Immune Response in Humans: The Role of Learning and Expectation. *PLoS ONE*, *7*(11). https://doi.org/10.1371/journal.pone.0049477

Amanzio, M., Benedetti, F., Porro, C. A., Palermo, S., & Cauda, F. (2013). Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Human Brain Mapping*, *34*(3), 738–752. https://doi.org/10.1002/hbm.21471

Amanzio, M., Corazzini, L. L., Vase, L., & Benedetti, F. (2009). A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain*, *146*(3), 261–269. https://doi.org/10.1016/j.pain.2009.07.010

Anderson, S. R., Gianola, M., Perry, J. M., & Reynolds Losin, E. A. (2020). Clinician-patient racial/ethnic concordance influences racial/ethnic minority pain: Evidence from simulated clinical interactions. *Pain Medicine*, *21*(11), 3109–3125. https://doi.org/10.1093/PM/PNAA258

Aslaksen, P. M., & Flaten, M. A. (2008). The roles of physiological and subjective stress in the effectiveness of a placebo on experimentally induced pain. *Psychosomatic Medicine*, *70*(7), 811–818. https://doi.org/10.1097/PSY.0b013e31818105ed

Aslaksen, P. M., Zwarg, M. L., Eilertsen, H. I. H., Gorecka, M. M., & Bjørkedal, E. (2015). Opposite effects of the same drug: Reversal of topical analgesia by nocebo information. *Pain*, *156*(1), 39–46. https://doi.org/10.1016/j.pain.0000000000000004

Atlas, L. Y., & Wager, T. D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. In F. Benedetti (Ed.), *Placebo. Handbook of Experimental Pharmacology* (pp. 37–69). Springer. Link: https://link.springer.com/chapter/10.1007/978-3-662-44519-8_3

Bąbel, P. (2020). Operant conditioning as a new mechanism of placebo effects. *European Journal of Pain*, *24*(5), 902–908. https://doi.org/10.1002/ejp.1544

Bąbel, P., Bajcar, E. A., Adamczyk, W., Kicman, P., Lisińska, N., Świder, K., & Colloca, L. (2017). Classical conditioning without verbal suggestions elicits placebo analgesia and nocebo hyperalgesia. *PLoS ONE*, *12*(7). https://doi.org/10.1371/journal.pone.0181856

Bajcar, E. A., & Bąbel, P. (2018). How does observational learning produce placebo effects? A model integrating research findings. *Frontiers in Psychology*, *9*(2041). https://doi.org/10.3389/fpsyg.2018.02041

Bajcar, E. A., Wiercioch-Kuzianik, K., Adamczyk, W. M., & Bąbel, P. (2020). To Experience or to Be Informed? Classical Conditioning Induces Nocebo Hyperalgesia even when Placebo Analgesia Is Verbally Suggested - Results of a Preliminary Study. *Pain Medicine*, *21*(3), 548–560. https://doi.org/10.1093/pm/pnz123

Barrett, J. E., King, M. G., & Pang, G. (2000). Conditioning rhinitis in allergic humans. *Annals of the New York Academy of Sciences*, *917*, 853–859. https://doi.org/10.1111/j.1749-6632.2000.tb05451.x

Benedetti, F. (2014). Drugs and placebos: What's the difference?: Understanding the molecular basis of the placebo effect could help clinicians to better use it in clinical practice. *EMBO Reports*, *15*(4), 329–332. https://doi.org/10.1002/embr.201338399

Benedetti, F., Amanzio, M., Vighetti, S., & Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *Journal of Neuroscience*, *26*(46), 12014–12022. https://doi.org/10.1523/JNEUROSCI.2947-06.2006

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open Versus Hidden Medical Treatments: The Patient's Knowledge About a Therapy Affects the Therapy Outcome. *Prevention & Treatment*, *6*(1). https://doi.org/https://doi.org/10.1037/1522-3736.6.1.61a

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. *J Neurosci*, *23*(10), 4315–4323. https://doi.org/10.1523/JNEUROSCI.23-10-04315.2003

Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., & Tracey, I. (2011). The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil. *Science Transl Med*, *3*(70). https://doi.org/10.1126/scitranslmed.3001244

Bonaz, B., Sinniger, V., & Pellissier, S. (2017). The vagus nerve in the neuro-immune axis: Implications in the pathology of the gastrointestinal tract. *Frontiers in Immunology*, *8*(1452). https://doi.org/10.3389/fimmu.2017.01452

Borrell-Carrió, F., Suchman, A. L., & Epstein, R. M. (2004). The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. *The Annals of Family Medicine*, *2*(6), 576-582. https://doi.org/10.1370/afm.245

Bräscher, A. K., Kleinböhl, D., Hölzl, R., & Becker, S. (2017). Differential classical conditioning of the nocebo effect: Increasing heat-pain perception without verbal suggestions. *Frontiers in Psychology*, *8*(2163). https://doi.org/10.3389/fpsyg.2017.02163

Büchel, C., Geuter, S., Sprenger, C., & Eippert, F. (2014). Placebo analgesia: A predictive coding perspective. *Neuron*, *81*(6), 1223–1239. https://doi.org/10.1016/j.neuron.2014.02.042

Buske-Kirschbaum, A. N. G. E. L. I. K. A., Kirschbaum, C., Stierle, H., Lehnert, H., & Hellhammer, D. I. R. K. (1992). Conditioned increase of natural killer cell activity (NKCA) in humans. *Psychosomatic Medicine, 54*(2), 123-132. Link: https://journals.lww.com/psychosomaticmedicine/abstract/1992/03000/Conditioned_increase_of_natural_killer_cell.1.aspx

Byerly, H. (1976). Explaining and exploiting placebo effects. *Perspect Biol Med, 19*(3), 423-436. https://doi.org/10.1353/pbm.1976.0038

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behavioral and Brain Sciences*, *36*(3), 181–204. https://doi.org/10.1017/S0140525X12000477

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., & Colloca, L. (2015). The placebo effect: from concepts to genes. *Neuroscience, 307*, 171-190. https://doi.org/10.1016/j.neuroscience.2015.08.017

Colagiuri, B., & Quinn, V. F. (2018). Autonomic Arousal as a Mechanism of the Persistence of Nocebo Hyperalgesia. *Journal of Pain*, *19*(5), 476–486. https://doi.org/10.1016/j.jpain.2017.12.006

Colagiuri, B., & Zachariae, R. (2010). Patient expectancy and post-chemotherapy nausea: a meta-analysis. *Annals of Behavioral Medicine, 40*(1), 3-14. https://doi.org/10.1007/s12160-010-9186-4

Coleshill, M. J., Sharpe, L., Colloca, L., Zachariae, R., & Colagiuri, B. (2018). Placebo and Active Treatment Additivity in Placebo Analgesia: Research to Date and Future Directions. *International Review of Neurobiology*, *139*, 407–441. https://doi.org/10.1016/bs.irn.2018.07.021

Colloca, L. (2024). The Nocebo Effect. *Annual Review of Pharmacology and Toxicology*, *64*, 171–190. https://doi.org/10.1146/annurev-pharmtox-022723-112425

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain*, *124*(1–2), 126–133. https://doi.org/10.1016/j.pain.2006.04.005

Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *Pain*, *144*(1–2), 28–34. https://doi.org/10.1016/j.pain.2009.01.033

Colloca, L., & Miller, F. G. (2011). How placebo responses are formed: A learning perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366*(1572), 1859–1869. https://doi.org/10.1098/rstb.2010.0398

Colloca, L., & Miller, F. G. (2011). The nocebo effect and its relevance for clinical practice. *Psychosomatic medicine*, *73*(7), 598-603. 10.1097/PSY.0b013e3182294a50 Link: https://journals.lww.com/psychosomaticmedicine/fulltext/2011/09000/the_nocebo_effect_and_its_relevance_for_clinical.12.aspx?casa_token=Xj6U36_t-hEAAAAA:6FmJmHvi4BdPFAT4KT99p-PWc5JHeILPhwIZSu7kVBK1dWgCPv6PVSr9Y4GM5z9gC6qDEQIqo-XuQpYIusdoK0UX9lQhRRY

Colloca, L., Sigaudo, M., & Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *PAIN®*, *136*(1-2), 211-218. https://doi.org/10.1016/j.pain.2008.02.006

Crow, R., Gage, H., Hampson, S., Hart, J., Kimber, A., & Thomas, H. (1999). The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health Technol Assess*, *3*(3), 1–96. http://hdl.handle.net/2299/12604

Dhabhar, F. S., Malarkey, W. B., Neri, E., & McEwen, B. S. (2012). Stress-induced redistribution of immune cells-From barracks to boulevards to battlefields: A tale of three hormones - Curt Richter Award Winner. *Psychoneuroendocrinology*, *37*(9), 1345–1368. https://doi.org/10.1016/j.psyneuen.2012.05.008

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet*, *357*(9258), 757–762. https://doi.org/10.1016/S0140-6736(00)04169-6

Elsenbruch, S., Roderigo, T., Enck, P., & Benson, S. (2019). Can a brief relaxation exercise modulate placebo or nocebo effects in a visceral pain model? *Frontiers in Psychiatry*, *10*(144). https://doi.org/10.3389/fpsyt.2019.00144

Faria, V., Åhs, F., Appel, L., Linnman, C., Bani, M., Bettica, P., Pich, E. M., Fredrikson, M., & Furmark, T. (2014). Amygdala-frontal couplings characterizing SSRI and placebo response in social anxiety disorder. *International Journal of Neuropsychopharmacology*, *17*(8), 1149–1157. https://doi.org/10.1017/S1461145714000352

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Placebo effects: biological, clinical and ethical advances. *Lancet*, *375*(9715), 686. https://doi.org/10.1016%2FS0140-6736(09)61706-2

Frakes, M. D., & Gruber, J. (2022). Racial concordance and the quality of medical care: Evidence from the military (No. w30767). *National Bureau of Economic Research*. https://www.nber.org/papers/w30767

Frisaldi, E., Piedimonte, A., & Benedetti, F. (2015). Placebo and Nocebo Effects: A Complex Interplay Between Psychological Factors and Neurochemical Networks. *American Journal of Clinical Hypnosis*, *57*(3), 267–284. https://doi.org/10.1080/00029157.2014.976785

Fu, J., Wu, S., Liu, C., Camilleri, J. A., Eickhoff, S. B., & Yu, R. (2021). Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *Neuroimage*, *231*, 117833. https://doi.org/10.1016/j.neuroimage.2021.117833

Geers, A. L., Close, S., Caplandies, F. C., & Vase, L. (2019a). A Positive Mood Induction for Reducing the Formation of Nocebo Effects from Side Effect Information. *Annals of Behavioral Medicine*, *53*(11), 999–1008. https://doi.org/10.1093/abm/kaz005

Geers, A. L., Close, S., Caplandies, F. C., Vogel, C. L., Murray, A. B., Pertiwi, Y., Handley, I. M., & Vase, L. (2019b). Testing a positive-affect induction to reduce verbally induced nocebo hyperalgesia in an experimental pain paradigm. *Pain*, *160*(10), 2290–2297. https://doi.org/10.1097/j.pain.0000000000001618

Geers, A. L., Faasse, K., Guevarra, D. A., Clemens, K. S., Helfer, S. G., & Colagiuri, B. (2021). Affect and emotions in placebo and nocebo effects: What do we know so far? *Social and Personality Psychology Compass*, *15*(1). https://doi.org/10.1111/spc3.12575

Haanstra, T. M., Van Den Berg, T., Ostelo, R. W., Poolman, R. W., Jansma, I. P., Cuijpers, P., & de Vet, H. C. W. (2012). Systematic review: Do patient expectations influence treatment outcomes in total knee and total hip arthroplasty? *Health and Quality of Life Outcomes*, *10*(152). https://doi.org/10.1186/1477-7525-10-152

Hadamitzky, M., Engler, H., & Schedlowski, M. (2013). Learned immunosuppression: Extinction, renewal, and the challenge of reconsolidation. *Journal of Neuroimmune Pharmacology*, *8*(1), 180–188. https://doi.org/10.1007/s11481-012-9388-6

Hadamitzky, M., Lückemann, L., Pacheco-López, G., & Schedlowski, M. (2020). Pavlovian conditioning of immunological and neuroendocrine functions. *Physiological reviews*, *100*(1), 357-405. https://doi.org/10.1152/physrev.00033.2018

Hall, O. T., Jordan, A., Teater, J., Dixon-Shambley, K., McKiever, M. E., Baek, M., Garcia, S., Rood, K. M., & Fielin, D. A. (2022). Experiences of racial discrimination in the medical setting and associations with medical mistrust and expectations of care among black patients

seeking addiction treatment. *Journal of Substance Abuse Treatment*, *133*(108551). https://doi.org/10.1016/j.jsat.2021.108551

Hechler, T., Endres, D., & Thorwart, A. (2016). Why harmless sensations might hurt in individuals with chronic pain: About heightened prediction and perception of pain in the mind. *Frontiers in Psychology*, *7*(1638). https://doi.org/10.3389/fpsyg.2016.01638

Herkenham, M., & Kigar, S. L. (2017). Contributions of the adaptive immune system to mood regulation: Mechanisms and pathways of neuroimmune interactions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *79*(Pt A), 49–57. https://doi.org/10.1016/j.pnpbp.2016.09.003

Howe, L. C., Leibowitz, K. A., & Crum, A. J. (2019). When your doctor "Gets it" and "Gets you": The critical role of competence and warmth in the patient-provider interaction. *Frontiers in Psychiatry*, *10*(475). https://doi.org/10.3389/fpsyt.2019.00475

Howe, L., Goyer, J., & Crum, A. (2017). Harnessing the Placebo Effect: Exploring the Influence of Physician Characteristics on Placebo Response. *Health Psychology*, *36*(11), 1074–1082. https://doi.org/10.1037/hea0000499.supp

Huneke, N. T. M., Aslan, I. H., Fagan, H., Phillips, N., Tanna, R., Cortese, S., Garner, M., & Baldwin, D. S. (2022). Functional neuroimaging correlates of placebo response in patients with depressive or anxiety disorders: A systematic review. I*nternational Journal of Neuropsychopharmacology*, *25*(6), 433–447. https://doi.org/10.1093/ijnp/pyac009

Illari, P. M. K., & Williamson, J. (2012). What is a mechanism? Thinking about mechanisms across the sciences. *European Journal for Philosophy of Science*, *2*(1), 119–135. https://doi.org/10.1007/s13194-011-0038-2

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., Kirsch, I., Schyner, R. N., Bong, H. N., Nguyen, L. T., Park, M., Rivers, A. L., McManus, C., Kokkotou, E., Drossman, D. A., Goldman, P., & Lembo, A. J. (2008). Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *BMJ*, *336*(7651), 999–1003. https://doi.org/10.1136/bmj.39524.439618.25

Kirchhof, J., Petrakova, L., Brinkhoff, A., Benson, S., Schmidt, J., Unteroberdörster, M., Wilde, B., Kaptchuk, T. J., Witzke, O., & Schedlowski, M. (2018). Learned immunosuppressive placebo responses in renal transplant patients. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(16), 4223–4227. https://doi.org/10.1073/pnas.1720548115

Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American psychologist*, *40*(11), 1189. https://psycnet.apa.org/doi/10.1037/0003-066X.40.11.1189

Kirsch, I. E. (1999). How expectancies shape experience. American Psychological Association.

Ku, L., & Vichare, A. (2023). The association of racial and ethnic concordance in primary care with patient satisfaction and experience of care. *Journal of general internal medicine*, *38*(3), 727-732. https://doi.org/10.1007/s11606-022-07695-y

Kugler, J., & Verghese, A. (2010). The physical exam and other forms of fiction. *Journal of General Internal Medicine*, *25*(8), 756–757. https://doi.org/10.1007/s11606-010-1400-3

Laveist, T. A., & Nuru-Jeter, A. (2002). Is Doctor-Patient Race Concordance Associated with Greater Satisfaction with Care? *Journal of Health and Social Behavior*, *43*(3), 296–306. https://doi.org/https://doi.org/10.2307/3090205

Levine, J. D., Gordon, N. C., & Howard, L. F. (1978). The Mechanism of Placebo Analgesia. *The Lancet*, *312*(8091), 654–657. https://doi.org/https://doi.org/10.1016/S0140-6736(78)92762-9

McKay, K. M., Imel, Z. E., & Wampold, B. E. (2006). Psychiatrist effects in the psychopharmacological treatment of depression. *Journal of Affective Disorders*, *92*(2–3), 287–290. https://doi.org/10.1016/j.jad.2006.01.020

Meeuwis, S. H., Wasylewski, M. T., Bajcar, E. A., Bieniek, H., Adamczyk, W. M., Honcharova, S., ... & Bąbel, P. (2023). Learning pain from others: a systematic review and meta-analysis of studies on placebo hypoalgesia and nocebo hyperalgesia induced by observational learning. Pain, 164(11), 2383-2396. 10.1097/j.pain.0000000000002943 Link: https://journals.lww.com/pain/fulltext/2023/11000/learning_pain_from_others__a_systematic_review_and.1.aspx?context=featuredarticles&collectionid=2

Meeuwis, S. H., Middendorp, H. V., Veldhuijzen, D. S., Van Laarhoven, A. I., Houwer, J. D., Lavrijsen, A. P., & Evers, A. W. (2018). Placebo effects of open-label verbal suggestions on itch. https://repository.ubn.ru.nl/bitstream/handle/2066/190969/190969.pdf

Miller, A. N., Duvuuri, V. N. S., Vishanagra, K., Damarla, A., Hsiao, D., Todd, A., & Toledo, R. (2023). The Relationship of Race/Ethnicity Concordance to Physician-Patient Communication: A Mixed-Methods Systematic Review. *Health Communication*, 1-15. https://doi.org/10.1080/10410236.2023.2223402

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *Pain*, *72*(1–2), 107–113. https://doi.org/10.1016/s0304-3959(97)00016-x

Moore, R. A., Cai, N., Skljarevski, V., & Tölle, T. R. (2014). Duloxetine use in chronic painful conditions - Individual patient data responder analysis. *European Journal of Pain*, *18*(1), 67–75. https://doi.org/10.1002/j.1532-2149.2013.00341.x

Morales-Quezada, L., Mesia-Toledo, I., Estudillo-Guerra, A., O'Connor, K. C., Schneider, J. C., Sohn, D. J., Crandell, D. M., Kaptchuk, T., & Zafonte, R. (2020). Conditioning open-label placebo: A pilot pharmacobehavioral approach for opioid dose reduction and pain control. *Pain Reports*, *5*(4). https://doi.org/10.1097/PR9.0000000000000828

Murray, D., & Stoessl, A. J. (2013). Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacology and Therapeutics*, *140*(3), 306–318. https://doi.org/10.1016/j.pharmthera.2013.07.009

Ongaro, G., & Kaptchuk, T. J. (2019). Symptom perception, placebo effects, and the Bayesian brain. *Pain*, *160*(1), 1–4. https://doi.org/10.1097/j.pain.0000000000001367

O'Reilly, J. X., Jbabdi, S., & Behrens, T. E. J. (2012). How can a Bayesian approach inform neuroscience? *European Journal of Neuroscience*, *35*(7), 1169–1179. https://doi.org/10.1111/j.1460-9568.2012.08010.x

Overduin, J., Jansen, A., & Jansen, A. (1997). Conditioned Insulin and Blood Sugar Responses in Humans in Relation to Binge Eating. *Physiology & Behavior*, *61*(4), 569–575. https://doi.org/10.1016/s0031-9384(96)00504-5

Papakostas, G. I., & Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *European Neuropsychopharmacology*, *19*(1), 34–40. https://doi.org/10.1016/j.euroneuro.2008.08.009

Ploghaus, A., Narain, C., Beckmann, C. F., Clare, S., Bantick, S., Wise, R., Matthews, P. M., Nicholas, J., Rawlins, P., & Tracey, I. (2001). Exacerbation of Pain by Anxiety Is Associated with Activity in a Hippocampal Network. *J Neurosci*, *21*(24), 9896–9903. https://doi.org/10.1523/JNEUROSCI.21-24-09896.2001

Pollo, A., Amanzio, M., Arslanian, A., Casadio, C., Maggi, G., & Benedetti, F. (2001). Response expectancies in placebo analgesia and their clinical relevance. *PAIN*, *93*(1), 77–84. https://doi.org/10.1016/S0304-3959(01)00296-2

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.*, *59*, 565-590. https://doi.org/10.1146/annurev.psych.59.113006.095941

Quan, N. (2014). In-depth conversation: Spectrum and kinetics of neuroimmune afferent pathways. *Brain, Behavior, and Immunity*, *40*(1–8), 1–8. https://doi.org/10.1016/j.bbi.2014.02.006

Quattrone, A., Barbagallo, G., Cerasa, A., & Stoessl, A. J. (2018). Neurobiology of placebo effect in Parkinson's disease: What we have learned and where we are going. *Movement Disorders, 33*(8), 1213–1227. https://doi.org/10.1002/mds.27438

Rief, W., Avorn, J., & Barsky, A. J. (2006). Medication-Attributed Adverse Effects in Placebo Groups Implications for Assessment of Adverse Effects. *Arch Intern Med, 166*(2), 155–160. https://doi.org/10.1001/archinte.166.2.155

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of Affective Disorders, 118*(1–3), 1–8. https://doi.org/10.1016/j.jad.2009.01.029

Rodriguez-Raecke, R., Doganci, B., Breimhorst, M., Stankewitz, A., Büchel, C., Birklein, F., & May, A. (2010). Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. *Journal of Neuroscience, 30*(34), 11363-11368. https://doi.org/10.1523/JNEUROSCI.2197-10.2010

Romanella, S. M., Mencarelli, L., Burke, M. J., Rossi, S., Kaptchuk, T. J., & Santarnecchi, E. (2023). Targeting neural correlates of placebo effects. *COGNITIVE AFFECTIVE & BEHAVIORAL NEUROSCIENCE, 23*(1), 217–236. https://doi.org/10.3758/s13415-022-01039-3

Roese, N. J., & Sherman, J. W. (2023). Expectancies. https://escholarship.org/uc/item/90v8b07m

Rutherford, B. R., Sneed, J. R., & Roose, S. P. (2009). Does study design influence outcome? - The effects of placebo control and treatment duration in antidepressant trials. *Psychotherapy and Psychosomatics, 78*(3), 172–181. https://doi.org/10.1159/000209348

Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. *Pharmacological Reviews, 67*(3), 697–730. https://doi.org/10.1124/pr.114.009423

Schedlowski, M., & Pacheco-López, G. (2010). The learned immune response: Pavlov and beyond. *Brain, Behavior, and Immunity, 24*(2), 176–185. https://doi.org/10.1016/j.bbi.2009.08.007

Segerdahl, A. R., Mezue, M., Okell, T. W., Farrar, J. T., & Tracey, I. (2015). The dorsal posterior insula subserves a fundamental role in human pain. *Nature neuroscience, 18*(4), 499-500. https://doi.org/10.1038/nn.3969

Skvortsova, A., Veldhuijzen, D. S., Van Dillen, L. F., Zech, H., Derksen, S. M., Sars, R. H., ... & Evers, A. W. (2023). Influencing the Insulin System by Placebo Effects in Patients With Diabetes Type 2 and Healthy Controls: A Randomized Controlled Trial. *Psychosomatic Medicine, 85*(6), 551-560. Link:

https://journals.lww.com/psychosomaticmedicine/fulltext/2023/07000/influencing_the_insulin_system_by_placebo_effects.12.aspx

Stockhorst, U., De Fries, D., Steingrueber, H. J., & Scherbaum, W. A. (2011). Unconditioned and conditioned effects of intranasally administered insulin vs placebo in healthy men: A randomised controlled trial. *Diabetologia*, *54*(6), 1502–1506. https://doi.org/10.1007/s00125-011-2111-y

Stockhorst, U., Mahl, N., Krueger, M., Huenig, A., Schottenfeld-Naor, Y., Huebinger, A., Berresheim, H. W., Steingrueber, H. J., & Scherbaum, W. A. (2004). Classical conditioning and conditionability of insulin and glucose effects in healthy humans. *Physiology and Behavior*, *81*(3), 375–388. https://doi.org/10.1016/j.physbeh.2003.12.019

Świder, K., & Bąbel, P. (2013). The effect of the sex of a model on nocebo hyperalgesia induced by social observational learning. *PAIN®, 154*(8), 1312-1317. https://doi.org/10.1016/j.pain.2013.04.001

Szpunar, K. K. (2010). Episodic future thought: An emerging concept. *Perspectives on Psychological Science, 5*(2), 142-162. https://doi.org/10.1177/1745691610362350

Takahashi, K. J., & Earl, A. (2020). Effect of Extraneous Affect on Health Message Reception. *Personality and Social Psychology Bulletin*, *46*(2), 270–284. https://doi.org/10.1177/0146167219855042

Tekampe, J., van Middendorp, H., Sweep, F. C., Roerink, S. H., Hermus, A. R., & Evers, A. W. (2018). Human pharmacological conditioning of the immune and endocrine system: challenges and opportunities. *International review of neurobiology, 138*, 61-80. https://doi.org/10.1016/bs.irn.2018.01.002

Tekampe, J., van Middendorp, H., Meeuwis, S. H., van Leusden, J. W., Pacheco-López, G., Hermus, A. R., & Evers, A. W. (2017). Conditioning immune and endocrine parameters in humans: a systematic review. *Psychotherapy and psychosomatics, 86*(2), 99-107. https://doi.org/10.1159/000449470

Tyng, C. M., Amin, H. U., Saad, M. N. M., & Malik, A. S. (2017). The influences of emotion on learning and memory. *Frontiers in Psychology*, *8*(1454). https://doi.org/10.3389/fpsyg.2017.01454

Van den Bergh, O., Witthöft, M., Petersen, S., & Brown, R. J. (2017). Symptoms and the body: Taking the inferential leap. *Neuroscience and Biobehavioral Reviews*, *74*(Pt A), 185–203. https://doi.org/10.1016/j.neubiorev.2017.01.015

Van de Sand, M. F., Menz, M. M., Sprenger, C., & Büchel, C. (2018). Nocebo-induced modulation of cerebral itch processing – An fMRI study. *NeuroImage*, *166*, 209–218. https://doi.org/10.1016/j.neuroimage.2017.10.056

Verghese, A., Brady, E., Cari, ;, Kapur, C., & Horwitz, R. I. (2011). The Bedside Evaluation: Ritual and Reason. *Ann Intern Med*, *155*(8), 550–553. https://doi.org/10.7326/0003-4819-155-8-201110180-00013

Vlemincx, E., Sprenger, C., & Büchel, C. (2021). Expectation and dyspnoea: The neurobiological basis of respiratory nocebo effects. *European Respiratory Journal*, *58*(3). https://doi.org/10.1183/13993003.03008-2020

Vögtle, E., Barke, A., & Kröner-Herwig, B. (2013). Nocebo hyperalgesia induced by social observational learning. *Pain*, *154*(8), 1427–1433. https://doi.org/10.1016/j.pain.2013.04.041

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of Medicine*, *368*(15), 1388–1397. https://doi.org/10.1056/nejmoa1204471

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. *Science*, *20*(303(5661)), 1162–1167. https://doi.org/10.1126/science.1093065

Wechsler, M. E., Kelley, J. M., Boyd, I. O. E., Dutile, S., Marigowda, G., Kirsch, I., Israel, E., & Kaptchuk, T. J. (2011). Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med*, *365*(2), 119–126. https://doi.org/10.1056/NEJMoa1103319

Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. I*nternational anesthesiology clinics*, *45*(2), 27-37. 10.1097/AIA.0b013e318034194e Link: https://journals.lww.com/anesthesiaclinics/fulltext/2007/04520/Cytokines,_Inflammation,_and_Pain.4.aspx?casa_token=xk2t7tKFkJQAAAAA:MZXErLssYYxwJ_RqV10kwcSfE5Wt0BXvKliegLCBwAIWkkF_0EEYnaos7TDw2mvib90Du0vMSJ363uui1Yol1axMFQ

Zunhammer, M., Bingel, U., & Wager, T. D. (2018). Placebo Effects on the Neurologic Pain Signature: A Meta-analysis of Individual Participant Functional Magnetic Resonance Imaging Data. *JAMA Neurology*, *75*(11), 1321–1330. https://doi.org/10.1001/jamaneurol.2018.2017

Zunhammer, M., Spisák, T., Wager, T. D., Bingel, U., Atlas, L., Benedetti, F., Büchel, C., Choi, J. C., Colloca, L., Duzzi, D., Eippert, F., Ellingsen, D. M., Elsenbruch, S., Geuter, S., Kaptchuk, T. J., Kessner, S. S., Kirsch, I., Kong, J., Lamm, C., … Zeidan, F. (2021). Meta-analysis of neural

systems underlying placebo analgesia from individual participant fMRI data. *Nature Communications, 12*(1), 1–11. https://doi.org/10.1038/s41467-021-21179-3

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PANACEA Learning Materials

Module 3: Assessing placebo/nocebo effects and responses

Module information

One of the primary objectives of this Module is to equip with the essential tools to evaluate and quantify observed changes in symptoms, discerning whether they stem from placebo/nocebo effects or responses. By the end of this module, a comprehensive understanding of how to differentiate and interpret these effects accurately will be obtained, enhancing the ability to navigate and evaluate clinical outcomes effectively.

3.1. Overview

The assessment of placebo and nocebo effects and responses involves distinguishing these phenomena from other factors that may contribute to changes in health. Identifying whether an observed change in symptoms is a result of a placebo or nocebo effect, or if it is due to other influences, requires careful evaluation of the underlying mechanisms and conditions. The magnitude of placebo or nocebo responses and effects can be measured in various ways, taking into account not only the individual's self-reported experience but also clinical observations and objective physiological markers. Outcome measures for assessing placebo and nocebo effects typically include self-report questionnaires, clinician-assessed evaluations, and physiological measures, each providing valuable insights into the nature and extent of the effects. By comparing these different types of measures, researchers can gain a comprehensive understanding of the placebo and nocebo phenomena, helping to refine the methods used to evaluate and manage them in both clinical and experimental settings.

3.2. How to differentiate between placebo/nocebo effects from other factors responsible of health changes

Introduction

From Module 1, we learned that placebo and nocebo *effects* are positive and negative health changes that occur specifically due to mechanisms activated by the psychosocial context surrounding the patient and stemming from expectations

influenced by learning from direct experience, verbal suggestion, or observing others (Evers et al., 2018). Differently, the placebo or nocebo *response* includes all health changes occurring after administration of an inert treatment, such as a placebo pill, as in clinical trials or open label placebo (see Module 8 for details). It includes placebo effects but also other non-specific factors (Evers et al., 2018).

Module 1 also taught us that in the field of pharmacology, the specific effects of a drug are those directly linked to its pharmacological action. In contrast, non-specific drug effects are those not directly linked to the drug's mechanism of action but caused by other aspects of the drug's administration (including placebo/nocebo effects). Placebo and nocebo *responses* can be understood as the sum of the specific and non-specific effects of an inert treatment.

Specifically, potential components of placebo/nocebo responses include 1) natural fluctuations of symptoms, also known as the *natural history* of a disease, where symptoms naturally vary over time; or 2) statistical phenomena, such as *regression to the mean*. Extreme values, such as intense pain, tend to revert to average values, like moderate pain, upon subsequent measurements. For example, consider patients who are recruited into clinical trials when their symptoms are particularly severe. Due to the high level of pain, they are experiencing at the time of recruitment, their initial pain scores are extreme. However, as time goes on, it is likely that their pain will decrease to some degree simply due to the natural fluctuation in their symptoms. As a result, their pain scores at later times will be closer to the average level of pain, demonstrating regression to the mean. This phenomenon helps explain why symptom scores often decrease over the course of a trial, even if the treatment being tested is not particularly effective. Thus, instances of regression to the mean (e.g., reduced pain) might be misconstrued as placebo effects (e.g., placebo-induced pain relief). Moreover, 3) *response bias*, caused by a conscious or unconscious preference for one response over others, may also contribute to placebo responses. For example, participants may overstate the positive effects of a placebo to please researchers or healthcare professionals. All these incidental phenomena can, but should not, be confused as improvements caused by a drug or placebo effects. Therefore, researchers and clinicians must know how to separate them from the specific, intended effects of a drug or placebo mechanism. Finally, 4) *co-interventions* can enhance symptom improvement beyond the effects of the primary therapy. For instance, changes in the patient's lifestyle, such as adopting a healthier diet, and increasing physical activity, can significantly contribute to

symptoms' variation. Additionally, other factors like social support, and complementary therapies (e.g., psychotherapy) can also play a crucial role in symptom relief and overall health improvement.

3.3. Determining placebo/nocebo responses and effects

Introduction

Placebo and nocebo effects and responses are mainly studied in two settings*: randomized controlled trials (RCTs)* and *basic research on placebo/nocebo mechanism*. Most often, RCTs use placebo interventions as controls to test the effectiveness of active treatments, whereas mechanism studies explore the underlying psychological, social, and physiological processes that cause placebo/nocebo effects.

How to determine whether an observed change in symptoms is a placebo/nocebo effect or response

To show a placebo/nocebo effect, it is necessary to separate the effects specifically caused by the placebo mechanisms from the effects that are not specific to the placebo. This is done by comparing a group given an inert treatment with a group that receives no treatment, often referred to as a *natural history* or *no-treatment group*. The no-treatment group accounts for effects unrelated to the placebo mechanism, such as the natural course of disease. The placebo or nocebo response is measured by comparing symptoms within a placebo pill group before and after the intervention. The placebo/nocebo effect is part of this response, but to clearly separate it, the no-treatment control group is needed.

Placebo group is compared with natural history group and depending on the direction of the difference between them (increase or decrease of the symptoms), researchers infer whether the placebo or nocebo effect was induced.

Analogously as above - placebo and nocebo response are the effect of placebo intervention; the direction of the effect decides on which type of response was induced.

How to determine the magnitude of a placebo/nocebo response

In RCTs of medical treatments, the interest is usually focused more on the active treatment than the placebo. Therefore, most RCTs include a placebo group but not a

no-treatment group. As we discussed above, this setup allows for measuring placebo/nocebo responses, but not placebo/nocebo effects.

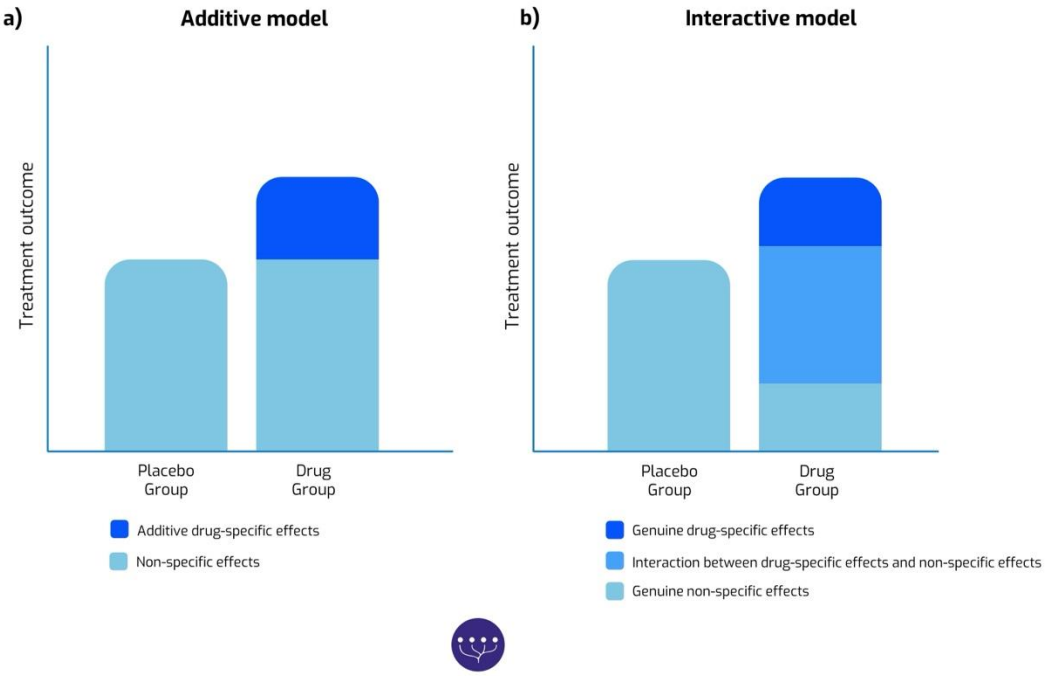
RCTs have two main objectives. The first objective is to separate the specific effects of the active treatment from the non-specific ones. By comparing a group receiving the active treatment with one receiving an inert treatment (e.g. a placebo pill), researchers can identify which symptom changes are directly caused by the active treatment and which ones are placebo responses.

In RCTs, the placebo group is thus used to measure the non-specific effects of a treatment (i.e., the placebo response), while the active-treatment group measures both the specific effects *and* the non-specific effects. Therefore, the difference between the active treatment and placebo group is seen as the true effect of the active treatment.

You may have noticed that this method assumes that the treatment effect and the placebo response add up (see Fig. 3.1: a). However, some experts theorize that the specific and non-specific effects of a treatment are more likely to be interactive than additive (Kube & Rief, 2017). These authors suggest that the specific effects, such as the pharmacokinetics of a drug, and non-specific effects, such as the patient's expectations about the drug, interact. For example, if the drug causes noticeable physical changes, it might increase a patient's belief in the drug's effectiveness, thus enhancing the drug's positive effects (Kube & Rief, 2017; see Fig. 3.1: b).

Figure 3.1

A comparison of the additive model and the interactive model



Note. (a) The additive model assumes that the total effect in the drug group additively comprises drug-specific and non-specific effects. (b) By contrast to the additive model, the interactive model considers an interaction between drug-specific and non-specific effects in addition to genuine drug-specific effects and genuine non-specific effects. Figure copied from Kube & Rief, 2017.

The second objective of RCTs is to assess symptom changes before and after treatment. This comparison helps researchers understand the overall effect of the active treatment. Likewise, by comparing symptoms in the placebo group before and after treatment, researchers can obtain the overall response to the placebo (rather than how it compares to the active treatment). Therefore, the magnitude of the placebo or nocebo response is determined by comparing symptoms before and after treatment within a placebo group (see Box 3.1.).

Box 3.1. Example of an RCT measuring the placebo/nocebo response

In a seminal RCT, Cobb and colleagues (1959) investigated the effectiveness of mammary artery ligation for treating angina pectoris. In the study, one group was subjected to a simple skin incision. This is a fake, or a *sham,* surgery. The other group received the actual surgery. When the two groups were compared, the surgery did not demonstrate greater effectiveness than the sham surgery. In fact, both groups improved significantly (Cobb et al., 1959). Therefore, the effect of the active treatment was small, while the placebo response was substantial.

How to determine the magnitude of a placebo/nocebo effect

Some RCTs not only account for the placebo response but also specifically study the placebo effect (see Box 3.2.). In these trials, comparing a placebo group with a no-treatment control group helps researchers distinguish the placebo-related changes from non-specific changes that would happen naturally, without any intervention. Thus, the magnitude of the placebo or nocebo effect is determined by the difference in symptoms between a placebo group and a no-treatment group.

It should be noted that RCTs in general seem to underestimate the magnitude of the placebo effect. This is because participants in RCTs are typically informed that they might be receiving inactive treatment. This can reduce how much people expect to experience treatment effects, thus reducing the difference between the placebo group and the no-treatment group (Colagiuri, et al., 2010; Vase et al., 2002).

Box 3.2. Example of an RCT measuring the placebo effect

In an RCT, Kaptchuk and colleagues (2010) studied how an open-label placebo affected irritable bowel syndrome (IBS) symptoms. Patients with IBS were split into two groups: one received a placebo openly (they knew the pills were inactive) and the other group received no treatment. Both groups had the same level of interaction with healthcare providers, including a 15-minute information session about the placebo effect. The placebo group took two placebo pills daily for 21 days. At the end of the study, the placebo group showed significantly improved IBS symptoms compared the no-treatment group, indicating a strong placebo effect (Kaptchuk et al., 2010).

Placebo/nocebo mechanism studies focus on the specific effects of a placebo, and thus also typically compare a placebo group with a no-treatment control group to identify the specific placebo effect. However, mechanism studies often employ unique and creative research designs tailored to each study to adequately address the complex and specific research questions they seek to answer (see Box 3.3.).

Box 3.3. Example of a mechanism study measuring the placebo effect

In a placebo mechanism study by Wager and colleagues (2004), healthy participants had an inactive cream applied to their arms. One group, the placebo group, was told the cream was a painkiller and that it would reduce the pain associated with an electrical stimulus. The other group, the no-treatment control, received no information about the cream. Despite both groups receiving the same inert cream and identical electrical stimuli, the placebo group reported less pain. This indicates that the mere expectation of pain relief can lead to actual pain relief, implicating positive expectations as a mechanism explaining the placebo effect (Wager et al., 2004).

3.4. Outcome measures of placebo/nocebo effects/responses

Introduction

Placebo and nocebo effects are present in many clinical conditions, and ultimately, there are as many ways to measure them as there are research questions in clinical studies. Generally, the methods and measures for assessing the effects, responses, and mechanisms of placebos resemble those used for testing the effectiveness of active treatments.

The reason for this overlap is that placebo interventions can cause changes in self-reported experiences, clinical outcomes, and physiological responses, similar to those caused by active treatments (Ortega et al., 2022; Schedlowski et al., 2015). It is important to highlight that the RCTs themselves do not aim to assess placebo responses, but researchers investigate these responses later. Researchers assess placebo responses in the same outcomes used to assess the effectiveness of pharmacological interventions, which are usually measured in self-report, and physiological or biological measures.

In the next section, we will detail some common outcome measures in placebo research, including examples of how these have been used in experiments. We will focus on pain, depression, and Parkinson's disease, as the majority of placebo and nocebo research centers on these conditions (Schedlowski et al., 2015).

The measurement of placebo and nocebo effects thus involves a combination of self-report assessed, clinician-assessed, and physiological measures.

Self-report measures

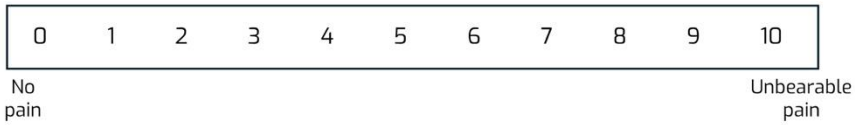
With self-report measures, information about the personal experiences of patients or research participants is obtained directly from them. Key types of self-report measures include:

1. *Visual Analog Scales (VAS)*: Here, participants rate their experiences on a continuous scale. This method is frequently used for assessing pain intensity (see below for an example; see Box 3.4.).

Visual Analogue Scale (VAS)

2. *Numerical Rating Scales (NRS)*: In this approach, participants use a scale with distinct numerical points to specify the intensity or frequency of their experiences (see below for an example).

Numerical Rating Scale (NRS)



3. *Questionnaires* involve participants answering a set of structured, standardized questions. These include validated scales for conditions, such as pain or depression. These questionnaires are carefully designed to elicit quantifiable responses, which can be analyzed to get a better understanding of a person's clinical condition (see Box 3.5.). In measuring nocebo effects, patients are prompted to report any potential symptoms (e.g. side effects) either openly or by selecting them from a provided list. Additionally, they may be asked to assess by scale the intensity of these symptoms if necessary.

Box 3.4. Example of a study measuring the placebo/nocebo effect using a Visual Analog Scale

In a placebo/nocebo mechanism study by Tu and colleagues (2021), participants were told they would receive a pain-relieving (lidocaine) cream on one part of their arm and a pain-increasing (capsaicin) cream on another. In reality, both creams were inert, with the "lidocaine" cream colored blue and the "capsaicin" cream colored pink.

Initially, experimenters applied mild heat pain to the "lidocaine" area and intense heat pain to the "capsaicin" area. Participants rated their pain on a Visual Analog Scale. On a later date, with the same cream applied in the same two colors, both areas received moderate, equal heat pain. Participants reported their pain on the Visual Analog Scale again. Despite the pain stimuli being equally intense, pain reports were lower for the "lidocaine" area than the "capsaicin" area, indicating placebo pain *relief* in the "lidocaine" area and nocebo pain *increases* in the "capsaicin" area (Tu et al., 2021).

Box 3.5. Example of a study measuring the placebo effect using a standardized questionnaire

Peciña and colleagues (2015) investigated placebo effects in depression. Participants were split into two groups. One group received a deceptive placebo, taking two inert pills daily for a week under the belief that the pills were a fast-acting antidepressant. The other group also took two inert pills daily for a week, but knew they were inactive.

Both groups' depression severity was measured using the 16-Item Quick Inventory of Depressive Symptomatology (Rush et al., 2003), before and after the intervention. Results showed a significant decrease in depression symptoms from the beginning to the end of the intervention, in the group that believed they were taking antidepressants compared to the group who were aware they were taking placebos (Peciña et al., 2015).

Potential problems with self-report measures

Some research suggests that using subjective measures to assess placebo/nocebo effects might lead to *bias* (Hróbjartsson et al., 2011). In research, bias refers to systematic errors due to conscious or unconscious preference for a certain outcome. For instance, participants might overstate placebo effects or downplay nocebo effects to please researchers or appear in a better light (Hróbjartsson & Gøtzsche, 2001). On the other hand, other data shows that placebo effects are comparable regardless of whether they are measured subjectively or objectively (Wampold et al., 2005)

Clinician-assessed measures

Assessed measures involve evaluations made by someone other than the patient or research participant, most often a researcher or clinician. These measures in a clinical or research setting might include interviews or direct observation to evaluate changes in a patient's condition following a placebo intervention.

Doctors and researchers often use *standardized scales* to assess changes in a patient's symptoms in response to an intervention. For instance, Parkinson's disease symptoms can be evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987). This scale assesses various aspects of Parkinson's disease, including mood, daily activities, motor skills, muscle stiffness, speech, and walking (see Box 3.6.).

Box 3.6. Example of a study measuring the placebo effect using a clinician assessed questionnaire

In an RCT by Freed and colleagues (2001), one group of Parkinson's disease patients underwent dopamine cell transplantation surgery, while another group had sham surgery. The UPDRS scores of both groups were measured before the surgery and again at 4, 8, and 12 months afterward.

The results showed significant differences in UPDRS scores between the transplantation and sham surgery groups, but this was only true for patients under 60 years old. Based on the difference in outcomes between the treatment and placebo groups, the study concluded that dopamine cell transplantation could effectively treat Parkinson's disease in younger, but not older patients (Freed et al., 2001).

Potential problems with assessed measures

Like self-report measures, the expectations and biases of researchers and clinicians can also unintentionally affect their observations and assessments. These biases can lead to either overestimating or underestimating the effects of placebos (Cohen et al., 2004).

To counter this, blinding in research is crucial. Blinding refers to keeping certain information hidden from one or more parties in a study, to prevent bias. For instance, in single-blind studies, participants do not know which treatment they are getting. In double-blind studies, both participants and researchers are unaware of the treatment allocation. Triple-blind studies extend blinding to include data analysts and others who might influence the study's results. However, maintaining blinding in placebo-controlled studies can be difficult, particularly when the active treatment has noticeable effects or side effects.

Physiological measures

Physiological measures involve using lab tests or devices that do not rely, or rely less, on patients' or observers' perceptions. They complement self-reported, and clinician assessed measurements, providing insights into the biological and chemical processes underlying the placebo effect. While self-reports capture participants' personal experiences, physiological measures reveal how the body and brain react to placebo interventions.

Neuroimaging

Neuroimaging technologies can be used to observe changes in brain activity triggered by a placebo intervention. The most common neuroimaging methods involve:

Functional magnetic resonance imaging (fMRI), which measures changes in blood flow in the brain, thus providing information about neural activity, and can be used to identify brain regions activated or deactivated during placebo interventions (see Box 3.7).

Box 3.7. Example of a study measuring the placebo effect using fMRI

In the Wager et al. (2004) study, where participants reported less pain after being told an inert cream was a painkiller, experimenters also used fMRI to measure brain activity. They discovered that the placebo group, compared to the control group (who received no information about the cream), showed reduced activity in brain areas responsive to pain during the pain exposure. These brain areas included the thalamus, insula, and anterior cingulate cortex.

Additionally, the researchers observed increased activity in the prefrontal cortex, a brain region linked to expectation management (Miller & Cohen, 2001), in the placebo group when they anticipated pain. These findings suggest a neural basis for placebo analgesia: the prefrontal cortex modulates activity in pain-sensitive areas, leading to a reduced pain sensation due to the placebo (Wager et al., 2004).

Positron emission topography (PET) involves injecting participants with a radioactive tracer to provide information on neurotransmitter release and brain metabolism in response to placebos, offering insights into the neurochemical aspects of placebo/nocebo effects (see Box 3.8).

Box 3.8. Example of a study measuring the placebo effect using PET

A study by Lidstone and colleagues (2010), examined the impact of expectations on dopamine release in Parkinson's disease patients. Participants were divided into four groups, each given a different likelihood (25%, 50%, 75%, 100%) of receiving Parkinson's medication (levodopa). In reality, all groups received a placebo.

Using PET scans, the researchers found that those who believed there was a 75% chance of receiving levodopa showed a significant release of endogenous dopamine in dopaminergic brain regions including the putamen and ventral striatum. This indicated that the strength of expectation about symptom improvement can directly affect neurochemical release in response to a placebo (Lidstone et al., 2010).

Electroencephalography (EEG) records electrical activity generated by neuronal firing, via electrodes on the scalp, and can be used to examine neural oscillations and event-related potentials. It thus offers insight into the electrophysiological activity associated with placebo and nocebo effects (see Box 3.9).

Box 3.9. Example of a study measuring the placebo effect using EEG

In a study by Wager and colleagues (2006) similar to the one mentioned earlier (Wager et al., 2004), participants had inert cream applied to two areas on their arms. They were told that one area had a pain-relieving cream and that the other had a neutral cream.

Painful laser stimuli were then applied to these areas, with participants believing that both areas received high-intensity pain. The placebo area was exposed to low-intensity pain, while the control area was exposed to high-intensity pain. Later, both areas were subjected to moderate-intensity lasers, with participants expecting high-intensity pain.

EEG results showed that the laser pain on the placebo-treated area resulted in a lower amplitude in the P2 waveform, an event-related potential associated with pain perception (Iannetti et al., 2004). These results suggested a neural mechanism for placebo pain relief at the electrophysiological level (Wager et al., 2006).

Biochemistry

Psychological processes can affect our health even at the molecular level (Ortega et al., 2022). Thus, laboratory tests can be used to assess how placebo interventions impact different biochemical functions. For instance, the brain interacts with the *immune system* via cytokine-signaling pathways (see Box 3.10), among other signaling molecules (Capuron & Miller, 2011). Additionally, placebos can stimulate

hormone release (see Box 3.11), indicating that *endocrine responses* also play a role in placebo effects (Benedetti et al., 2003).

Box 3.10. Example of a study measuring the placebo effect using measures of immune function

In a study by Prossin and colleagues (2021), healthy participants received two consecutive 20-minute saline injections. The first one was painless, and the second one was painful. During the experiment, participants also received a third saline injection every 4 minutes, which was also painless. They were told that this third injection might relieve their pain (placebo). Importantly, participants could see when the placebo injection was given.

The researchers measured a pro-inflammatory, pro-nociceptive molecule called interleukin-18 in the participants' blood to check for inflammation. They found that interleukin-18 decreased significantly when the placebo was given, compared to when it was not given, during the painful phases of the experiment. This suggests that immune functions can play a role in placebo pain relief (Prossin et al., 2022).

Box 3.11. Example of a study measuring the placebo effect using measures of endocrine responses

In a study by Benedetti and colleagues (2003), two groups of participants received an injection of sumatriptan – a medication that stimulates the release of growth hormone. On another day, they received a saline injection as a placebo. One group was told the placebo would increase their growth hormone levels, while the other was told it would decrease them. Two additional groups did not get sumatriptan but got the same placebo injections with the same growth hormone information.

Researchers measured growth hormone levels using blood samples. The results showed that the placebo injections raised growth hormone levels in both groups that had received sumatriptan, but not in the groups that only got the placebo. This suggests that placebo effects may be stronger when people have previous experience with an active treatment, especially when the placebo

Comparing self-report, clinician-assessed, and physiological measures

Generally, research suggests that symptoms, which can be evaluated by self-reports, such as mood and pain, show larger placebo effects than those measured by clinician assessed or physiological measures (Hróbjartsson & Gøtzsche, 2010). Apart from the above-mentioned potential for bias in these measures (Hróbjartsson et al., 2011), symptoms that can be measured by self-reports are often also consciously accessible and can thus be sensitive to people's expectations about a treatment (Benedetti et al., 2003; Colloca & Miller, 2011).

Conversely, physiological events, measured with physiological outcome measures, such as hormone secretion, often cannot be consciously experienced, and thus do not change because of people's expectations alone (Benedetti et al., 2003; Colloca & Miller, 2011). Indeed, it seems physiological measures generally require direct experience with an active treatment to show a placebo effect (Benedetti et al., 2003).

For these reasons, self-report measures are often considered less objective than other measures. However, some studies have challenged this view by directly comparing self-reports, clinician assessments, and physiological measures. For example, rheumatoid arthritis RCTs consistently find that clinician assessed placebo effects tend to be larger than patient self-reports and physiological measures. Furthermore, patient self-reports and physiological measures in these trials have been found to correlate (Cohen et al., 2004; Strand et al., 2004; Vollert et al., 2020; see also Box 3.12.).

Importantly, meta-analytic results showed that the choice between self-report and physiological outcome measures can impact results, with less subjectivity usually resulting in smaller observed effects, for example in conditions such as asthma (Radziwill & Kruszewski, 2011), allergic rhinitis (Radziwill & Kruszewski, 2011), alcohol use disorders (Del Re et al., 2013), restless leg syndrome (Silva et al., 2017), osteoarthritis (Huang et al., 2019; Zhang et al., 2008), allergic skin diseases (Ali et al., 2020), and surgical trials (Wartolowska et al., 2016, 2017). Exploration of the influence of self-report and physiological measures on placebo responses in sleep-related disorders has yielded inconsistent findings, with some meta-analyses suggesting a reliance on self-report bias for self-report measures with greater placebo responses (Labarca et al., 2023; McCall et al., 2003; Yeung et al., 2018), while others indicate smaller placebo responses in self-report compared to physiological measures (He et al., 2020), or no differences (Jiang et al., 2020; Muench et al., 2023), underscoring the importance of employing both types of measures. It is noteworthy that, within self-report measurement in psychiatric disorders, discrepancies exist between observer ratings and self-ratings when assessing clinical outcomes, as clinician-rated evaluations yielded higher placebo response rates compared to patient-reported data (Ahmadzad-Asl et al., 2022; Meister et al., 2020; Rief et al., 2009). This discrepancy may arise from individuals with depression or anxiety being unable to accurately perceive minor mood changes, or it could be due to clinicians potentially overestimating patient

improvements, underscoring again the importance of using diverse assessment methods.

Box 3.12. Example of a study comparing self-report- and physiological measures

Vollert and colleagues (2020) compared the self-reports and physiological outcomes of the placebo groups of five double-blind RCTs examining the effectiveness of drugs for rheumatoid arthritis. All trials measured self-reported pain levels and inflammation markers (C-reactive protein and erythrocyte sedimentation rate) at the start, and 12 and 24 weeks after the intervention.

In all five placebo groups, both outcome measures showed similar improvements. Specifically, patients reported less pain, and their inflammation markers decreased significantly. These improvements were still significant after 12 and 24 weeks. These results suggest that in rheumatoid arthritis trials, patient reports can be considered as accurate as physiological measures.

3.5. Conclusion

In summary, we have explored the distinctions between placebo/nocebo effects and placebo/nocebo responses, the methods for determining their magnitude, and some of the common ways of measuring them. Self-report measures capture personal experiences and psychological states, while clinician assessed measures involve external evaluation of a person's symptoms. Physiological measures, on the other hand, offer insights into the neurobiological and biochemical mechanisms of placebo/nocebo effects. Although research suggests that self-reports are more responsive to placebos than clinician assessments and physiological measures, rheumatoid arthritis and sleep-disorders trials consistently paint a different picture, challenging the view that physiological measures are necessarily more objective than patient reports.

References

Ahmadzad-Asl, M., Davoudi, F., Mohamadi, S., Hadi, F., Nejadghaderi, S. A., Mirbehbahani, S. H., Jabbarinejad, R., Saneh, S., Arshadi, M., Naserbakht, M., Sinyor, M., Kabir, A., & Shamshiri, A. (2022). Systematic review and meta-analysis of the placebo effect in panic disorder: Implications for research and clinical practice. *Aust. New Zealand J. Psychiatry, 56*(9), 1130–1141. https://doi.org/10.1177/00048674211068793

Ali, A. A., Seng, E. K., Alavi, A., & Lowes, M. A. (2020). Exploring changes in placebo treatment arms in hidradenitis suppurativa randomized clinical trials: A systematic review. *JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, 82*(1), 45–53. https://doi.org/10.1016/j.jaad.2019.05.065

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. *J Neurosci*, *23*(10), 4315–4323. https://doi.org/10.1523/JNEUROSCI.23-10-04315.2003

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology and Therapeutics*, *130*(2), 226–238. https://doi.org/10.1016/j.pharmthera.2011.01.014

Cobb, L., Thomas, G., Dillard, G., Merendino, K., & Bruce, R. (1959). An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med*, *260*(22), 1115–1118. https://doi.org/10.1056/NEJM195905282602204

Cohen, S. B., Strand, V., Aguilar, D., & Ofman, J. J. (2004). Patient- versus physician-reported outcomes in rheumatoid arthritis patients treated with recombinant interleukin-1 receptor antagonist (anakinra) therapy. *Rheumatology*, *43*(6), 704–711. https://doi.org/10.1093/rheumatology/keh152

Colagiuri, B. (2010). Participant expectancies in double-blind randomized placebo-controlled trials: potential limitations to trial validity. *Clinical Trials, 7*(3), 246-255. https://doi.org/10.1177/1740774510367916

Colloca, L., & Miller, F. G. (2011). How placebo responses are formed: a learning perspective. P*hilosophical Transactions of the Royal Society B: Biological Sciences, 366*(1572), 1859-1869. https://doi.org/10.1098/rstb.2010.0398

Del Re, A., Maisel, N., Blodgett, J., Wilbourne, P., & Finney, J. (2013). Placebo group improvement in trials of pharmacotherapies for alcohol use disorders: A multivariate meta-analysis examining change over time. J *Clin Psychopharmacol, 33*(5), 649–657. 10.1097/JCP.0b013e3182983e73 Link: https://journals.lww.com/psychopharmacology/fulltext/2013/10000/Placebo_Group_Improvement_in_Trials_of.10.aspx?casa_token=X2IGQg_GjFkAAAAA:fD026UKgi2wqwgG838yuQgspeE4ZnpJdR9RzuOTQ5JyIFlSeWAzrNzNLgWRZ0DKWdNWh4FQJWaktOyueTQ5FFyVoxi1l3tg

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Fahn S., Elton R. L., & Members of the UPDRS Development Committee. (1987). Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne D, & Holstein N (Eds.), *Recent developments in Parkinson's disease* (Vol. 2, pp. 153–163). Macmillian Healthcare Information.

Freed, C., Greene, P., Breeze, R., Tsai, W., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J., Eidelberg, D., & Fahn, S. (2001). Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med*, *344*(10), 710–719. https://doi.org/10.1056/NEJM200103083441002

He, D., Jiang, B., Guo, Z., Mu, Q., & McClure, M. A. (2020). Biphasic feature of placebo response in primary insomnia: Pooled analysis of data from randomized controlled clinical trials of orexin receptor antagonists. *Sleep, 43*(3). https://doi.org/10.1093/sleep/zsz238

Hróbjartsson, A., Kaptchuk, T. J., & Miller, F. G. (2011). Placebo effect studies are susceptible to response bias and to other types of biases. J*ournal of clinical epidemiology, 64*(11), 1223-1229. https://doi.org/10.1016/j.jclinepi.2011.01.008

Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med*, *344*(21), 1594–1602. https://doi.org/10.1056/NEJM200105243442106

Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews*, *2010*(1). https://doi.org/10.1002/14651858.CD003974.pub3

Huang, Z., Chen, J., Hu, Q. S., Huang, Q., Ma, J., Pei, F. X., Shen, B., & Kraus, V. B. (2019). Meta-analysis of pain and function placebo responses in pharmacological osteoarthritis trials. *Arthritis Res. Ther., 21*(1). https://doi.org/10.1186/s13075-019-1951-6

Iannetti, G. D., Leandri, M., Truini, A., Zambreanu, L., Cruccu, G., & Tracey, I. (2004). Aδ nociceptor response to laser stimuli: Selective effect of stimulus duration on skin temperature, brain potentials and pain perception. *Clinical Neurophysiology*, *115*(11), 2629–2637. https://doi.org/10.1016/j.clinph.2004.05.023

Jiang, B., He, D., Guo, Z., & Gao, Z. (2020). Dynamic features of placebo effects addressing persistent insomnia disorder: A meta-analysis of placebo-controlled randomized clinical trials. *Journal of Sleep Research, 29*(4), 1–7. https://doi.org/10.1111/jsr.12997

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE*, *5*(12). https://doi.org/10.1371/journal.pone.0015591

Kube, T., & Rief, W. (2017). Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discovery Today*, *22*(4), 729–735. https://doi.org/10.1016/j.drudis.2016.11.022

Labarca, G., Montenegro, R., Oscullo, G., Henriquez-Beltran, M., Uribe, J. P., Gómez-Olivas, J. D., Garcia-Ortega, A., & Martínez-García, M. Á. (2023). Placebo response in objective and subjective measures of hypersomnia in randomized clinical trials on obstructive sleep apnea. A systematic review and meta-analysis. *Sleep Medicine Reviews*, *67*, 101720. https://doi.org/10.1016/j.smrv.2022.101720

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. *Arch Gen Psychiatry*, *67*(8), 857–865. https://doi.org/10.1001/archgenpsychiatry.2010.88

McCall, W. V., D'Agostino, R., & Dunn, A. (2003). A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. *Sleep Medicine*, *4*(1), 57–62. https://doi.org/10.1016/s1389-9457(02)00242-3

Meister, R., Abbas, M., Antel, J., Peters, T., Pan, Y., Bingel, U., Nestoriuc, Y., & Hebebrand, J. (2020). Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. *European Child and Adolescent Psychiatry*, *29*(3), 253–273. https://doi.org/10.1007/s00787-018-1244-7

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*, *24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Muench, A., Giller, J., Morales, K. H., Culnan, E., Khader, W., Kaptchuk, T. J., McCall, W. V., & Perlis, M. L. (2023). Do Placebos Primarily Affect Subjective as Opposed to Objective Measures? A Meta-Analysis of Placebo Responses in Insomnia RCTs. *Behavioral Sleep Medicine*, *21*(4), 500–512. https://doi.org/10.1080/15402002.2022.2115046

Ortega, Á., Salazar, J., Galban, N., Rojas, M., Ariza, D., Chávez-Castillo, M., Nava, M., Riaño-Garzón, M. E., Díaz-Camargo, E. A., Medina-Ortiz, O., & Bermúdez, V. (2022). Psycho-Neuro-Endocrine-Immunological Basis of the Placebo Effect: Potential Applications beyond Pain Therapy. *International Journal of Molecular Sciences*, *23*(8). https://doi.org/10.3390/ijms23084196

Peciña, M., Bohnert, A. S. B., Sikora, M., Avery, E. T., Langenecker, S. A., Mickey, B. J., & Zubieta, J. K. (2015). Association between placebo-activated neural systems and antidepressant responses neurochemistry of placebo effects in major depression. *JAMA Psychiatry*, *72*(11), 1087–1094. https://doi.org/10.1001/jamapsychiatry.2015.1335

Prossin, A., Koch, A., Campbell, P., Laumet, G., Stohler, C. S., Dantzer, R., & Zubieta, J. K. (2022). Effects of placebo administration on immune mechanisms and relationships with

central endogenous opioid neurotransmission. *Molecular Psychiatry*, *27*(2), 831–839. https://doi.org/10.1038/s41380-021-01365-x

Radziwill, K., & Kruszewski, J. (2011). Evaluation of the size of the placebo effect in treatments of allergic diseases and asthma based on a meta-analysis of efficacy trials of drugs. *Postepy Dermatologii i Alergologii*, 28(5), 372–377. https://www.termedia.pl/Original-paper-Evaluation-of-the-size-of-the-placebo-effect-in-treatments-of-allergic-diseases-and-asthma-based-on-a-meta-analysis-of-efficacy-trials-of-drugs,7,17687,0,1.html

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of Affective Disorders*, *118*(1), 1–8. https://doi.org/10.1016/j.jad.2009.01.029

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., & Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): A Psychometric Evaluation in Patients with Chronic Major Depression. *Biol Psychiatry*, *54*, 573–583. https://doi.org/10.1016/S0006-3223(03)01866-8

Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. *Pharmacological Reviews*, *67*(3), 697–730. https://doi.org/10.1124/pr.114.009423

Silva, M. A., Duarte, G. S., Camara, R., Rodrigues, F. B., Fernandes, R. M., Abreu, D., Mestre, T., Costa, J., Trenkwalder, C., & Ferreira, J. J. (2017). Placebo and nocebo responses in restless legs syndrome: A systematic review and meta-analysis. *Neurology*, *88*(23), 2216–2224. https://doi.org/10.1212/WNL.0000000000004004

Strand, V., Cohen, S., Crawford, B., Smolen, J. S., & Scott, D. L. (2004). Patient-reported outcomes better discriminate active treatment from placebo randomized controlled trials in rheumatoid arthritis. *Rheumatology*, *43*(5), 640–647. https://doi.org/10.1093/rheumatology/keh140

Tu, Y., Wilson, G., Camprodon, J., Dougherty, D. D., Vangel, M., Benedetti, F., Kaptchuk, T. J., Gollub, R. L., & Kong, J. (2021). Manipulating placebo analgesia and nocebo hyperalgesia by changing brain excitability. *PNAS*, *118*(19). https://doi.org/10.1073/pnas.2101273118/-/DCSupplemental

Vase L, Riley JL 3rd, Price DD. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*, *99*(3), 443-452. https://doi.org/10.1016/S0304-3959(02)00205-1

Vollert, J., Cook, N. R., Kaptchuk, T. J., Sehra, S. T., Tobias, D. K., & Hall, K. T. (2020). Assessment of Placebo Response in Objective and Subjective Outcome Measures in Rheumatoid Arthritis Clinical Trials. *JAMA Network Open*, *3*(9). https://doi.org/10.1001/jamanetworkopen.2020.13196

Wager, T. D., Matre, D., & Casey, K. L. (2006). Placebo effects in laser-evoked pain potentials. *Brain, Behavior, and Immunity*, *20*(3), 219–230. https://doi.org/10.1016/j.bbi.2006.01.007

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. *Science*, *20*(303(5661)), 1162–1167. https://doi.org/10.1126/science.1093065

Wampold, B. E., Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. J*ournal of clinical psychology, 61*(7), 835-854. https://doi.org/10.1002/jclp.20129

Wartolowska, K. A., Gerry, S., Feakins, B. G., Collins, G. S., Cook, J., Judge, A., & Carr, A. J. (2017). A meta-analysis of temporal changes of response in the placebo arm of surgical randomized controlled trials: An update. *Trials, 18*(1), 1–7. https://doi.org/10.1186/s13063-017-2070-9

Yeung, V., Sharpe, L., Glozier, N., Hackett, M. L., & Colagiuri, B. (2018). A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Medicine Reviews, 38*, 17–27. https://doi.org/10.1016/j.smrv.2017.03.006

Zhang, W., Robertson, J., Jones, A. C., Dieppe, P. A., & Doherty, M. (2008). The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *ANNALS OF THE RHEUMATIC DISEASES, 67*(12), 1716–1723. https://doi.org/10.1136/ard.2008.092015

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PANACEA Learning Materials

Module 4: Placebo and nocebo in clinical trials and clinical practice

Module information

This module will explore the evidence surrounding the placebo phenomenon as observed in clinical research, particularly in randomized controlled trials (RCTs), and its implications for everyday clinical practice. Drawing on insights from basic research into the mechanisms underlying placebo responses, we will discuss the prevalence and significance of placebo phenomena in these contexts. Our goal is to provide a comprehensive understanding of placebo phenomena, deepening our exploration of its role in the clinical context, with a focus on both clinical research and everyday clinical practice.

4.1 Overview

Placebos as an inert treatment (i.e. pure placebo) are utilized in clinical research to distinguish the pharmacological effects of a drug under study from effects attributable to disease progression (i.e. natural history) or other incidental factors. This practice allows for a clear determination of a drug's efficacy and safety. Additionally, optimizing placebo effects in clinical practice can offer significant advantages, enhancing overall treatment outcomes by leveraging psychological and contextual factors that positively influence patient health. However, there is an ongoing debate concerning the ethical use of placebo interventions and the administration of health treatments without scientific evidence ("off-label"), particularly due to regulatory issues and associated risks.

The clinical benefits derived from the psychosocial context surrounding the patients and the therapy first became apparent in randomized controlled trials (RCTs), where participants in placebo groups (treatments without active ingredients) often showed significant symptom improvements. Interest in the placebo phenomenon arises precisely from the substantial and robust evidence from clinical trials demonstrating improvements in clinical outcomes even in patients assigned to the

sham treatment arm. Around the 1980s, neuroscientists began to shift their focus from what is 'missing' in the placebo arm (i.e., the active ingredient) to what is present. They started examining all the factors capable of modifying symptoms that are not attributable to the active effect of the treatment, such as the pharmacologically active principle. This paradigm shift has led to a deeper understanding of the psychological, biological, and contextual elements that contribute to the placebo effect.

In some health conditions, such as pain and psychiatric disorders, placebo effects can be so large that they make it difficult to prove the effectiveness of active treatments in RCTs (Enck et al., 2013). In clinical research (i.e., clinical trials), the goal is often to minimize placebo effects to measure the magnitude of the drug effect and to optimize drug-placebo differences (Enck et al., 2013). This optimization of drug-placebo differences is referred to as assay sensitivity. In basic research (e.g. placebo mechanism studies), instead, the goal is to understand how placebo effects are established. Insights from basic research into the mechanisms underlying the placebo phenomenon can then be translated into clinical practice to minimize the placebo effect in clinical trials and maximize the placebo effect to optimize patient outcomes (Weimer & Enck, 2014). In this module, we will discuss how placebos are commonly used in RCTs and in everyday clinical practice.

4.2. Applications in clinical trials

Introduction

Clinical trials are essential for determining the safety and efficacy of new treatments. These studies involve systematically testing new drugs, therapies, or medical procedures in participants to gather data that supports their use. One crucial aspect of these trials is the use of a comparison group to ensure that any observed effects are due to the treatment itself and no other factors. This brings us to the concept of the placebo as an experimental paradigm/intervention. In this context we refer to placebo as an inert substance or sham treatment that resembles the active treatment but has no therapeutic effect. The purpose of using a placebo is to create a control group that receives an identical-looking intervention without the active ingredient. By comparing the outcomes of participants receiving

the active treatment to those receiving the placebo, researchers can determine the actual effectiveness of the new treatment. The treatment comparison with a placebo allows researchers to account for the placebo response, a phenomenon where patients experience changes in their health thanks to the activations of placebo mechanism (see Module 1 and Module 2).

Conducting Placebo-Controlled Trials

The most common placebo-controlled trial is the randomized double-blind trial, where participants are randomly assigned to either the active treatment group or the placebo group at a 50:50 drug-placebo ratio. The term "double-blind" means that neither the participants nor the researchers know who is receiving the active treatment and who is receiving the placebo as the inert treatment.

While this standard research design is highly effective, the substantial nature of placebo response has led researchers to develop various types of trial designs and features to further minimize these effects and optimize assay sensitivity (Enck et al., 2013). By understanding and implementing these design variants and features, researchers can enhance the reliability of clinical trial results, ultimately leading to the development of effective and evidence-based treatments.

In the following sections, we will explore these types of trial designs in detail, providing insights into how they work, their advantages, and potential challenges associated with their implementation. Understanding these techniques will equip healthcare students and healthcare professionals with the knowledge to critically evaluate and design clinical trials that yield more reliable and meaningful results.

Types of trial designs

To control placebo responses and ensure the reliability of clinical trial results, several experimental designs can be adopted. Each design aims to isolate the true effects of the treatment from the placebo response and other confounding factors. Here, we'll explore some of the primary methods utilized.

Adding no-treatment control groups

One approach involves adding a no-treatment control group, which means that a third group of participants does not receive any intervention. This comparison

allows researchers to distinguish placebo effects from regression to the mean and the natural course of the disease. Including a no-treatment control group poses significant ethical concerns, as it involves withholding potential treatment from participants. Denying patients' treatment, especially when an effective standard exists, can be considered unethical. However, this strategy remains crucial for differentiating between placebo effects and other non-specific effects. Spontaneous symptom fluctuations occur in all medical conditions, and significant portions of the placebo response often result from spontaneous remission of symptoms (Krogsbøll et al., 2009). One potential solution, inspired by psychotherapy RCTs, is to use a waitlist control group. In this design, patients randomly assigned to the waitlist control group receive active treatment after a delay, once the active treatment group has completed their course. However, this strategy is only ethical if the waitlist period is shorter than the typical wait time for routine services (Elliott & Brown, 2002). Challenges with waitlist control groups arise despite their ability to mitigate some ethical concerns by eventually providing treatment to all participants. For one, patients may be resistant to joining a study where they may not receive immediate treatment. Additionally, even participants on the waitlist may experience placebo responses due to their anticipation of future treatment. Moreover, the delay in receiving treatment can lead to higher dropout rates among waitlisted participants. Finally, waitlist control groups cannot be blinded, potentially introducing bias into the study. While including a no-treatment control group or a waitlist control group introduces ethical and practical challenges, it remains a valuable method for accurately distinguishing between actual treatment effects, placebo effects, and the natural progression of disease.

Crossover designs

In crossover designs, patients receive both active and inert treatment in separate phases. They either receive the active drug first, in Phase I, and the inert treatment in Phase II, or vice versa. The order should be randomized and double-blinded. Furthermore, there is a washout period between the two phases, during which the active drug is cleared from the participants' systems. This design has the advantage of allowing each participant to serve as their own control, which can increase the overall statistical power of the study. Crossover designs can increase participant motivation because all participants will receive active treatment at some point (Weimer & Enck, 2014). Some limitations in crossover design must be acknowledged. Receiving the active drug in Phase I can lead to conditioning effects in

Phase II when participants receive the inert treatment after the active one (Colloca & Benedetti, 2006; Kessner et al., 2013). This can increase placebo effects and thus reduce assay sensitivity. Another challenge is that receiving both placebo and active treatment allows participants to compare their experiences between the two phases. If the drug has noticeable (side) effects, this can cause participants to become un-blind in Phase II when they receive the inert treatment, which can then lead to dropout (Weimer & Enck, 2014).

Given these limitations, crossover designs overall do not seem to improve assay sensitivity and may introduce additional biases (Weimer & Enck, 2014).

Comparative effectiveness research

In comparative effectiveness research, novel treatments are compared with existing treatments already on the market to test for non-inferiority, that is, whether they are at least as effective as the currently available treatment. The upside of this strategy is that it allows all participants in a clinical trial to receive active medication.

However, as we have already learned in Module 2, a 100% chance of receiving an active treatment increases its effectiveness (Sinyor et al., 2010). Furthermore, since placebo effects are present in the overall effects of most medications, omitting a placebo group means these effects are still there, but uncontrolled. This can lead to an overestimation of the active treatment's effectiveness. More statistical power, namely a much larger sample size, is needed in a non-inferiority trial compared to a placebo-controlled trial to demonstrate effectiveness of medicines over placebo. This requirement conflicts with the Declaration of Helsinki, which advocates for minimizing the number of participants in clinical trials (World Medical Association, 2013). Therefore, experts in the field argue against the omission of placebo groups in RCTs (Enck & Klosterhalfen, 2019). However, the relevance of this argument depends on the research objective. If the goal is to match the efficacy of another treatment or even to outperform it, the inclusion of a placebo group might seem less critical. Despite this, one potential issue arises when a novel, experimental treatment is compared with a well-established and believed effective medication. In such cases, expectations about efficacy can differ significantly between treatments. Existing research (see PANACEA Scoping Review) might not always address the

influence of differential expectations on outcomes, which could potentially skew results.

Design features

In this section, we explore the design features to minimize placebo responses providing insights into their characteristics, their advantages, and potential challenges associated with their implementation.

Randomization

The most common method for assigning participants to drug or placebo groups in clinical trials is balanced randomization, where participants are randomly allocated to each group at a 50:50 ratio. However, there are various reasons for using unbalanced randomization, where more participants are assigned to one of the groups – most often the active treatment group. This approach can allow more patients to receive active treatment, which is more ethical, and this in turn can increase participant motivation and facilitate recruitment (Weimer & Enck, 2014).

However, as we learned in Module 2, increasing the chance of receiving active treatment enhances responses to both active and inert treatments (Lidstone et al., 2010; Papakostas & Fava, 2009; Sinyor et al., 2010). In line with this, research suggests that a 50:50 randomization ratio produces the largest differences between active treatment and placebo groups (Weimer et al., 2015a, 2015b; Weimer & Enck, 2014). On the one hand, as many patients as possible should receive the active treatment, on the other; this reduces assay sensitivity and requires a larger sample size to demonstrate the active treatment's effect. This conflicts with the World Medical Associations' Declaration of Helsinki (2013), which advocates for minimizing the number of participants in clinical trials (World Medical Association, 2013). Therefore, a 50:50 randomization remains the recommended approach (Enck et al., 2013).

Blinding

As we briefly discussed in Module 3, blinding in research is crucial to prevent biased results (i.e., systematic errors because of conscious or unconscious preferences for a certain outcome). Blinding refers to keeping certain information hidden from one or more parties in a study (Figure 4.1).

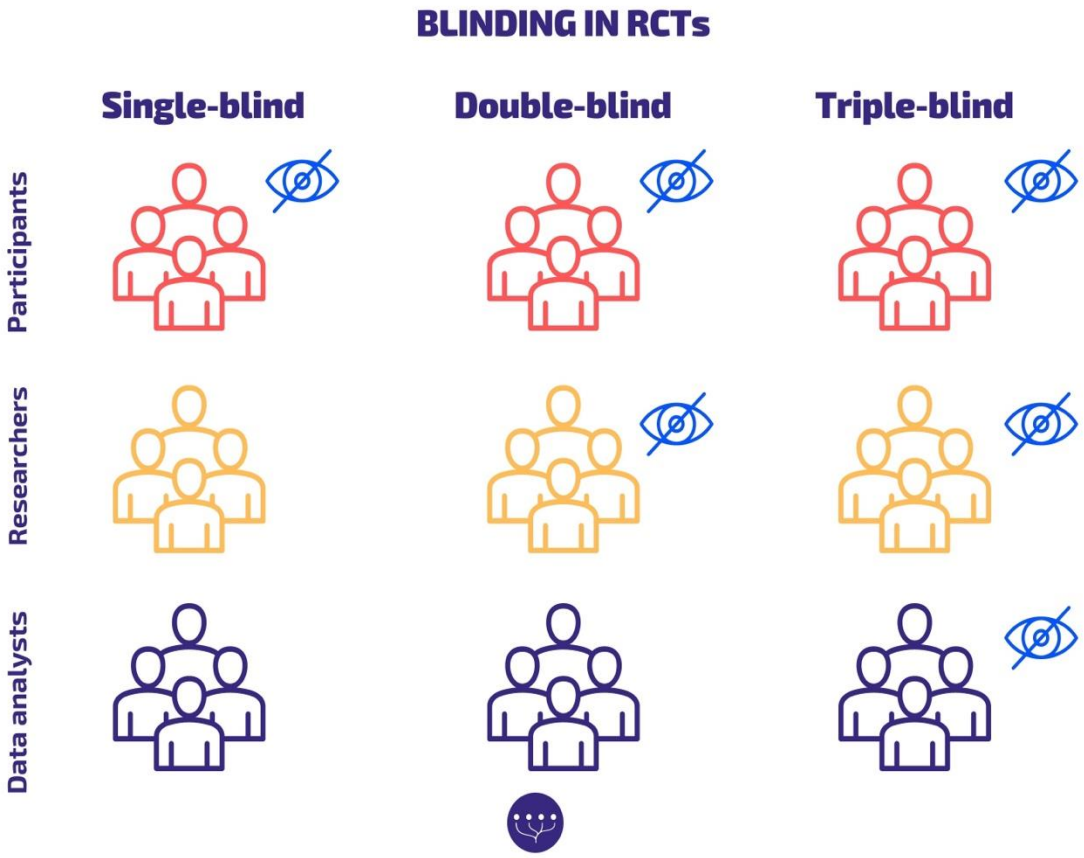
In single-blind studies, participants do not know which treatment they are receiving, but the researchers do. This helps to mitigate participants' expectations from influencing the results. However, it does not eliminate the potential bias introduced by researchers who may inadvertently treat participants differently based on their knowledge of the treatment allocation.

In double-blind studies, both participants and researchers are unaware of which treatment the participants are receiving. This minimizes biases from both parties, providing a more robust and unbiased evaluation of the treatment's efficacy. Double-blind placebo interventions are considered the benchmark for establishing a treatment's efficacy in clinical trials.

Triple-blind studies take this a step further by extending blinding to data analysts and others who might influence the study's outcomes. In this setup, participants, researchers, and those analyzing the data are all blinded to the treatment allocation, ensuring that bias is minimized at every stage of the study.

Figure 4.1

Type of blinding in RCTs



Maintaining blinding in placebo-controlled studies can be difficult, especially when the active treatment has noticeable effects or side effects. Although RCTs are typically set up to be double-blinded and report as such, the *effectiveness* of blinding is rarely assessed or reported (Hróbjartsson et al., 2007). The effectiveness of blinding can be evaluated, for example, by asking patients or data collectors to guess which group specific participants were in. In 2007, Hróbjartsson and colleagues assessed, from a random sample of 1599 RCTs, how often RCTs report on the success of blinding and found that only 2% of clinical trials assessed blinding effectiveness, and of those, less than half (45%) found blinding to be successful. Thus, more systematic assessment and reporting on the effectiveness of blinding in RCTs is needed.

Placebo run-ins

One common method of minimizing placebo effects in RCTs is to identify and exclude placebo responders through psychological or genetic tests. Placebo responders are participants who exhibit a significant improvement in symptoms

when receiving an inert treatment, while non-responders show little to no symptomatic improvement under the same conditions. This is often done in *placebo run-in phases*, during which all participants receive an inert treatment, and are made aware of this during informed consent. Those participants who show symptom improvement during this phase are excluded. The remaining participants are randomized to the active or inert treatment group (Enck et al., 2013; Weimer & Enck, 2014).

There is little evidence for the effectiveness of this method (Lee et al., 2004; Simpson et al., 2014), and this effect seems to be limited to non-specific effects, such as reducing the regression to the mean and, thus, placebo responses. However, since being a placebo responder or non-responder does not seem to be a stable trait (see Module 5), this method does not eliminate the possibility of placebo effects occurring during the actual trial.

A further problem with this method is that it compromises *ecological validity*, as having such a highly selective study population makes the findings less applicable to the real world (Enck et al., 2013). For example, lower disease severity often predicts placebo effects in RCTs (Weimer et al., 2015a, 2015b). If placebo responders are excluded at the start of a trial, the trial may mostly include patients with more severe or persistent symptoms. These patients might respond differently to the active treatment than those with milder symptoms, who could still end up taking the drug once it is on the market. This exclusion of so-called placebo responders could therefore lead to trial results that do not accurately reflect how the drug will work for the wider population, including those with milder symptoms (Enck et al., 2013).

Active placebos

To prevent un-blinding, inert treatments in clinical trials should closely match the active treatment in the way they look, feel, smell, and taste. A further step to preventing un-blinding is to match the side effects of the inert treatment with those of the active drug. This can be done by using *active placebos*, which are otherwise inert treatments containing substances that mimic the side effects of the active drug without producing its therapeutic effects. However, active placebos can be difficult to produce, which has contributed to a lack of data on their effectiveness

(Weimer & Enck, 2014). That being said, some researchers in placebo mechanism studies have come up with simple methods to create active placebos. For example, Rief and Glombiewski (2012) added a small amount of capsaicin to an inert nasal spray, to increase participants' belief in its effectiveness in producing pain relief. This subsequently increased placebo analgesia towards a heat pain stimulus (Rief & Glombiewski, 2012). Nonetheless, a recent systematic review and meta-analysis of 21 RCTs found no significant difference in participant-reported outcomes between RCTs using active and inert placebos (Laursen et al., 2023). However, the results of the RCTs varied widely, indicating that this overall finding was relatively weak. The authors concluded that researchers should carefully consider the type of placebos they use in clinical trials.

One of the most used active placebos is atropine, mainly used in antidepressant trials, because it mimics the anticholinergic effects of tricyclic antidepressants by causing dry mouth. A meta-analysis by Moncrieff and colleagues (2004) reviewed nine studies comparing atropine with various antidepressants (e.g., amitriptyline, imipramine). They found that while antidepressants were generally more effective than atropine, the effect size was smaller compared to trials using inert placebos. The authors concluded that un-blinding in clinical trials using inert placebos might overestimate the efficacy of antidepressants (Moncrieff et al., 2004). In light of these findings, researchers in RCT methodology advocate for the incorporation of active placebos to mitigate un-blinding risks and enhance the reliability of trial outcomes (Enck et al., 2013). This underscores the evolving landscape within clinical trial design, emphasizing the importance of robust blinding strategies to uphold the methodological rigor and accuracy of study findings.

Regulatory and Ethics implications

When conducting clinical research, the ethical use of placebos must be carefully considered, underscoring the importance of safeguarding participant welfare. Regulatory bodies base their assessments on established guidelines such as the Belmont Report, the Helsinki Declaration, and Good Clinical Practice (EMA, 2016).

The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best existing interventions, except under specific circumstances:

1) when no proven intervention exists, the use of placebo or no intervention is acceptable; 2) when, for compelling and scientifically sound methodological reasons, the use of an intervention less effective than the best proven one, a placebo, or no intervention is necessary to determine the efficacy or safety of an intervention. In such cases, the patients who receive these less effective interventions, placebo, or no intervention must not be exposed to additional risks of serious or irreversible harm due to the absence of the best proven intervention.

Extreme care must be taken to avoid abuse of this option (World Medical Association, 2013). Informed consent becomes an essential tool in clinical trials, ensuring participants are fully aware of the nature and purpose of the study. Therefore, the necessity of using a placebo-controlled study must be carefully evaluated on a case-by-case basis by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) (NCPHS, 1979).

This careful balance ensures that clinical research adheres to ethical standards while advancing scientific knowledge and patient care.

4.3. Nocebo responses in clinical trial

Introduction

Nocebo responses in clinical trials are measurable in the side effects reported by patients in the placebo group, which can be strikingly similar to those experienced by participants receiving active treatments. It is important to note that the absence of the active ingredient in the placebo group suggests that even some adverse effects observed in the active treatment arm may be attributable to nocebo mechanisms. These side effects are frequently influenced by the information provided during the informed consent process, leading to expectations that result in nocebo effects (Barsky et al., 2002). This phenomenon is particularly important in the context of treatment discontinuation, as nocebo effects can lead to a higher rate of dropout in clinical trials, complicating the interpretation of trial outcomes (Myers et al., 1987). Furthermore, the ethical challenge of communicating side effects to participants has emerged, as providing information about potential side effects may

inadvertently induce them, while withholding such information may compromise informed consent.

Side effects

Patients in the placebo groups of RCTs often report similar side effects to those reported by participants in the active treatment group. Such non-specific side effects seem to result from the information given to participants during informed consent, and they can thus be viewed as nocebo effects (Barsky et al., 2002).

In a systematic review of adverse events reported in anti-migraine RCTs, Amanzio and colleagues (2009) found that the side effects of inert treatments differed between RCTs and mirrored the side effects of the different classes of anti-migraine drugs they were being tested against (triptans, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs). For example, inert treatments in anticonvulsant trials produced side effects similar to those of anticonvulsants, such as memory problems, while inert treatments in NSAID trials caused side effects similar to those of NSAIDs, such as gastrointestinal symptoms (Amanzio et al., 2009).

Similarly, Rief and colleagues (2009) compared side effects in the placebo groups of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). TCAs are believed to induce more side effects than SSRIs (Trindade et al., 1998; Wilson & Mottram, 2004). Accordingly, the placebo groups of TCA trials reported significantly more side effects than the placebo groups of SSRI trials, and these side effects mirrored the type of drug being tested. Furthermore, the rate of reported side effects was influenced by the expectations of both experimenters and patients, thus further suggesting a link between informed consent and side effects (Rief et al., 2009).

Research indicates that other factors unrelated to the active ingredient of a drug can impact the occurrence of side effects, revealing the nocebo effect. Some research suggests that how side effects are measured in RCTs can significantly influence results. In a systematic review of adverse events in RCTs of statins (a class of cholesterol-lowering medication), Rief and colleagues (2006) assessed methodologies for measuring side effects and found that these methods varied widely between studies. Consequently, adverse event rates also varied greatly,

which the authors attributed partly to the lack of comparability between assessment methods (Rief et al., 2006).

In their study of antidepressant RCTs, Rief and colleagues (2009) found that the method of measuring side effects significantly influenced the rates of reported side effects. Specifically, structured methods, such as checklists or rating scales with lists of common symptoms, revealed higher rates of side effects compared to less structured methods, such as open-ended questions. The authors concluded that a more systematic assessment of side effects appears to be more reliable and is therefore recommended (Rief et al., 2006, 2009).

Treatment discontinuation

Side effects in RCTs are problematic because they can lead to patients discontinuing treatment. Myers and colleagues (1987) conducted a post hoc analysis on data from an RCT investigating aspirin and sulfinpyrazone for treating angina pectoris. They found that mentioning potential gastrointestinal side effects in the informed consent form significantly increased the reporting of these side effects in both the active treatment and placebo groups. Crucially, this resulted in six times more participants discontinuing treatment compared to when these side effects were not mentioned in the informed consent (Myers et al., 1987). More recent systematic reviews and meta-analyses found that nocebo effects could account for up to 9%, 10%, and 13% of dropouts in migraine (Kokoti et al., 2020), Parkinson's disease (Rato et al., 2019), and fibromyalgia (Häuser et al., 2012) RCTs, respectively. Thus, nocebo effects can create significant practical challenges for RCTs.

How to communicate about side effects in RCTs

Communicating possible drug side effects thus presents an ethical dilemma. On one hand, informing patients about side effects can cause them to experience those side effects. On the other hand, clinicians and researchers are required to provide truthful information for patients to be able to make informed decisions about participating in RCTs.

Potential solutions to this dilemma include the "authorized concealment" approach (Box 4.1), where participants consent to not being informed about potential mild side effects and are only informed about potential serious or irreversible ones (Geers et al., 2024). Alternatively, information about side effects can be framed to minimize

nocebo effects by stressing that side effects are a small possibility, or by focusing on the small proportion of patients who experience side effects and highlighting the large proportion of patients who do not (Peters et al., 2011; Woloshin & Schwartz, 2011). The minimization of nocebo effects through communication will be discussed in more detail in Module 6.

Box 4.1. Authorized concealment

Authorized concealment is an ethical strategy proposed to reduce nocebo-related side effects, particularly those that are mild and self-limiting. It involves a shared decision-making process in which patients voluntarily choose not to be informed about certain non-serious side effects of a treatment. This approach has been suggested by bioethicists but remains largely theoretical, with limited empirical testing so far.

How it works:

- **The clinician informs the patient about the nocebo effect and its potential to amplify symptoms through negative expectations.**
- **The patient is asked whether they prefer not to be told about certain mild or common side effects (e.g., headache, fatigue).**
- **If the patient agrees, this constitutes an informed waiver of their right to receive selected risk information.**

Ethical principles:

- **Respect for autonomy: Patients explicitly consent to limited disclosure.**
- **Non-maleficence: Information about serious or irreversible risks is never withheld, as this would undermine informed consent**

Critics argue that knowing one is not fully informed may increase curiosity or anxiety, potentially leading to information-seeking and enhanced nocebo responses (Blease, 2015).

As of now, authorized concealment remains a theoretical proposal, and no randomized controlled trials have evaluated its clinical effectiveness.

4.4. Applications in clinical practice

Introduction

Research shows that doctors use placebo interventions in their clinical practice. The term "placebo intervention" can be ambiguous, because it may be used to refer to both "pure placebos" and "impure placebos." Pure placebos refer specifically to treatments that are purely inactive, that is, sugar pills or saline injections, which have no direct effect on a disease. In contrast, impure placebos are active treatments, which nonetheless have no influence over the specific ailment under treatment. These can be, for example, vitamins prescribed in the absence of a vitamin deficiency, or antibiotics prescribed for viral infections. This section outlines evidence on how often, in what way, and why clinicians use placebo interventions in their practice.

Frequency of placebo use in clinical practice

Linde and colleagues (2018) conducted a systematic review and meta-analysis of surveys on general practitioners' (GPs) use of placebo interventions in clinical practice. The review included 16 surveys from 13 countries, including 2981 GPs in total. The findings revealed high variability across surveys in the reported frequency of placebo use. Twenty-nine to 97% of GPs had used some form of placebo (pure or impure) at least once in their career, with 46% to 95% reporting having done so within the past year. Fifteen to 89% reported having prescribed a placebo within the past month, and 1% to 75% reported having used placebos within the past week.

For pure placebos, 2% to 15% of GPs reported monthly use, while 1% to 3% reported using them weekly. In contrast, impure placebos were used more commonly, with 53% to 89% of GPs reporting having used them monthly and 16% to 75% reporting using them weekly. The authors attributed the high variability between studies to cultural differences, such as different understandings of what constitutes a placebo, and to differences in the methods used to ask about placebo use, such as whether the term “placebo” or “non-specific therapy” was used (Babel, 2012). Indeed, Linde and colleagues (2018) argue that many doctors may not consider the use of a “non-disease-specific treatment” as placebo use.

Additionally, in a survey of 78 nurses in the Netherlands, 53.8% reported using *placebo effects* by inducing positive expectations (Smits et al., 2022). This is in contrast to using pure or impure placebos, as it does not involve prescribing inert or non-disease-specific treatments, but rather, taking advantage of placebo

mechanisms, such as learning processes and the provider-patient relationship (Evers et al., 2018). In the same study, a survey of 47 healthcare professionals, including psychologists and medical doctors, revealed that 17.4% reported using pure placebos, while 30.4% reported using impure placebos (Smits et al., 2022). Furthermore, an earlier systematic review from Fässler and colleagues (2010) found that nurses in hospitals reported using placebos more than doctors did, possibly due to nurses having to deal with a larger number of difficult patients (Fässler et al., 2010).

In line with previous studies, a study conducted by the PANACEA consortium at a European level (O'Keefe et al., accepted), involving various healthcare professionals regardless of their clinical discipline, revealed a high prevalence of placebo interventions in clinical practice (71.7% of respondents), highlighting the implicit recognition of its potential to enhance treatment outcomes.

These findings indicate that the rates of placebo use in clinical settings varies widely. Nevertheless, impure placebos seem to be used more commonly, at least in primary care settings. Furthermore, there is some indication that nurses use placebos (or take advantage of placebo effects) more frequently than doctors. However, due to the limited evidence and large variability between surveys, the estimates from these studies should be interpreted with caution.

Types of placebos used in clinical practice

Research suggests that the most typical pure placebo interventions in clinical practice are placebo pills made from sugar or another inactive substance, such as lactose, and saline injections (Fässler et al., 2010; Linde et al., 2018). In contrast, the most commonly used *impure* placebo interventions include vitamins and supplements, homeopathic remedies, antibiotics for viral infections, and painkillers for non-pain conditions, such as sleep (Fässler et al., 2010; Linde et al., 2018; Smits et al., 2022).

Other placebo interventions (or non-specific treatments) reported by medical professionals include diagnostic procedures, such as non-essential physical examinations or physiotherapy in the absence of a specific indication for it (Fässler et al., 2010). Furthermore, some research suggests that when it is provided as a

survey response option, clinicians will also report using positive suggestion or other strategies that induce placebo effects (Howick et al., 2013; Meissner et al., 2012; Smits et al., 2022).

Reasons of placebo use in clinical practice

In their systematic review, Fässler and colleagues (2010) found that in hospital settings, placebos were mostly prescribed for pain, insomnia, anxiety, and risk of substance abuse. The primary motivation given for using placebos in hospitals was to manage difficult or demanding patients. In primary care, GPs most commonly prescribe (impure) placebos to satisfy patient requests for prescriptions. Other reported reasons included eliciting placebo effects, avoiding conflicts, supplementing active treatment, addressing non-specific or unexplained symptoms, and to avoid the need to tell patients that their treatment options were exhausted. Some GPs and nurses also used pure placebos diagnostically with the aim of distinguishing between organic and functional symptoms. However, this practice varied greatly between studies and had also declined in more recent years.

Consistent with these findings, Linde and colleagues (2018) found that clinicians primarily use placebo interventions to manage the challenges of busy daily practice, such as handling patient expectations. Together, these findings suggest that placebo interventions in clinical practice are currently mostly used for reasons other than eliciting placebo effects, *per se*.

Using placebo interventions to support active treatments

Finally, in the future, placebo interventions could be used to reduce drug intake in the clinic. Specifically, conditioning open-label placebos (COLP) is a promising avenue for reducing drug intake without compromising therapeutic outcomes (Morales-Quezada et al., 2020). In COLP, an active treatment is paired with an open-label placebo, to train the body to react to the placebo in a similar way it would to the active treatment. In this way, patients can progressively reduce drug intake by replacing dosages of the active drug with the conditioned placebo treatment. This approach has shown potential in reducing opioid consumption in patients with pain. For example, in the study of Morales-Quezada and colleagues (2020), opioid intake in patients recovering from spinal cord injury and polytrauma was significantly

reduced while effective pain control was maintained. However, such pharmaco-conditioning requires further research before it can be integrated into standard clinical care.

4.5 Placebo and Nocebo Phenomena Across Clinical Conditions

Introduction

Placebo and nocebo phenomena exert effects across a multitude of clinical conditions, reflecting their significant influence in the medical field (Benedetti, 2014; Colloca & Barsky, 2020; Rossettini et al., 2020). While these effects are particularly marked in conditions where subjective experiences, such as pain and emotional distress, are major components (Colloca & Barsky, 2020), their reach extends beyond self-reported perceptions by also affecting objective clinical measures, including immune responses and motor performance (Benedetti, 2008). This blurring of the line between self-reported and clinician-assessed outcomes emphasizes that both aspects are crucial in comprehensive patient care.

Clinical conditions

Historically, research has largely focused on pain management (Atlas, 2021), but the scope of placebo and nocebo effects is expansive, influencing a variety of symptomatology and disorders. Neurological disorders like Parkinson's disease, migraine, dementia, and ADHD (Benedetti, 2008; Colloca & Barsky, 2020), as well as psychiatric conditions such as depression, anxiety, and addiction (Papakostas & Fava, 2009; Enck et al., 2013; Haas et al., 2020), are all susceptible to placebo and nocebo effects. Similarly, these phenomena impact gynecological issues including premenstrual dysphoric disorder and menopausal hot flushes (Pan et al., 2020), cardiovascular conditions such as cardiomyopathy and hypertension (Colloca & Barsky, 2020; Rossettini et al., 2020), and gastrointestinal disorders including irritable bowel syndrome, Crohn's disease, and nausea (Benedetti, 2014; Jairath et al., 2017). Dermatological conditions (e.g., itch, atopic dermatitis, psoriasis), respiratory issues (e.g., cough, dyspnea), immunological challenges (e.g., allergy, asthma), and sleep disorders (e.g., insomnia) also demonstrate significant responses to placebo and nocebo influences (Frisaldi et al., 2023; Bagnis et al., 2025).

In line with the findings of the PANACEA consortium study (O'Keefe et al., accepted), the clinical domains most frequently reported as benefiting from placebo effects

included general medicine, neurology, psychiatry, gynecology, cardiology, gastroenterology, and dermatology, further aligning with the wide range of conditions under which placebo effects have been documented (Bagnis et al., 2025).

Across different clinical settings, disease characteristics such as baseline severity, symptom duration, and disorder subtype significantly determine the placebo and nocebo responses and effects observed. For instance, lower baseline severity correlates with higher placebo responses in conditions like schizophrenia, depression, and neuropathic pain, while higher severity is linked to greater responses in alcohol use disorder and arthritis. Gastroenterological studies reveal that active disease or prolonged disease duration tends to associate with lower placebo response rates, underscoring the need for thorough patient evaluation and tailored therapeutic interventions. These findings illustrate the importance of considering the clinical profile of a disease in placebo research, supporting more personalized and effective patient care strategies (Benedetti, 2008; Enck et al., 2013; Kaptchuk & Miller, 2015).

The PANACEA consortium evidence notable variations in the understanding, application and management of placebo and nocebo across different disciplines and clinical areas (O'Keefe et al., accepted). Healthcare professionals generally attribute placebo effects to patient beliefs independent of specific treatment properties, emphasizing their perceived utility, especially in conditions lacking specific treatments. However, this perspective may reflect an underestimation of the healthcare professional's own role in influencing placebo effects through communication and interaction.

The extensive range of conditions responsive to placebo and nocebo effects underscores their clinical significance and the necessity for further exploration to fully harness their therapeutic potential.

4.6 Conclusion

In sum, research shows that clinicians use placebos at highly varying rates, with impure placebos seemingly being more common. Rather than aiming to induce placebo effects, *per se*, clinicians report prescribing placebos for such reasons as managing patient expectations and addressing non-specific symptoms. Furthermore, in the future, placebos may be used in clinical practice to reduce drug

intake. However, further research is needed to better understand and standardize placebo use in clinical settings.

References

Amanzio, M., Corazzini, L. L., Vase, L., & Benedetti, F. (2009). A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain, 146*(3), 261–269. https://doi.org/10.1016/j.pain.2009.07.010

Atlas, L. Y. (2021). A social affective neuroscience lens on placebo analgesia. *Trends in Cognitive Sciences, 25*(11), 992-1005. https://doi.org/10.1016/j.tics.2021.07.016

Babel, P. (2012). The Effect of Question Wording in Questionnaire Surveys on Placebo Use in Clinical Practice. E*valuation and the Health Professions, 35*(4), 447–461. https://doi.org/10.1177/0163278711420285

Barsky, A. J., Saintfort, R., Rogers, M. P., & Borus, J. F. (2002). Nonspecific Medication Side Effects and the Nocebo Phenomenon. *JAMA, 287*(5), 622–627. https://doi.org/10.1001/jama.287.5.622

Benedetti, F. (2014). Placebo effects: from the neurobiological paradigm to translational implications. *Neuron, 84*(3), 623-637. https://doi.org/10.1016/j.neuron.2014.10.023

Benedetti, F. (2008). Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu. Rev. Pharmacol. Toxicol., 48*(1), 33-60. https://doi.org/10.1146/annurev.pharmtox.48.113006.094711

Colloca, L., & Barsky, A. J. (2020). Placebo and nocebo effects. *New England Journal of Medicine, 382*(6), 554-561. https://www.nejm.org/doi/abs/10.1056/NEJMra1907805

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain, 124*(1–2), 126–133. https://doi.org/10.1016/j.pain.2006.04.005

Elliott, S. A., & Brown, J. S. L. (2002). What are we doing to waiting list controls?. *Behaviour research and therapy, 40*(9), 1047-1052. https://doi.org/10.1016/S0005-7967(01)00082-1

Enck, P., Bingel, U., Schedlowski, M., & Rief, W. (2013). The placebo response in medicine: Minimize, maximize or personalize? *Nature Reviews Drug Discovery, 12*(3), 191–204. https://doi.org/10.1038/nrd3923

Enck, P., & Klosterhalfen, S. (2019). Placebos and the Placebo Effect in Drug Trials. In J. Barrett, C. Page, & M. Michel (Eds.), *Concepts and Principles of Pharmacology. Handbook of Experimental Pharmacology* (Vol. 260, pp. 400–425). Springer, Cham. https://doi.org/https://doi.org/10.1007/164_2019_269

European Medicine Agency (2016) Committee for Human Medicinal Products Guideline for good clinical practice E6 (R2). EMA/CHMP/ICH/135/1995 Committee for Human Medicinal Products. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics, 87*(4), 204–210. https://doi.org/10.1159/000490354

Fässler, M., Meissner, K., Schneider, A., & Linde, K. (2010). Frequency and circumstances of placebo use in clinical practice - a systematic review of empirical studies. *BMC Medicine*, 8. https://doi.org/10.1186/1741-7015-8-15

Frisaldi, E., Shaibani, A., Benedetti, F., & Pagnini, F. (2023). Placebo and nocebo effects and mechanisms associated with pharmacological interventions: an umbrella review. *BMJ open, 13*(10), e077243. 10.1136/bmjopen-2023-077243

Geers, A. L., Spotts, E. K., Vang, M., Mayer, S. R., & Miller, F. G. (2024). The Use of Authorized Concealment to Minimize Nocebo Side Effects: A Survey of US Public Attitudes. *Psychotherapy and Psychosomatics, 92*(6), 391–398. https://doi.org/10.1159/000535011

Haas, J. W., Rief, W., Glombiewski, J. A., Winkler, A., & Doering, B. K. (2020). Expectation-induced placebo effect on acute sadness in women with major depression: an experimental investigation. *Journal of affective disorders, 274*, 920-928. https://doi.org/10.1016/j.jad.2020.05.056

Häuser, W., Bartram, C., Bartram-Wunn, E., & Tölle, T. (2012). Adverse Events Attributable to Nocebo in Randomized Controlled Drug Trials in Fibromyalgia Syndrome and Painful Diabetic Peripheral Neuropathy Systematic Review. C*lin J Pain, 28*(5). https://doi.org/10.1097/AJP.0b013e3182321ad8

Howick, J., Bishop, F. L., Heneghan, C., Wolstenholme, J., Stevens, S., Hobbs, F. D. R., & Lewith, G. (2013). Placebo Use in the United Kingdom: Results from a National Survey of Primary Care Practitioners. *PLoS ONE, 8*(3). https://doi.org/10.1371/journal.pone.0058247

Hróbjartsson, A., Forfang, E., Haahr, M. T., Als-Nielsen, B., & Brorson, S. (2007). Blinded trials taken to the test: An analysis of randomized clinical trials that report tests for

the success of blinding. *International Journal of Epidemiology*, *36*(3), 654–663. https://doi.org/10.1093/ije/dym020

Jairath, V., Zou, G., Parker, C. E., MacDonald, J. K., Mosli, M. H., AlAmeel, T., ... & Feagan, B. G. (2017). Systematic review with meta-analysis: placebo rates in induction and maintenance trials of Crohn's disease. *Alimentary Pharmacology & Therapeutics*, *45*(8), 1021-1042. https://doi.org/10.1111/apt.13973

Kaptchuk, T. J., & Miller, F. G. (2015). Placebo effects in medicine. *N Engl J Med*, *373*(1), 8-9. 10.1056/NEJMp1504023

Kessner, S., Wiech, K., Forkmann, K., Ploner, M., & Bingel, U. (2013). The Effect of Treatment History on Therapeutic Outcome: An Experimental Approach. *JAMA Intern Med*, *173*(15), 1468–1469. https://doi.org/10.1001/jamainternmed.2013.6705

Kokoti, L., Drellia, K., Papadopoulos, D., & Mitsikostas, D. D. (2020). Placebo and nocebo phenomena in anti-CGRP monoclonal antibody trials for migraine prevention: a meta-analysis. *Journal of Neurology*, *267*(4), 1158-1170. https://doi.org/10.1007/s00415-019-09673-7

Krogsbøll, L. T., Hrábjartsson, A., & Gøtzsche, P. C. (2009). Spontaneous improvement in randomised clinical trials: Meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Medical Research Methodology*, *9*(1). https://doi.org/10.1186/1471-2288-9-1

Laursen, D. R. T., Nejstgaard, C. H., Bjørkedal, E., Frost, A. D., Hansen, M. R., Paludan-Müller, A. S., Prosenz, J., Werner, C. P., & Hróbjartsson, A. (2023). Impact of active placebo controls on estimated drug effects in randomised trials: a systematic review of trials with both active placebo and standard placebo. In *Cochrane Database of Systematic Reviews* (Vol. 2023, Issue 3). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.MR000055.pub2

Lee, S., Walker, J. R., Jakul, L., & Sexton, K. (2004). Does elimination of placebo responders in a placebo run-in increase the treatment effect in randomized clinical trials? A meta-analytic evaluation. *Depression and Anxiety*, *19*(1), 10–19. https://doi.org/10.1002/da.10134

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. *Arch Gen Psychiatry*, *67*(8), 857–865. https://doi.org/10.1001/archgenpsychiatry.2010.88

Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PLoS ONE, 13*(8). https://doi.org/10.1371/journal.pone.0202211

Meissner, K., Höfner, L., Fässler, M., & Linde, K. (2012). Widespread use of pure and impure placebo interventions by GPs in germany. *Family Practice, 29*(1), 79–85. https://doi.org/10.1093/fampra/cmr045

Moncrieff, J., Wessely, S., & Hardy, R. (2004). Active placebos versus antidepressants for depression. In *Cochrane Database of Systematic Reviews* (Vol. 2017, Issue 12). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD003012.pub2

Morales-Quezada, L., Mesia-Toledo, I., Estudillo-Guerra, A., O'Connor, K. C., Schneider, J. C., Sohn, D. J., Crandell, D. M., Kaptchuk, T., & Zafonte, R. (2020). Conditioning open-label placebo: A pilot pharmacobehavioral approach for opioid dose reduction and pain control. *Pain Reports, 5*(4). https://doi.org/10.1097/PR9.0000000000000828

Myers, M. G., Cairns, J. A., & Singer, J. (1987). The consent form as a possible cause of side effects. *Clinical Pharmacology and Therapeutics, 42*(3), 250–253. https://doi.org/10.1038/clpt.1987.142

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (NCPHS) Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Federal Register. 1979; 44:23192–23197. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Pan, Y., Meister, R., Löwe, B., Kaptchuk, T. J., Buhling, K. J., & Nestoriuc, Y. (2020). Open-label placebos for menopausal hot flushes: a randomized controlled trial. *Scientific reports, 10*(1), 20090. https://doi.org/10.1038/s41598-020-77255-z

Papakostas, G. I., & Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *European Neuropsychopharmacology, 19*(1), 34–40. https://doi.org/10.1016/j.euroneuro.2008.08.009

Peters, E., Hart, P. S., & Fraenkel, L. (2011). Informing patients: The influence of numeracy, framing, and format of side effect information on risk perceptions. *Medical Decision Making, 31*(3), 432–436. https://doi.org/10.1177/0272989X10391672

Rato, M. L., Duarte, G. S., Ferreira, A. N., Alves, M., Mainoli, B., Teodoro, T., ... & Ferreira, J. J. (2019). Nocebo response in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism & Related Disorders, 65*, 13-19. https://doi.org/10.1016/j.parkreldis.2019.04.015

Rief, W., Avorn, J., & Barsky, A. J. (2006). Medication-Attributed Adverse Effects in Placebo Groups: Implications for Assessment of Adverse Effects. *Arch Intern Med, 166*(2), 155–160. https://doi.org/10.1001/archinte.166.2.155

Rief, W., & Glombiewski, J. A. (2012). The hidden effects of blinded, placebo-controlled randomized trials: An experimental investigation. *Pain*, *153*(12), 2473–2477. https://doi.org/10.1016/j.pain.2012.09.007

Rief, W., Nestoriuc, Y., Von Lilienfeld-Toal, A., Dogan, I., Schreiber, F., Hofmann, S. G., Barsky, A. J., & Avorn, J. (2009). Differences in Adverse Effect Reporting in Placebo Groups in SSRI and Tricyclic Antidepressant Trials: A Systematic Review and Meta-Analysis. *Drug Saf, 32*(11), 1041–1056. https://doi.org/10.2165/11316580-000000000-00000

Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., & Testa, M. (2020). Context matters: the psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Archives of Physiotherapy, 10*, 1-12. https://doi.org/10.1186/s40945-020-00082-y

Simpson, D. M., Rice, A. S. C., Emir, B., Landen, J., Semel, D., Chew, M. L., & Sporn, J. (2014). A randomized, double-blind, placebo-controlled trial and open-label extension study to evaluate the efficacy and safety of pregabalin in the treatment of neuropathic pain associated with human immunodeficiency virus neuropathy. *Pain*, *155*(10), 1943–1954. https://doi.org/10.1016/j.pain.2014.05.027

Sinyor, M., Levitt, A. J., Cheung, A. H., Schaffer, A., Kiss, A., Dowlati, Y., & Lanctôt, K. L. (2010). Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. *Journal of Clinical Psychiatry*, *71*(3), 270–279. https://doi.org/10.4088/JCP.08r04516blu

Smits, R. M., Veldhuijzen, D. S., van Middendorp, H., van der Heijden, M. J. E., van Dijk, M., & Evers, A. W. M. (2022). Integrating Placebo Effects in General Practice: A Cross-Sectional Survey to Investigate Perspectives From Health Care Professionals in the Netherlands. *Frontiers in Psychiatry*, 12. https://doi.org/10.3389/fpsyt.2021.768135

Trindade, E., Menon, D., Topfer, L.-A., & Coloma, C. (1998). Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *CMAJ, 159*(10), 1245–1252. https://doi.org/PMC1229819

Weimer, K., Colloca, L., & Enck, P. (2015a). Age and sex as moderators of the placebo response - An evaluation of systematic reviews and meta-analyses across medicine. *Gerontology, 61*(2), 97–108. https://doi.org/10.1159/000365248

Weimer, K., Colloca, L., & Enck, P. (2015b). Placebo effects in psychiatry: mediators and moderators. The *Lancet Psychiatry, 2*(3), 246-257. https://doi.org/10.1016/S2215-0366(14)00092-3

Weimer, K., & Enck, P. (2014). Traditional and innovative experimental and clinical trial designs and their advantages and pitfalls. In F. Benedetti, P. Enck, E. Frisaldi, & M. Schedlowski (Eds.), *Placebo. Handbook of Experimental Pharmacology* (Vol. 225, pp. 237–272). Springer. https://doi.org/10.1007/978-3-662-44519-8_14

Wilson, K., & Mottram, P. (2004). A comparison of side effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in older depressed patients: A meta-analysis. *International Journal of Geriatric Psychiatry, 19*(8), 754–762. https://doi.org/10.1002/gps.1156

Woloshin, S., & Schwartz, L. M. (2011). Communicating Data About the Benefits and Harms of Treatment: A Randomized Trial. *Ann Intern Med, 155*(2), 87–96. https://doi.org/10.7326/0003-4819-155-2-201107190-00004

World Medical Association. (2013). World Medical Association declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*, *310*(20), 2191–2194. https://doi.org/10.1001/jama.2013.281053

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PANACEA Learning Materials

Module 5: Factors that influence placebo phenomena

Module information

This module articulates factors involved in modulating placebo effects and responses and strategies for ethically optimizing the placebo effect to improve patient outcomes considering the intricate interplay of individual differences, and psychological and contextual factors. Notably, ensuring an ethical approach is paramount when harnessing the power of placebo effects to enhance patient outcomes (see Module 7).

5.1 Overview

Numerous studies have demonstrated that placebo effects do not occur in a vacuum, but rather emerge from the complex interplay between individual, psychological, and contextual factors. Research has shown that individual characteristics—such as age, sex, race, genetic and neurobiological profiles, as well as relatively stable psychological dispositions like personality traits and enduring beliefs—can significantly shape the magnitude and nature of placebo responses. However, findings in this area are still mixed and sometimes inconsistent, suggesting that this line of research is still developing. Therefore, caution is warranted when interpreting results related to individual differences, and further empirical work is essential to draw more definitive conclusions. In contrast, psychological processes such as learning from experiences, expectations, and emotional states have been more consistently linked to placebo effects, with mechanisms like classical conditioning and anticipatory responses emerging as key pathways. Finally, contextual and environmental factors—ranging from the clinical setting to the symbols of medical care—act as powerful cues that can enhance or diminish placebo responses. Together, these lines of research underscore the multidimensional nature of placebo effects and highlight the need to consider a wide range of variables when studying or applying them in clinical settings.

5.2 Individual differences

Introduction

A line of research has attempted to identify individual characteristics that shape susceptibility to placebo effects, delineating a complex interplay of individual differences such as age, sex, race, genetic profiles, neurobiological factors, and personality traits. However, the reader needs to bear in mind that the literature has not

provided any robust evidence regarding individual differences in placebo effects. Considering the limited evidence regarding individual differences in the placebo effect, it is important to note that there are likely numerous studies that did not find significant effects. Future studies are needed to delve into these aspects further to draw more certain conclusions. Nevertheless, some potentially interesting results from a few studies are listed below.

Age, Sex, Race

Age, sex, and race may play a role in influencing susceptibility to placebo response and effects in individuals, as suggested by several meta-analyses and systematic reviews. First, meta-analyses on RCTs indicate that younger age is associated with greater placebo responses in obsessive-compulsive disorder (Mohamadi et al., 2023), schizophrenia (Agid et al., 2013; Fraguas et al., 2019; Leucht et al., 2019), bipolar disorder (Dodd et al., 2019), epilepsy (Rheims et al., 2008), neuropathic pain (Arakawa et al., 2015), genetically determined intellectual disability (Curie et al., 2015), fibromyalgia (Mitsikostas et al., 2012), asthma (Yang et al., 2014), and non-alcoholic steatohepatitis (Ng et al., 2022). In gastroenterological diseases, age seems to have less impact on placebo responses, and with the opposite effect. For example, it has been shown that placebo responses increased with the mean age in participants with chronic idiopathic constipation (Nee et al., 2019).
It is important to mention that a larger placebo response could also indicate that nonspecific effects (e.g., regression to the mean) may be more pronounced in younger people, or it might be attributed to the placebo effect. An experimental study comparing children and adults shows equal magnitudes of placebo effects in pain, but a larger impact of learning on subsequent experiences in children (Wrobel et al., 2015). The impact of sex appears even less consistent. Reduced placebo responses and adverse events rate in placebo arms with a greater proportion of males have been shown in bipolar (Yildiz et al., 2011) and depressive (Meister et al., 2017) disorders. Instead, increased placebo responses and effects on pain (Vambheim & Flaten, 2017) and itch (Lee et al., 2020) were found in studies with male predominance. These contrasting results suggest that sex differences that may influence placebo responses are disease- and symptoms-specific. Moreover, it has been found that the placebo responses in nausea (Quinn & Colagiuri, 2015) and pain (Vambheim & Flaten, 2017) varied depending on sex, with men more susceptible to suggestion and women to conditioning. Finally, the experimenter's or clinician's sex on placebo response may play a role as well. Indeed, it has been shown that participants reported lower pain when tested by an experimenter of the opposite sex (Daniali & Flaten, 2019).
Although not extensively studied, belonging to specific racial or ethnic groups could reduce the likelihood of patients experiencing placebo effects during medical interactions. A study by Okusogu et al. (2020), examining racial effects on placebo hypoalgesia in both patients with temporomandibular disorders (TMD) and healthy

participants, found that White participants experienced greater conditioning effects, relief expectations, and placebo effects than African American/Black participants. Although racial effects on placebo in TMD were small and short-lived, they were influenced by conditioning strength. Additionally, matching the experimenter and participant by race enhanced placebo hypoalgesia in TMDs, while differing sexes did so in healthy participants.

In Module 2, we explored how the doctor-patient relationship influences placebo effects, playing a crucial role in patient outcomes. The main drivers of placebo effects, such as expectations and conditioning, are likely influenced by the warmth and empathy expressed by physicians, as well as the level of support and engagement from patients (Howe et al., 2019). A substantial body of literature highlights that these elements of the clinical encounter occur less frequently in interactions with racial and ethnic minority patients, resulting in healthcare disparities (for a review, see Friesen & Blease, 2018). This implies that individuals from racial and ethnic minority backgrounds may obtain fewer therapeutic benefits from placebo effects.

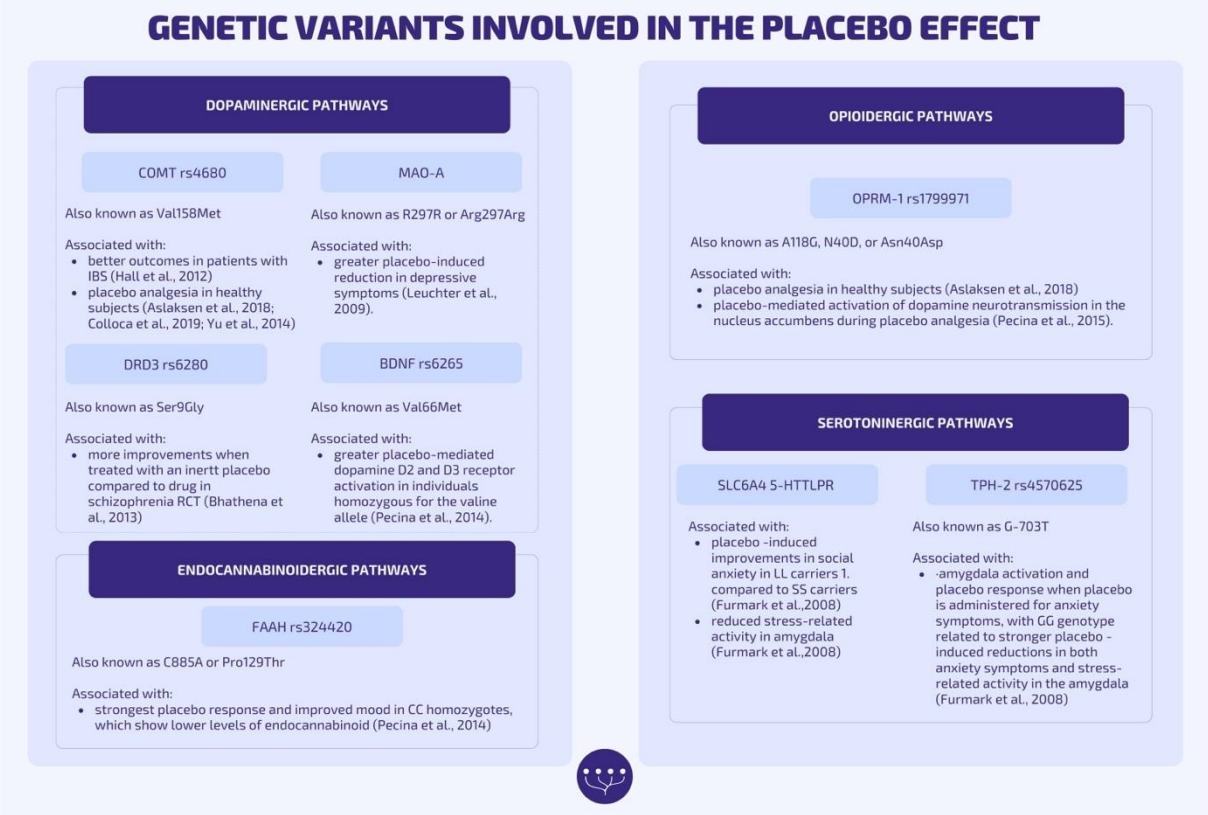
While individual characteristics have been subject to investigation, their definitive association with susceptibility to the placebo response and effect remains uncertain. Due to the limited body of research in this domain, it is advisable to approach conclusions regarding the influence of race or ethnicity on placebo responses and effects with caution.

Genetic profiles

There is tentative evidence that genetic variation potentially predicts placebo effects. Exploring the influence of various genes on the placebo response may offer potential insights into customizing treatment strategies to optimize individual outcomes using the placebo effect. Notably, investigations into the genetic variants involved in the placebo effect have primarily focused on four key systems: the dopaminergic, opioidergic, serotoninergic, and endocannabinoidergic pathways (Colagiuri et al., 2015). See Figure 5.1.

Figure 5.1

Genetic variants involved in the placebo effect by pathways.



Neurobiological factors

In recent years, various brain imaging techniques (Box 5.1) have been employed to explore how individual differences in brain structure and function influence placebo effects, especially in placebo analgesia investigation (Koban et al., 2013; Wager et al., 2011). However, it is important to note that recent studies in neuroimaging have consistently shown that these group averages are not necessarily representative of individual differences (e.g., Kohoutová et al., 2023; Siddiqi et al., 2022; Gratton et al., 2018). It is crucial to interpret these findings in the context of individual variability rather than assuming uniform effects across populations.

Notably, functional magnetic resonance imaging (fMRI) studies showed correlations with placebo analgesia in brain regions not primarily implicated in nociceptive processing, such as somatosensory areas, dorsal anterior cingulate cortex (ACC), anterior insula, and medial thalamus (Apkarian et al., 2005; Bushnell et al., 1999; Iannetti & Mouraux, 2010; Rainville et al., 1997). Conversely, individual differences in placebo analgesia are associated with neural activity in regions like the parietal and prefrontal cortex, as well as brainstem areas (Atlas et al., 2012; Petrovic et al., 2010; Scott et al., 2008; Wager et al., 2004).

Moreover, in healthy individuals, it was found that during the rest phase increased connectivity between the same brain networks mentioned above was associated with

greater modulation of pain by expectancy cues, while decreases in activity during painful stimulation correlated with changes in pain ratings (Kong et al., 2013).
In studies using measurements of brain structures (e.g., voxel-based morphometry, diffusion tensor imaging), correlations between grey matter density in the nucleus accumbens (NAc), insula, and dorsolateral prefrontal cortex (dlPFC) and placebo effects were found (Schweinhardt et al., 2009). Furthermore, individual placebo analgesia was linked to increased white matter integrity in rostral ACC and in left dlPFC and stronger fiber tract connections between these regions and the periaqueductal grey, highlighting the significance of cortical prefrontal regions in endogenous pain regulation (Stein et al., 2012).
Molecular imaging via positron emission tomography (PET) allows the examination of neurotransmitter activity and its association with placebo analgesia, with evidence from pharmacological and brain imaging studies implicating opioidergic and dopaminergic systems in regions like the NAc and prefrontal areas. Studies by Peciña et al. (2013) and Scott et al. (2008) link individual differences in opioid and dopamine activity to variations in placebo analgesia, suggesting a relationship between these neurotransmitter systems and placebo responsiveness.
Finally, while imaging studies reveal brain regions involved in pain processing and their modulation by placebos, electroencephalography (EEG) offers higher temporal. Studies measuring event-related potentials (ERPs) show that placebo leads to a reduction in the amplitude of laser-evoked potentials, particularly the N2 and/or P2 components, suggesting that early modulation in neurophysiological processing correlated with the subjectively experienced analgesic effect (Colloca et al., 2008; Lyby et al., 2010; Morton et al., 2010). Interestingly, the placebo effects on P2 were reduced for participants with high fear of pain, in line with a reduced analgesic effect for highly anxious individuals (Lyby et al., 2010).

Taken together, the activation of neurophysiological systems associated with valuation and reward processing, particularly the nucleus accumbens (NAc)/ventral striatum, orbitofrontal areas, and ventromedial prefrontal cortex (vmPFC) has been recurrently found. These activations have been linked to variations in reward learning and traits such as novelty seeking, which may indicate differences in dopaminergic activity among participants. Individuals exhibiting heightened functional activity and structural integrity in these regions may be particularly susceptible to placebo analgesia, as they effectively learn to associate medical contexts and treatment cues with pain relief and reward value.
However, it is important to note that while some consistent findings have emerged across multiple studies using different techniques, recent research in neuroimaging has underscored the individual variability in these effects.

Box 5.1 Brain imaging techniques

Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging technique that measures brain activity by detecting changes in blood flow and oxygenation levels in response to neural activity. It provides insight into brain function by mapping the spatial distribution of these changes, allowing researchers to identify regions of the brain associated with specific tasks or cognitive processes.

Voxel-Based Morphometry (VBM) is a neuroimaging technique used to analyze differences in brain anatomy between groups of individuals or changes within the same individual over time. It involves segmenting structural MRI images into small units called voxels and comparing their density or volume across groups or conditions, enabling the identification of regional differences in brain structure.

Diffusion Tensor Imaging (DTI) is a neuroimaging technique used to visualize the white matter tracts in the brain and assess the microstructural integrity of these pathways. DTI measures the diffusion of water molecules within the brain, providing information about the direction and magnitude of water diffusion in different tissue types. This data is used to reconstruct white matter tracts and analyze properties such as fractional anisotropy, which reflects the coherence and organization of white matter fibers. DTI is valuable for studying brain connectivity and assessing changes in white matter integrity associated with various neurological conditions.

Positron Emission Tomography (PET) is a neuroimaging technique that detects gamma rays emitted by a radioactive tracer injected into the body. The tracer, typically a small amount of a radioactive substance attached to a biologically active molecule, emits positrons that collide with electrons in the body, producing pairs of gamma rays. PET scanners detect these gamma rays and use them to create three-dimensional images of the distribution of the tracer in the body, providing information about physiological processes such as metabolism, blood flow, and neurotransmitter activity. PET is commonly used in clinical diagnosis, research, and drug development.

Personality traits and relatively stable attitudes

The idea that individual responsiveness to placebo effects can be explained, to some extent, by stable psychological factors, such as personality, has a long history. Researchers have questioned the existence of a "placebo personality" and even the notion of individual consistency in placebo responsiveness (Buckalew et al., 1981; Kaptchuk et al., 2008).
In clinical trials, high placebo responses contribute to many clinical trials failing to find significant drug effects. To address this issue, clinical trials have used various methods to reduce, or control for, placebo response rates, such as trying to identify (and sometimes exclude) people who would respond favorably to placebos. After the emergence of randomized controlled trials in the 1940s to 1950s, it was soon suggested that individuals may show a consistent tendency to respond ("placebo responders") or not respond ("placebo non-responders") positively to placebo interventions and that this tendency may be explained by personality traits (see Box 5.2).

Box 5.2 Early influential study on "placebo personality"

Researchers employed Rorschach interviews with patients undergoing treatment for post-operative pain and discovered that individuals exhibiting consistent placebo responses tended to display traits such as being talkative, attending church regularly, experiencing anxiety, demonstrating self-centered tendencies, showing heightened awareness of bodily sensations, and being emotionally labile, in contrast to non-responders. The researchers suggested that these characteristics might indicate a greater reliance on external stimuli rather than internal mental processes for alleviating anxiety and tension, thereby predisposing them to positive responses to placebo interventions (Lasagna et al., 1954).

As mentioned above and explored in Module 2, positive expectations of a therapeutic outcome are commonly considered as a key mechanism of the placebo effect. Correspondingly, dispositional optimism has been proposed to promote placebo effects by increasing the expectancy of a positive therapeutic outcome (e.g., Geers et al., 2005, 2010; Kern et al., 2020). Also, individuals high in openness to experience may exhibit greater receptivity to placebo interventions due to their propensity for cognitive flexibility and receptiveness to novel experiences. For example, Kelley et al. (2009) have found that the personality traits extraversion, openness to experience, and agreeableness were associated with a placebo response in IBS when the patient-clinician interaction was augmented with warmth and empathy. Conversely, trait anxiety, which is sometimes negatively associated with optimism and related to negative expectancy bias, has been suggested as a negative predictor of placebo responsiveness (Horing et al., 2014; Peciña et al., 2013). Similarly, neuroticism (Peciña et al., 2013), pain catastrophizing (Ballou et al., 2022; Sullivan et al., 2008; Weng et al., 2022) and fear of pain (Lyby et al., 2010) have been linked to placebo effects as a negative predictor.
It is important to note, however, that numerous studies did not find significant effects. For instance, in a study conducted by Ballou et al. 2022, they did not find any significant effects of age, sex, extraversion, or openness to experience, neither in double-blind placebo conditions nor in open-label placebo (OLP) conditions. Similarly, a recent meta-analysis by Kang and colleagues (Kang et al., 2023) found that personality traits like behavioral inhibition, reward responsiveness, optimism, and anxiety do not appear to influence susceptibility to placebo effects, challenging the notion that personality influences responsiveness to placebos and contradicting its utility for identifying placebo "responders" and "non-responders." However, it is important to note that this meta-analysis only included a fraction of the studies that actually assess personality traits and placebo effects (e.g., they only considered studies with within-subjects designs, any between-subjects or mixed model studies were excluded).

The evidence generally tends to lean towards inconsistent or null findings. This should be highlighted, along with several methodological considerations regarding the assessment of moderating variables, such as personality, for placebo effects. These considerations include issues like lack of power and the types of samples used (e.g., healthy participants or students).

5.3 Psychological Factors

Introduction

The placebo effect represents a unique convergence of psychological, environmental, and interpersonal elements that significantly enhance therapeutic outcomes. Its strategic application, alongside active medical treatments and under ethical guidelines, provides an unparalleled opportunity to maximize the efficacy of health interventions.

Expanding on the insights from earlier modules (see Module 2, which intricately explores the mechanisms driving placebo effects, and Module 4, which describes the applications of the placebo in medical research and clinical practice), a multitude of factors come into play. Learning from experiences, expectations, emotions, and environmental cues collectively wield a substantial influence over the placebo effect. Delving into mechanism studies holds promise in offering deeper insights into the variability of placebo effects and thus the possibility for optimizing placebo effects in clinical practice or even minimizing them when necessary, such as in pharma-clinical trials.
Health professionals play a pivotal role in directly shaping these mechanisms through their communication strategies and patient interactions, making these mechanisms key agents in optimizing treatment outcomes in clinical settings.

Learning from experience and expectations

Research has demonstrated that the individual's learning from experiences—whether direct, through direct experience with treatments (classic and operant conditioning), or indirect, through social observation (observational learning) or verbal instruction (instructed learning), or the interaction between these different types of learning—plays a crucial role in shaping both placebo effects and response. (Bąbel, 2020; Colagiuri et al., 2015; Finniss et al., 2010; Forsberg et al., 2017; Meeuwis et al., 2023; Petersen et al., 2014; Thomaidou et al., 2023). Expectations, with varying degrees of awareness, are a key element emerging from these different forms of learning. Research highlights the crucial role of expectations in placebo effects, emphasizing how these anticipations, molded through diverse learning pathways, significantly influence responses to treatments and interventions. Crucially, a patient's positive expectations and belief in a treatment's efficacy can profoundly increase their response to it, regardless of whether the treatment possesses active therapeutic properties (Atlas, 2021, Bingel, 2020).
There is growing and robust scientific pharmacological evidence that supports the beneficial application of placebo effects by bolstering elements that shape patient learning and expectations toward positive outcomes (Bishop et al., 2017; Blease & DesRoches, 2022; Price et al., 2008).

Classical and operant conditioning

Patients' prior experiences with treatments, acquired through multiple learning mechanisms—including classical conditioning (partially independent of explicit awareness) and operant conditioning, both derived from direct experiences—play a critical role in shaping patient's expectations and responses to subsequent therapies (Bąbel, 2020; Colagiuri et al., 2015). These learning experiences predispose patients to anticipate certain results, significantly enhancing the treatment's efficacy when positive.

As described in Module 2, classical conditioning concerns an association between events by associating a neutral stimulus with an unconditioned stimulus (US) that naturally triggers an unconditioned response (UR), converting the neutral stimulus into a conditioned stimulus (CS). As a result, the CS gains the ability to provoke a response that is alike or connected to the UR. This response is called a conditioned response (CR). Exposure to a CS–US pairing leads to the development of a general unconscious or conscious expectation that the CS will be followed by the US. When later exposed to the CS, a specific expectation that the US will follow arises, resulting in the production of the conditioned response (CR).

When applying the conditioning framework to the placebo effect, the drug or active ingredient serves as the US. Elements of treatment administration, such as the timing of drug intake, the people present during administration, the locations where the drug is used, therapeutic rituals, intervention procedures, and the tastes or odors present at the time of use, serve as CS capable of triggering a physiological response associated with the US. Notably, not all stimuli have the same potential to be conditioned.

According to the principles of classical conditioning, some associations are more likely to form than others. The strength of the association depends on several factors including the frequency with which the stimuli has been linked to a positive or negative outcome, the intensity of adverse effects in past experiences, and the prominence and evolutionary relevance of the stimulus. These factors together influence how effectively a particular stimulus can be conditioned to elicit a response. Classical conditioning principles involve i) generalization, where learning from specific cues can extend to similar ones, allowing placebo effects triggered by cues sharing certain features; and ii) extinction that involves reducing a conditioned response by presenting the cue without the expected outcome until the response weakens. Reactivating a conditioned response can occur through spontaneous recovery or reinstatement techniques.

Health professionals must keep in mind the basic principles of classical conditioning when considering the placebo effect since these principles may moderate and optimize

the placebo effect. However, robust clinical applications are undefined, indicating potential but unproven benefits in healthcare settings.

Classical conditioning, the most extensively studied learning process producing placebo effects, has led to key research areas including conditioned immunopharmacological effects, conditioned drug tolerance, and conditioned pain, each exploring how associations with specific stimuli can alter immune responses, drug tolerance, and pain perception (Bąbel, 2019).

Classically conditioned immunosuppression stands out as one of the most notable examples of how conditioning principles can be harnessed to optimize placebo effects. This concept involves mirroring drug effects by pairing a neutral stimulus, such as a novel taste or scent, with an immunomodulating drug. The subsequent exposure to this conditioned stimulus alone can trigger immune responses that replicate those induced by the drug, even in the drug's absence (Hadamitzky et al., 2013; 2018). Kirchhof and colleagues (2018) provided compelling evidence of conditioned immunosuppression in kidney transplant patients. Initially treated with immunosuppressants like cyclosporine A or tacrolimus paired with a novel taste, patients later exhibited significant reductions in T lymphocyte activity when the taste was paired with a placebo. This conditioned response closely mirrored the drug's effects and highlighted the potential for conditioned stimuli to enhance drug efficacy without altering the dosage.
Given these promising findings, further investigation into conditioned immunosuppression is crucial for clinical practice.

Classical conditioning significantly contributes to drug addiction by developing tolerance, where the drug's effects decrease after repeated use. When cues associated with the drug (CSs) are repeatedly paired with the drug itself (US), compensatory responses develop to counteract the drug's effects, leading to tolerance. In this phenomenon, an organism is administered a drug in a particular environment where tolerance gradually develops. During a subsequent test in the same environment, tolerance is evident with reduced drug effects. However, if the drug is administered in a different environment, tolerance is either diminished or fully reinstated, showcasing the role of environmental cues in drug response modulation. This phenomenon has been observed across various drugs, effects, and species, reinforcing the impact of environmental context on drug tolerance (Siegel, 2005). Understanding drug tolerance can help clinicians optimize treatment strategies. By considering the situational specificity of tolerance, healthcare providers could tailor treatment environments to enhance or mitigate drug effects effectively.

Finally, classical conditioning paradigms have been extensively used to induce placebo analgesia in laboratory settings for decades (Bąbel et al., 2017). A typical experiment designed to evoke placebo effects through classical conditioning involves an initial exposure where participants experience standardized painful stimulation. Subsequently, they receive a positive cue, such as a placebo treatment, and are re-exposed to pain stimuli. During this second exposure, however, the intensity of the pain stimuli is covertly reduced. This deceptive approach leads participants to believe that the placebo treatment acts as an effective analgesic. Following this learning phase, when participants are re-exposed to the original pain stimuli alongside the placebo treatment, they typically report experiencing less pain than before.
In clinical contexts, various contextual factors can influence pain variations by eliciting responses similar to those produced by active drugs. This drug-mimicking response can occur as a conditioned response due to the association between a pain-relief experience and a contextual stimulus (such as the environment, specific sounds, or even the presence of medical personnel). Identifying these elements, or conditioned stimuli, that modify pain perception may be crucial for developing effective pain management programs. However, because of substantial differences between experimental and clinical environments, further research is needed before translating laboratory findings into clinical practice.

Also, operant conditioning plays a significant role in placebo effects by shaping behaviors through consequences, thereby optimizing the placebo response or the placebo effects (Bąbel, 2020). Unlike classical conditioning where responses are triggered by preceding stimuli, operant behaviors are influenced by their outcomes. In operant conditioning, a behavior linked to a reinforcer increases in likelihood, while association with a punisher diminishes the behavior.
In the context of placebo effect, the administration of an inert treatment can increase their future application based on positive (e.g., improved activity) or negative reinforcement (e.g., pain relief). Recent research has successfully induced long-lasting placebo analgesia through operant conditioning, demonstrating its potential as a mechanism for enhancing the placebo effect (Adamczyk et al., 2019). Placebo response is stronger when preceded by preconditioning with a pharmaceutical agent, and the effect of a drug also benefits from rewarding. Based on these findings, operant conditioning emerges as a crucial mechanism contributing to and optimizing placebo effects.
Research has demonstrated that the lasting impact of a treatment's perceived efficacy can significantly shape health outcomes even beyond the immediate treatment period. For instance, in the realm of chronic pain management, patients who hold a positive perception of their pain-relief treatments often experience not only reduced pain levels during the treatment phase but also enhanced pain management outcomes in the long term. Similarly, in post-operative care, patients who are confident in the effectiveness

of their recovery regime tend to exhibit better rehabilitation progress and overall quality of life post-surgery, indicating the profound influence of sustained treatment perceptions on health outcomes (Atlas, 2021).
This strategic reinforcement not only boosts patient compliance and overall satisfaction but also enhances the therapeutic efficacy by leveraging the robust framework of learned associations and expectations from previous experiences and instructed knowledge (Wager & Atlas, 2015).

Observational Learning

Observational learning plays a crucial role by facilitating the acquisition of behaviors and expectations through the observation of others' actions, experiences, and outcomes. In the context of optimizing placebo effects, observational learning becomes a powerful tool. By witnessing individuals experience pain relief after a certain intervention, observers may undergo placebo hypoalgesia—a phenomenon essential for enhancing treatment responses in chronic pain conditions. Understanding the contributing factors is vital for developing effective strategies to optimize placebo effects. Studies indicated that observing a model demonstrates pain relief or exacerbation post a sham intervention can induce similar responses in observers later when the same placebo is administered (Vase et al., 2002). Research indicates that the magnitude of placebo hypoalgesia may vary depending on the specific observational learning employed (Meeuwis et al., 2023). The efficacy of observational learning can be influenced by various factors such as how people observe effects, whether through direct interactions, video demonstrations, or alternative methods. Verbal and behavioral modeling play a critical role in shaping an individual's perception of pain. Verbal modeling involves translating observed pain ratings into personal expectations, whereas behavioral modeling occurs through direct observation or video representation of pain experiences. Symbolic modeling, through platforms like television, also influences pain perception (Hunter et al., 2014). Understanding the impact of these different modes of observational learning on placebo and nocebo effects is crucial for enhancing treatment outcomes and improving patient experiences in healthcare settings (Meeuwis et al., 2023). Directing patients' attention towards observed treatment effectiveness in others offers a valuable strategy in healthcare. Emphasizing positive treatment outcomes witnessed through observational learning enhances the placebo effect, boosting patient confidence, engagement, and leading to improved treatment responses and overall health outcomes.

These research avenues highlight the potential of learning paradigms to significantly impact medical treatment and patient outcomes (Box 5.3). Recognizing the influence of environmental cues and learning experience emphasizes the importance of

personalized treatment plans. Complex individual responses, diverse environmental contexts, and the intricate nature of addiction necessitate cautious consideration. Clinicians must contextualize research findings within each patient's unique circumstances and exercise care when applying these concepts in real-world settings. Further research is crucial to effectively translate laboratory discoveries in optimizing placebo effects into clinical practice.

Box 5.3 How Learning Processes May Optimize Placebo Effects

Scientific Evidence	Practical Implication
The number of learning trials can impact the magnitude of the placebo effect (Colloca et al., 2010).	Regular exposure to contextual cues paired with symptom relief during treatment can enhance therapy effects in their presence.
Negative exposure or experiences with a placebo before actual treatment can reduce the effectiveness of placebo learning (Colloca et al., 2006).	To achieve the best outcomes, avoid exposing patients to any negative contextual stimuli that can be associated with their future treatment.
The conditioning schedule influences resistance to placebo effect extinction (Yeung et al., 2014).	Utilizing a partial reinforcement schedule may reduce interventions needed to maintain treatment effects, aiding in optimizing treatment strategies. This can help in drug dose regulation.
Generalization of placebo and nocebo effects (Kampermann et al., 2021; Koban et al., 2018).	Consistency in treatment environments for positive outcomes but distinct environments for treatment with significant side effects can optimize treatment effects.
Acquisition of placebo effects through observational learning (Meeuwis et al., 2023).	Enhancing treatment effects through exposing patients to similar contextual cues in the presence of which another person demonstrated improvement can optimize placebo effects.

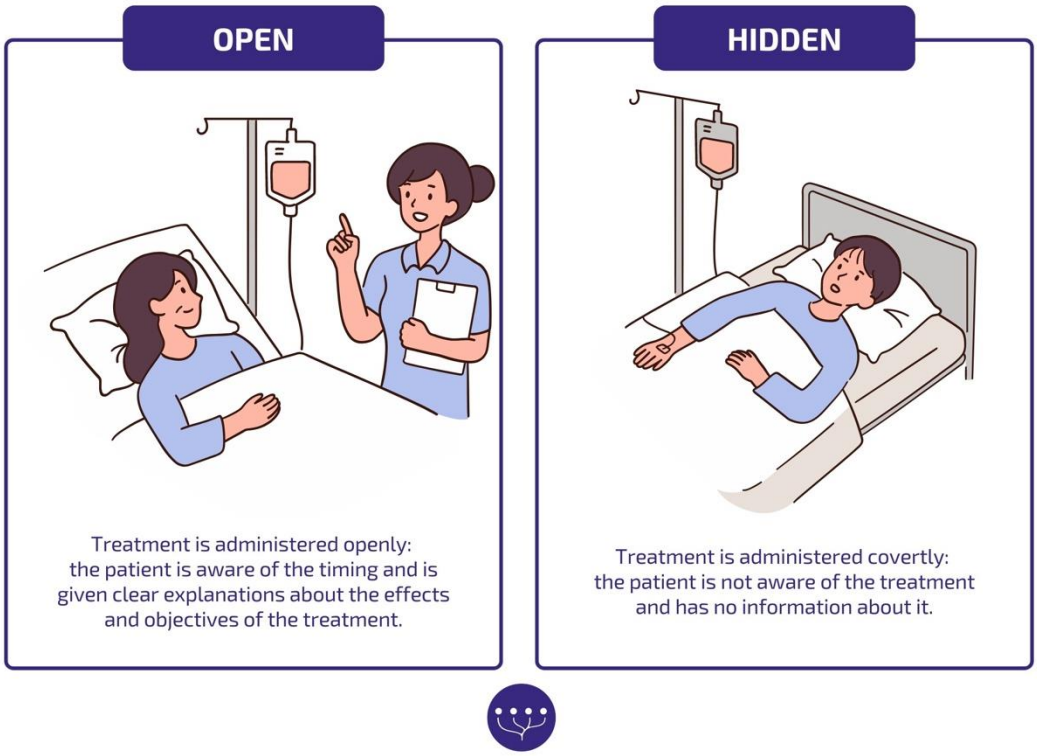
Verbal suggestions/instruction

Learning through verbal instruction stands out as the most direct and efficient method for a health professional to optimize placebo effects in their practice. Verbal instructions, when used appropriately, can set expectations that increase the effects of actual treatments. For example, informing patients about the potential benefits of a medication can positively impact their efficacy and satisfaction.
The open-hidden paradigm (Fig 5.2), which strategically manipulates the awareness of treatment administration, underscores the significant impact of the treatment context on therapeutic outcomes (Price et al., 2008). In this approach, treatments administered openly, where patients are not only aware of the timing but are also provided with clear, comprehensive explanations about the effects and objectives of the treatment, consistently yield better therapeutic results compared to those administered without

patient awareness (hidden administration). This finding highlights the critical role of therapeutic interaction and the setting in which a patient receives treatment (Finniss et al., 2010, Wager & Atlas, 2015). By fully informing patients and ensuring the treatment process is visible, healthcare providers can optimize these crucial factors, thereby enhancing patient engagement, trust, and overall treatment efficacy.

Figure 5.2

The open-hidden administration



Moreover, communication that addresses patient expectations and belief systems can significantly alter treatment outcomes. Tailoring realistic communication to assure patients of the potential benefits of a treatment can harness the placebo effect ethically and may enhance the overall therapeutic impact (Peederman et al., 2021). Positive, empathetic, and engaging interactions can significantly elevate patient trust and compliance, key components that synergize with the placebo effect (Bensing et al., 2011; Hojat et al., 2011). Regular effective communication, active listening, and showing empathy are crucial techniques practitioners must employ to optimize this interaction (see PANACEA Clinical Recommendations for more details). Furthermore, understanding and explaining placebo effects to patients might play a significant role in shaping treatment efficacy, overall health, and symptom perception (Evers et al.,

2018, 2020). Informing patients about how placebo mechanisms work—specifically, how expectations, prior experiences, and the healthcare environment interact to influence treatment efficacy and health outcomes—could potentially encourage greater engagement and proactivity in their treatment processes. This involves not only explaining the treatment process but also drawing the patient's attention to the beneficial effects observed in previous experiences with the treatment or similar therapies
(see PANACEA Clinical Recommendations for more details).
Such knowledge could empower patients by illuminating the significant role their mindsets and beliefs play in their healing journeys. This, in turn, can enhance the effectiveness of treatments by aligning physiological responses with positive expectations and beliefs, ultimately improving perceived and actual health outcomes (Benedetti, 2013).
By integrating an understanding of these mental mechanisms, healthcare providers can more effectively harness the full spectrum of therapeutic tools available, bridging the gap between mind and body in patient care.

Emotions

While some theoretical accounts tend to centralize cognitive processes like expectations and learning in placebo responses, it is increasingly recognized that placebo effects extend beyond mere cognitive processes. Emotion, as both a process and a moderator, plays a pivotal role in shaping placebo responses and has significant implications for optimizing the placebo effect. Patients often turn to treatments in times of distress, seeking relief from negative emotions like anxiety, fear, and stress. The treatment ritual itself can alleviate suffering not just by influencing expectations or the specific illness being treated, but also by targeting emotional well-being. While beliefs and expectations remain crucial, studies are increasingly recognizing the significant role of emotions and mood in shaping placebo response and effect (Atlas, 2021). By reducing negative affect and fostering positive emotions such as trust, hope, and a sense of support, the placebo effect has shown the potential to mitigate suffering (Kaptchuk et al., 2009; Kube et al., 2019). Various research works have indicated that the placebo effect indeed can diminish negative emotions. Examples include placebo analgesia being associated with lower levels of fear and anxiety compared to control conditions in both healthy individuals and patients with neuropathic pain (Coen & Mao, 2014; Benedetti 2014).

5.4 Contextual Factors and Environmental Cues

Introduction

Contextual factors and environmental cues have been widely recognized in the literature as critical modulators of placebo effects. These elements encompass the entire therapeutic context in which a treatment is delivered, ranging from the appearance of the medication (e.g., pill color and shape) to the demeanor and communication style of the healthcare provider, and even the design of the clinical environment. The context in which treatment takes place can convey powerful implicit messages about efficacy, safety, and care, which in turn shape patients' expectations and experiences. For instance, a warm and confident provider-patient interaction has been shown to enhance placebo analgesia (Kaptchuk et al., 2008), while clinical settings perceived as sterile or impersonal may reduce its magnitude (Benedetti, 2014). These cues act as conditioned stimuli or social signals that trigger neurobiological mechanisms related to reward, attention, and emotion regulation. Overall, contextual and environmental factors are not mere background features, but active ingredients that can amplify or attenuate therapeutic outcomes through their influence on patients' psychological and physiological responses.

Context

In exploring contextual factors influencing placebo effects, interpersonal relationships have been identified as significant contributors to treatment outcomes. The quality of the clinical encounter and the therapeutic alliance with healthcare providers, as explained before, play a crucial role in shaping placebo effects as highlighted by the role of communication and verbal instructions. Beyond these relationships, the broader social context, including the presence and support of affective others, familiar people, or meeting, and chatting with other patients undergoing the same therapy with positive results, can also impact placebo effects and therapy outcomes positively (Atlas, 2021; Bagnis et al., 2023).

Moreover, focusing on non-interpersonal contextual factors, expectations, beliefs, and attitudes of caregivers and healthcare providers emerges as paramount as well. The beliefs and behaviors of practitioners hold sway over patient experiences and treatment results. Healthcare professionals who convey confidence in their prescribed treatments can bolster the placebo effect (Price et al., 2008).

Environment

The environment in which the placebo effect occurs plays a pivotal role in influencing the magnitude and direction of these effects. The setting in which care is provided (e.g. hospital setting or at home) shapes patient perceptions and responses, together with the specific features of the treatment itself. Research has demonstrated that the physical environment within healthcare settings can positively influence the healing process and contribute to patients' overall sense of well-being. Particularly beneficial effects have been identified in relation to sunlight, windows, pleasant odors, and seating arrangements (Dijkstra et al., 2006).

As mentioned earlier, equally important are the characteristics of the treatment administered openly and visibly, where patients are fully aware of the procedure's timing and process. Treatments perceived as sophisticated or cutting-edge, injections, surgery, or high-tech therapies, tend to elicit more pronounced placebo effects compared to simpler interventions like pills. Specifically, it has been shown that the route of administration plays a significant role, with placebo responses in acute (Macedo et al., 2006) and chronic (Swerts et al., 2022) migraine preventive treatment being greater when placebo had been administered by subcutaneous and head injection, respectively. Similarly, the type of placebo treatment appears to play a role in the magnitude of improvement, with sham acupuncture and sham surgery showing more pronounced reductions in migraine frequency (Meissner et al., 2013), intra-articular and topical placebo being more effective in osteoarthritis trials (Bannuru et al., 2015), and injectable agonists in patients with Type 2 diabetes mellitus (de Wit et al., 2016) compared to oral administration. These results underscore the relationship between patients' expectations and treatment outcomes, highlighting that the method and type of placebo administration can influence the perceived efficacy of the treatment.
Finally, the frequency and thoroughness of follow-up appointments and symptom monitoring further impact the overall treatment experience and outcomes (Bishop et al., 2017). Numerous studies underscore the significance of establishing an environment where patients feel valued, informed, and monitored, consistently evaluating patients' post-intervention/experiment, and engaging in explicit discussions about official guidelines and treatment protocols to underscore the legitimacy of the intervention (Bishop et al., 2017).

5.5 Conclusion

Optimizing the placebo effect in clinical practice requires a comprehensive approach that considers the intricate interactions between patient and practitioner characteristics, the healthcare delivery environment, and the specific attributes of treatments. Ethically harnessing these placebo mechanisms, through thoughtful patient-practitioner interactions and strategic communication (see PANACEA Clinical Recommendations for more details), offers a robust avenue to enhance the holistic efficacy of medical treatments. Each stakeholder in the healthcare pathway has a role to play in nurturing these mechanisms and effects to improve the overall quality of healthcare and patient outcomes.

References

Adamczyk, W. M., Wiercioch-Kuzianik, K., Bajcar, E. A., & Bąbel, P. (2019). Rewarded placebo analgesia: a new mechanism of placebo effects based on operant conditioning. *European Journal of Pain, 23*(5), 923-935. https://doi.org/10.1002/ejp.1360

Agid, O., Siu, C. O., Potkin, S. G., Kapur, S., Watsky, E., Vanderburg, D., Zipursky, R. B., & Remington, G. (2013). Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. *American Journal of Psychiatry, 170*(11), 1335–1344. https://doi.org/10.1176/appi.ajp.2013.12030315

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*(4), 463–484. https://doi.org/10.1016/J.EJPAIN.2004.11.001

Arakawa, A., Kaneko, M., & Narukawa, M. (2015). An Investigation of Factors Contributing to Higher Levels of Placebo Response in Clinical Trials in Neuropathic Pain: A Systematic Review and Meta-Analysis. *Clinical Drug Investigation*, *35*(2), 67–81. https://doi.org/10.1007/s40261-014-0259-1

Aslaksen, P. M., Forsberg, J. T., & Gjerstad, J. (2018). The opioid receptor mu 1 (OPRM1) rs1799971 and catechol-O-methyltransferase (COMT) rs4680 as genetic markers for placebo analgesia. *Pain, 159*(12), 2585-2592. https://doi.org/10.1097/j.pain.0000000000001370

Atlas, L. Y. (2021). A social affective neuroscience lens on placebo analgesia. *Trends in Cognitive Sciences*, *25*(11), 992–1005. https://doi.org/10.1016/j.tics.2021.07.016

Atlas, L. Y., Whittington, R. A., Lindquist, M. A., Wielgosz, J., Sonty, N., & Wager, T. D. (2012). Dissociable Influences of Opiates and Expectations on Pain. *Journal of Neuroscience*, *32*(23), 8053–8064. https://doi.org/10.1523/JNEUROSCI.0383-12.2012

Bąbel, P. (2020). Operant conditioning as a new mechanism of placebo effects. *European Journal of Pain (United Kingdom)*, *24*(5), 902–908. https://doi.org/10.1002/ejp.1544

Bąbel, P. (2019). Classical conditioning as a distinct mechanism of placebo effects. *Frontiers in psychiatry, 10*, 449. https://doi.org/10.3389/fpsyt.2019.00449

Bąbel, P., Bajcar, E. A., Adamczyk, W., Kicman, P., Lisińska, N., Świder, K., & Colloca, L. (2017). Classical conditioning without verbal suggestions elicits placebo analgesia and nocebo hyperalgesia. *PLoS One, 12*(7), e0181856. https://doi.org/10.1371/journal.pone.0181856

Bagnis, A., Todorov, A., Altizio, I., Colonnello, V., Fanti, S., Russo, P. M., & Mattarozzi, K. (2023). Familiarity From Facial Appearance Leads to Hypoalgesia. *The Journal of Pain*, *24*(11), 2040–2051. https://doi.org/10.1016/J.JPAIN.2023.06.012

Ballou, S., Haas, J.W., Iturrino, J., Nee, J., Kirsch, I., Rangan, V., Cheng, V., Lembo, A., Kaptchuk, T.J., & Kelley, J.M. (2022). Psychological Predictors of Response to Open-label versus Double-blind Placebo in a Randomized Controlled Trial in Irritable

Bowel Syndrome. *Psychosomatic Medicine, 84*(6), 738-746. https://doi.org/10.1097/psy.0000000000001078

Bannuru, R. R., McAlindon, T. E., Sullivan, M. C., Wong, J. B., Kent, D. M., & Schmid, C. H. (2015). Effectiveness and implications of alternative placebo treatments: A systematic review and network meta-analysis of osteoarthritis trials. *Annals of Internal Medicine*, *163*(5), 365–392. https://doi.org/10.7326/M15-0623

Benedetti, F. (2013). Placebo and the new physiology of the doctor-patient relationship. *Physiological Reviews*, *93*(3), 1207–1246. https://doi.org/10.1152/physrev.00043.2012

Benedetti, F. (2014). Placebo effects: from the neurobiological paradigm to translational implications. *Neuron, 84*(3), 623-637. https://doi.org/10.1016/j.neuron.2014.10.023

Benedetti, F. (2014). *Placebo Effects: Understanding the mechanisms in health and disease* (2nd ed.). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780198705086.001.0001

Bensing, J. M., Deveugele, M., Moretti, F., Fletcher, I., van Vliet, L., Van Bogaert, M., & Rimondini, M. (2011). How to make the medical consultation more successful from a patient's perspective? Tips for doctors and patients from lay people in the United Kingdom, Italy, Belgium and the Netherlands. *Patient education and counseling, 84*(3), 287-293. https://doi.org/10.1016/j.pec.2011.06.008

Bhathena, A., Wang, Y., Kraft, J. B., Idler, K. B., Abel, S. J., Holley-Shanks, R. R., ... & Katz, D. A. (2013). Association of dopamine-related genetic loci to dopamine D3 receptor antagonist ABT-925 clinical response. *Translational psychiatry, 3*(4), e245-e245. https://doi.org/10.1038/tp.2013.22

Bingel, U. (2020). Placebo 2.0: the impact of expectations on analgesic treatment outcome. *Pain, 161*, S48-S56. https://doi.org/10.1097/j.pain.0000000000001981

Bishop, F. L., Coghlan, B., Geraghty, A. W. A., Everitt, H., Little, P., Holmes, M. M., Seretis, D., & Lewith, G. (2017). What techniques might be used to harness placebo effects in non-malignant pain? A literature review and survey to develop a taxonomy. *BMJ Open*, *7*(6), e015516. https://doi.org/10.1136/bmjopen-2016-015516

Blease, C., & DesRoches, C. M. (2022). Open notes in patient care: confining deceptive placebos to the past? *Journal of Medical Ethics*, *48*(8), 572–574. https://doi.org/10.1136/MEDETHICS-2021-107746

Buckalew, L. W., Ross, S., & Starr, B. J. (1981). Nonspecific Factors in Drug Effects: Placebo Personality. *Psychological Reports, 48*(1), 3-8. https://doi.org/10.2466/pr0.1981.48.1.3

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J. I., & Carrier, B. (1999). Pain perception: Is there a role for primary somatosensory cortex? *Proceedings of the National Academy of Sciences*, *96*(14), 7705–7709. https://doi.org/10.1073/PNAS.96.14.7705

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: mechanisms and their clinical implications. *Bmj*, 348. https://doi.org/10.1136/bmj.f7656

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., & Colloca, L. (2015). The placebo effect: From concepts to genes. *Neuroscience*, *307*, 171–190. https://doi.org/10.1016/j.neuroscience.2015.08.017

Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *Pain*, *144*(1–2), 28–34. https://doi.org/10.1016/j.pain.2009.01.033

Colloca, L., Tinazzi, M., Recchia, S., Le Pera, D., Fiaschi, A., Benedetti, F., & Valeriani, M. (2008). Learning potentiates neurophysiological and behavioral placebo analgesic responses. *Pain*, *139*(2), 306–314. https://doi.org/10.1016/J.PAIN.2008.04.021

Colloca, L., Wang, Y., Martinez, P. E., Chang, Y. P. C., Ryan, K. A., Hodgkinson, C., … & Dorsey, S. G. (2019). OPRM1 rs1799971-COMT rs4680-FAAH rs324420 genes interact with placebo procedures to induce hypoalgesia. *Pain, 160*(8), 1824. https://doi.org/10.1097/j.pain.0000000000001578

Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M., & Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *Pain, 151*(2), 430-439. 10.1016/j.pain.2010.08.007 Link: https://journals.lww.com/pain/fulltext/2010/11000/How_the_number_of_learning_trials_affects_placebo.27.aspx?casa_token=FOInJm6vLLgAAAAA:InorNcFyzFtUvdoL0b79-lcNtxD6YJp4gNPeB-DWL9D2CukTd_qvTbmcVffN6hOt0eqhsrGw-sVDhIEkJlnpXpq8Eih0

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain, 124*(1-2), 126-133. https://doi.org/10.1016/j.pain.2006.04.005

Curie, A., Yang, K., Kirsch, I., Gollub, R. L., Des Portes, V., Kaptchuk, T. J., & Jensen, K. B. (2015). Placebo Responses in Genetically Determined Intellectual Disability: A Meta-Analysis. *PLOS ONE*, *10*(7), e0133316. https://doi.org/10.1371/JOURNAL.PONE.0133316

Daniali, H., & Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00242

de Wit, H. M., te Groen, M., Rovers, M. M., & Tack, C. J. (2016). The placebo response of injectable GLP-1 receptor agonists vs. oral DPP-4 inhibitors and SGLT-2 inhibitors: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology*, 301–314. https://doi.org/10.1111/bcp.12925

Dijkstra, K., Pieterse, M., & Pruyn, A. (2006). Physical environmental stimuli that turn healthcare facilities into healing environments through psychologically mediated effects: systematic review. *Journal of Advanced Nursing*, *56*(2), 166–181. https://doi.org/10.1111/J.1365-2648.2006.03990.X

Dodd, S., Walker, A. J., Brnabic, A. J. M., Hong, N., Burns, A., & Berk, M. (2019). Incidence and characteristics of the nocebo response from meta-analyses of the placebo arms of clinical trials of olanzapine for bipolar disorder. *Bipolar Disorders*, *21*(2), 142–150. https://doi.org/10.1111/bdi.12662

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L.,

Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Evers, A. W. M., Colloca, L., Blease, C., Gaab, J., Jensen, K. B., Atlas, L. Y., Beedie, C. J., Benedetti, F., Bingel, U., Büchel, C., Bussemaker, J., Colagiuri, B., Crum, A. J., Finniss, D. G., Geers, A. L., Howick, J., Klinger, R., Meeuwis, S. H., Meissner, K., … Kirsch, I. (2020). What Should Clinicians Tell Patients about Placebo and Nocebo Effects? Practical Considerations Based on Expert Consensus. *Psychotherapy and Psychosomatics*, *90*(1), 49–56. https://doi.org/10.1159/000510738

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical, and ethical advances of placebo effects. *The Lancet*, *375*(9715), 686–695. https://doi.org/10.1016/S0140-6736(09)61706-2

Forsberg, J. T., Martinussen, M., & Flaten, M. A. (2017). The placebo analgesic effect in healthy individuals and patients: a meta-analysis. *Psychosomatic medicine, 79*(4), 388-394. https://doi.org/10.1097/psy.0000000000000432

Fraguas, D., Díaz-Caneja, C. M., Pina-Camacho, L., Umbricht, D., & Arango, C. (2019). Predictors of placebo response in pharmacological clinical trials of negative symptoms in schizophrenia: A meta-regression analysis. *Schizophrenia Bulletin*, *45*(1), 57–68. https://doi.org/10.1093/schbul/sbx192

Friesen, P., & Blease, C. (2018). Placebo effects and racial and ethnic health disparities: an unjust and underexplored connection. *J Med Ethics*, *44*, 774–781. https://doi.org/10.1136/medethics-2018-104811

Furmark, T., Appel, L., Henningsson, S., Åhs, F., Faria, V., Linnman, C., … & Fredrikson, M. (2008). A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. *Journal of Neuroscience, 28*(49), 13066-13074. https://doi.org/10.1523/JNEUROSCI.2534-08.2008

Geers, A. L., Helfer, S. G., Kosbab, K., Weiland, P. E., & Landry, S. J. (2005). Reconsidering the role of personality in placebo effects: Dispositional optimism, situational expectations, and the placebo response. *Journal of Psychosomatic Research*, *58*(2), 121–127. https://doi.org/10.1016/J.JPSYCHORES.2004.08.011

Geers, A. L., Wellman, J. A., Fowler, S. L., Helfer, S. G., & France, C. R. (2010). Dispositional Optimism Predicts Placebo Analgesia. *The Journal of Pain*, *11*(11), 1165–1171. https://doi.org/10.1016/J.JPAIN.2010.02.014

Gratton, C., Laumann, T. O., Nielsen, A. N., Greene, D. J., Gordon, E. M., Gilmore, A. W., … & Petersen, S. E. (2018). Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron, 98*(2), 439-452. https://doi.org/10.1016/j.neuron.2018.03.035

Hadamitzky, M., Engler, H., & Schedlowski, M. (2013). Learned immunosuppression: extinction, renewal, and the challenge of reconsolidation. *Journal of Neuroimmune Pharmacology, 8*, 180-188. https://doi.org/10.1007/s11481-012-9388-6

Hadamitzky, M., Sondermann, W., Benson, S., & Schedlowski, M. (2018). Placebo effects in the immune system. *International review of neurobiology, 138*, 39-59. https://doi.org/10.1016/bs.irn.2018.01.001

Hall, K. T., Lembo, A. J., Kirsch, I., Ziogas, D. C., Douaiher, J., Jensen, K. B., ... & 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

Hojat, M., Louis, D. Z., Markham, F. W., Wender, R., Rabinowitz, C., & Gonnella, J. S. (2011). Physicians' empathy and clinical outcomes for diabetic patients. *Academic Medicine, 86*(3), 359-364. https://doi.org/10.1097/acm.0b013e3182086fe1

Horing, B., Weimer, K., Muth, E. R., & Enck, P. (2014). Prediction of placebo responses: A systematic review of the literature. *Frontiers in Psychology, 5*. https://doi.org/10.3389/fpsyg.2014.01079

Howe, L. C., Leibowitz, K. A., & Crum, A. J. (2019). When your doctor "Gets it" and "Gets you": The critical role of competence and warmth in the patient-provider interaction. *Frontiers in Psychiatry, 10*(JULY). https://doi.org/10.3389/FPSYT.2019.00475

Hunter, T., Siess, F., & Colloca, L. (2014). Socially induced placebo analgesia: A comparison of a pre-recorded versus live face-to-face observation. *European Journal of Pain, 18*(7), 914-922. https://doi.org/10.1002/j.1532-2149.2013.00436.x

Iannetti, G. D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research, 205*(1), 1–12. https://doi.org/10.1007/S00221-010-2340-1/METRICS

Kampermann, L., Tinnermann, A., & Büchel, C. (2021). Generalization of placebo pain relief. Pain, 162(6), 1781-1789. 10.1097/j.pain.0000000000002166 Link: https://journals.lww.com/pain/fulltext/2021/06000/generalization_of_placebo_pain_relief.20.aspx?casa_token=iX2a1dz5-3IAAAAA:RDqyDgf6qGFp_GfBjWqLUkJuNZcWgcwztHaDI5Qm_XX6MVia-UNwOoa7XZuTGeXY-AM0T7Tm3WWjbAScbuTdxoLuCJWV

Kang, H., Miksche, M. S., & Ellingsen, D.-M. (2023). Association between personality traits and placebo effects: a preregistered systematic review and meta-analysis. *PAIN, 164*(3), 494–508. https://doi.org/10.1097/j.pain.0000000000002753

Kaptchuk, T. J., Kelley, J. M., Deykin, A., Wayne, P. M., Lasagna, L. C., Epstein, I. O., Kirsch, I., & Wechsler, M. E. (2008). Do "placebo responders" exist? *Contemporary Clinical Trials, 29*(4), 587–595. https://doi.org/10.1016/j.cct.2008.02.002

Kaptchuk, T. J., Shaw, J., Kerr, C. E., Conboy, L. A., Kelley, J. M., Csordas, T. J., ... & Jacobson, E. E. (2009). "Maybe I made up the whole thing": placebos and patients' experiences in a randomized controlled trial. *Culture, Medicine, and Psychiatry, 33*, 382-411. https://doi.org/10.1007/s11013-009-9141-7

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., ... & Lembo, A. J. (2008). Components of placebo effect: Randomised controlled trial in

patients with irritable bowel syndrome. *BMJ*, 336(7651), 999–1003. https://doi.org/10.1136/bmj.39524.439618.25

Kelley, J. M., Lembo, A. J., Ablon, J. S., Villanueva, J. J., Conboy, L. A., Levy, R., ... & Kaptchuk, T. J. (2009). Patient and practitioner influences on the placebo effect in irritable bowel syndrome. *Psychosomatic medicine, 71*(7), 789-797. https://doi.org/10.1097/psy.0b013e3181acee12

Kern, A., Kramm, C., Witt, C. M., & Barth, J. (2020). The influence of personality traits on the placebo/nocebo response: A systematic review. *Journal of Psychosomatic Research*, *128*, 109866. https://doi.org/10.1016/j.jpsychores.2019.109866

Kirchhof, J., Petrakova, L., Brinkhoff, A., Benson, S., Schmidt, J., Unteroberdörster, M., Wilde, B., Kaptchuk, T. J., Witzke, O., & Schedlowski, M. (2018). Learned immunosuppressive placebo responses in renal transplant patients. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(16), 4223–4227. https://doi.org/10.1073/PNAS.1720548115/SUPPL_FILE/PNAS.1720548115.ST08.DOCX

Koban, L., Ruzic, L., & Wager, T. D. (2013). Brain predictors of individual differences in placebo responding. In *Placebo and Pain* (pp. 89-102). Academic Press. https://doi.org/10.1016/B978-0-12-397928-5.00010-6

Koban, L., Kusko, D., & Wager, T. D. (2018). Generalization of learned pain modulation depends on explicit learning. *Acta psychologica, 184*, 75-84. https://doi.org/10.1016/j.actpsy.2017.09.009

Kohoutová, L., Atlas, L. Y., Büchel, C., Buhle, J. T., Geuter, S., Jepma, M., ... & Woo, C. W. (2022). Individual variability in brain representations of pain. *Nature neuroscience, 25*(6), 749-759. https://doi.org/10.1038/s41593-022-01081-x

Kong, J., Jensen, K., Loiotile, R., Cheetham, A., Wey, H. Y., Tan, Y., Rosen, B., Smoller, J. W., Kaptchuk, T. J., & Gollub, R. L. (2013). Functional connectivity of the frontoparietal network predicts cognitive modulation of pain. *PAIN®*, *154*(3), 459–467. https://doi.org/10.1016/J.PAIN.2012.12.004

Krummenacher, P., Candia, V., Folkers, G., Schedlowski, M., & Schönbächler, G. (2010). Prefrontal cortex modulates placebo analgesia. *PAIN®*, *148*(3), 368–374. https://doi.org/10.1016/J.PAIN.2009.09.033

Kube, T., Blease, C., Ballou, S. K., & Kaptchuk, T. J. (2019). Hope in medicine: applying multidisciplinary insights. *Perspectives in biology and medicine, 62*(4), 591-616. https://doi.org/10.1353/pbm.2019.0035

Lasagna, L., Mosteller, F., Von Felsinger, J. M., & Beecher, H. K. (1954). A study of the placebo response. The *American journal of medicine, 16*(6), 770-779. https://doi.org/10.1016/0002-9343(54)90441-6

Lee, H. H., Patel, K. R., Rastogi, S., Singam, V., Vakharia, P. P., Chopra, R., & Silverberg, J. I. (2020). Placebo responses in randomized controlled trials for systemic therapy in atopic dermatitis: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, *82*(1), 62–71. https://doi.org/10.1016/j.jaad.2019.05.102

Leucht, S., Chaimani, A., Mavridis, D., Leucht, C., Huhn, M., Helfer, B., Samara, M., Cipriani, A., Geddes, J. R., & Davis, J. M. (2019). Disconnection of drug-response and placebo-response in acute-phase antipsychotic drug trials on schizophrenia? Meta-regression analysis. *Neuropsychopharmacology*, *44*(11), 1955–1966. https://doi.org/10.1038/s41386-019-0440-6

Leuchter, A. F., McCracken, J. T., Hunter, A. M., Cook, I. A., & Alpert, J. E. (2009). Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder. *Journal of clinical psychopharmacology*, *29*(4), 372-377. https://doi.org/10.1097/jcp.0b013e3181ac4aaf

Lui, F., Colloca, L., Duzzi, D., Anchisi, D., Benedetti, F., & Porro, C. A. (2010). Neural bases of conditioned placebo analgesia. *PAIN®*, *151*(3), 816–824. https://doi.org/10.1016/J.PAIN.2010.09.021

Lyby, P. S., Aslaksen, P. M., & Flaten, M. A. (2010). Is fear of pain related to placebo analgesia? *Journal of Psychosomatic Research*, *68*(4), 369–377. https://doi.org/10.1016/J.JPSYCHORES.2009.10.009

Macedo, A., Farré, M., & Baños, J. E. (2006). A meta-analysis of the placebo response in acute migraine and how this response may be influenced by some of the characteristics of clinical trials. *European Journal of Clinical Pharmacology*, *62*(3), 161–172. https://doi.org/10.1007/s00228-005-0088-5

Meeuwis, S. H., Wasylewski, M. T., Bajcar, E. A., Bieniek, H., Adamczyk, W. M., Honcharova, S., Di Nardo, M., Mazzoni, G., & Bąbel, P. (2023). Learning pain from others: A systematic review and meta-analysis of studies on placebo hypoalgesia and nocebo hyperalgesia induced by observational learning. *Pain*, *164*(11), 2383–2396. https://doi.org/10.1097/j.pain.0000000000002943

Meissner, K., Fässler, M., Rücker, G., Kleijnen, J., Hróbjartsson, A., Schneider, A., Antes, G., & Linde, K. (2013). Differential effectiveness of placebo treatments: A systematic review of migraine prophylaxis. *JAMA Internal Medicine*, *173*(21), 1941–1951. https://doi.org/10.1001/jamainternmed.2013.10391

Meister, R., Jansen, A., Härter, M., Nestoriuc, Y., & Kriston, L. (2017). Placebo and nocebo reactions in randomized trials of pharmacological treatments for persistent depressive disorder. A meta-regression analysis. *Journal of Affective Disorders*, *215*, 288–298. https://doi.org/10.1016/j.jad.2017.03.024

Mitsikostas, D. D., Chalarakis, N. G., Mantonakis, L. I., Delicha, E. M., & Sfikakis, P. P. (2012). Nocebo in fibromyalgia: Meta-analysis of placebo-controlled clinical trials and implications for practice. *European Journal of Neurology*, *19*(5), 672–680. https://doi.org/10.1111/j.1468-1331.2011.03528.x

Mohamadi, S., Ahmadzad-Asl, M., Nejadghaderi, S. A., Jabbarinejad, R., Mirbehbahani, S. H., Sinyor, M., Richter, M. A., & Davoudi, F. (2023). Systematic Review and Meta-Analysis of the Placebo Effect and its Correlates in Obsessive Compulsive Disorder. *Canadian Journal of Psychiatry*, *68*(7), 479–494. https://doi.org/10.1177/07067437221115029

Morton, D. L., El-Deredy, W., Watson, A., & Jones, A. K. P. (2010). Placebo analgesia as a case of a cognitive style driven by prior expectation. *Brain Research*, *1359*, 137–141. https://doi.org/10.1016/J.BRAINRES.2010.08.046

Nee, J., Sugarman, M. A., Ballou, S., Katon, J., Rangan, V., Singh, P., Zubiago, J., Kaptchuk, T. J., & Lembo, A. (2019). Placebo response in chronic idiopathic constipation: A systematic review and meta-analysis. *Am. J. Gastroenterol.*, *114*(12), 1838–1846. https://doi.org/10.14309/ajg.0000000000000399

Ng, C. H., Xiao, J., Lim, W. H., Chin, Y. H., Yong, J. N., Tan, D. J. H., Tay, P., Syn, N., Foo, R., Chan, M., Chew, N., Tan, E. X., Huang, D. Q., Dan, Y. Y., Tamaki, N., Siddiqui, M. S., Sanyal, A. J., Loomba, R., Noureddin, M., & Muthiah, M. D. (2022). Placebo effect on progression and regression in NASH: Evidence from a meta-analysis. *Hepatology*, *75*(6), 1647–1661. https://doi.org/10.1002/hep.32315

Okusogu, C., Wang, Y., Akintola, T., Haycock, N. R., Raghuraman, N., Greenspan, J. D., ... & Colloca, L. (2020). Placebo hypoalgesia: racial differences. *Pain*, *161*(8), 1872-1883. https://doi.org/10.1097/j.pain.0000000000001876

Peciña, M., Azhar, H., Love, T. M., Lu, T., Fredrickson, B. L., Stohler, C. S., & Zubieta, J. K. (2013). Personality trait predictors of placebo analgesia and neurobiological correlates. *Neuropsychopharmacology*, *38*(4), 639–646. https://doi.org/10.1038/npp.2012.227

Peciña, M., Martinez-Jauand, M., Hodgkinson, C., Stohler, C. S., Goldman, D., & Zubieta, J. K. (2014). FAAH selectively influences placebo effects. *Molecular psychiatry*, *19*(3), 385-391. https://doi.org/10.1038/mp.2013.124

Peciña, M., Bohnert, A. S., Sikora, M., Avery, E. T., Langenecker, S. A., Mickey, B. J., & Zubieta, J. K. (2015). Association between placebo-activated neural systems and antidepressant responses: neurochemistry of placebo effects in major depression. *JAMA psychiatry*, *72*(11), 1087-1094. 10.1001/jamapsychiatry.2015.1335 Link: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2443355

Peerdeman, K. J., Geers, A. L., Della Porta, D., Veldhuijzen, D. S., & Kirsch, I. (2021). Underpredicting pain: an experimental investigation into the benefits and risks. *Pain*, *162*(7), 2024-2035. https://doi.org/10.1097/j.pain.0000000000002199

Petersen, G. L., Finnerup, N. B., Colloca, L., Amanzio, M., Price, D. D., Jensen, T. S., & Vase, L. (2014). The magnitude of nocebo effects in pain: a meta-analysis. *Pain®*, *155*(8), 1426-1434. https://doi.org/10.1016/j.pain.2014.04.016

Petrovic, P., Kalso, E., Petersson, K. M., Andersson, J., Fransson, P., & Ingvar, M. (2010). A prefrontal non-opioid mechanism in placebo analgesia. *PAIN*, *150*(1), 59–65. https://doi.org/10.1016/J.PAIN.2010.03.011

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology*, *59*, 565–590. https://doi.org/10.1146/annurev.psych.59.113006.095941

Quinn, V. F., & Colagiuri, B. (2015). Placebo Interventions for Nausea: a Systematic Review. *Annals of Behavioral Medicine*, *49*(3), 449–462. https://doi.org/10.1007/s12160-014-9670-3

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain Affect Encoded in Human Anterior Cingulate But Not Somatosensory Cortex. *Science*, *277*(5328), 968–971. https://doi.org/10.1126/SCIENCE.277.5328.968

Rheims, S., Cucherat, M., Arzimanoglou, A., & Ryvlin, P. (2008). Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Medicine*, *5*(8), 1223–1237. https://doi.org/10.1371/journal.pmed.0050166

Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H., & Bushnell, M. C. (2009). The Anatomy of the Mesolimbic Reward System: A Link between Personality and the Placebo Analgesic Response. *Journal of Neuroscience*, *29*(15), 4882–4887. https://doi.org/10.1523/JNEUROSCI.5634-08.2009

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry*, *65*(2), 220–231. https://doi.org/10.1001/archgenpsychiatry.2007.34

Siddiqi, S. H., Kording, K. P., Parvizi, J., & Fox, M. D. (2022). Causal mapping of human brain function. *Nature reviews neuroscience*, *23*(6), 361-375. https://doi.org/10.1038/s41583-022-00583-8

Siegel, S. (2005). Drug tolerance, drug addiction, and drug anticipation. *Current Directions in psychological science*, *14*(6), 296-300. https://doi.org/10.1111/j.0963-7214.2005.00384.x

Stein, N., Sprenger, C., Scholz, J., Wiech, K., & Bingel, U. (2012). White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. *PAIN®*, *153*(11), 2210–2217. https://doi.org/10.1016/J.PAIN.2012.07.010

Sullivan, M. J. L., Lynch, M. E., Clark, A. J., Mankovsky, T., & Sawynok, J. (2008). Catastrophizing and treatment outcome: differential impact on response to placebo and active treatment outcome. *Contemporary Hypnosis*, *25*(3–4), 129–140. https://doi.org/10.1002/CH.365

Swerts, Di. B., Benedetti, F., & Peres, M. F. P. (2022). Different routes of administration in chronic migraine prevention lead to different placebo responses: A meta-analysis. *Pain*, *163*(3), 415–424. https://doi.org/10.1097/j.pain.0000000000002365

Thomaidou, M. A., Blythe, J. S., Peerdeman, K. J., Van Laarhoven, A. I., Van Schothorst, M. M., Veldhuijzen, D. S., & Evers, A. W. (2023). Learned nocebo effects on cutaneous sensations of pain and itch: a systematic review and meta-analysis of experimental behavioral studies on healthy humans. *Psychosomatic Medicine*, *85*(4), 308-321. https://doi.org/10.1097/psy.0000000000001194

Vambheim, S. M., & Flaten, M. A. (2017). A systematic review of sex differences in the placebo and the nocebo effect. *J. Pain Res.*, *10*, 1831–1839. https://doi.org/10.2147/JPR.S134745

Vase, L., Riley III, J. L., & Price, D. D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain, 99*(3), 443-452. https://doi.org/10.1016/S0304-3959(02)00205-1

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

Wager, T. D., Atlas, L. Y., Leotti, L. A., & Rilling, J. K. (2011). Predicting Individual Differences in Placebo Analgesia: Contributions of Brain Activity during Anticipation and Pain Experience. *Journal of Neuroscience*, *31*(2), 439–452. https://doi.org/10.1523/JNEUROSCI.3420-10.2011

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. *Science*, *303*(5661), 1162–1167. https://doi.org/10.1126/SCIENCE.1093065/SUPPL_FILE/WAGER.SOM.PDF

Weng, L., van Laarhoven, A. I. M., Peerdeman, K. J., & Evers, A. W. M. (2022). Do individual psychological characteristics predict induction and generalization of nocebo and placebo effects on pain and itch? *Frontiers in Psychiatry*, *13*, 838578. https://doi.org/10.3389/FPSYT.2022.838578/BIBTEX

Wrobel, N., Fadai, T., Sprenger, C., Hebebrand, J., Wiech, K., & Bingel, U. (2015). Are children the better placebo analgesia responders? An experimental approach. *The Journal of Pain, 16*(10), 1005-1011 https://doi.org/10.1016/j.jpain.2015.06.013

Yang, S., Gomeni, R., & Beerahee, M. (2014). Does short-term placebo response predict the long-term observation? Meta-analysis on forced expiratory volume in 1 second from asthma trials. T*he Journal of Clinical Pharmacology, 54*(11), 1207-1213. https://doi.org/10.1002/jcph.329

Yeung, S. T. A., Colagiuri, B., Lovibond, P. F., & Colloca, L. (2014). Partial reinforcement, extinction, and placebo analgesia. *Pain, 155*(6), 1110-1117 https://doi.org/10.1016/j.pain.2014.02.022

Yildiz, A., Vieta, E., Tohen, M., & Baldessarini, R. J. (2011). Factors modifying drug and placebo responses in randomized trials for bipolar mania. *International Journal of Neuropsychopharmacology*, *14*(7), 863–875. https://doi.org/10.1017/S1461145710001641

Yu, R., Gollub, R. L., Vangel, M., Kaptchuk, T., Smoller, J. W., & Kong, J. (2014). Placebo analgesia and reward processing: integrating genetics, personality, and intrinsic brain activity. *Human brain mapping, 35*(9), 4583-4593. https://doi.org/10.1002/hbm.22496

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PANACEA Learning Materials

Module 6: Factors that influence nocebo phenomena

Module information

Drawing on evidence-based research and clinical practices and expanding from insights from earlier modules (see Module 2 and Module 4), here we provide an overview t of factors that influence nocebo phenomena, focusing on: characteristics that may make people susceptible to nocebo effects, and strategies enhancing patient-provider communication, setting balanced treatment expectations, and environmental cues. This information is particularly pertinent as it enables healthcare providers to identify individuals who may be vulnerable and respond appropriately. Managing and reducing nocebo effects is crucial for enhancing the efficacy of therapy, increasing treatment continuity, avoiding drop-out or unnecessary changes in medication, decreasing the intensity and occurrence of adverse effects, and ultimately improving the overall health of the individual.

6.1 Overview

Nocebo effects, where individual and contextual factors lead to negative health changes (e.g., treatment's adverse reactions), significantly impact clinical outcomes and patient adherence (see Module 1). Unlike iatrogenic effects, which are unintended negative consequences directly caused by medical treatments (see Module 1 for more details), nocebo effects arise from various nonpharmacological factors. These include patient expectations, previous negative experiences with medications, instructions provided by healthcare providers, and psychosocial influences like media reports and socially transmitted beliefs (Barsky et al., 2002). For instance, media reports and socially transmitted information, such as exaggerated portrayals of COVID-19 severity or unfounded concerns about vaccine safety, can contribute to the amplification of nocebo effects and influence patient health outcomes in significant ways (Mattarozzi et al., 2023). Nocebo effects can be unintentionally triggered, and by providing education on this topic, awareness can be raised regarding how these effects manifest and how they can be mitigated.

6.2 Individual Differences

Introduction

Individual differences could play a significant role in how people respond to nocebo effects. Although this line of nocebo research is less explored than susceptibility to

placebo effects (see Module 5), several factors seem to contribute to these individual differences, including age, sex and race, genetic profiles, neurobiological factors, and personality traits. However, it is important for the reader to bear in mind that the literature has not provided robust evidence regarding individual differences in nocebo effects. Future studies are needed to delve into these aspects further to draw more certain conclusions. Nevertheless, some potentially interesting results from a few studies are listed below.

Age, Sex, Race

Age-related differences in susceptibility to nocebo effects have been documented, with some evidence suggesting that older adults may be more vulnerable to these phenomena. For example, meta-analyses have shown that older patients with ADHD (Ramírez-Saco et al., 2022) and osteoporosis (Kravvariti et al., 2023; Yavropoulou et al., 2024) showed higher nocebo response.
This is unsurprising given that various aspects of aging and healthcare can increase vulnerability to the nocebo response. For example, elderly individuals often experience a higher incidence of mental health conditions, particularly anxiety and depression, which are recognized for fostering and intensifying the occurrence of nocebo effects (Kravvariti et al., 2021). Even in the absence of diagnosed mental illness, older adults commonly exhibit heightened health anxiety (Barsky et al., 2002), and other psychological vulnerabilities, such as loneliness (Sheehan & Banerjee, 1999), making older individuals more likely to manifest emotional distress through physical symptoms, which is linked to a heightened susceptibility to nocebo effects (Kravvariti et al., 2021.) Furthermore, older adults, who often have more extensive experience with medical interventions and medications, may be more likely to develop negative expectations based on prior experiences, thereby increasing their susceptibility to nocebo effects (Kravvariti et al., 2021). Finally, challenges in patient-physician communication, influenced by older adults' expectations and stereotypes about physician behavior, may increase their susceptibility to the nocebo effect (Kravvariti et al., 2021). Also, addressing caregivers instead of patients when discussing treatment risks and benefits could further strain the therapeutic alliance and diminish patient trust in the physician and prescribed treatments (Kravvariti et al., 2021).

It is important to note that nocebo responses are usually assessed by the rate of adverse events in the placebo group. However, adverse events encompass any negative occurrences (e.g., a car accident or a fall), regardless of whether they are related to the investigational drug. The number of adverse events may increase with age, as older individuals may be more prone to incidents such as car accidents and falls.

Sex differences in susceptibility to nocebo effects have been reported in the literature, although findings have been inconsistent. Some studies suggest that women may be more susceptible to nocebo effects compared to men. For example, it has been found that women exhibited greater susceptibility to nocebo-induced symptoms following administration of an inert substance compared to men (Bagarić et al., 2022; Vambheim & Flaten, 2017). However, differences in nocebo responding may be due to the induction method. In fact, it has been found that females responded with larger nocebo responses than males when a conditioning procedure was used, whereas males responded with larger nocebo responses than females when verbal instructions were used (Klosterhalfen et al., 2009). Similarly, Swider and Babel showed that social observational modeling induced larger nocebo hyperalgesic responses in females than in males and suggested that this difference was due to larger increases in anxiety in females than in males (Świder & Bąbel, 2013).
Potential explanations for sex differences in susceptibility to nocebo effects include differences in pain perception and hormonal influences. Women have been shown to exhibit greater sensitivity to experimental pain stimuli compared to men (Fillingim et al., 2009). Additionally, hormonal fluctuations across the menstrual cycle may modulate pain sensitivity and perception in women, potentially influencing their susceptibility to nocebo effects (Riley et al., 1999).

Research on racial differences in susceptibility to nocebo effects is relatively limited, but there is emerging evidence suggesting potential differences across racial and ethnic groups (Yetman et al., 2021). As we have learned in Module 5, the clinical encounter is quite different depending on racial membership. For example, physicians were found to be more verbally dominant and less engaged in patient-centered communication during medical visits with Black patients as compared to White patients (Johnson et al., 2004). Moreover, Black patients tend to express greater general medical mistrust compared to White patients (Boulware et al., 2003). Additionally, research findings reveal that Black patients consistently report lower levels of trust in their personal physicians (Musa et al., 2009). These differences in communication and trust in medical providers across racial and ethnic groups may contribute to variations in the formation and modulation of negative expectations, thereby influencing susceptibility to nocebo effects.

Also, it is important to highlight that these findings on differences between Black and White patients are based on samples from the USA. As these differences likely relate to social factors and physician treatment practices, we cannot generalize these findings to Black and White populations worldwide, particularly in non-Western countries.

Genetic profiles

Genetic variations may contribute to individual differences in susceptibility to nocebo effects, particularly through their influence on neurotransmitter systems implicated in nocebo responses (Colagiuri et al., 2015). One such gene of interest is the catechol-O-methyltransferase (COMT) gene, which codes for an enzyme involved in the breakdown of catecholamines, including dopamine. The COMT polymorphism, specifically the Val158 variant, is associated with increased somatosensory amplification and higher nocebo responses, both in drug and placebo treatment, indicating genetic influence on susceptibility to nocebo effects (Wendt et al., 2014).
However, caution should be warranted due to the lack of successful replications in this area.

Neurobiological factors

In Module 2, we have learned the neurobiological mechanisms underlying nocebo effects, especially in nocebo hyperalgesia. Although still under investigation, some of these mechanisms may be involved in individual variability to nocebo responses (Kleine-Borgmann & Bingel, 2018). For example, neurobiological factors underlying susceptibility to nocebo effects may involve complex interactions between brain regions implicated in emotional regulation and the processing of expectation and pain perception.
Research indicates that nocebo hyperalgesia is influenced, at least partially, by descending inhibitory pathways that involve the body's natural opioid and dopamine systems (Geuter & Büchel, 2013; Scott et al., 2006). Positron emission tomography studies have demonstrated decreased activity of dopamine and opioid neurotransmitters in networks responsible for processing and regulating pain during nocebo interventions (Scott et al., 2008). Anxiety and stress were highlighted as key components of nocebo effects, as suggested by the involvement of cholecystokinin (CCK), a transmitter associated with anxiety and panic, in nocebo hyperalgesia (Benedetti & Amanzio, 1997). Subsequent research found activation of the hypothalamic-pituitary-adrenal axis in nocebo hyperalgesia, strengthening the link between anxiety and this phenomenon (Benedetti et al., 2006). Neuroimaging studies have linked nocebo hyperalgesia with increased activity and connectivity in the hippocampus and amygdala, supporting the role of anxiety-related brain circuitry in this process (Bingel et al., 2011; Kong et al., 2008). As such, individuals with higher levels of anxiety may exhibit abnormal alterations in these brain circuits, potentially rendering them more susceptible to the effects of the nocebo phenomenon.
Changes in posterior insula activity, along with the parietal operculum, correspond to changes in pain perception intensity and influence future pain perception (Rodriguez-Raecke et al., 2010; Segerdahl et al., 2015). Moreover, the dorsal anterior cingulate cortex (dACC) is crucial for processing negative affect and pain, suggesting a possible association between heightened dACC activation and nocebo hyperalgesia processing (Fu et al., 2021).

These findings underscore the role of individual differences in susceptibility to nocebo effects, as variations in brain activity in these regions may contribute to differences in nocebo response among individuals. However, most studies may be outdated as newer research highlights significant individual variations, warranting caution in interpretation.

Personality traits and relatively stable attitudes

Personality traits and stable attitudes such as suggestibility, catastrophizing, neuroticism, anxiety, and pessimism have been consistently linked to increased susceptibility to nocebo effects (Blasini et al., 2017). The evidence is quite mixed, but among all the traits studied previously, these show the most consistent findings (although the evidence remains somewhat weak).
Suggestibility, which is a trait that enhances sensitivity to bodily sensations (such as physical suggestibility), has been associated with the occurrence of nocebo effects (Corsi et al., 2016). Catastrophizing, a significant psychological factor in pain management therapies that involves an intense and exaggerated negative response to pain, including feelings of helplessness and persistent focus on pain sensations, has also been identified as relevant to nocebo effects, where it can lead individuals to perceive moderate pain as more intense and harmful (Vögtle et al., 2013). Individuals high in neuroticism tend to experience negative emotions more frequently and intensely, leading them to interpret ambiguous situations in a negative light (Tackett & Lahey, 2016). This negative bias can predispose them to expect adverse outcomes, thereby enhancing the likelihood of experiencing nocebo effects. Moreover, trait anxiety, characterized by a tendency to perceive situations as threatening or dangerous, is associated with heightened vigilance to potential harm (Elwood et al., 2012). Individuals with high trait anxiety may be more prone to anticipate negative outcomes and consequently experience heightened physiological and psychological responses, contributing to increased susceptibility to nocebo effects. Additionally, pessimistic individuals, who habitually expect negative outcomes and view the world through a negative lens, are more likely to interpret ambiguous stimuli in a negative manner (Forgeard & Seligman, 2012). This negative cognitive bias may predispose them to anticipate adverse effects from treatments or interventions, thereby amplifying the occurrence of nocebo effects.

6.3 Strategies to Minimize Nocebo Effects

Introduction

The key to minimizing nocebo effects often revolves around the reduction of negative emotions and affect, and the optimization of outcome expectations. Minimizing nocebo effects requires a multi-faceted approach involving careful communication, patient education, and thoughtful informed consent procedures. Delving deep into the

strategies that can effectively mitigate nocebo effects is crucial to understand that these tactics are specifically crafted based on the main mechanisms (i.e. patient's emotions, affect, and patient's learning from experience and expectations) responsible for eliciting nocebo effects and responses.

Literature strongly highlights that the interactions and communication between patients and clinicians can significantly influence patient perceptions and expectations, thereby amplifying or reducing the likelihood of nocebo effects (Colloca & Finniss, 2019; Manai et al., 2019). The power of well-crafted communication cannot be overstated—it is fundamental not only for conveying information, but also for building cooperative behavior and a therapeutic alliance that supports a positive psychological framework for patients, thereby facilitating better health outcomes and a more gratifying healthcare experience (Colloca & Miller, 2011). This interaction style not only builds trust but also helps in clarifying any ambiguities that might contribute to nocebo effects.

During interactions and communication between patients and clinician, crucial phases for identifying and addressing nocebo effects include the initial prescription of the treatment—where patients' expectations and potential side effects should be carefully managed by clinicians—and during follow-up visits where the treatment's efficacy and side effects are assessed. At the stage of choosing and prescribing treatment, it is crucial to prevent nocebo effects to enhance the efficacy of the treatment, to minimize potential side effects, and to ensure patient adherence (Pagnini, 2019). Differently, during follow-up visits, it is essential to recognize signs of nocebo effects.

Prescription of the treatment and the prevention of nocebo effect

Ensuring that the patient clearly understands the objectives and potential benefits of the medication is a critical step. Effective communication between healthcare providers and patients is paramount both in maximizing treatment efficacy (see Module 5 for details) and in minimizing the occurrence and impact of nocebo effects in clinical practice. Previous research indicates that nocebo hyperalgesia can often be triggered more readily through verbal suggestions compared to placebo hypoalgesia (Reicherts et al., 2016; Schwarz et al., 2016). Merely disclosing the potential to experience higher pain can itself produce negative expectations and worsening of pain outcomes (Benedetti et al., 2016; Blasini et al., 2017). Furthermore, studies have noted a tendency for a negative social transmission bias where negative information is more effectively retained and shared among individuals (Bebbington et al., 2017; Mattarozzi et al., 2023).

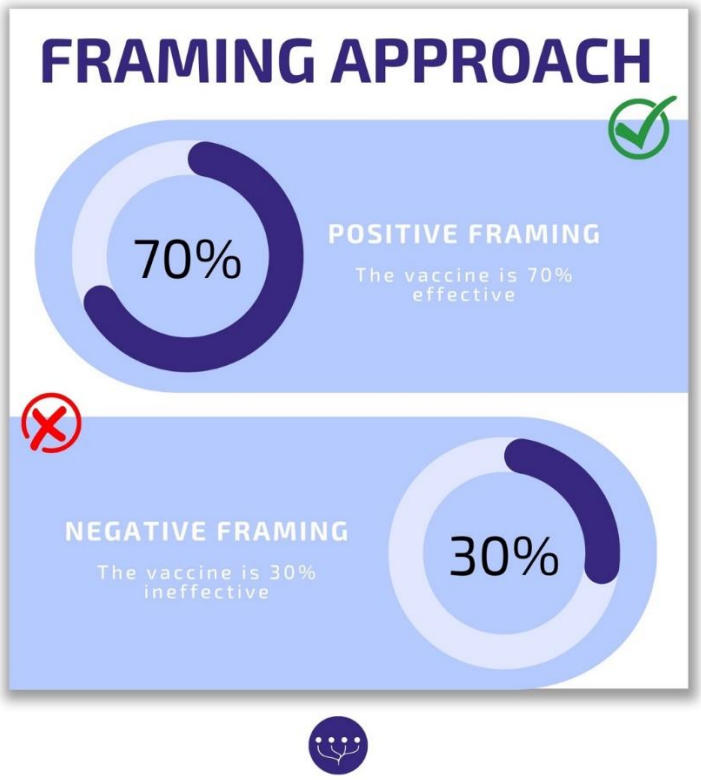
At this stage minimizing the potential activation of nocebo effects involves a strategic balance of communication, particularly in communicating the risks associated with potential adverse effects alongside the benefits of treatments. Comprehensive

information that covers diagnoses, potential side effects, and the ins and outs of the treatment process helps ensure patients have a thorough understanding of their medical journey, which is instrumental in preventing misconceptions and relieving anxiety (Palermo et al., 2015). When healthcare providers communicate the factual benefits and realistic outcomes of treatments, highlighting their effectiveness in others with similar conditions, patient focus can shift from fear to informed optimism.

The framing approach (Fig. 6.1) can be an effective strategy to minimize nocebo effects by presenting treatment side effect information in a positive light. Research shows that framing information positively—such as stating that a vaccine is 70% effective rather than 30% ineffective—leads to more favorable views of treatment efficacy. Similarly, presenting drug side effect information positively, by highlighting the proportion of patients who remain free from side effects, can reduce perceived treatment risks compared to focusing on the negative aspects. Utilizing positive framing techniques can help shape patient expectations more favorably, thereby minimizing nocebo effects and enhancing overall treatment outcomes (Faasse et al., 2019; Manai et al., 2019; Pan et al, 2019).

Figure 6.1

The framing approach



Such discussions should not merely convey information, but should actively involve patients in their care process, bolstering their comfort and trust levels (Klinger et al., 2017; Petrie & Rief, 2019). See PANACEA Clinical Recommendations for more details.

Implementing active feedback mechanisms, where patients are encouraged to recapitulate what has been discussed, helps in confirming their understanding and clears any misunderstandings instantly. Addressing misconceptions arising from prior negative experiences or inaccurate information is essential in good practice. Addressing these misconceptions is crucial, as they can lead to negative expectations, thus increasing the risk of triggering nocebo effects.

The emotional burden experienced by patients, as noted in studies examining the impact of emotional and motivational states like anxiety, significantly influences the efficacy of pain management treatments (Benedetti et al., 2006). Healthcare providers must address these emotional factors, potentially by integrating psychological support or counseling into treatment plans. Proactively assessing and addressing patient concerns and anxieties, by understanding and discussing their specific worries, allow healthcare providers to tailor information and support strategies more effectively, thereby reducing potential nocebo effects (Geers et al., 2021). See PANACEA Clinical Recommendations for more details.

Conversations about potential adverse effects are most effective when framed concerning their likelihood and manageability, in relation to the therapeutic benefits expected. This framing can significantly reduce anxiety-driven responses. Training patients on how to effectively manage possible side effects equips them to handle their treatments better (Bodenheimer et al., 2002; Petrie & Rief, 2019). Further, enhancing resources such as web-based platforms and revising drug leaflets to present information in patient-friendly formats, like graphical representations, can simplify complex medical data, making it less daunting. The role of educational materials in medical settings cannot be underestimated, especially regarding their impact on patient perceptions and expectations (Klinger et al., 2017; Petrie & Rief, 2019).

Additionally, the utilization of media, such as instructional videos depicting the successful management of treatment and side effects by others, can foster a more positive outlook and readiness in patients to manage their symptoms similarly (Meeuwis et al., 2023).

Follow-up visits and the recognition of nocebo effect

Recognizing the nocebo effect in clinical practice during follow-up visits is essential to ensure that patients receive the best possible care and maintain trust in their treatment plans (Bingel, 2014). It is important to caution healthcare providers that

differentiating between nocebo effects and actual treatment side effects can be very challenging. Therefore, careful consideration and sensitivity are required when addressing potential nocebo effects, avoiding premature conclusions and ensuring that any approach to mitigate them is thoughtfully and cautiously implemented.

One important indicator that may suggest the presence of the nocebo effect is the occurrence of non-specific side effects. These side effects do not align specifically with the known pharmacological profile of the treatment and may manifest as generalized symptoms such as fatigue, discomfort, or pain that have no clear link to the therapy being administered. Another key indicator is the early onset of side effects. It is crucial to be aware of side effects that appear unusually soon after the initiation of therapy, especially those occurring potentially before the treatment could have caused any real effects. This premature onset can often suggest that the side effects are driven more by the patient's expectations rather than the actual treatment itself. Furthermore, considering the patient's history and their subjective reports of side effects from similar treatments is significant. Patients who have experienced side effects in the past may be more likely to anticipate and, consequently, experience those same side effects again, irrespective of the actual treatment being administered.

When addressing patient-reported side effects, it is important first to confirm whether these symptoms are directly caused by the medication. Once medication-related causes have been ruled out, consider other potential factors, including the possibility of nocebo effects. This comprehensive approach ensures accurate assessment before making changes to therapy or dosage. Engage in thorough initial consultations that not only explore medical history but also delve into previous experiences with healthcare and treatments and psychological profiles. This can help identify potential biases towards negative expectations. Consider the patient's history of negative side effects. Patients with prior negative experiences may have reduced trust in treatments and expect poor outcomes. This skepticism can potentiate the nocebo effect, where they may report more side effects or perceive the treatment as less effective. Pay close attention to the patient's psychological profile and if they are particularly high in anxiety, pessimism, hostility, anger, distrust, or dissatisfaction (Geers et al., 2021). These psychological traits can predispose individuals to anticipate negative outcomes, which can manifest as nocebo responses. Patients who arrive with misinformation—particularly those who believe in and relay incorrect or exaggerated side effects or negative outcomes from treatments—can be more susceptible to experiencing nocebo effects. Such false beliefs need to be addressed directly to manage expectations and improve treatment outcomes (Klinger et al., 2017).

While scientific evidence has demonstrated the mechanisms responsible for nocebo effects, it is not yet capable of definitively distinguishing whether drug side effects are due to nocebo mechanisms or to the drug's active ingredient. Therefore, although we understand how nocebo effects arise and can provide guidelines to prevent and

minimize them, recognizing nocebo effects in clinical practice with certainty remains a challenge based on current research.

To effectively address and mitigate side effects stemming from a nocebo mechanism, several strategies (see Box 6.1) can be implemented (Petrie & Rief, 2019; Pan et al.,2019).

Box 6.1 Strategies to address and mitigate nocebo side effects

- Provide a thorough explanation to the patient, specifically addressing how these symptoms may be influenced by the underlying nocebo mechanism and guide them in reassessing their interpretations of these symptoms
- Informe patients about nocebo mechanisms and let them to become more aware of the potential impact of negative expectations by explaining how their mindsets and beliefs can influence their health
- Distinguishing between symptoms driven by the nocebo effect and those genuinely caused by the treatment, so that patients can better manage their symptoms and anxiety
- Provide accurate and scientifically backed information to counter any misinformation the patient might have encountered to help alleviate worries and reduce the impact of nocebo effects
- Emphasize the positive aspects and successful outcomes of the treatment, balancing the communication of potential negative effects with positive information to create a more optimistic and realistic view, positively influencing the patient's perceptions and expectations, and resulting in better outcomes
- Regularly inquiring about the patient's treatment experience and satisfaction to gain valuable insights into the patient's mindset and expectations, and to prevent further negative expectations and improve patient adherence and outcome

Contextual and environmental cues

Studies demonstrate how contextual and environmental cues can trigger nocebo responses, particularly through learned associations such as classical conditioning (Petrie & Rief, 2019). For instance, the anticipation of side effects upon arrival at the outpatient therapy setting, even before having taken any medication. Understanding the psychological mechanisms of expectancy and learning, as described in these studies, healthcare providers can prevent these conditioned responses by altering the environmental cues and framing techniques employed during clinical interactions (Schwarz et al., 2016).
Other people can be present in the healthcare context. Observational learning plays a significant role in how individuals perceive and react to their own health symptoms. When individuals observe others reporting a worsening of symptoms, they may also experience a worsening of their own symptoms through a process known as "social contagion" (Benedetti, 2013). This phenomenon is particularly evident with unpleasant emotional experiences such as pain. Observing others express discomfort or pain can unintentionally prime an individual to expect or exacerbate their own pain, essentially spreading the unpleasant experience through social interactions (Świder & Bąbel, 2013; Vögtle et al., 2016; Yoshida et al., 2013). Healthcare providers should carefully monitor

and manage the social interactions that patients have with others in similar treatment settings, such as support groups or common areas in clinics. Ensuring that these interactions are positive and encouraging can help reduce the likelihood of nocebo effects induced by negative reports from other patients.

6.4 Conclusion

The nocebo effect, with its notable presence and clinical impact, prompts a critical exploration into methods capable of mitigating its adverse consequences. Although various strategies have been debated, research into effective interventions remains relatively scarce. Contextualized informed consent has been suggested to tailor the communication of potential side effects, thereby potentially lessening the nocebo responses in vulnerable patients. Despite its utility, this method faces ethical concerns regarding the full transparency required by informed consent.
Another promising approach involves optimizing expectations by balancing the presentation of adverse effects with the benefits of treatments. By positively framing side effect information and proactively addressing patient anxiety, this strategy not only informs but reassures, leading to better outcomes as evidenced in clinical trials such as those examining reactions to influenza vaccines. Such an approach maintains the integrity of informed consent while simultaneously attempting to minimize nocebo responses by portraying medical information in a manner that highlights the relative rarity of negative effects.

Furthermore, educating patients about the nocebo effect itself represents an innovative strategy. Providing a straightforward explanation of the nocebo effect and its relevance to their treatment experience can empower patients, giving them a more comprehensive understanding of how expectations might influence their symptoms. However, the timing and manner of delivering this information require careful consideration. Patients may benefit from this knowledge at different stages of treatment, depending on their individual needs and understanding. It is crucial to use empathetic and reassuring language to prevent self-blame and encourage open communication. Healthcare providers should emphasize that all symptoms are valid and encourage patients to report any concerns, even if they suspect they might be influenced by the nocebo effect, to ensure that no potential side effects are overlooked or dismissed.
Ultimately, while no single strategy has emerged as universally superior, the integration of these methods—mindful tailoring of information, positive framing, and direct education about the nocebo effect—may offer a multifaceted approach to reducing nocebo-driven disturbances in medical treatments. It emphasizes the necessity of not only managing patient expectations effectively but also navigating the ethical considerations inherent in patient communication. As research progresses, these methods may evolve and potentially revolutionize the way healthcare providers

manage and mitigate the nocebo effect, improving patient care outcomes across various medical contexts.

References

Bagarić, B., Jokić-Begić, N., & Sangster Jokić, C. (2022). The Nocebo Effect: A Review of Contemporary Experimental Research. *International Journal of Behavioral Medicine*, *29*(3), 255–265. https://doi.org/10.1007/s12529-021-10016-y

Barsky, A. J., Saintfort, R., Rogers, M. P., & Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *JAMA*, *287*(5), 622–627. https://doi.org/10.1001/jama.287.5.622

Bebbington, K., MacLeod, C., Ellison, T. M., & Fay, N. (2017). The sky is falling: evidence of a negativity bias in the social transmission of information. *Evolution and Human Behavior*, *38*(1), 92–101. https://doi.org/10.1016/J.EVOLHUMBEHAV.2016.07.004

Benedetti, F. (2013). Responding to nocebos through observation: Social contagion of negative emotions. *Pain*, *154*(8), 1165. https://doi.org/10.1016/j.pain.2013.05.012

Benedetti, F., & Amanzio, M. (1997). The neurobiology of placebo analgesia: From endogenous opioids to cholecystokinin. *Progress in Neurobiology*, *52*(2), 109–125. https://doi.org/10.1016/S0301-0082(97)00006-3

Benedetti, F., Amanzio, M., Vighetti, S., & Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(46), 12014–12022. https://doi.org/10.1523/JNEUROSCI.2947-06.2006

Benedetti, F., Carlino, E., & Piedimonte, A. (2016). Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *The Lancet Neurology*, *15*(7), 736–747. https://doi.org/10.1016/S1474-4422(16)00066-1

Bingel, U. (2014). Avoiding nocebo effects to optimize treatment outcome. *JAMA*, *312*(7), 693–694. https://doi.org/10.1001/jama.2014.8342

Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Science Translational Medicine*, *3*(70). https://doi.org/10.1126/SCITRANSLMED.3001244

Blasini, M., Corsi, N., Klinger, R., & Colloca, L. (2017). Nocebo and pain: An overview of the psychoneurobiological mechanisms. *Pain Reports*, *2*(2), 1–9. https://doi.org/10.1097/PR9.0000000000000585

Bodenheimer, T., Lorig, K., Holman, H., & Grumbach, K. (2002). Patient self-management of chronic disease in primary care. *Jama*, *288*(19), 2469-2475. 10.1001/jama.288.19.2469 Link: https://jamanetwork.com/journals/jama/article-abstract/195525?casa_token=WUT63p6Y19gAAAAA:TmVn06qDUlFv68p-lDCYsG5QF-clyJL4B2pOszoFWK71-Xh1_L6kRLAUKrEu6WIPJo2ghU8

Boulware, L. E., Cooper, L. A., Ratner, L. E., LaVeist, T. A., & Powe, N. R. (2003). Race and Trust in the Health Care System. *Public Health Reports*, *118*(4), 358–365. https://doi.org/10.1093/PHR/118.4.358

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., & Colloca, L. (2015). The placebo effect: From concepts to genes. *Neuroscience*, *307*, 171–190. https://doi.org/10.1016/j.neuroscience.2015.08.017

Colloca, L., & Finniss, D. (2019). Effects, Nocebo Communication, Patient-clinician Outcomes, Therapeutic. *Jama*, *307*(6), 567–568. https://doi.org/10.1001/jama.2012.115

Colloca, L., & Miller, F. G. (2011). The nocebo effect and its relevance for clinical practice. In *Psychosomatic Medicine* (Vol. 73, Issue 7, pp. 598–603). NIH Public Access. https://doi.org/10.1097/PSY.0b013e3182294a50

Corsi, N., Emadi Andani, M., Tinazzi, M., & Fiorio, M. (2016). Changes in perception of treatment efficacy are associated to the magnitude of the nocebo effect and to personality traits. *Scientific Reports*, *6*. https://doi.org/10.1038/SREP30671

De La Cruz, M., Hui, D., Parsons, H. A., & Bruera, E. (2010). Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. *Cancer*, *116*(3), 766–774. https://doi.org/10.1002/CNCR.24751

Elwood, L. S., Wolitzky-Taylor, K., & Olatunji, B. O. (2012). Measurement of anxious traits: A contemporary review and synthesis. *Anxiety, Stress and Coping*, *25*(6), 647–666. https://doi.org/10.1080/10615806.2011.582949

Faasse, K., Huynh, A., Pearson, S., Geers, A. L., Helfer, S. G., & Colagiuri, B. (2019). The influence of side effect information framing on nocebo effects. *Annals of Behavioral Medicine*, *53*(7), 621-629. https://doi.org/10.1093/abm/kay071

Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley, J. L. (2009). Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *The Journal of Pain*, *10*(5), 447–485. https://doi.org/10.1016/J.JPAIN.2008.12.001

Forgeard, M. J. C., & Seligman, M. E. P. (2012). Seeing the glass half full: A review of the causes and consequences of optimism. *Pratiques Psychologiques*, *18*(2), 107–120. https://doi.org/10.1016/J.PRPS.2012.02.002

Fu, J., Wu, S., Liu, C., Camilleri, J. A., Eickhoff, S. B., & Yu, R. (2021). Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *NeuroImage*, *231*. https://doi.org/10.1016/j.neuroimage.2021.117833

Geers, A. L., Faasse, K., Guevarra, D. A., Clemens, K. S., Helfer, S. G., & Colagiuri, B. (2021). Affect and emotions in placebo and nocebo effects: What do we know so far? *Social and Personality Psychology Compass*, *15*(1), e12575. https://doi.org/10.1111/spc3.12575

Geuter, S., & Büchel, C. (2013). Facilitation of pain in the human spinal cord by nocebo treatment. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(34), 13784–13790. https://doi.org/10.1523/JNEUROSCI.2191-13.2013

Johnson, R. L., Roter, D., Powe, N. R., & Cooper, L. A. (2004). Patient race/ethnicity and quality of patient-physician communication during medical visits. *American Journal of Public Health*, *94*(12), 2084–2090. https://doi.org/10.2105/AJPH.94.12.2084

Kleine-Borgmann, J., & Bingel, U. (2018). Nocebo Effects: Neurobiological Mechanisms and Strategies for Prevention and Optimizing Treatment. *International Review of Neurobiology*, *138*, 271–283. https://doi.org/10.1016/BS.IRN.2018.02.005

Klinger, R., Blasini, M., Schmitz, J., & Colloca, L. (2017). Nocebo effects in clinical studies: Hints for pain therapy. In *Pain Reports* (Vol. 2, Issue 2). Pain Rep. https://doi.org/10.1097/PR9.0000000000000586

Klosterhalfen, S., Kellermann, S., Braun, S., Kowalski, A., Schrauth, M., Zipfel, S., & Enck, P. (2009). Gender and the nocebo response following conditioning and expectancy. *Journal of Psychosomatic Research*, *66*(4), 323–328. https://doi.org/10.1016/J.JPSYCHORES.2008.09.019

Kong, J., Gollub, R. L., Polich, G., Kirsch, I., LaViolette, P., Vangel, M., Rosen, B., & Kaptchuk, T. J. (2008). A functional magnetic resonance imaging study on the neural mechanisms of

hyperalgesic nocebo effect. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(49), 13354–13362. https://doi.org/10.1523/JNEUROSCI.2944-08.2008

Kravvariti, E., Kotsani, M., Mitsikostas, D. D., & Sfikakis, P. P. (2021). Nocebo phenomena may be enhanced in aging: Implications for clinical practice. *Maturitas*, *143*, 10–16. https://doi.org/10.1016/j.maturitas.2020.07.011

Kravvariti, Evrydiki, Kasdagli, M. I., Diomatari, K. M., Mouratidou, P., Daskalakis, K., Mitsikostas, D. D., Sfikakis, P. P., & Yavropoulou, M. P. (2023). Meta-analysis of placebo-arm dropouts in osteoporosis randomized-controlled trials and implications for nocebo-associated discontinuation of anti-osteoporotic drugs in clinical practice. *Osteoporosis International*, *34*(3), 585–598. https://doi.org/10.1007/s00198-022-06658-7

Manaï, M., van Middendorp, H., Veldhuijzen, D. S., Huizinga, T. W., & Evers, A. W. (2019). How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *Pain reports*, *4*(3), e699. 10.1097/PR9.0000000000000699 Link: https://journals.lww.com/painrpts/fulltext/2019/06000/how_to_prevent,_minimize,_or_extinguish_nocebo.23.aspx

Mattarozzi, K., Bagnis, A., Kłosowska, J., Bąbel, P., Cremonini, V., De Palma, A., Fabbri, A., Farinella, E., Puccini, L., Sambri, V., Semprini, S., & Russo, P. M. (2023). No(cebo) Vax: COVID-19 Vaccine Beliefs Are Important Determinants of Both Occurrence and Perceived Severity of Common Vaccines' Adverse Effects. *Psychological Science*, *34*(5), 603–615. https://doi.org/10.1177/09567976231163875

Meeuwis, S. H., Wasylewski, M. T., Bajcar, E. A., Bieniek, H., Adamczyk, W. M., Honcharova, S., Di Nardo, M., Mazzoni, G., & Bąbel, P. (2023). Learning pain from others: A systematic review and meta-analysis of studies on placebo hypoalgesia and nocebo hyperalgesia induced by observational learning. *Pain*, *164*(11), 2383–2396. https://doi.org/10.1097/j.pain.0000000000002943

Musa, D., Schulz, R., Harris, R., Silverman, M., & Thomas, S. B. (2009). Trust in the health care system and the use of preventive health services by older black and white adults. *American Journal of Public Health*, *99*(7), 1293–1299. https://doi.org/10.2105/AJPH.2007.123927

Pagnini, F. (2019). The potential role of illness expectations in the progression of medical diseases. *BMC Psychology*, *7*(1), 1–5. https://doi.org/10.1186/s40359-019-0346-4

Palermo, S., Benedetti, F., Costa, T., & Amanzio, M. (2015). Pain anticipation: An activation likelihood estimation meta-analysis of brain imaging studies. *Human Brain Mapping*, *36*(5), 1648–1661. https://doi.org/10.1002/HBM.22727

Pan, Y., Kinitz, T., Stapic, M., & Nestoriuc, Y. (2019). Minimizing drug adverse events by informing about the nocebo effect—an experimental study. *Frontiers in Psychiatry*, *10*, 504. https://doi.org/10.3389/fpsyt.2019.00504

Petrie, K. J., & Rief, W. (2019). Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. *Annual Review of Psychology*, *70*(August 2018), 599–625. https://doi.org/10.1146/annurev-psych-010418-102907

Ramírez-Saco, D., Barcheni, M., Cunill, R., Sáez, M., Farré, M., & Castells, X. (2022). Nocebo Response in Attention Deficit Hyperactivity Disorder: Meta-Analysis and Meta-Regression

of 105 Randomized Clinical Trials. *Journal of Attention Disorders*, *26*(11), 1412–1421. https://doi.org/10.1177/10870547221075845

Reicherts, P., Gerdes, A. B. M., Pauli, P., & Wieser, M. J. (2016). Psychological Placebo and Nocebo Effects on Pain Rely on Expectation and Previous Experience. *The Journal of Pain*, *17*(2), 203–214. https://doi.org/10.1016/J.JPAIN.2015.10.010

Riley, J. L., Robinson, M. E., Wise, E. A., & Price, D. (1999). A meta-analytic review of pain perception across the menstrual cycle. *Pain*, *81*(3), 225–235. https://doi.org/10.1016/S0304-3959(98)00258-9

Rodriguez-Raecke, R., Doganci, B., Breimhorst, M., Stankewitz, A., Büchel, C., Birklein, F., & May, A. (2010). Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. *Journal of Neuroscience*, *30*(34), 11363–11368. https://doi.org/10.1523/JNEUROSCI.2197-10.2010

Schwarz, K. A., Pfister, R., & Büchel, C. (2016). Rethinking Explicit Expectations: Connecting Placebos, Social Cognition, and Contextual Perception. *Trends in Cognitive Sciences*, *20*(6), 469–480. https://doi.org/10.1016/j.tics.2016.04.001

Scott, D. J., Heitzeg, M. M., Koeppe, R. A., Stohler, C. S., & Zubieta, J. K. (2006). Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(42), 10789–10795. https://doi.org/10.1523/JNEUROSCI.2577-06.2006

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry*, *65*(2), 220–231. https://doi.org/10.1001/archgenpsychiatry.2007.34

Segerdahl, A. R., Mezue, M., Okell, T. W., Farrar, J. T., & Tracey, I. (2015). The dorsal posterior insula subserves a fundamental role in human pain. *Nature Neuroscience*, *18*(4), 499–500. https://doi.org/10.1038/NN.3969

Sheehan, B., & Banerjee, S. (1999). Review: Somatization in the elderly. *International Journal of Geriatric Psychiatry*, *14*(12), 1044–1049. https://doi.org/10.1002/(SICI)1099-1166(199912)14:12%3C1044::AID-GPS55%3E3.0.CO;2-0

Świder, K., & Bąbel, P. (2013). The effect of the sex of a model on nocebo hyperalgesia induced by social observational learning. *PAIN®*, *154*(8), 1312–1317. https://doi.org/10.1016/J.PAIN.2013.04.001

Tackett, J., & Lahey, B. (2016). *Neuroticism* (T. Widiger (ed.)). https://scholar.google.it/scholar?as_q=neuroticism&as_epq=&as_oq=&as_eq=&as_occt=any&as_sauthors=Tackett&as_publication=&as_ylo=2016&as_yhi=2016&hl=it&as_sdt=0%2C5

Vambheim, S. M., & Flaten, M. A. (2017). A systematic review of sex differences in the placebo and the nocebo effect. *Journal of Pain Research*, *10*, 1831–1839. https://doi.org/10.2147/JPR.S134745

Vögtle, E., Barke, A., & Kröner-Herwig, B. (2013). Nocebo hyperalgesia induced by social observational learning. *Pain*, *154*(8), 1427–1433. https://doi.org/10.1016/j.pain.2013.04.041

Vögtle, E., Kröner-Herwig, B., & Barke, A. (2016). Nocebo hyperalgesia: Contributions of social observation and body-related cognitive styles. *Journal of Pain Research*, *9*, 241–249. https://doi.org/10.2147/JPR.S96228

Wendt, L., Albring, A., Benson, S., Engler, H., Engler, A., Hinney, A., Rief, W., Witzke, O., & Schedlowski, M. (2014). Catechol-O-Methyltransferase Val158Met Polymorphism Is Associated with Somatosensory Amplification and Nocebo Responses. *PLOS ONE*, *9*(9), e107665. https://doi.org/10.1371/JOURNAL.PONE.0107665

Yavropoulou, M. P., Kasdagli, M. I., Makras, P., Diomatari, K. M., Anastasilakis, A. D., Mitsikostas, D. D., Kassi, E., Sfikakis, P. P., & Kravvariti, E. (2024). Nocebo-associated treatment discontinuation with subcutaneous anti-osteoporotic drugs. A systematic review and meta-analysis of placebo-arm dropouts in randomized-controlled trials. *Maturitas*, *179*. https://doi.org/10.1016/j.maturitas.2023.107874

Yetman, H. E., Cox, N., Adler, S. R., Hall, K. T., & Stone, V. E. (2021). What Do Placebo and Nocebo Effects Have to Do With Health Equity? The Hidden Toll of Nocebo Effects on Racial and Ethnic Minority Patients in Clinical Care. *Frontiers in Psychology*, *12*, 788230. https://doi.org/10.3389/fpsyg.2021.788230

Yoshida, W., Seymour, B., Koltzenburg, M., & Dolan, R. J. (2013). Uncertainty Increases Pain: Evidence for a Novel Mechanism of Pain Modulation Involving the Periaqueductal Gray. *Journal of Neuroscience*, *33*(13), 5638–5646. https://doi.org/10.1523/JNEUROSCI.4984-12.2013

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PANACEA Learning Materials

Module 7: Ethics and critical evaluation of placebo and nocebo

Module information

Module 7 explores the ethical conditions required for implementing placebo interventions in both clinical trials and practice. In the section on clinical trials, it covers the core principles of bioethics and how research protocols are ethically evaluated, with a focus on determining when it is acceptable to use placebo controls. It also emphasizes the importance of informed consent and compares placebo controls with active treatments to ensure patient welfare. In clinical practice, the module examines ethical regulations and principles surrounding placebo intervention, addressing the potential issues of deception and the ethical validity of open-label placebos (OLPs). It assesses the efficacy of OLPs compared to no treatment and how placebo effects can be ethically induced through contextual and environmental factors.

7.1 Overview

The ethical application of placebo interventions, whether in clinical research or practice, has been the subject of extensive debate in both medical ethics and placebo literature. In clinical trials, the use of pure placebos must adhere to core bioethical principles (respect for autonomy, beneficence, non-maleficence, and justice), which serve as the foundation for evaluating research protocols. Ethical scrutiny focuses especially on the justification for using placebo controls instead of active comparators, particularly when withholding effective treatment might pose risks to participants. Informed consent plays a crucial role in ensuring transparency and protecting participants' rights, yet poses unique challenges in placebo-controlled designs.

In clinical practice, the ethical landscape becomes even more complex. While regulatory frameworks and ethical guidelines aim to safeguard patient welfare, the use of deceptive placebo intervention (i.e., administered without patient awareness) raises concerns about trust and autonomy. This has spurred growing interest in alternative approaches such as open-label placebos, which have been shown to elicit positive outcomes even when patients are aware of the nature of the treatment. In addition, ethically acceptable strategies to harness placebo effects through

contextual and communicative factors (without deception) are gaining recognition as a promising avenue to enhance care while preserving patient rights. Overall, the literature emphasizes that ethical placebo use requires careful balancing of scientific validity, therapeutic benefit, and respect for individuals' informed choices.

7.2. Conditions needed for placebo interventions to be carried out ethically in clinical trials

Introduction

In Module 4, we learned that placebos are often used in randomized controlled trials (RCTs) as controls to test the efficacy of novel active treatments. Throughout this module, we will refer to RCTs using a placebo control group, as placebo-controlled RCTs or *PCTs* (placebo-controlled trials). As we learned in Modules 1 and 4, PCTs are considered the gold standard of clinical trials, because they offer the most assay sensitivity, that is, accurate differentiation between the efficacy of active and inert treatments.

However, clinical research must consider not only the rigor of its methodology, but also the protection and rights of its human participants. In particular, if an effective, approved treatment already exists, comparing a novel treatment for that same disease to a placebo intervention can raise ethical concerns, because assigning participants to the placebo group denies them access to established and effective care. Therefore, using a PCT design must always be ethically justified. In the first part of this module, we will describe how to determine the ethicality of a PCT.

The principles of bioethics

Autonomy, beneficence, non-maleficence, and justice are the main ethical principles that must guide both researchers in RCTs and doctors in their routine clinical practice. In the context of RCTs, *autonomy* refers to respecting a research participant's right to make free and informed decisions about participating in a trial. For example, this would mean ensuring that participants are fully informed about the aims, risks, and benefits of participating in a PCT (World Medical Association, 2024), including that there is a chance of receiving a placebo intervention instead of the active treatment. *Beneficence* refers to the researcher's obligation to act with the participant's best interest in mind, with the aim of maximizing participant benefits. *Non-maleficence* refers to avoiding harm to participants. These two become particularly important when considering withholding standard treatment

from participants in a placebo control group. Finally, *justice* refers to fair and equal distribution of the benefits and burdens of research (Varkey, 2021). In the case of a PCT, this could include fully randomized assigning of participants into treatment groups, or ensuring that the population who is included in a trial is the same population who will ultimately benefit from the research.

Ethical evaluation of research protocols

The need for ethical evaluations in human biomedical research was given rise to after the 1945 Nuremberg Judgement, where Nazi doctors were prosecuted for their experiments on death camp prisoners, resulting in the Nuremberg Code (1947-1949) (BMJ, 1996). The current reference guideline, originally derived from the Nuremberg Code (Shuster, 1997), is the Declaration of Helsinki of human rights in medical research. It was published by the World Medical Association in 1964 and has been revised several times since then (World Medical Association, 2024). Concerning the use of placebos, the guidelines (art. 33) currently state that:

Box 7.1 Declaration of Helsinki on use of placebo

"The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

If no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

If for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and the participants who receive any intervention other than the best proven one(s), placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option."

Based on the guidelines, it is generally considered both scientifically and ethically appropriate to use a PCT in certain situations. We are going to clarify and specify these circumstances, addressing when the use of a placebo control is warranted.

First, PCTs are acceptable when no proven treatment for a disease exists. In a similar vein, they are also generally considered ethical in the event of *clinical*

equipoise. Clinical equipoise refers to "*a state of honest, general disagreement within the expert medical community*," concerning the preferred treatment for a disease (Freedman, 1987; Hey & Weijer, 2013, p. 4). In clinical trials, equipoise means that researchers are unsure about the potential benefits or risks of assigning a patient to one of the experimental groups. For example, this could be when there is not enough evidence that a novel active treatment is more effective than a placebo intervention. This would also include cases where findings on the efficacy of a treatment for one disease cannot be generalized to the disease of interest. For example, investigating whether an existing anti-depressant would also work for post-traumatic stress disorder (Raskind et al., 2013).

Employing a placebo control group when a proven effective treatment exists, conflicts with the bioethical principles of beneficence and non-maleficence, because assigning participants to the placebo control group deprives these patients of competent medical care (Freedman 1990; Weijer and Miller 2004). In contrast, it is not considered ethically problematic to compare a placebo intervention to a novel treatment when they are added to an established treatment, as patients are still receiving at least standard care.

Second, using a placebo control group is permissible when the potential risks of going untreated are negligible. For example, because male pattern baldness or allergic rhinitis do not pose immediate or serious risks to a patient's health, it would be acceptable to use a placebo control group to investigate the effectiveness of treatments for these conditions (Olsen et al., 2012; Patel et al., 2014).

Finally, it is often justifiable to use a placebo control group when investigating treatments for health conditions with highly fluctuating symptoms and/or conditions that are known to respond strongly to placebo interventions (Millum & Grady, 2013). For example, depression has fluctuating symptoms, but also shows large placebo effects (Rief et al., 2009). Showing that a novel anti-depressant is equally effective as an established one might mean that the novel drug is as effective as the existing drug, or that neither was more effective than a placebo intervention. In these cases, a placebo control group may be necessary to reliably demonstrate the efficacy of the novel treatment.

Risk-benefit assessment

Nevertheless, even when a placebo control group would be necessary to demonstrate a novel treatment's efficacy, this is not in itself sufficient to justify its

use. The level of risk that participants are exposed to in a clinical trial must be balanced by the social value of the expected knowledge (Millum & Grady, 2013). Therefore, it is important to first consider the severity of the condition being studied. If the risks of going untreated are too high, a placebo control group cannot be justified under any circumstances. Furthermore, it is important to identify who will ultimately benefit from the research. In most cases, this should be the population which the study is being conducted on.

However, although it may be possible to sufficiently answer research questions *without* placebos, PCTs often require a smaller sample size than active control studies do. Furthermore, they can usually detect treatment effects earlier than active control studies. This may be especially relevant when participant recruitment is slow, such as in cases of rare diseases. PCTs, therefore, can be more efficient in achieving their goals, and have fewer costs, thus increasing their social value (Millum & Grady, 2013). Ultimately, the decision of which type of control group to use must prioritize the protection of participants and the social (before than scientific) value of the knowledge gained.

Informed consent

Informed consent is a comprehensive process aimed at ensuring that patients understand the details of their participation in clinical trials, including potential risks, benefits, and their rights as participants (Grant, 2021). In the name of participant autonomy, researchers are responsible for obtaining voluntary and well-informed consent from patients before they can be included in a trial. The informed consent procedure must include descriptions of the aims, methods, sources of funding, conflicts of interest, affiliations of the researcher, and the possible risks and benefits of participating (World Medical Association, 2024). Other information that should be provided includes the constraints and discomforts posed by the research, such as the length of participation, number of medical tests, descriptions of medical tests, etc. (Chassany & Duračinský, 1999).

However, such descriptions can often be very technical, and research shows that patients often only barely understand the explanations provided of trial methodology (Falagas et al., 2009). This can result in refusal to participate, but most importantly, it poses the risk of violating participant autonomy, due to participants not fully understanding what they are consenting (Blease et al., 2017; Reijula et al., 2015). This common failure of researchers to ensure that participants understand the fundamental aspects of clinical trials is known as *therapeutic*

misconception (Appelbaum et al., 2004). A systematic review of studies of informed consent processes found that in only half of the reviewed studies, participants adequately understood the aims and methods of the trials in which they participated (Falagas et al., 2009). This has led to calls for researchers to find appropriate and simple ways of explaining concepts, such as placebo control, randomization, double blinding, etc. (Blease et al., 2017; Chassany & Duračinský, 1999).

Informed consent and placebo control

Adequate information about placebos and their function needs to be provided to research participants, or else they cannot be fully informed about the potential risks and benefits of a study (World Medical Association, 2024).

However, where research participants are usually given extensive information on the possible risks and benefits of the active treatment under investigation, information about placebos is often incomplete and sometimes inaccurate (Blease et al., 2017). One reason for this disparity may be that biomedical researchers are not adequately educated on the science of placebo effects (Falagas et al., 2009). However, as we have learned in this course, a substantial body of literature exists that could be used in informed consent procedures to ensure that research participants are fully informed about the use of placebos in PCTs.

For example, as we learned in Modules 2 and 3, placebo effects are most likely to influence symptoms that can be experienced and self-reported. Indeed, while placebo interventions cannot cause tumors to regress, they can influence the self-reported symptoms of oncological disease, such as nausea, fatigue, or hot flushes (Chvetzoff & Tannock, 2003; Tramèr et al., 1998). Informing patients that they might experience health benefits and/or adverse events even if they receive the placebo intervention would correct the false beliefs that placebo interventions have no effects, would allow participants to make fully informed choices about participating, and would help those in placebo control groups to make sense of their experiences during PCTs (Blease et al., 2017).

There may be theoretical justifications for not informing patients about placebo effects. For instance, telling participants about placebo effects could affect their expectations and thus increase or reduce responses to the placebo or active treatment, possibly biasing the results of the study (Blease et al., 2017). Nonetheless, even in this case, ethical concerns should always override methodological ones (Blease et al., 2017).

What should be included in informed consent about placebo control?

Participants should always be told what is in the placebo treatment. For example, placebo pills in clinical trials often include lactose or gluten, which can potentially cause harm to some participants (Golomb et al., 2010). Furthermore, researchers should actively involve patients in the development of materials that provide clear and engaging information about placebo control groups, as well as placebo and nocebo effects. These materials could take the form of concise and accessible leaflets and online resources, such as videos (Blease et al., 2017).

Furthermore, the information given to participants about placebo and nocebo effects should be specific to their disease. For conditions where placebo and nocebo effects are common, participants should be told that research indicates they may experience such effects in the form of symptom improvement, worsening, or side effects. In contrast, for conditions where placebo or nocebo effects are unlikely, participants could be told that the placebo intervention is not expected to influence their symptoms, and that its primary purpose is to help researchers accurately interpret the results of the study (Blease et al., 2017).

Informed consent and nocebo effects

Finally, participants should be informed not only about the possible side effects of the treatment under investigation, but that these side effects can occur due to expectations of side effects, also in the placebo control group. However, nocebo effects in RCTs create a dilemma between patient autonomy and non-maleficence, because, as we learned in Module 4, informing participants about potential side effects can increase the chance that they experience those negative health changes.

One suggestion is that participants should be given the choice of how much information they wish to receive about potential side effects. This approach respects the principle of autonomy by allowing individuals to decide how they want to be informed and communicated with. However, serious side effects must always be disclosed. When participants wish to be fully informed, autonomy takes precedence over other considerations. This approach may reduce *unnecessary* nocebo effects. That is, it means that participants who prefer not to know about *all* potential side effects might be less likely to experience these effects (Howick, 2012, 2021).

Furthermore, even when participants are informed about all potential side effects, the way this information is communicated can minimize the chance of nocebo effects occurring. Empathetic communication can generally help reduce these

effects (De Brochowski et al., 2024; Howe et al., 2017). Moreover, framing the information positively, while still being accurate and complete, is another effective strategy. For example, in one study, healthy volunteers were informed about the risks of a placebo intervention in two different ways. One group was told that the side effects were common, affecting 1 in 10 people. The other group received the same information, but it was positively framed, stating that side effects are uncommon and 90% of people are not affected. Those in the positive framing group reported fewer nocebo effects than those given the standard risk information (Barnes et al., 2019).

Ultimately, nocebo effects exist and can cause harm, making it essential to acknowledge them to adhere to the principle of non-maleficence. While some nocebo effects are inevitable, others can be mitigated by avoiding unnecessarily negative communication and instead adopting a more positive and empathetic approach.

To deepen the understanding of strategies to minimize nocebo effects, Module 6 provides a detailed exploration of effective techniques and approaches.

Placebo control vs active control

Next, we aim to directly compare the most common arguments for using a PCT design or an active control design. As stated in the Declaration of Helsinki, the effectiveness of a novel treatment must be tested against the best, approved treatment (World Medical Association, 2024). An active control study compares a novel active treatment to an existing active treatment, rather than a placebo. The three main types of active control study are *superiority trials*, *equivalence trials*, and *non-inferiority trials*. Each has distinct objectives regarding the comparison between a new treatment and an established one. Superiority trials are designed to demonstrate that a new treatment is significantly more effective than active control. Equivalence trials, on the other hand, aim to establish that the new treatment effects are statistically like those of the established treatment within a defined margin, indicating no meaningful difference. Non-inferiority trials seek to show that the new treatment is not substantially less effective than the standard treatment, remaining within an acceptable margin of efficacy. Statistically, PCTs and superiority trials both focus on detecting significant differences between treatments. By contrast, equivalence and non-inferiority trials emphasize that the new treatment is "not unacceptably worse" than the existing standard. This approach allows researchers to assess whether the new intervention offers

comparable effectiveness, often with potential additional benefits, such as fewer side effects, reduced costs, or greater convenience for patients (D'Agostino et al., 2003).

PCTs are scientifically informative

Placebo controlled trials are considered scientifically more informative than active control trials because the placebo control provides a clear reference point to which compare the effectiveness of the novel active treatment (Temple, 1997). Temple & Ellenberg (2000) argue that, in contrast to PCTs, interpreting the results of an active control study requires the assumption that, if a placebo group had been included, it would have performed worse than the active control group. This assumption is appropriate in certain cases, such as with medications that have consistently outperformed placebo controls in clinical trials (e.g., many medications for cardiovascular conditions; Chou et al., 2022; Wei et al., 2020). However, for many health conditions, especially those with fluctuating symptoms or strong placebo effects (e.g., depression; La Vaque & Rossiter, 2001), this assumption is hard to prove (Temple & Ellenberg, 2000).

Furthermore, where PCTs focus on detecting significant differences between a novel treatment and an inert one, equivalence and non-inferiority trials focus on showing that a treatment is "not unacceptably worse" than an existing treatment (Hey & Weijer, 2013, 2016). Demonstrating a significant difference between treatments is statistically more challenging than demonstrating equivalence or non-inferiority, where small differences are often deemed acceptable (Schumi & Wittes, 2011). Therefore, PCTs may require stronger study designs to confirm their hypotheses, whereas researchers aiming to show a lack of difference between treatments may have less incentive to optimize their study design and data quality (Schumi & Wittes, 2011; Temple & Ellenberg, 2000).

This is of course not the case with superiority trials, which aim to show a significant difference between a novel active treatment and an existing active treatment. However, active control trials, and superiority trials especially, require much larger sample sizes than PCTs do (Enck et al., 2013; Leon, 2011). In fact, as mentioned above, in PCTs, the comparison is between a treatment and a placebo, where the difference in effect size is expected to be relatively large (since placebos typically have little to no therapeutic effect). In active control trials, however, the new treatment is being compared with an existing, effective treatment, so the expected difference in

efficacy (effect size) is much smaller. To detect a statistically meaningful difference (or a lack of significant difference, as in equivalence or non-inferiority studies), a much larger sample is needed to achieve adequate statistical power. This means that using an active control study increases the number of participants potentially exposed to an ineffective, or even harmful, novel treatment (Temple, 1997; Temple & Ellenberg, 2000). Thus, PCTs may be more appealing to researchers due to the smaller sample sizes required, the more clearly interpretable comparison, and lower costs (Millum & Grady, 2013).

Active control studies are ethical and practically informative

Active control trials are more ethically sound than PCTs because they avoid the issue of non-treatment associated with placebo control groups. This is because in active control trials, all participants receive a treatment designed to address their condition, ensuring that no patient is denied effective care. From a clinical perspective, active control trials are also considered more practically useful. Instead of merely testing whether a novel treatment is better than an inert one, they help determine which of the two *active* treatments is more effective. This is generally more helpful for clinicians to decide on the best treatment for their patients (Hey & Weijer, 2013, 2016).

This is a crucial distinction between PCTs and active control trials. Schwartz and Lellouch (1967) distinguish between *pragmatic trials*, which compare treatments to find out which works better in real-world practice, and *explanatory trials*, which aim to understand how treatments work biologically. Following this reasoning, the choice of control should align with the specific research question. If the goal is to understand how a treatment works, a PCT may be appropriate, but if the aim is to identify which treatment is better for clinical use, an active control study may be more informative (Hey & Weijer, 2013; Schwartz & Lellouch, 1967).

Thus, the choice between a PCT and an active control trial is complex and must be guided by the scientific and ethical considerations of each specific trial. PCTs offer scientific advantages in certain situations, such as with conditions that show large placebo effects, but they raise ethical concerns about denying some participants access to competent medical care. Active control trials may be more ethically sound and practically informative, but they face challenges related to statistical rigor and sample size. Balancing these trade-offs is essential, and, ultimately, no single trial design is inherently better. Instead, the design should align with the specific

research question at hand and should take into account the ethical and practical qualities of the disease or treatment under investigation.

In summary, conducting PCTs ethically requires careful consideration of both scientific rigor and participant wellbeing. While PCTs are often considered the gold standard for clinical trials due to clearly differentiating between active and inert treatments, they must be ethically justified, especially when effective treatments exist and when testing treatments for severe conditions. Researchers must consider the risks of withholding standard care against the scientific and social value of the study and ensure that participants are fully informed about the potential risks and benefits, including those that come with placebo control groups. Ethical principles such as autonomy, beneficence, non-maleficence, and justice should guide the decision-making process to protect participants and ensure that research outcomes benefit the populations being studied. Ultimately, when ethically justified, PCTs can provide important scientific knowledge, but their use must always prioritize participant wellbeing and the fair distribution of benefits.

7.3. Conditions needed for placebo interventions to be carried out ethically in clinical practice

Introduction

As we learned in Module 4, many healthcare providers report using placebo interventions in one way or another in the clinic. Maximizing the synergistic effect of placebo mechanisms in conjunction with active treatments, which are supported by scientific evidence as core therapies, is crucial and an ethical imperative (see Module 5 for further details). Contextual placebo interventions focus on aspects related to the therapeutic environment, such as the patient-provider relationship, communication style, and overall treatment setting. These factors can shape a patient's perception and response to the treatment, thereby enhancing the effects of active treatments and contributing to positive health changes and improved clinical outcomes.

However, the ethical considerations become more complex when it comes to tangible placebo interventions (vs. Contextual intervention). These interventions involve physical substances or procedures that may lack inherent therapeutic effects but are administered in a manner mimicking real treatments. Tangible placebos can be categorized into: i) pure placebo: interventions with no active therapeutic components, such as sugar pills, saline injections, or sham surgeries;

and ii) impure placebo: such as active therapies that are not intended to address the specific symptoms for which they are prescribed, such as antibiotics for viral infections, vitamin pills, or medications dosed too low to produce pharmacological effects. Both pure and impure placebos have the capacity to induce a placebo response, resulting in positive health changes and improved clinical outcomes. When considering the ethical use of placebo interventions in clinical practice, two primary ethical questions arise concerning: whether there is robust scientific evidence that placebo interventions provide clinically meaningful benefits in comparison to no treatment, and whether informed consent can be obtained honestly and transparently, ensuring that the patient understands the nature and purpose of the placebo treatment.

Traditionally, the most potent placebo effects have been believed to occur when placebo interventions are prescribed deceptively, that is, by claiming that a prescribed placebo intervention is an active treatment. Another approach, perhaps more commonly used in clinical practice, is to withhold precise information and avoid explicitly labeling the intervention as a placebo. This method involves providing incomplete information, which can still capitalize on placebo effects without engaging in outright deception (Foddy, 2009; Miller & Colloca, 2009; Pollo et al., 2001). This practice leads to an ethical dilemma: while it may maximize the benefits of placebo interventions (aligning with the principle of beneficence), it conflicts with the principles of transparency and respect for patient autonomy. Some theorists propose that, under certain circumstances, there may be an ethical imperative to use deceptive placebo interventions (Foddy, 2009; Pugh, 2015). However, deceptive use of placebo interventions in the clinic goes against current ethical guidelines. It is important to note that even withholding information from the patient, without giving false information, is a form of deception and therefore unethical. In the following text, we will discuss the current ethical perspectives concerning deceptive and honest use of placebo interventions in the clinic.

Regulations and principles

As earlier discussed, healthcare providers in clinical practice are guided by the same ethical principles as researchers in RCTs, that is, autonomy, beneficence, non-maleficence, and justice. In clinical practice, autonomy refers to respecting a patient's right to make informed decisions about their treatment. Thus, clinicians must ensure that patients understand the aims, risks, and benefits of any treatment prescribed. Beneficence requires clinicians to act in the patient's best interest, aiming

to maximize positive outcomes, whereas non-maleficence refers to avoiding causing harm to patients. Justice obliges clinicians to treat all patients fairly and equally (Varkey, 2021).

According to the American Medical Association (AMA) Code of Medical Ethics, placebo interventions can only be prescribed if the patient is informed and consents to it (American Medical Association, 2006). Using placebo interventions deceptively is viewed as a breach of professional standards and may even require disciplinary action (see '*Legal issues with deceptive placebos*'). Furthermore, the code states that clinicians should avoid prescribing placebo interventions simply to satisfy difficult patients and ease their own work, but instead with the aim of maximizing the welfare of the patient. Thus, the use of placebo interventions in clinical practice must always align with ethical principles that prioritize patient autonomy and beneficence, and the integrity of the clinician-patient relationship.

Deception

Doctors have used placebo interventions without patient knowledge throughout history, often to soothe patients with complex diagnoses or physically unexplained symptoms, or as a diagnostic tool to determine whether symptoms might have a psychological basis (Annoni, 2020). Such prescribing of placebo interventions, although deceptive, can be well intentioned, pursuing the principle of beneficence (i.e. aiming to produce beneficial placebo effects in patients). However, as we learned in Module 4, clinicians often also report using placebo interventions to deal with difficult patients (Fässler et al., 2010; Linde et al., 2018). In such cases, placebos are used to ease the job of the clinician, and to please patients that, for example, insist on specific treatments (e.g. antibiotics) that the clinician knows will operate through placebo mechanisms in that clinical condition. This approach is often employed without a clear evaluation of the cost-benefit balance for the patient's wellbeing rather than maximizing the patient's beneficence. Whether well intentioned or not, most clinicians and theorists agree, in line with the AMA Code of Ethics, that deceptive placebo interventions cannot be ethically justified (Annoni, 2018; Barnhill, 2011).

The primary concern with using placebo interventions deceptively is that it breaches the bioethical principle of autonomy, preventing a patient from making informed decisions about their own healthcare. Such diminished autonomy also reduces patient involvement in their own treatment decisions, conflicting with modern medicine's shift towards patient-centered care and shared decision-making (Brock,

1991; Miller & Colloca, 2009). Furthermore, deceptive use of placebo interventions can make patients feel betrayed and lead to mistrust, which can harm the doctor-patient relationship, undermine a patient's faith in the healthcare system as a whole, and reduce adherence to future treatments (Bostick et al., 2008; Miller & Colloca, 2009). An additional risk is that patients might choose the same placebo treatments for other clinical conditions where effective, evidence-based treatments are available, potentially compromising the quality of their care. Finally, deception may even result in physical harm to a patient if placebo interventions mask or delay accurate diagnosis and treatment of an underlying medical condition (Bostick et al., 2008).

Can transparency compromise efficacy?

Open-label placebos (OLPs) have emerged as a response to the ethical concerns associated with deception. As we will learn in Module 8, these are placebo interventions administered honestly, with patients made aware that they are receiving a pure or impure placebo treatment. Although this approach offers an ethical alternative to deceptive placebo interventions, some authors question the effectiveness of OLPs (Foddy, 2009). The argument is that, because placebo effects tend to be strongest when patients expect an effective treatment, the strength of placebo interventions may be significantly diminished when patients are made aware of their inert nature.

While several studies on healthy samples comparing the efficacy of OLPs with deceptive placebo interventions report mixed findings (Druart et al., 2024; Friehs et al., 2022; Kube et al., 2020; Mundt et al., 2017), similar research in clinical samples is limited. Some studies did not find statistical differences between OLP and conventional (i.e., deceptive or double-blind) placebo (Disley et al., 2021; Lembo et al., 2021). However, as these studies did not test for equivalence, we cannot conclude from the findings that the two interventions were equally efficacious. This standard was so far only met by a very recent but small study that found OLPs to be indeed non-inferior to a deceptive placebo intervention—but, again, referring to a non-clinical sample (Druart et al., 2024). Therefore, while OLPs may be an ethically sound option (see '*The ethics of open-label placebos*' below for a discussion on the ethicality of OLPs), whether they are as effective as deceptively prescribed placebo interventions remains to be determined, especially in clinical samples. However, whether this is a practically relevant question is arguable, given that deceptive placebo interventions in clinical practice contradict current guidelines.

One solution to the dilemma of transparency versus efficacy is an authorized concealment approach, where the clinician obtains permission from the patient to replace the active treatment with a placebo intervention, but the clinician does not disclose when this is done. Such an approach is in line with the AMA code of ethics, and respects patient autonomy while allowing the patient's expectations to remain ambiguous (Stoessl, 2020).

Legal issues with deceptive placebos

The use of placebo interventions in clinical practice is not specifically regulated, although national laws or guidelines may apply depending on the country. However, informed consent is required for any medical intervention (with exceptions made for emergencies; The European Convention on Human Rights and Biomedicine, 1997). Therefore, the legal requirements for prescribing placebo interventions may be best interpreted through the principles that govern informed consent.

In general (see Cave, 2017 for differences by countries), doctors are legally obliged to disclose all "material" information related to a patient's treatment. Material information includes the nature and purpose of the treatment, the potential risks and benefits of the treatment, available alternatives, and consequences of refusing treatment (Cave, 2017). Exceptions may be given under *therapeutic privilege*. This concept allows physicians to withhold information about a patient's diagnosis or treatment if they believe that sharing this information would hinder recovery or cause unnecessary emotional suffering (Cave, 2017). Legally, failure to meet the obligations of informed consent can be considered a case of medical negligence (Ng, 2024).

A case study and legal analysis of deceptive placebo use

As discussed above, there are no universal laws governing the use of placebo interventions in clinical practice. When issues arise, they are generally addressed on a case-by-case basis, depending on the specific laws and regulations of the country (Bolcato et al., 2024). To give an example, we describe a medico-legal case study, where complaints were filed against a doctor and nurses for deceptively prescribing and administering a placebo intervention (Rich, 2003).

In this case, a 14-year-old boy (the patient) suffering from post-traumatic, persistent migraines following a football injury, had his morphine treatment replaced with a placebo intervention (a saline solution) by his neurologist, who did not inform the patient or his mother of this switch. The placebo intervention was administered by

nurses, and the patient recovered and was discharged soon after. When the patient's mother later found out about the switch to the placebo intervention, she filed complaints against the neurologist and the nurses. The medical board ultimately did not take action against the neurologist due to the lack of clear ethical guidelines on the use of placebo interventions in clinical settings. The nursing board initially charged the nurses for violating the requirement for informed consent. However, the nurses successfully challenged these charges by arguing that deceptive use of placebo interventions was still common practice.

The case raises important legal questions concerning informed consent. The neurologist could have argued that he acted under therapeutic privilege and in consideration of the patient's beneficence, highlighting the potential risks associated with prolonged morphine use, particularly in young people, such as dependency, tolerance, and potential side effects However, the therapeutic privilege doctrine is meant for cases where disclosing information might cause immediate harm. Since the patient was not in immediate danger, this would be a weak defense. Legally, the case's central challenge revolved around proving damage. Specifically, although the patient's autonomy was breached, he did not suffer any measurable physical, psychological, emotional, or financial harm. Thus, the lack of tangible harm led to the case being dismissed.

This case illustrates the gap that existed at the time between ethical standards and legal regulations, showing that while deceptive placebo use may violate ethical norms, it was (and may still be) difficult to pursue legal action without tangible and provable damages (Rich, 2003). Of note, this case study is old, and a similar case may be approached differently in the current time.

The ethics of open-label placebos

OLPs present a possible ethical solution to the issue of deception. We will further explore OLPs in Module 8; here we will focus specifically on the ethical issues surrounding OLPs. Although OLPs seem to sidestep the ethical problems of deception inherent to the traditional use of placebo interventions, there are concerns that even OLPs might involve subtle deception due to the complex mechanisms underlying placebo effects (Blease et al., 2016). For example, even if patients are informed about the inert nature of OLPs, communication could remain incomplete or ambiguous, leading to multiple potential interpretations about how they function and what they are used for.

For example, a common description given to participants in OLP research is that "placebos are powerful" (Blease, 2019; Charlesworth et al., 2017). However, this could be misleading because most of the data showing the efficacy of placebo interventions comes from placebo mechanism studies where participants were deceived or from RCTs where participants partially expected receiving an active treatment (Blease et al., 2016). Blease and colleagues (2016) argue that, whether this ambiguity is ethically acceptable largely depends on whether patients are comfortable with it and with OLPs in general. As we will see in Module 8, there is some evidence to suggest that patients do find OLPs acceptable, suggesting they could become an ethical and widely used treatment option in the future (Haas et al., 2020; Hull et al., 2013).

However, there are several ethical issues surrounding the clinical use of OLPs that extend beyond deception (Specker Sullivan, 2021). Historically, the use of placebo interventions often involved medical paternalism, and this was particularly the case for marginalized groups. Additionally, OLP studies frequently involve conditions that are considered to primarily affect women, such as irritable bowel syndrome and chronic fatigue (Jason et al., 2009; Lovell & Ford, 2012). This focus could perpetuate historical biases and injustices in medical research and care. To ensure true ethical integrity, clinical researchers and practitioners must consider not just informed consent but also other criteria, such as whether their goals and practices address or maintain structural injustices. If OLPs become more widely used, researchers and clinicians should carefully evaluate whom they include in studies or prescribe OLPs to, what conditions they focus on, and why they choose those conditions and populations (Specker Sullivan, 2021).

Efficacy of OLPs compared to no treatment

As stated above, to be ethical, placebo interventions need to be effective. Given that deceptive placebo interventions are not in line with current guidelines, we will not discuss the efficacy of deceptive placebo interventions here. However, a number of clinical trials of OLPs (see Module 8 for further details) have been performed for various conditions, such as irritable bowel syndrome, chronic lower back pain, episodic migraine, and cancer-related fatigue, etc. (e.g., Carvalho et al., 2016; Hoenemeyer et al., 2018; Kam-Hansen et al., 2014; Kaptchuk et al., 2010). These studies have provided promising results as compared to no treatment. Nonetheless, these findings should be interpreted with caution, given the early state of research in this field and thus, small number of studies with heterogeneity in methods and

quality (von Wernsdorff et al., 2021). Thus, more evidence on the effectiveness of OLPs is still warranted to fully justify their widespread use in clinical practice (Blease, 2019).

Inducing placebo effects through contextual factors

As we learned in Module 2, many factors within the treatment context, beyond inert pills, injections, and procedures, can trigger placebo and nocebo effects. Rather than limiting placebo interventions to substances or procedures, experts argue for enhancing treatment outcomes by triggering the mechanisms underlying placebo and nocebo effects, particularly through fostering a positive doctor-patient relationship (Evers et al., 2018). For example, empathetic communication by clinicians can induce positive emotions and expectations, leading to improved treatment outcomes. Conversely, negative communication that induces anxiety or negative expectations can increase nocebo effects, worsening outcomes (Howe et al., 2019). That being said, it is also important to avoid creating unrealistically positive expectations (see Module 5 and the guidelines for more details on optimizing placebo effects).

Given that the behavior of healthcare professionals can directly influence treatment outcomes, there is an ethical imperative for clinicians to take advantage of this to maximize placebo effects and minimize nocebo effects (Evers et al., 2018). Clinicians must navigate the delicate balance between fostering hope and maintaining honesty about treatment limitations. This requires ethical sensitivity to patients' vulnerabilities and an understanding of the potential impact of their communication style on patient outcomes. Misleading patients, even unintentionally, can erode trust and violate ethical principles of autonomy and informed consent. Therefore, while clinicians should leverage positive communication to enhance treatment effects, they must also commit to transparency and integrity in their interactions, ensuring that patients have realistic expectations and are fully informed about their treatment options. This approach not only respects patient autonomy but also promotes a more ethical practice environment where patients feel valued and supported (Annoni & Miller, 2016).

7.4 Conclusion

In summary, the ethical use of placebo interventions in clinical practice necessitates a delicate balance between transparency and patient autonomy. Central to this ethical framework are the principles of beneficence, non-maleficence, autonomy,

and justice. Healthcare providers have a clear ethical obligation to enhance the beneficial effects of treatments, thereby maximizing placebo effects while minimizing nocebo effects, without compromising patient trust. Respect for autonomy requires that patients are adequately informed, and their decisions are honored, even when navigating placebo use.

The potential of open-label placebos, which are administered with transparency about their inert nature, is an ongoing area of research. This approach presents a promising means to align placebo intervention with ethical standards, particularly in situations where an active, evidence-based treatment does not exist. By offering open-label placebos, healthcare providers can enhance patient outcomes through placebo effects while maintaining transparency and upholding ethical principles such as autonomy and informed consent.

Ultimately, ethical guidelines for placebo interventions should prioritize the patient's autonomy and wellbeing, guided by the principles of beneficence (acting in the best interest of the patient), non-maleficence (avoiding harm), justice (ensuring fairness in treatment), and respecting patient autonomy. By adhering to these principles, healthcare professionals can make informed decisions about the use of placebo interventions that are ethically sound and patient-centered.

References

American Medical Association. (2006). *Use of Placebo in Clinical Practice*. AMA Code of Ethics. https://code-medical-ethics.ama-assn.org/ethics-opinions/use-placebo-clinical-practice

Annoni, M. (2018). The Ethics of Placebo Effects in Clinical Practice and Research. *International Review of Neurobiology*, *139*, 463–484. https://doi.org/10.1016/bs.irn.2018.07.031

Annoni, M. (2020). Better than nothing: A historical account of placebos and placebo effects from modern to contemporary medicine. *International Review of Neurobiology*, *153*, 3–26. https://doi.org/10.1016/bs.irn.2020.03.028

Annoni, M., & Miller, F. G. (2016). Placebo effects and the ethics of therapeutic communication: a pragmatic perspective. *Kennedy Institute of Ethics Journal, 26*(1), 79-103. https://doi.org/10.1353/ken.2016.0004

Appelbaum, P. S., Lidz, C. W., & Grisso, T. (2004). Therapeutic Misconception in Clinical Research: Frequency and Risk Factors. *IRB: Ethics & Human Research*, *26*(2), 1–8. https://doi.org/https://www.jstor.org/stable/3564231

Barnes, K., Faasse, K., Geers, A. L., Helfer, S. G., Sharpe, L., Colloca, L., & Colagiuri, B. (2019). Can Positive Framing Reduce Nocebo Side Effects? Current Evidence and Recommendation for Future Research. *Frontiers in Pharmacology*, *10*. https://doi.org/10.3389/fphar.2019.00167

Barnhill, A. (2011). What it takes to defend deceptive placebo use. *Kennedy Institute of Ethics Journal*, *21*(3), 219–250. https://doi.org/10.1353/ken.2011.0015

Blease, C. R., Colloca, L., & Kaptchuk, T. J. (2016). Are open-Label Placebos Ethical? Informed Consent and Ethical Equivocations. *Bioethics*, *30*(6), 407–414. https://doi.org/10.1111/bioe.12245

Blease, C. R. (2019). The role of placebos in family medicine: Implications of evidence and ethics for general practitioners. *Australian Journal of General Practice*, *48*(10). https://doi.org/10.31128/AJGP-05-19-4939

Blease, C. R., Bishop, F. L., & Kaptchuk, T. J. (2017). Informed consent and clinical trials: Where is the placebo effect? *BMJ*, *356*. https://doi.org/10.1136/bmj.j463

BMJ. (1996). The Nuremberg Code (1947). *BMJ*, *313*, 1448. https://doi.org/https://doi.org/10.1136/bmj.313.7070.1448

Bolcato, V., Franzetti, C., Fassina, G., Basile, G., Martinez, R. M., & Tronconi, L. Pietro. (2024). Comparative study on informed consent regulation in health care among Italy, France, United Kingdom, Nordic Countries, Germany, and Spain. *Journal of Forensic and Legal Medicine*, *103*. https://doi.org/10.1016/j.jflm.2024.102674

Bostick, N. A., Sade, R., Levine, M. A., & Stewart, Jr. D. M. (2008). Placebo Use in Clinical Practice: Report of the American Medical Association Council on Ethical and Judicial Affairs. *The Journal of Clinical Ethics*, *19*(1). https://doi.org/10.1086/JCE200819109

Brock, D. W. (1991). The ideal of shared decision making between physicians and patients. *Kennedy Institute of Ethics Journal*, *1*(1), 28–47. https://doi.org/10.1353/ken.0.0084

Carvalho, C., Caetano, J. M., Cunha, L., Rebouta, P., Kaptchuk, T. J., & Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: A randomized controlled trial. *Pain*, *157*(12), 2766–2772. https://doi.org/10.1097/j.pain.0000000000000700

Cave, E. (2017). The ill-informed: Consent to medical treatment and the therapeutic exception. *Common Law World Review*, *46*(2), 140–168. https://doi.org/10.1177/1473779517709452

Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*(2), 97–107. https://doi.org/10.1111/jebm.12251

Chassany, O., & Duračinský, M. (1999). Ethics and clinical trials. *Fundamental and Clinical Pharmacology*, *13*(4), 437–444. https://doi.org/10.1111/j.1472-8206.1999.tb00001.x

Chou, R., Cantor, A., Dana, T., Wagner, J., Ahmed, A. Y., Fu, R., & Ferencik, M. (2022). Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*, *328*(8), 754–771. https://doi.org/10.1001/jama.2022.12138

Chvetzoff, G., & Tannock, I. F. (2003). Placebo Effects in Oncology. *Journal of the National Cancer Institute*, *95*(1), 19–29. https://doi.org/https://doi.org/10.1093/jnci/95.1.19

D'Agostino Sr, R. B., Massaro, J. M., & Sullivan, L. M. (2003). Non-inferiority trials: design concepts and issues–the encounters of academic consultants in statistics. *Statistics in Medicine*, *22*(2), 169-186. https://doi.org/10.1002/sim.1425

De Brochowski, V., Rubin, G. J., & Webster, R. K. (2024). The effect of nocebo explanation and empathy on side-effect expectations of medication use following a fictional GP consultation. *Psychology, Health and Medicine*, *29*(4), 809–821. https://doi.org/10.1080/13548506.2023.2240072

Disley, N., Kola-Palmer, S., & Retzler, C. (2021). A comparison of open-label and deceptive placebo analgesia in a healthy sample. *Journal of Psychosomatic Research*, *140*. https://doi.org/10.1016/j.jpsychores.2020.110298

Druart, L., Graham Longsworth, S. E., Terrisse, H., Locher, C., Blease, C. R., Rolland, C., & Pinsault, N. (2024). If only they knew! A non-inferiority randomized controlled trial comparing deceptive and open-label placebo in healthy individuals. *European Journal of Pain*, *28*(3), 491–501. https://doi.org/10.1002/ejp.2204

Enck, P., Bingel, U., Schedlowski, M., & Rief, W. (2013). The placebo response in medicine: Minimize, maximize or personalize? *Nature Reviews Drug Discovery*, *12*(3), 191–204. https://doi.org/10.1038/nrd3923

Evers, A. W. M., Colloca, L., Blease, C. R., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Falagas, M. E., Korbila, I. P., Giannopoulou, K. P., Kondilis, B. K., & Peppas, G. (2009). Informed consent: how much and what do patients understand? *American Journal of Surgery*, *198*(3), 420–435. https://doi.org/10.1016/j.amjsurg.2009.02.010

Fässler, M., Meissner, K., Schneider, A., & Linde, K. (2010). Frequency and circumstances of placebo use in clinical practice - a systematic review of empirical studies. *BMC Medicine*, *8*. https://doi.org/10.1186/1741-7015-8-15

Foddy, B. (2009). A duty to deceive: Placebos in clinical practice. *American Journal of Bioethics*, *9*(12), 4–12. https://doi.org/10.1080/15265160903318350

Freedman, B. (1987). Equipoise and the ethics of clinical research. *The New England Journal of Medicine*, *317*(3), 141–145. https://doi.org/10.1056/NEJM198707163170304

Friehs, T., Rief, W., Glombiewski, J. A., Haas, J., & Kube, T. (2022). Deceptive and non-deceptive placebos to reduce sadness: A five-armed experimental study. *Journal of Affective Disorders Reports*, *9*, 100349. https://doi.org/10.1016/j.jadr.2022.100349

Golomb, B. A., Erickson, L. C., Koperski, S., Sack, D., Enkin, M., & Howick, J. (2010). What's in Placebos: Who Knows? Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine*, *153*(8), 532–535. https://doi.org/10.7326/0003-4819-153-8-201010190-00010

Grant, S. C. (2021). Informed consent—We can and should do better. *JAMA Network Open*, *4*(4), e2110848-e2110848. 10.1001/jamanetworkopen.2021.10848

Haas, J. W., Rief, W., & Doering, B. K. (2021). Open-label placebo treatment: Outcome expectations and general acceptance in the lay population. *International Journal of Behavioral Medicine*, *28*, 444-454. https://doi.org/10.1007/s12529-020-09933-1

Hey, S. P., & Weijer, C. (2013). Assay sensitivity and the epistemic contexts of clinical trials. *Perspectives in Biology and Medicine*, *56*(1), 1–17. https://doi.org/10.1353/pbm.2013.0002

Hey, S. P., & Weijer, C. (2016). What questions can a placebo answer? *Monash Bioethics Review*, *34*(1), 23–36. https://doi.org/10.1007/s40592-016-0057-z

Hoenemeyer, T. W., Kaptchuk, T. J., Mehta, T. S., & Fontaine, K. R. (2018). Open-Label Placebo Treatment for Cancer-Related Fatigue: A Randomized-Controlled Clinical Trial. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-20993-y

Howe, L. C., Leibowitz, K. A., & Crum, A. J. (2019). When your doctor "Gets it" and "Gets you": The critical role of competence and warmth in the patient-provider interaction. *Frontiers in Psychiatry*, *10*(475). https://doi.org/10.3389/fpsyt.2019.00475

Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the Placebo Effect: Exploring the Influence of Physician Characteristics on Placebo Response. *Health Psychology*, *36*(11), 1074–1082. https://doi.org/10.1037/hea0000499.supp

Howick, J. (2012). Saying Things the "Right" Way: Avoiding "Nocebo" Effects and Providing Full Informed Consent. *American Journal of Bioethics*, *12*(3), 33–34. https://doi.org/10.1080/15265161.2012.656799

Howick, J. (2021). Unethical informed consent caused by overlooking poorly measured nocebo effects. *Journal of Medical Ethics*, *47*(9), 590–594. https://doi.org/10.1136/medethics-2019-105903

Hull, S. C., Colloca, L., Avins, A., Gordon, N. P., Somkin, C. P., Kaptchuk, T. J., & Miller, F. G. (2013). Patients' attitudes about the use of placebo treatments: telephone survey. *BMJ*, 347. https://doi.org/10.1136/bmj.f3757

Jason, L. A., Porter, N., Brown, M., Anderson, V., Brown, A., Hunnell, J., & Lerch, A. (2009). CFS: A Review of Epidemiology and Natural History Studies. *Bulletin of IACFS ME*, *17*(3), 88–106. https://doi.org/https://doi.org/10.1016/j.cgh.2021.08.039

Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine*, *6*(218). https://doi.org/10.1126/scitranslmed.3006175

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS one*, *5*(12). https://doi.org/10.1371/journal.pone.0015591

Kube, T., Rief, W., Vivell, M. B., Schäfer, N. L., Vermillion, T., Körfer, K., & Glombiewski, J. A. (2020). Deceptive and nondeceptive placebos to reduce pain: an experimental study in healthy individuals. The Clinical *Journal of Pain, 36*(2), 68-79.

10.1097/AJP.0000000000000781 https://journals.lww.com/clinicalpain/abstract/2020/02000/deceptive_and_nondeceptive_placebos_to_reduce.2.aspx

La Vaque, T. J., & Rossiter, T. (2001). The Ethical Use of Placebo Controls in Clinical Research: The Declaration of Helsinki. *Applied Psychophysiology and Biofeedback*, *26*(1), 23–37. https://doi.org/10.1023/a:1009563504319

Lembo, A., Kelley, J. M., Nee, J., Ballou, S., Iturrino, J., Cheng, V., ... & Kaptchuk, T. J. (2021). Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. *Pain, 162*(9), 2428-2435. 10.1097/j.pain.0000000000002234 https://journals.lww.com/pain/abstract/2021/09000/open_label_placebo_vs_double_blind_placebo_for.13.aspx

Leon, A. C. (2011). Evolution of psychopharmacology trial design and analysis: Six decades in the making. *The Journal of Clinical Psychiatry, 72*(3), 6831. https://doi.org/10.4088/JCP.10r06669

Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PLoS one*, *13*(8). https://doi.org/10.1371/journal.pone.0202211

Lovell, R. M., & Ford, A. C. (2012). Effect of gender on prevalence of irritable bowel syndrome in the community: Systematic review and meta-analysis. *American Journal of Gastroenterology*, *107*(7), 991–1000. https://doi.org/10.1038/ajg.2012.131

Miller, F. G., & Colloca, L. (2009). The legitimacy of placebo treatments in clinical practice: Evidence and ethics. *American Journal of Bioethics*, *9*(12), 39–47. https://doi.org/10.1080/15265160903316263

Millum, J., & Grady, C. (2013). The ethics of placebo-controlled trials: Methodological justifications. *Contemporary Clinical Trials*, *36*(2), 510–514. https://doi.org/10.1016/j.cct.2013.09.003

Mundt, J. M., Roditi, D., & Robinson, M. E. (2017). A comparison of deceptive and non-deceptive placebo analgesia: efficacy and ethical consequences. A*nnals of Behavioral Medicine*, *51*(2), 307-315. https://doi.org/10.1007/s12160-016-9854-0

Ng, I. K. S. (2024). Informed consent in clinical practice: Old problems, new challenges. *Journal of the Royal College of Physicians of Edinburgh*, *54*(2), 153–158. https://doi.org/10.1177/14782715241247087

Olsen, E. A., Whiting, D. A., Savin, R., Rodgers, A., Johnson-Levonas, A. O., Round, E., Rotonda, J., & Kaufman, K. D. (2012). Global photographic assessment of men aged 18 to 60 years with male pattern hair loss receiving finasteride 1 mg or placebo. *Journal of the American Academy of Dermatology*, *67*(3), 379–386. https://doi.org/10.1016/j.jaad.2011.10.027

Patel, P., Holdich, T., Fischer Von Weikersthal-Drachenberg, K. J., & Huber, B. (2014). Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *Journal of Allergy and Clinical Immunology*, *133*(1). https://doi.org/10.1016/j.jaci.2013.05.032

Pollo, A., Amanzio, M., Arslanian, A., Casadio, C., Maggi, G., & Benedetti, F. (2001). Response expectancies in placebo analgesia and their clinical relevance. *Pain*, *93*(1), 77–84. https://doi.org/10.1016/S0304-3959(01)00296-2

Pugh, J. (2015). Ravines and sugar pills: Defending deceptive placebo use. *Journal of Medicine and Philosophy*, *40*(1), 83–101. https://doi.org/10.1093/jmp/jhu045

Raskind, M. A., Peterson, K., Williams, T., David Hoff, L. J., Kimberly Hart, P., Hollie Holmes, P., Dallas Homas, B., Hill, J., Daniels, C., Calohan, J., Steven Millard, P. P., Rohde, K., James, R. O., Denise Pritzl, M., Kevin Feiszli, L., Eric Petrie, B. C., Gross, C., Mayer, C. L., Michael Freed, D. C., … Peskind, E. R. (2013). A Trial of Prazosin for Combat Trauma PTSD With Nightmares in Active-Duty Soldiers Returned From Iraq and Afghanistan. *The American Journal of Psychiatry*, *170*(9), 1003–1010. https://doi.org/10.1176/appi.ajp.2013.12081133

Reijula, E., Halkoaho, A., Pietilä, A. M., Selander, T., Kälviäinen, R., & Keränen, T. (2015). Therapeutic misconception correlates with willingness to participate in clinical drug trials among patients with epilepsy; need for better counseling. *Epilepsy and Behavior*, *48*, 29–34. https://doi.org/10.1016/j.yebeh.2015.05.013

Rich, B. A. (2003). A placebo for the pain: A medico-legal case analysis. *Pain Medicine*, *4*(4), 366–372. https://doi.org/10.1111/j.1526-4637.2003.03046.x

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of Affective Disorders*, *118*(1–3), 1–8. https://doi.org/10.1016/j.jad.2009.01.029

Schumi, J., & Wittes, J. T. (2011). Through the looking glass: Understanding non-inferiority. *Trials*, *12*. https://doi.org/https://doi.org/10.1186/1745-6215-12-106

Schwartz, D., & Lellouch, J. (1967). Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Chronic Diseases*, *20*(8), 637–648. https://doi.org/10.1016/0021-9681(67)90041-0

Shuster, E. (1997). Fifty Years Later: The Significance of the Nuremberg Code. *New England Journal of Medicine*, *337*(20), 1436–1440. https://doi.org/10.1056/NEJM199711133372006

Specker Sullivan, L. (2021). More than consent for ethical open-label placebo research. *Journal of Medical Ethics*, *47*(12), E7. https://doi.org/10.1136/medethics-2019-105893

Stoessl, A. J. (2020). Deception and the ethics of placebo. *International Review of Neurobiology*, *153*, 147–163. https://doi.org/10.1016/bs.irn.2020.03.030

Temple, R. J. (1997). When Are Clinical Trials of a Given Agent vs. Placebo No Longer Appropriate or Feasible? *Controlled Clinical Trials*, *18*, 613–620. https://doi.org/https://doi.org/10.1016/S0197-2456(97)00058-5

Temple, R. J., & Ellenberg, S. S. (2000). Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments Part 1: Ethical and Scientific Issues. *Annals of Internal Medicine*, *133*, 455–463. https://doi.org/10.7326/0003-4819-133-6-200009190-00015

The European Convention on Human Rights and Biomedicine. (1997). *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. https://www.coe.int/en/web/bioethics/oviedo-convention

Tramèr, M. R., Reynolds, D. J. M., Stoner, N. S., Moore, R. A., & Mcquay, H. J. (1998). Efficacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: A quantitative systematic review. *European Journal of Cancer*, *34*(12), 1836–1844. https://doi.org/https://doi.org/10.1016/S0959-8049(98)00161-0

Varkey, B. (2021). Principles of Clinical Ethics and Their Application to Practice. *Medical Principles and Practice*, *30*(1), 17–28. https://doi.org/10.1159/000509119

Wei, J., Galaviz, K. I., Kowalski, A. J., Magee, M. J., Haw, J. S., Narayan, K. M. V., & Ali, M. K. (2020). Comparison of Cardiovascular Events among Users of Different Classes of Antihypertension Medications: A Systematic Review and Network Meta-analysis. *JAMA Network Open*, *3*(2). https://doi.org/10.1001/jamanetworkopen.2019.21618

Weijer, C., & Miller, P. B. (2004). When are research risks reasonable in relation to anticipated benefits?. *Nature medicine*, *10*(6), 570-573. https://doi.org/10.1038/nm0604-570

von Wernsdorff, M., Loef, M., Tuschen-Caffier, B., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. *Scientific Reports, 11*(1), 3855. https://doi.org/10.1038/s41598-021-83148-6

World Medical Association. (2024). World Medical Association declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*. Published online October 19, 2024. doi:10.1001/jama.2024.21972 (see attachment)

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PANACEA Learning Materials

Module 8: Open-label placebo

Module information

In this Module, we will describe the open-label placebo (OLP) research. By the end of this chapter, you will gain a comprehensive understanding of open-label placebo, including their ethical considerations, historical development, significant research findings, and potential implications for clinical practice.

8.1 Overview

Placebos have long been a cornerstone of clinical research and practice; however, their application is often fraught with ethical concerns stemming from the deception commonly associated with traditional placebo use (see Module 7). This deception raises significant issues regarding patient autonomy and informed consent and has led to the historical assumption that concealment is necessary for placebos to be effective.
The use of placebos is marked by variability and conceptual confusion in clinical practice, as highlighted by existing literature (Linde et al., 2018). Diverse attitudes among healthcare professionals contribute to this ambiguity (Linde et al., 2011), and confusion persists in defining and applying terms like 'placebo' and 'placebo effect' (Louhiala, 2012; Tilburt et al., 2008) (see Module 1 and Glossary for concept definition). In the U.S., many physicians frequently resort to the use of impure placebos, particularly for managing pain and functional disorders (Fässler et al., 2010).

In this context, it is crucial to understand the distinct meanings of pure and impure placebos, as both play different roles in discussions regarding placebo use. Pure placebos are substances that contain no active therapeutic ingredients and are used solely for their psychological effect, examples being sugar pills and saline injections. These are employed to elicit placebo responses by leveraging the power of belief and expectation.
Conversely, impure placebos are active treatments prescribed for their ability to activate placebo effects rather than for their direct pharmacological effects on the condition being treated. Examples include vitamins given to patients without deficiencies or antibiotics prescribed for viral infections. While impure placebos may possess some pharmacological activity, their primary purpose is to cultivate positive expectations in patients, leading to placebo effects that can result in actual symptom improvement.

The use of impure placebos poses its own ethical challenges; although they are somewhat more defensible than pure placebos, they can still involve deception or a lack of transparency, potentially undermining the trust between patient and provider.
Both pure and impure placebos harness the power of patient belief and expectation to yield beneficial outcomes, yet their ethical implications differ, particularly concerning transparency and informed consent.

Open-label placebos (OLPs) represent an effort to address these ethical challenges by fully informing patients about the nature of the treatment they receive. By doing so, OLPs aim to enhance transparency, potentially increasing trust between patients and providers while still leveraging the beneficial psychological effects of placebo treatments.
Specifically, OLPs are prescribed transparently and honestly, allowing patients to be fully aware that they are receiving a placebo. Remarkably, patients can still experience therapeutic benefits from this approach. This shift invites a reconsideration of the essential elements that contribute to the effectiveness of a placebo, marking a transformative development in our understanding of placebo utilization in clinical practice.

8.2 The Evolution of OLP Research

Introduction

OLP research has emerged over the past decades as a transformative development in placebo science, challenging the long-held assumption that deception is necessary for placebo effects to occur. In contrast to traditional placebo intervention (where patients are unaware they are receiving an inert treatment), OLPs are given openly, with full disclosure that the treatment has no active pharmacological ingredient.

This line of research has not only expanded our understanding of the psychological and neurobiological mechanisms underlying placebo effects but also offered ethically acceptable ways to harness them in clinical practice—circumventing the need for deception. The evolution of OLP studies reflects an important paradigm shift, moving from proof-of-concept trials in highly controlled settings to more ecologically valid studies in real-world clinical populations.

1965 – 2010

The exploration of OLP research began in 1965 with the pioneering investigation of nonblind placebos by Park and Covi. This early work laid the foundation for questioning the necessity of deception in placebo administration. However, it

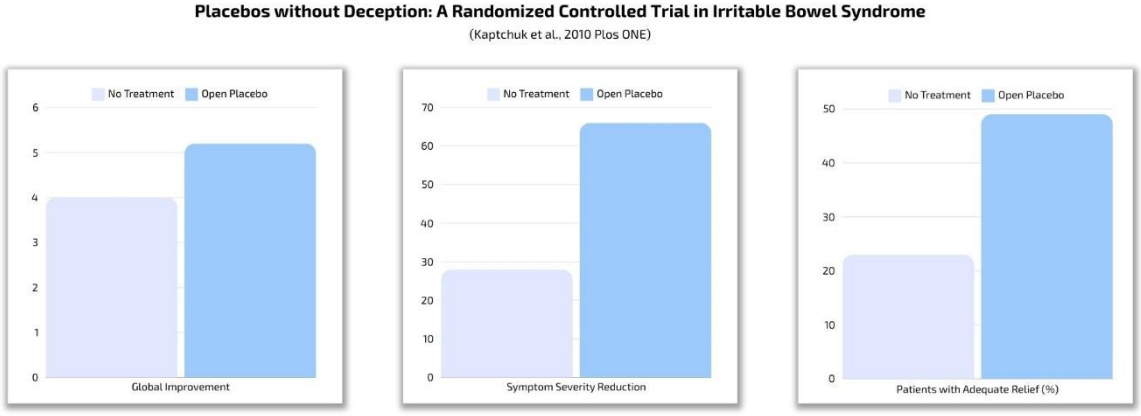
wasn't until 2008 that OLP entered the clinical spotlight, thanks to Sandler and Bodfish's innovative use of OLP as a dose-extender in children with ADHD. This study provided preliminary evidence that even when patients are aware they are taking a placebo, there can be observable therapeutic benefits.

2010

The field took a significant leap forward in 2010 when researchers of the Harvard Medical School conducted the first randomized controlled trial (RCT) specifically comparing OLP to no treatment in adults. Under the leadership of Ted Kaptchuk, the study involved 80 patients with irritable bowel syndrome (IBS), a condition notorious for its susceptibility to placebo effects. The participants were divided into two groups: one received the OLP treatment, while the other received no treatment. The OLP treatment involved taking a placebo pill twice daily for three weeks, with patients fully informed that these pills were inert. A warm patient-provider relationship was established for both groups. Clinicians did not rely on scripted or standardized dialogue when prescribing OLP. Instead, they engaged in open and honest conversations with patients, focusing on several key points (Kaptchuk et al., 2010; Kaptchuk, 2018). They emphasized the robust placebo responses observed in IBS trials while candidly admitting the uncertainty regarding the efficacy of OLP, thereby removing any associated stigma. Discussions included the neurobiological mechanisms underlying placebo effects, such as neurotransmitters and brain-gut connections, without suggesting that positive thinking was necessary for effectiveness. Patients were also encouraged to maintain a skeptical or curious attitude, allowing them to explore the treatment without the pressure of needing to believe for it to work. Additionally, patients were instructed on the importance of adhering to the pill regimen, as the benefits might manifest gradually or immediately.
This non-suggestive approach was critical in shaping subsequent OLP studies, which often adopted and standardized these discussion points. However, some researchers later incorporated elements intended to evoke positive expectations, reflecting varied interpretations and applications of the original framework.
The results were notable (Figure 8.1). Already at the midpoint of treatment, but also after the full three weeks, participants of the OLP group showed significantly higher global improvement (with large effect sizes), significantly reduced symptom severity and more adequate relief than the no-treatment group. Remarkably, 60% reported adequate relief compared to just 35% in the control group. This stark difference underscored the potential efficacy of OLP in clinical settings and challenged the deeply held belief that deception was a necessary component of the placebo effect.

Figure 8.1

Main results by Kaptchuk and collaborators (2010)



2010 – Today

Inspired by these findings, several OLP trials were carried out in the following years to investigate this novel approach in different conditions. In 2017, the first meta-analysis on the effects of OLP was conducted by Charlesworth and colleagues, consolidating the burgeoning evidence base. Today (July 2024), there are around 200 research entries on Google Scholar, reflecting the growing interest and ongoing debates regarding the mechanisms and potential for healthcare implementation of OLP. Despite the promising results, much remains to be explored and understood.

8.3 Evidence of OLP Outcomes Across Conditions

Introduction

The growing body of research into OLPs has demonstrated their potential benefits across a diverse range of conditions. The following paragraphs give an insight into clinical OLP research by presenting a selection of studies conducted across different countries and different conditions. As this selection is not a complete overview of all available data on OLP effects, the findings of meta-analyses on OLP are described afterwards.

Individual studies

Notably, in the field of IBS, the initial 2010 study by Kaptchuk et al. showed promise, and this was further supported by a larger study in 2021 by Lembo et al., involving 308 patients over six weeks, which reaffirmed a significant treatment effect on IBS severity.

In chronic low back pain, studies reported improvements in disability and pain severity (Carvalho et al., 2016; Kleine-Borgmann et al., 2019). However, another study noted that OLP provided no additional benefit when patients were already receiving comprehensive multimodal treatment (Ikemoto et al., 2020).

OLP has also demonstrated efficacy in migraine headache management. A study with 66 patients found a notable decrease in pain when OLP was administered 30 minutes after headache onset compared to untreated attacks (Kam-Hansen et al., 2014).

Research into cancer-related fatigue has consistently shown that OLP can significantly alleviate symptoms, both in cancer survivors and in patients with advanced cancer, with studies reporting effect sizes ranging from medium to large (Hoenemeyer et al., 2018; Zhou et al., 2018; Yennurajalingam, 2022).

In major depression, studies have shown mixed results. A 2012 study with 20 patients receiving two weeks of treatment with a waitlist control followed by another four weeks of OLP showed no significant treatment effect on depression severity (Kelley et al., 2012). Similarly, a 2020 study involving 38 patients over four weeks of treatment with treatment-as-usual (TAU) control and another four weeks of OLP showed no significant overall effect, but suggested OLP to be effective for patients younger than 50 years with early onset of depression (Nitzan et al., 2020). A study in 2020 with 94 patients found that OLP protected against induced sadness (Haas, Rief, Glombiewski et al., 2020).

When examining insomnia, a study (Haas, Winkler et al., 2022) involving 68 patients assessed sleep over two nights with a placebo pill before the second night. No significant effect was observed on subjective or objective sleep measures, although the study's experimental nature, rather than a clinical setting, may have influenced results.

OLP has been tested across many other conditions including allergic rhinitis (Schaefer et al., 2016; Schaefer, Zimmermann et al., 2023), menopausal hot flushes (Pan et al., 2020), knee osteoarthritis (Olliges et al., 2022), test anxiety (Schaefer et al., 2019), and ADHD (Sandler et al., 2010; Sandler & Bodfish, 2008). Sandler's work demonstrated that ADHD medication doses could be halved when OLP was introduced, maintaining stable symptom improvement. Similarly,

children with functional abdominal pain or IBS reported less abdominal pain and reduced usage of rescue medication (Nurko et al., 2022).

Meta-analyses

Meta-analyses have further analyzed the efficacy of OLP. A 2017 meta-analysis (Charlesworth et al., 2017) involving clinical samples across five studies with 260 participants showed a significant positive effect with a large effect size (SMD = 0.88, $p < .001$). A 2021 analysis (von Wernsdorff et al., 2021) of 11 studies with 654 participants confirmed this with a medium effect size (SMD = 0.72, $p < .001$). OLP effects in non- and subclinical samples were summarized by a meta-analysis across 17 studies with 1201 participants (Spille et al., 2023). Examples for conditions that have been investigated in the included studies with healthy participants are acute pain, sadness, itch, wound healing, well-being, stress, or physical performance, indicating diverse potential applications of OLP across various experimental and clinical settings. This meta-analysis found a significant effect on self-reported outcomes with a small effect size (SMD = 0.43, $p < .01$) but no significant effect on objective outcomes. This means that OLP effects seem to be more powerful in clinical than in non-clinical conditions (Box 8.1).

Box 8.1 How Strong Are Open-Label Placebo Effects?

Two recent meta-analyses have systematically assessed the effects of open-label placebos (OLPs), highlighting consistent findings across both clinical and non-clinical populations, yet with notable differences in effect size.

- **In clinical samples**, von Wernsdorff et al. (2021) reviewed randomized controlled trials involving patients with medical or psychological conditions. Their meta-analysis found a **large and significant effect** of OLPs on self-reported outcomes, with an aggregated **standardized mean difference (SMD) of 0.72**.
- **In non-clinical (healthy) samples**, Spille et al. (2023) conducted a meta-analysis of experimental studies. While OLPs were still effective, the effects were **moderate**, with a pooled **SMD of 0.43** for self-reported outcomes.

This discrepancy suggests that individuals experiencing clinical symptoms may be more susceptible to placebo effects. Why?

- In clinical settings, the **therapeutic context** is more salient, characterized by empathetic communication, trust, and hope for relief.
- Patients may have **stronger expectations and motivation** for improvement than healthy volunteers.
- The **rituals of care** and symbolic meaning of treatment might amplify OLP responses.

These findings reinforce the idea that **OLPs can be effective**, but their impact is shaped by the broader **clinical context and patient characteristics**.

Another 2023 network meta-analysis (Buergler et al., 2023) differentiated between clinical and non-clinical samples and found that only nasal OLPs (i.e., nasal sprays) were significantly better than no treatment in healthy samples, whereas only OLP pills were better than no treatment in clinical samples. However, these findings might be biased by confounding variables and need to be treated with caution. In general, the network meta-analysis confirmed the above mentioned larger OLP effects in clinical populations compared to non-clinical ones.

In summary, the evidence suggests that OLP treatments have beneficial effects for several conditions and appear to produce larger effects in clinical samples compared to non-clinical ones. However, further research is needed to understand the long-term effects of OLP and to compare their efficacy to that of conventional placebos.

8.4 Mechanisms of OLP

Introduction

Understanding the mechanisms underlying OLP is essential to advancing both theoretical models of placebo responses and their ethical application in clinical settings. Research in this area has focused on multiple, interrelated domains. Neurobiological investigations explore how brain activity and endogenous systems may be engaged even in the absence of deception. Cognitive and psychological mechanisms, such as treatment expectations, prior therapeutic experiences, and individual differences in beliefs, are also considered central to explaining OLP responses. Additionally, patient-related factors, including personality traits and emotional states, have been examined for their potential to influence responsiveness to OLPs. Finally, growing attention has been devoted to the role of healthcare providers, with studies exploring how clinicians' attitudes, verbal and nonverbal communication, and the way OLPs are presented can shape outcomes. Together, these lines of inquiry contribute to a multifaceted understanding of how open-label placebos exert their effects.

Neurobiology

Understanding how OLP works has intrigued researchers and clinicians alike. The neurobiological underpinnings of OLP reveal fascinating insights.
First, it has been found that OLP analgesia can be blocked by naloxone, an opioid antagonist, indicating that OLP shares mechanistic similarities with conventional placebo effects (Benedetti et al., 2023).

Brain imaging studies (Schaefer, Kühnel et al., 2023) have also shown that OLP administration activates areas associated with modulating affective states, such as the periaqueductal gray, bilateral anterior hippocampus, and anterior cingulate cortex. This activation is similar to that observed in conventional placebo effects. However, one notable difference lies in the prefrontal cortex, which is involved in expectancy and is activated in conventional placebo responses but not in OLP. This suggests that while positive expectations might enhance OLP's effectiveness, they are not a prerequisite.

Treatment Expectations and Experience

The role of treatment expectations in OLP is complex and varied. While certain studies, such as those involving IBS (Lembo et al., 2021), found no correlation between treatment expectancy and OLP effects, others indicated that providing a rationale for OLP could enhance its efficacy (Buergler et al., 2023). For instance, studies on acute pain relief in healthy participants showed that when a rationale was given, OLP was more successful (Locher et al., 2017).
However, the relationship between expectation and OLP does not dominate as it does with conventional placebo effects. Some studies have even observed OLP effects without any rationale or explanation, such as in migraine headaches or induced sadness in depression (Kam-Hansen et al., 2014; Haas, Rief, Glombiewski et al., 2020). This evidence suggests that while positive treatment expectations can be beneficial, OLP may operate through mechanisms that do not solely rely on expectancy.
Moreover, patients in OLP trials often mention hope rather than expectation (Kaptchuk et al., 2009; Kaptchuk, 2018; Haas, Ongaro et al., 2022). This distinction is crucial as hope implies a sense of suffering from symptoms, aligning with the finding that OLP effects tend to be more pronounced in clinical populations compared to healthy subjects.

Participants in OLP trials have shared a wide range of treatment experiences and perceptions. When interviewed, many participants reported having low treatment expectations or did not mention any expectations at all (Pan et al., 2022; Haas, Ongaro et al., 2022). Despite this, there was a common thread of hope, with individuals expressing optimism that the treatment might offer some benefit (Pan et al., 2022; Haas, Ongaro et al., 2022). Curiosity also played a significant role, as several participants indicated an openness and willingness to "see what happens" with this novel approach (Haas, Ongaro et al., 2022; Pan et al., 2022). However, ambivalence was not uncommon, with some participants expressing skepticism or mixed feelings about the treatment's potential efficacy (Haas, Ongaro et al., 2022). These trials also prompted participants to reflect on their cognitive and emotional processes, offering a unique opportunity for introspection (Haas, Ongaro et al., 2022). Moreover, the OLP treatment seemed to

foster a sense of proactivity and empowerment, enhancing participants' overall sense of control over their health and treatment journey (Pan et al., 2022; Haas, Ongaro et al., 2022).

Patients' Psychological Factors

Before an implementation of OLP into healthcare can be considered, it is important to begin to understand potential patient-level characteristics that may predict response to OLP treatment. Unlike conventional placebos, where personality traits such as optimism and positive thinking play significant roles (see Module 5), OLP effects appear less influenced by these factors (Locher et al., 2019; Zhou et al., 2018; Ballou et al., 2022). Exploratory studies suggest that patients' active engagement in OLP treatment is more crucial than passive commitment, which is often sufficient for blinded placebo efficacy (Ballou et al., 2022; Haas, Ongaro et al., 2022).
Acceptability of OLP is another critical dimension for a potential future application in practice. Laypersons tend to find OLP an acceptable treatment under certain circumstances, primarily driven by its anticipated effectiveness and perceived plausibility (Hull et al., 2013; Haas, Rief, & Doering, 2020; Schienle & Seibel, 2024). However, OLP is often viewed as less effective compared to deceptive placebos. Participants in OLP trials highlight the importance of trust in healthcare professionals, perceived treatment effectiveness, and minimized treatment risks, which are seen as significant advantages over conventional medication (Locher et al., 2021; Druart et al., 2022).

Physicians' Attitudes

Physicians' attitudes towards OLP have not yet been investigated sufficiently. The findings of a study that surveyed orthopedic surgeons indicate that while a majority of participating physicians consider OLP ethical, fewer believe it to be effective, and even fewer would consider prescribing it (Bernstein et al., 2021). This gap underscores the need for greater awareness and education among healthcare professionals about the potential benefits and ethical nature of OLP.

8.5 Conclusion

Several hurdles remain in the path of widespread healthcare implementation of OLP. Key questions include understanding the precise mechanisms of OLP, identifying predictors of its efficacy, determining who is likely to benefit most, and developing standardized yet flexible prescription methods. Addressing these challenges through comprehensive research and pragmatic clinical trials will be essential for integrating OLP into mainstream healthcare practice.

OLP represents a promising frontier in ethical medical treatment, offering substantial benefits without the ethical baggage of deception. The evidence, though still evolving, indicates that OLP can effectively manage a range of clinical conditions where elective treatments are not available. As research continues to unravel the mechanisms and optimization of OLP, it holds the potential to revolutionize patient care by harnessing the power of the mind in an open, transparent, and ethically sound manner.

References

Ballou, S., Haas, J. W., Iturrino, J., Nee, J., Kirsch, I., Rangan, V., Cheng, V., Lembo, A., Kaptchuk, T. J., & Kelley, J. M. (2022). Psychological Predictors of Response to Open-Label Versus Double-Blind Placebo in a Randomized Controlled Trial in Irritable Bowel Syndrome. *Psychosomatic Medicine*, *84*(6), 738–746. https://doi.org/10.1097/PSY.0000000000001078

Benedetti, F., Shaibani, A., Arduino, C., & Thoen, W. (2023). Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *PAIN*, *164*(5). https://journals.lww.com/pain/fulltext/2023/05000/open_label_nondeceptive_placebo_analgesia_is.7.aspx

Bernstein, M. H., Rosenfield, M., Fuchs, N., Magill, M., Blease, C. R., Beaudoin, F. L., Rich, J. D., Wartolowska, K., & Terek, R. M. (2021). How orthopedic surgeons view open label placebo pills: Ethical and effective, but opposed to personal use. *Journal of Psychosomatic Research*, *151*, 110638. https://doi.org/https://doi.org/10.1016/j.jpsychores.2021.110638

Buergler, S., Sezer, D., Gaab, J., & Locher, C. (2023). The roles of expectation, comparator, administration route, and population in open-label placebo effects: a network meta-analysis. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-39123-4

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics*, *85*(5), 270–288. https://doi.org/10.1159/000447034

Charlesworth, J. E. G., Onakpoya, I., Petkovic, G., Kelley, J. M., Hunter, M., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*, 97–107. https://doi.org/10.1111/jebm.12251

Druart, L., Vauthrin, O., Pinsault, N., Locher, C., & Blease, C. (2023). 'It's not my greengrocer, it's someone from the medical profession': A qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France. *British Journal of Health Psychology*, *28*(2), 273–290. https://doi.org/10.1111/bjhp.12624

Fässler, M., Meissner, K., Schneider, A., & Linde, K. (2010). Frequency and circumstances of placebo use in clinical practice - a systematic review of empirical studies. *BMC Medicine*, *8*, 15. https://doi.org/10.1186/1741-7015-8-15

Haas, J. W., Ongaro, G., Jacobson, E., Conboy, L. A., Nee, J., Iturrino, J., Rangan, V., Lembo, A., Kaptchuk, T. J., & Ballou, S. (2022). Patients' experiences treated with open-label placebo versus double-blind placebo: a mixed methods qualitative study. *BMC Psychology*, *10*(1). https://doi.org/10.1186/s40359-022-00731-w

Haas, J. W., Rief, W., & Doering, B. K. (2020). Open-Label Placebo Treatment: Outcome Expectations and General Acceptance in the Lay Population.

International Journal of Behavioral Medicine. https://doi.org/10.1007/s12529-020-09933-1

Haas, J. W., Rief, W., Glombiewski, J. A., Winkler, A., & Doering, B. K. (2020). Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *Journal of Affective Disorders*, *274*, 920–928. https://doi.org/10.1016/j.jad.2020.05.056

Haas, J. W., Winkler, A., Rheker, J., Doering, B. K., & Rief, W. (2022). No open-label placebo effect in insomnia? Lessons learned from an experimental trial. *Journal of Psychosomatic Research*, *158*. https://doi.org/10.1016/j.jpsychores.2022.110923

Hoenemeyer, T. W., Kaptchuk, T. J., Mehta, T. S., & Fontaine, K. R. (2018). Open-label placebo treatment for cancer-related fatigue: A randomized-controlled clinical trial. *Scientific Reports*, *8*, 2784. https://doi.org/10.1038/s41598-018-20993-y

Hull, S. C., Colloca, L., Avins, A., Gordon, N. P., Somkin, C. P., Kaptchuk, T. J., & Miller, F. G. (2013). Patients' attitudes about the use of placebo treatments: Telephone survey. *BMJ (Online)*, *347*(7915), 1–9. https://doi.org/10.1136/bmj.f3757

Ikemoto, T., Ueno, T., Arai, Y. C., Wakao, N., Hirasawa, A., Hayashi, K., & Deie, M. (2020). Open-Label Placebo Trial among Japanese Patients with Chronic Low Back Pain. *Pain Research and Management*, *2020*, 6636979. https://doi.org/10.1155/2020/6636979

Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine*, *6*(218), 1–9. https://doi.org/10.1126/scitranslmed.3006175

Kaptchuk, T. J. (2018). Open-label placebo: Reflections on a research agenda. *Perspectives in Biology and Medicine*, *61*(3), 311–334. https://doi.org/10.1353/pbm.2018.0045

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE*, *5*(12), e15591. https://doi.org/10.1371/journal.pone.0015591

Kaptchuk, T. J., Shaw, J., Kerr, C. E., Conboy, L. A., Kelley, J. M., Csordas, T. J., Lembo, A. J., & Jacobson, E. E. (2009). "Maybe I made up the whole thing": Placebos and patients' experiences in a randomized controlled trial. *Culture, Medicine and Psychiatry*, *33*(3), 382–411. https://doi.org/10.1007/s11013-009-9141-7

Kelley, J. M., Kaptchuk, T. J., Cusin, C., Lipkin, S., & Fava, M. (2012). Open-label placebo for major depressive disorder: A pilot randomized controlled trial. *Psychotherapy and Psychosomatics*, *81*(5), 5–8. https://doi.org/10.1159/000337053

Kleine-Borgmann, J., Schmidt, K., Hellmann, A., & Bingel, U. (2019). Effects of open-label placebo on pain, functional disability, and spine mobility in patients with

chronic back pain: a randomized controlled trial. *Pain*, *160*(12), 2891–2897. https://doi.org/10.1097/j.pain.0000000000001683

Lembo, A., Kelley, J. M., Nee, J., Ballou, S., Iturrino, J., Cheng, V., Rangan, V., Katon, J., Hirsch, W., Kirsch, I., Hall, K., Davis, R. B., & Kaptchuk, T. J. (2021). Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. *Pain*, *162*(9), 2428–2435. https://doi.org/10.1097/j.pain.0000000000002234

Linde, K., Atmann, O., Meissner, K., Schneider, A., Meister, R., Kriston, L., & Werner, C. (2018). How often do general practitioners use placebos and non-specific interventions? Systematic review and meta-analysis of surveys. *PLoS ONE*, *13*(8), 1–15. https://doi.org/10.1371/journal.pone.0202211

Linde, K., Fässler, M., & Meissner, K. (2011). Placebo interventions, placebo effects and clinical practice. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366*(1572), 1905–1912. https://doi.org/10.1098/rstb.2010.0383

Locher, C., Buergler, S., Frey Nascimento, A., Kost, L., Blease, C., & Gaab, J. (2021). Lay perspectives of the open-label placebo rationale: A qualitative study of participants in an experimental trial. *BMJ Open*, *11*(8). https://doi.org/10.1136/bmjopen-2021-053346

Locher, C., Frey Nascimento, A., Kossowsky, J., Meyer, A., & Gaab, J. (2019). Open-label placebo response – Does optimism matter? A secondary-analysis of a randomized controlled trial. *Journal of Psychosomatic Research*, *116*, 25–30. https://doi.org/10.1016/j.jpsychores.2018.11.009

Locher, C., Nascimento, A. F., Kirsch, I., Kossowsky, J., Meyer, A., & Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, *158*(12), 2320–2328. https://doi.org/10.1097/j.pain.0000000000001012

Louhiala, P. (2012). What do we really know about the deliberate use of placebos in clinical practice?. *Journal of Medical Ethics, 38*(7), 403-405. https://doi.org/10.1136/medethics-2011-100420

Nitzan, U., Carmeli, G., Chalamish, Y., Braw, Y., Kirsch, I., Shefet, D., Krieger, I., Mendlovic, S., Bloch, Y., & Lichtenberg, P. (2020). Open-label placebo for the treatment of unipolar depression: Results from a randomized controlled trial. *Journal of Affective Disorders*, *276*, 707–710. https://doi.org/10.1016/j.jad.2020.07.077

Nurko, S., Saps, M., Kossowsky, J., Zion, S. R., Di Lorenzo, C., Vaz, K., Hawthorne, K., Wu, R., Ciciora, S., Rosen, J. M., Kaptchuk, T. J., & Kelley, J. M. (2022). Effect of Open-label Placebo on Children and Adolescents With Functional Abdominal Pain or Irritable Bowel Syndrome: A Randomized Clinical Trial. *JAMA Pediatrics*, *176*(4), 349–356. https://doi.org/10.1001/jamapediatrics.2021.5750

Olliges, E., Stroppe, S., Haile, A., Reiß, F., Malhis, M., Funke, S. A., & Meissner, K. (2022). Open-Label Placebo Administration Decreases Pain in Elderly Patients

With Symptomatic Knee Osteoarthritis – A Randomized Controlled Trial. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.853497

Pan, Y., Frank, M. L., Kaptchuk, T. J., & Nestoriuc, Y. (2022). "Let's see what happens:"-Women's experiences of open-label placebo treatment for menopausal hot flushes in a randomized controlled trial. *PLoS ONE*, *17*(11 November). https://doi.org/10.1371/journal.pone.0276499

Pan, Y., Meister, R., Löwe, B., Kaptchuk, T. J., Buhling, K. J., & Nestoriuc, Y. (2020). Open-label placebos for menopausal hot flushes: a randomized controlled trial. *Scientific Reports*, *10*, 20090. https://doi.org/10.1038/s41598-020-77255-z

Park, L. C., & Covi, L. (1965). Nonblind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. *Archives of general psychiatry, 12*(4), 336-345. https://psycnet.apa.org/doi/10.1001/archpsyc.1965.01720340008002

Sandler, A. D., & Bodfish, J. W. (2008). Open-label use of placebos in the treatment of ADHD: A pilot study. *Child: Care, Health and Development*, *34*(1), 104–110. https://doi.org/10.1111/j.1365-2214.2007.00797.x

Sandler, A. D., Glesne, C. E., & Bodfish, J. W. (2010). Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder?. *Journal of Developmental & Behavioral Pediatrics, 31*(5), 369-375. https://doi.org/10.1097/dbp.0b013e3181e121ed

Schaefer, M., Denke, C., Harke, R., Olk, N., Erkovan, M., & Enge, S. (2019). Open-label placebos reduce test anxiety and improve self-management skills: A randomized-controlled trial. *Scientific Reports*, *9*(1), 2–7. https://doi.org/10.1038/s41598-019-49466-6

Schaefer, M., Harke, R., & Denke, C. (2016). Open-label placebos improve symptoms in allergic rhinitis: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *85*, 373–374. https://doi.org/10.1159/000447242

Schaefer, M., Kühnel, A., Schweitzer, F., Enge, S., & Gärtner, M. (2023). Neural underpinnings of open-label placebo effects in emotional distress. *Neuropsychopharmacology*, *48*(3), 560–566. https://doi.org/10.1038/s41386-022-01501-3

Schaefer, M., Zimmermann, K., & Enck, P. (2023). A randomized controlled trial of effects of open-label placebo compared to double-blind placebo and treatment-as-usual on symptoms of allergic rhinitis. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-34790-9

Schienle, A., & Seibel, A. (2024). Would You Take an Open-Label Placebo Pill or Give One to Your Child? Findings from a Cross-Sectional Survey. *Psychology Research and Behavior Management*, *17*, 393–400. https://doi.org/10.2147/PRBM.S439783

Spille, L., Fendel, J. C., Seuling, P. D., Göritz, A. S., & Schmidt, S. (2023). Open-label placebos—a systematic review and meta-analysis of experimental studies

with non-clinical samples. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-30362-z

Tilburt, J. C., Emanuel, E. J., Kaptchuk, T. J., Curlin, F. A., & Miller, F. G. (2008). Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. *BMJ*, 337. https://doi.org/10.1136/bmj.a1938

von Wernsdorff, M., Loef, M., Caffier, B. T., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. *Scientific Reports*, *11*, 3855. https://doi.org/10.1038/s41598-021-83148-6

Yennurajalingam, S., Azhar, A., Lu, Z., Rodriguez, A. J., Arechiga, A. B., Guerra-Sanchez, M., Stanton, P., Andersen, C. R., Urbauer, D. L., & Bruera, E. (2022). Open-Label Placebo for the Treatment of Cancer-Related Fatigue in Patients with Advanced Cancer: A Randomized Controlled Trial. *Oncologist*, *27*(12), 1081–1089. https://doi.org/10.1093/oncolo/oyac184

Zhou, E. S., Hall, K. T., Michaud, A. L., Blackmon, J. E., Partridge, A. H., & Recklitis, C. J. (2018). Open-label placebo reduces fatigue in cancer survivors: A randomized trial. *Supportive Care in Cancer*, *27*, 2179–2187. https://doi.org/10.1007/s00520-018-4477-6