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The Placebo Effect in Mental Health: Psychological, Neurobiological, and Ethical Aspects

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Abstract

The placebo effect is a psychobiological phenomenon in which patients' expectations, prior experiences, and social context influence health outcomes, even in the absence of active pharmacological treatment. Key mechanisms include expectancy, verbal suggestion, classical conditioning, and social-contextual factors, underpinned by neurobiological processes involving endogenous opioids, dopamine, and related neural circuits. In mental health and psychotherapy, placebo effects are particularly relevant, as the therapeutic alliance, empathy, and belief in treatment can significantly enhance outcomes. Ethical applications such as open-label and dose-extending placebos preserve patient autonomy while leveraging expectancy and learning to improve clinical results. Recognizing and integrating placebo mechanisms into clinical practice highlights the interaction of psychological, neurobiological, and ethical factors, offering a holistic approach to treatment and enhancing therapy outcomes in conditions like depression, anxiety, and chronic pain.

Key words: placebo effect, neurobiological aspects, psychological mechanisms, mental health, psychotherapy

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Introduction

The placebo effect is a well-documented phenomenon in which patients' expectations and perceptions can influence health outcomes, with important implications for psychology, neurobiology, and clinical practice. A placebo is an inert treatment intended to elicit a psychological or physiological response. The placebo effect refers to the measurable improvement in health outcomes due to such interventions, whereas the placebo response describes an individual's reaction to the treatment. In contrast, the nocebo effect occurs when negative expectations exacerbate symptoms (1).

The term "placebo" comes from the Latin word meaning "I will please," and in the Middle Ages it was used to describe fake treatments given to comfort patients. Historically, inert treatments have been used since ancient times, with scientific attention renewed in the 1940s following Henry Beecher's influential work (2–5). Typical examples include saline injections and sugar pills, which illustrate how expectancy can modulate outcomes (6).

Long regarded as a confounding factor in research, the placebo effect is increasingly recognized as a powerful modulator of treatment outcomes, especially in psychological domains. Placebo responses can be induced through verbal suggestion, prior experience, or conditioning, underscoring their role as determinants of health (7). Conditions especially sensitive to placebo effects include chronic pain, depression, anxiety, and migraines, reflecting the strong influence of subjective symptom reporting and patient expectations (1, 8).

Placebo responses are not always beneficial. The nocebo effect arises when negative expectations exacerbate symptoms or trigger adverse reactions. Both phenomena share similar psychological and neurobiological mechanisms, but in contrast, placebo responses confer benefit and nocebo effects may cause harm (9, 10).

From a psychological perspective, the placebo effect is not merely a "sham" intervention, but a complex psychobiological response shaped by anticipation, verbal framing, conditioning, and the therapeutic context. Mental disorders are particularly sensitive to placebo effects because symptom perception is largely subjective, and therapeutic outcomes are strongly influenced by patient expectations, therapist interaction, and the therapeutic context. Psychotherapy and psychiatric practice illustrate this significance, as patient expectations and the therapeutic alliance often determine clinical outcomes (11). Remarkably, even "open-label placebos," where patients are informed they are receiving an inert treatment, can elicit measurable clinical improvements when presented in a supportive context (12).

Accordingly, the placebo effect represents a bridge between biological and psychological processes, but also between scientific research and clinical practice. This narrative review aims to synthesize current evidence on psychological and neurobiological mechanisms underlying placebo effects, examine their relevance in psychotherapy and mental health interventions, and outline key ethical considerations related to their clinical use.

Methods

A comprehensive literature search was conducted to summarize current knowledge on the placebo effect and its underlying psychological and neurobiological mechanisms, with a particular focus on mental health and psychotherapy. Relevant articles were identified through a systematic search of the PubMed database covering the period from January 2010 to January 2025. The search combined keywords such as “placebo effect,” “psychological mechanisms,” “neurobiological aspects,” “mental health,” “psychotherapy,” “open-label placebo,” and “dose-extending placebo.” To ensure thoroughness, reference lists of selected articles were also screened for additional relevant studies.

Titles and abstracts were independently screened by multiple authors for relevance, and full-text articles were assessed according to the predefined inclusion criteria. The selected studies focused on placebo mechanisms in mental health interventions, explored psychological, neurobiological, or ethical aspects, and reported a clear study design and outcomes. The studies that were excluded were those lacking methodological transparency, non-peer-reviewed sources, animal studies without direct clinical relevance, and publications not related to mental health or psychotherapy.

Although this review is narrative in nature, methodological rigor was maintained to enhance transparency and reproducibility. Efforts were made to critically evaluate each study’s design, sample size, and reported outcomes, rather than simply summarizing prior reviews. Ultimately, 31 studies were included, representing a combination of original research and literature reviews that collectively informed our understanding of psychological and neurobiological mechanisms, clinical applications, and ethical considerations surrounding placebo interventions in mental health.

Contribution to Existing Literature

While numerous reviews have examined placebo effects from either neurobiological or clinical perspectives, this review uniquely integrates psychological mechanisms, neuroscientific evidence, and ethical considerations within a single mental health-focused framework. It explicitly connects placebo research with psychotherapeutic processes, emphasizing therapeutic alliance, expectancy, and learning as shared mechanisms across treatment modalities. In contrast to reviews centered on pharmacological trials, this article foregrounds ethically transparent applications, including open-label and dose-extending placebos, in psychotherapy and mental health care. By situating placebo mechanisms within real-world clinical interactions rather than solely experimental paradigms, this review advances a clinically applicable and ethically grounded perspective on placebo-informed mental health interventions.

Psychological and Neurobiological Mechanisms of the Placebo Effect

Placebo effects arise from the interplay of psychological and neurobiological factors. Figure 1 illustrates an integrated model of placebo mechanisms in mental health

treatment, highlighting the interaction between contextual factors, psychological and neurobiological processes, and therapeutic outcomes.

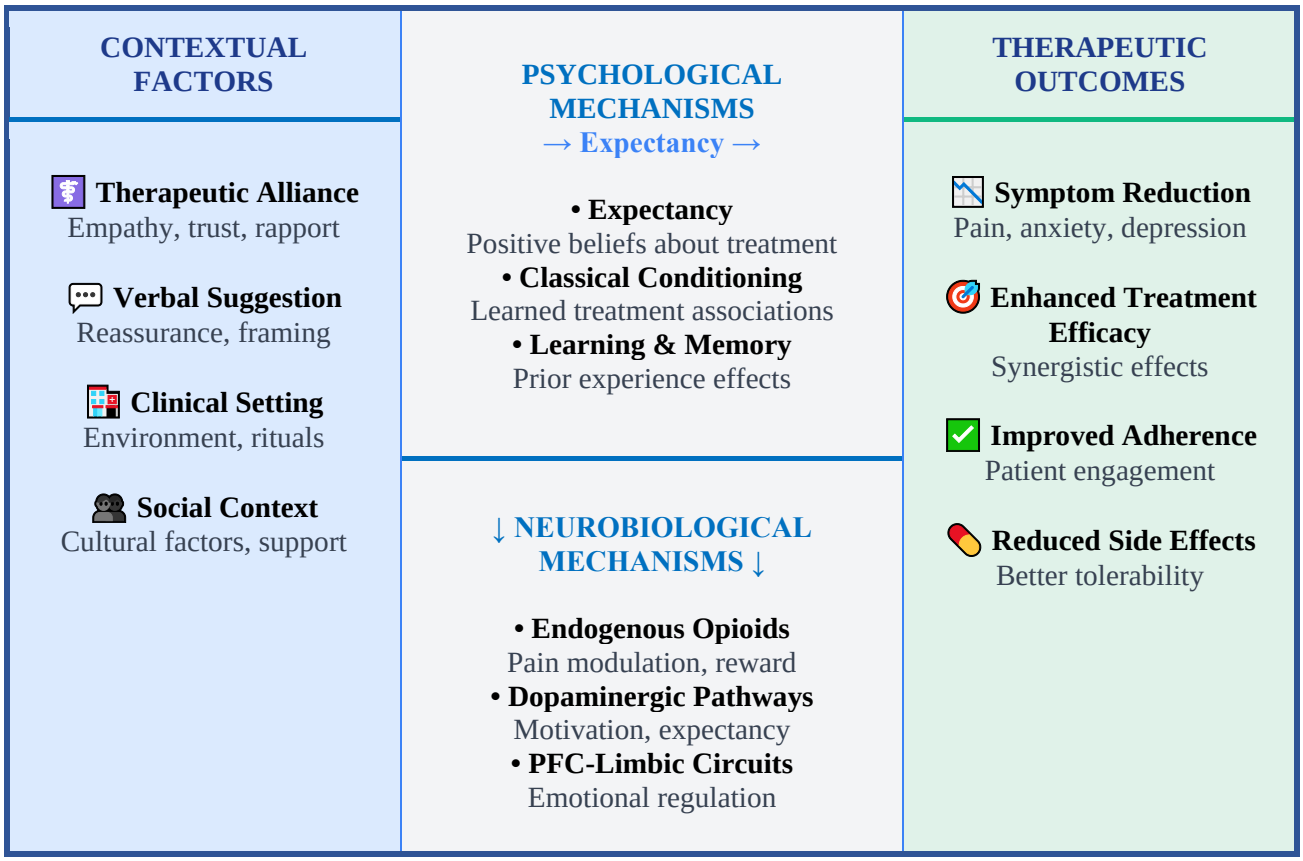

Figure 1. Integrated model of placebo mechanisms and therapeutic outcomes in mental health
Slika 1. Integrisani model placebo mehanizama i terapijskih ishoda u mentalnom zdravlju

While Figure 1 illustrates the dynamic interaction between contextual, psychological, and neurobiological factors, a more detailed overview of the individual mechanisms involved in the placebo effect is provided in Table I.

Table I Psychological and Neurobiological Mechanisms of the Placebo Effect

Tabela I Psihološki i neurobiološki mehanizmi placebo efekta

Mechanism	Description	Key Findings / Examples
Expectancy	Patient beliefs about treatment efficacy influence symptom perception	Pain reduction via anticipation of relief
Verbal suggestion	Clinician communication reinforces expectations	Improved anxiety or mood after positive framing
Classical conditioning	Learned associations with active treatments trigger responses	Inert pills producing analgesia
Social/contextual	Therapeutic environment, empathy, rituals	Enhanced outcomes in psychotherapy
Endogenous opioids	Activation of opioid pathways mediates analgesia	Naloxone reverses placebo analgesia
Dopaminergic system	Reward pathways enhance motor and cognitive functions	Dopamine release in Parkinson's disease

Psychological Mechanisms

From a psychological perspective, the placebo effect is primarily shaped by cognitive and social processes. The main mechanisms include expectancy, verbal suggestion, and classical conditioning, each contributing uniquely to symptom improvement. Expectancy refers to patients' beliefs and predictions regarding the efficacy of a treatment. Positive expectations can directly influence symptom perception, leading to reductions in pain, anxiety, or other distressing symptoms, even in the absence of active pharmacological agents (13). This mechanism operates through both conscious awareness and implicit cognitive processes, highlighting the complexity of mind–body interactions (2, 14).

Verbal suggestion involves information, reassurance, or framing provided by the clinician. Effective communication can strengthen patient confidence, enhance positive expectations, and facilitate symptom improvement. Verbal suggestion often interacts with expectancy, amplifying its effects by creating a psychologically supportive context (14).

Classical conditioning refers to learned associations between previously effective treatments and symptom relief. Repeated exposure to active interventions can establish automatic responses, such that inert treatments resembling the original intervention can evoke similar physiological or psychological improvements. Conditioning interacts with expectancy and verbal suggestion to produce robust placebo responses (15). Patient–clinician relationship ("placebo amplifier") plays a pivotal role in modulating placebo

effects. Empathy, trust, and therapeutic alliance significantly influence outcomes by enhancing expectancy and reinforcing conditioned responses. The quality of interpersonal interactions, including supportive and reassuring communication, can substantially amplify placebo effects, particularly in psychotherapeutic contexts (16).

Individual differences and contextual factors further shape placebo responsiveness. Personality traits such as optimism, suggestibility, and emotional stability, prior experiences with treatments, and cultural background can determine both the magnitude and duration of placebo responses. Contextual variables, including the therapeutic setting, ritualized procedures, and social cues, also modify outcomes by reinforcing expectations and conditioning processes (9).

Finally, the social and contextual aspects of care, including the therapeutic environment, the clinician's empathy, and the quality of the patient–practitioner relationship, significantly influence placebo outcomes. The symbolic significance of medical rituals and the relational framework of treatment can improve therapeutic effectiveness (16, 17).

Although expectancy and conditioning are well-established mechanisms, their relative contribution varies considerably across individuals and clinical contexts. Many studies rely on short-term experimental designs, which limits conclusions regarding the long-term clinical relevance and stability of placebo effects in real-world therapeutic settings.

Neurobiological Mechanisms

Placebo effects are grounded in well-characterized neurobiological pathways, in which psychological factors such as expectancy, learning, and social context translate into measurable changes in brain activity and neurotransmitter release (2, 6). Key brain regions involved include the prefrontal cortex (PFC), responsible for expectation and cognitive control; the anterior cingulate cortex (ACC), which modulates attention and affective aspects of pain; the nucleus accumbens, central to reward and motivation; the amygdala, critical for emotional processing; and the periaqueductal gray (PAG), essential for descending pain modulation (6, 18–21).

Neurotransmitter systems play a central role in mediating placebo responses. Endogenous opioids contribute to analgesic effects and can be blocked by naloxone, highlighting their role in placebo analgesia (17, 20). Dopaminergic pathways, particularly in reward-related regions such as the nucleus accumbens, mediate motor and motivational aspects of placebo responses, for example in Parkinson's disease (18, 19). In addition, the endocannabinoid system has been implicated in the modulation of pain and stress during placebo interventions (6).

Placebo responses are condition-specific. For example, placebo analgesia predominantly engages endogenous opioids and PAG circuits, whereas antidepressant placebo responses activate prefrontal-limbic circuits, including PFC, ACC, amygdala,

and nucleus accumbens (6, 11, 12). These examples demonstrate that placebo effects can act concurrently with active treatments, contributing to overall therapeutic efficacy.

The nocebo effect involves similar brain regions and neurotransmitter systems but in the opposite direction. Anticipation of negative outcomes increases activity in ACC, amygdala, and insula, and triggers the release of stress-related neurotransmitters, resulting in symptom exacerbation (9, 10). Thus, while placebo and nocebo effects share overlapping neural circuitry, the valence of expectations (positive vs. negative) determines whether the outcome is beneficial or harmful.

Taken together, these findings highlight the integrative nature of mind–brain interactions, showing that placebo responses arise from a dynamic interplay between psychological processes, neural circuits, and neurochemical systems. This perspective provides a neurobiological foundation for ethically leveraging placebo mechanisms in clinical and psychotherapeutic interventions (6, 18, 19).

Placebo in Psychotherapy and Mental Health

In psychotherapy and mental health, placebo mechanisms play a significant role due to the central importance of patient expectations, beliefs, and the therapeutic alliance. Psychotherapy, in contrast to pharmacological interventions, is based on verbal communication, symbolic processes, and the quality of the patient–therapist relationship, all of which overlap with mechanisms underlying placebo responses (11, 22). A central factor in psychotherapy is the therapeutic alliance, often regarded as one of the strongest predictors of clinical improvement across different modalities. Empathy, trust, and positive regard from the therapist can shape patient expectations and thereby enhance symptom reduction, mirroring the mechanisms of placebo responses. Similarly, the framing of therapeutic interventions, reinforcement of progress, and provision of hope contribute to beneficial outcomes beyond the specific techniques applied (23).

Clinical studies comparing placebo to psychopharmacological agents, particularly antidepressants, show that a substantial proportion of symptom improvement in mild-to-moderate depression can be attributed to placebo responses, while the pharmacological effect becomes more pronounced in severe depression. Pharmacological agents are required to demonstrate efficacy above placebo through standardized clinical trial designs, including double-blind, placebo-controlled protocols and validated outcome measures such as the HAM-D or MADRS scales. These findings contextualize the magnitude of placebo effects and underscore their relevance in understanding therapeutic outcomes (1, 11, 24).

Recent evidence also highlights the potential of open-label placebos in mental health interventions. Research has demonstrated that if an intervention is offered within a therapeutic framework that is both supportive and credible, symptom improvement can still occur even when patients are informed they are receiving an inert treatment (24–26). This discovery challenges the assumption that deception is necessary for placebo effects and opens opportunities for ethical integration of placebo mechanisms into psychotherapy.

Translating placebo research into clinical practice presents several challenges. Individual variability in response is influenced by biological factors, such as genetic predispositions and neurochemical differences (including endogenous opioid and non-opioid mechanisms), as well as psychological factors, including personality traits, prior experiences, and expectations (6, 13, 27). Contextual factors, such as the quality of the therapeutic alliance, communication style, and treatment setting, further modulate outcomes. Consequently, while experimental studies show the potential of placebo mechanisms, their expression in real-world clinical settings may vary widely among patients. Recognizing and ethically leveraging these mechanisms requires careful consideration of these individual differences to optimize treatment outcomes.

Overall, the convergence of psychotherapeutic procedures and placebo mechanisms emphasizes that placebo effects should be viewed as integral components of mental health treatment outcomes rather than as confounding factors. Using these systems in a morally and openly responsible way can improve treatment outcomes and support more comprehensive care models (11, 28, 29). Despite strong evidence supporting the overlap between placebo mechanisms and psychotherapeutic processes, conceptual challenges remain in distinguishing specific treatment effects from contextual and relational influences, highlighting the need for integrative models that acknowledge both technique-specific and common therapeutic factors.

Ethical Integration of Placebo Mechanisms in Clinical and Psychological Practice

Important ethical questions are brought up by our expanding knowledge of placebo mechanisms in both pharmacological and psychotherapeutic contexts. Even though placebo effects can improve treatment results, their application must strike a balance between patient autonomy, transparency, and clinical benefit. Historically, deceptive placebo use was widespread; for example, in 1807, Thomas Jefferson noted that one of the most successful physicians "used more bread pills, drops of colored water, and powder of hickory ashes, than of all other medication put together," describing the practice as a "pious fraud". Similar practices persisted into the 20th century, reflecting a long-standing tension between clinical pragmatism and ethical transparency (30, 31).

Contemporary research demonstrates that open-label placebos, where patients are informed about the inert nature of the intervention, can still produce meaningful clinical improvements when framed within a supportive therapeutic context (25, 26).

Research indicates that placebo-related practices, particularly the use of so-called "impure placebos," remain common in modern clinical practice. In the United States, 46–58% of internists and rheumatologists reported prior prescription of placebo-related interventions (32). In a cross-sectional mailed survey of 1,200 practicing physicians, 679 (57%) responded. About half of the respondents reported regularly prescribing pharmacologically active treatments in contexts where non-specific therapeutic effects were expected to contribute to clinical improvement, most commonly over-the-counter analgesics (41%) and vitamins (38%), while only a small proportion used saline (3%) or

sugar pills (2%). A minority reported prescribing antibiotics (13%) and sedatives (13%) in situations where their specific efficacy for the treated condition was uncertain. The majority (62%) considered the practice ethically permissible. Physicians most often described placebo treatments to patients as potentially beneficial medicines not typically used for the patients' conditions (68%), and rarely explicitly identified them as placebos (5%) (32).

Similarly, surveys of UK general practitioners revealed that placebo use is widespread, with 97% reporting administration of placebos at least once in their career, and 77% using them at least weekly (33). In a web-based survey of 1,715 general practitioners, 783 (46%) responded. The study distinguished between "pure" placebos, such as sugar pills or saline injections, and "impure" placebos, including interventions with known efficacy for certain conditions, but prescribed for ailments where their benefit is uncertain, such as antibiotics for suspected viral infections. Only 12% of the respondents had ever used pure placebos, while nearly all (97%) had used impure placebos. Weekly use of pure placebos was rare (1%), but impure placebos were employed weekly by 77% of the respondents. Most physicians considered placebo use ethically permissible in certain circumstances (66% for pure, 84% for impure placebos) (33).

These findings collectively highlight the persistent clinical relevance of placebo mechanisms, the widespread and varied use of both pure and impure placebos in practice, and the need for ongoing ethical guidance and further research to clarify benefits, harms, and cost-effective implementation strategies (32, 33).

Ethically integrating placebo mechanisms involves leveraging expectation, suggestion, and learning processes without compromising informed consent. Clinicians can enhance positive outcomes by fostering therapeutic alliance, providing credible explanations for interventions, and reinforcing adaptive behaviors, all while maintaining patient trust. This approach aligns with contemporary bioethical principles, emphasizing beneficence, autonomy, and non-maleficence (34).

Furthermore, strategically harnessing placebo mechanisms offers opportunities to optimize treatment efficacy, especially in conditions with a strong subjective component, such as pain, and anxiety. By ethically leveraging the psychological and neurobiological underpinnings of placebo responses, through expectation, conditioning, and social-contextual modulation, clinicians can create synergistic effects that complement active interventions, ultimately supporting more holistic and patient-centered care (11, 23).

Bridging Standard, Open-Label, and Dose-Extending Placebos

Recent evidence demonstrates that open-label and dose-extending placebos can produce meaningful clinical, behavioral, and biological outcomes without relying on deception. Open-label placebos, administered with full patient awareness, capitalize on expectation and conditioning within a supportive context, while preserving ethical transparency. Dose-extending placebos, given alongside active medications, can enhance therapeutic efficacy, reduce side effects, and support treatment adherence (35, 36).

Placebo Mechanisms in Mental Health: Future Directions and Clinical Integration

Recent developments in the study of placebo highlight its potential as a game-changing intervention for mental health treatment. With the goal of creating predictive models that can tailor interventions, future research should examine the interactions between unique cognitive, emotional, and neurobiological factors that affect placebo responsiveness. Studies on open-label and dose-extending placebos, which ethically use expectancy and conditioning to improve therapeutic results while preserving patient autonomy, are especially encouraging (36).

These approaches illustrate that placebo mechanisms can be harnessed deliberately to complement standard interventions, aligning clinical benefit with patient autonomy. Clinicians can ethically improve outcomes and provide opportunities for pragmatic studies to assess large-scale efficacy by incorporating open-label and dose-extending modalities into psychotherapy and medical practice. According to this perspective, placebo effects are intentionally and ethically used medicinal enhancers rather than confounding artifacts (36).

Recent original clinical and experimental studies support the integration of placebo mechanisms into mental health care strategies. In a randomized controlled trial, adjunctive open-label placebo combined with cognitive-behavioral therapy yielded greater reductions in depressive symptoms compared to CBT alone in adults with major depressive disorder, illustrating the potential of ethically applied placebo strategies in mood disorders (25). Emerging feasibility data further show beneficial effects of open-label placebo on fatigue in neurological populations, underscoring the broader applicability of expectancy-based interventions (37). Experimental evidence also indicates that psychological framing can enhance the effectiveness of standard treatments on sickness behavior and affective symptoms, highlighting the relevance of expectancy modulation in clinical outcomes (38). Additionally, recent meta-analytic work quantifying placebo responses across anxiety, obsessive-compulsive, and stress-related disorders emphasizes meaningful placebo contributions in psychiatric research and identifies moderators of placebo responsiveness (39). Collectively, these findings underscore the capacity of placebo-informed strategies to complement existing mental health interventions.

Placebo mechanisms can be strategically incorporated into psychotherapy to enhance the impact of evidence-based interventions. Utilizing expectation, learning, and social-contextual processes for clinical advantage can be achieved by strengthening the patient–therapist relationship, framing interventions with hope and credibility, and rewarding adaptive behaviors. These effects are supported by underlying mechanisms that connect mind–brain processes to symptom improvement, particularly through modulation of endogenous opioid and dopaminergic systems. Applying placebo principles ethically may reduce side effects, increase patient engagement, and decrease the burden of treatment, especially for conditions like pain and mood disorders that have

high subjective symptomatology. By combining these insights, a patient-centered approach is promoted where psychological, biological, and ethical aspects come together to change placebo effects from inadvertent side effects to intentional therapeutic benefits. This paradigm highlights the capacity of placebo mechanisms to serve not only as adjuncts to traditional treatments, but also as central contributors to mental health interventions, opening avenues for innovative, ethically robust, and neurobiologically informed clinical strategies (36).

Recent literature increasingly emphasizes the clinical relevance of placebo mechanisms in both experimental and real-world mental health settings (7, 22, 36).

In addition to summarizing current empirical evidence, we propose that placebo-informed strategies should be conceptualized as structured components of therapeutic optimization rather than incidental contextual influences. From a clinical perspective, systematic integration could involve three complementary levels: (1) communication-based expectancy enhancement through transparent and credible therapeutic framing, (2) learning-based reinforcement using conditioning principles to sustain treatment responses, and (3) context-based modulation through deliberate strengthening of therapeutic alliance and treatment-related rituals.

Importantly, such integration does not imply replacing evidence-based interventions, but rather augmenting them through ethically transparent methods, particularly through open-label placebo models and expectancy-focused psychoeducation. Future mental health frameworks may benefit from recognizing placebo responsiveness as a patient-specific characteristic that could inform individualized therapeutic planning. The development of standardized clinical recommendations for ethically leveraging placebo mechanisms, while preserving patient autonomy and informed consent, represents a promising direction for both research and clinical practice.

Critical Reflection and Limitations of Research

The placebo effect is well documented, but there are still issues with its comprehension and use. The majority of the evidence is derived from brief, controlled studies that don’t accurately capture the complexities of clinical practice, and cross-study comparisons are made more difficult by the wide variation in how placebo responses are defined and measured. Furthermore, not everyone experiences the same effects. Their intensity and persistence are significantly influenced by individual differences in personality, genetics, and cultural background. Lastly, although placebo is effective in treating conditions with subjective symptoms like pain and anxiety, its application in diseases with biological parameters that can be measured objectively is still limited. Future research that uses ecologically sound designs, takes individual variability into account, and incorporates multidisciplinary points of view is crucial, as these limitations require careful interpretation of current findings.

These limitations underscore the importance of cautious interpretation and reinforce the need for longitudinal and ecologically valid research designs.

Conclusion

Placebo mechanisms illustrate the profound influence of psychological processes – expectation, learning, and relational context – on both physiological and psychological outcomes. In mental health care, they underscore the pivotal role of perception, trust, and the quality of therapeutic interactions in shaping treatment success. When implemented ethically, placebo principles can enhance conventional therapies by improving efficacy, supporting adherence, and reducing side effects without deceiving patients. For conditions dominated by subjective experiences, such as pain, anxiety, and depression, deliberately leveraging these mechanisms allows clinicians to optimize therapeutic benefit. By recognizing placebo effects as intentional, ethically guided components of care, they are transformed from incidental phenomena into active contributors to mental well-being, bridging psychology, neuroscience, and clinical practice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

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Placebo efekat u mentalnom zdravlju: psihološki, neurobiološki i etički aspekti

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Kratak sadržaj

Placebo efekat je psihobiološki fenomen u kojem očekivanja pacijenta, prethodna iskustva i socijalni kontekst utiču na zdravstvene ishode, čak i kada tretman nema farmakološki aktivni sastojak. Ključni mehanizmi uključuju očekivanja, verbalnu sugestiju, klasično uslovljavanje i socijalno-kontekstualne faktore, podržane neurobiološkim procesima koji uključuju endogene opioide, dopamin i povezane moždane puteve. U mentalnom zdravlju i psihoterapiji placebo efekti su posebno značajni, jer odnos terapeut–pacijent, empatija i verovanje u tretman mogu značajno poboljšati ishode. Etički prihvatljive primene, poput otvorenog placeba i placeba za produženo doziranje, očuvavaju autonomiju pacijenta dok koriste očekivanja i učenje za unapređenje kliničkih rezultata. Prepoznavanje i integracija placebo mehanizama u kliničku praksu naglašava interakciju psiholoških, neurobioloških i etičkih faktora, pružajući holistički pristup lečenju i poboljšavajući terapijske rezultate kod stanja kao što su depresija, anksioznost i hronični bol.

Ključne reči: placebo efekat, neurobiološki aspekti, psihološki mehanizmi, mentalno zdravlje, psihoterapija