

Placebo and Nocebo Effects in Musculoskeletal Pain: A Narrative Review

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Abstract

Musculoskeletal pain disorders are among the leading causes of disability worldwide and represent a major public health challenge. Although treatment outcomes are often attributed to the specific effects of therapeutic interventions, increasing evidence suggests that contextual and psychosocial factors significantly influence pain perception and recovery. Placebo and nocebo effects are psychobiological phenomena that arise from patients' expectations, prior experiences, therapeutic relationships, and treatment contexts. The placebo effect results in symptom improvement independent of the active components of treatment, whereas the nocebo effect leads to symptom worsening due to negative expectations and contextual influences. Contemporary research demonstrates that these effects are mediated through complex neurobiological mechanisms involving endogenous opioid, dopaminergic, and endocannabinoid pathways. In musculoskeletal pain management, clinician communication, therapeutic alliance, environmental factors, and treatment rituals can substantially influence clinical outcomes. This narrative review examines the underlying mechanisms, current evidence, and clinical implications of placebo and nocebo effects in musculoskeletal pain, emphasizing strategies to optimize positive contextual factors while minimizing adverse nocebo responses.

Keywords: Placebo, Nocebo, Musculoskeletal Pain, Contextual Factors, Pain Management, Rehabilitation, Expectations.

Introduction:

Musculoskeletal disorders, including low back pain, neck pain, osteoarthritis, shoulder disorders, rheumatoid arthritis, and fibromyalgia, are among the most common causes of chronic pain and disability globally [1]. Despite advances in diagnosis and treatment, many patients continue to experience persistent symptoms, suggesting that factors beyond tissue pathology contribute to pain perception and recovery.

The contemporary biopsychosocial model recognizes pain as a multidimensional experience influenced by biological, psychological, and social determinants. Within this framework, placebo and nocebo effects have gained increasing attention as important contributors to treatment outcomes [2]. Historically regarded as confounding factors in clinical trials, placebo and nocebo responses are now recognized as genuine psychobiological phenomena capable of influencing neurophysiological processes associated with pain modulation [3].

In musculoskeletal rehabilitation, contextual factors such as clinician behaviour, communication style, treatment rituals, and patient expectations can significantly affect therapeutic outcomes ⁽¹⁾. Understanding these mechanisms is essential for optimizing patient-centered care and improving treatment effectiveness.

The purpose of this narrative review is to summarize current evidence regarding placebo and nocebo effects in musculoskeletal pain and discuss their implications for clinical practice.

Understanding Placebo and Nocebo Effects:

Placebo Effect:

The placebo effect refers to beneficial changes in symptoms, functioning, or well-being resulting from psychosocial and contextual factors associated with treatment rather than its specific physiological properties ^(2,4). Placebo responses occur when positive expectations activate endogenous pain-modulating systems, producing measurable reductions in pain and disability.

Importantly, placebo effects do not imply that symptoms are imaginary. Neuroimaging and neurochemical studies have demonstrated that placebo analgesia is associated with real biological changes in brain regions involved in pain processing and modulation [3,5].

Nocebo Effect:

The nocebo effect refers to the induction or worsening of symptoms caused by negative expectations, anxiety, or unfavourable contextual influences [6]. Nocebo responses may manifest as increased pain, heightened symptom awareness, reduced treatment effectiveness, or adverse effects unrelated to the active intervention.

In musculoskeletal practice, negative communication regarding prognosis, structural abnormalities, or treatment risks can inadvertently contribute to nocebo-induced symptom exacerbation [7].

Mechanisms Underlying Placebo and Nocebo Effects:

Expectancy- Expectation is considered the primary psychological mechanism driving placebo and nocebo responses [5,8]. Positive expectations can enhance pain relief through activation of descending inhibitory pathways, whereas negative expectations may increase pain sensitivity and symptom reporting.

Neuroimaging studies have identified changes in activity within the prefrontal cortex, anterior cingulate cortex, insula, and periaqueductal gray during expectancy-induced analgesia [5].

Classical Conditioning -Classical conditioning contributes significantly to placebo responses. Repeated associations between therapeutic interventions and symptom relief can lead patients to experience analgesia when exposed to treatment-related cues, even in the absence of active treatment [3, 9].

For example, patients who repeatedly experience pain reduction following physiotherapy may develop conditioned responses to the treatment environment itself.

Social Learning-Observational learning can influence treatment outcomes by shaping expectations. Observing positive treatment responses in others can enhance placebo effects, while witnessing negative experiences may trigger nocebo responses [3,6].

Social learning is particularly relevant in the era of online health information and social media, where patient perceptions are increasingly influenced by external narratives.

Neurobiological Basis:

Placebo Analgesia-Placebo-induced pain relief is mediated through several neurochemical systems:Endogenous Opioid System -The endogenous opioid system plays a central role in placebo analgesia. Studies have demonstrated that administration of naloxone, an opioid antagonist, can block placebo-induced pain relief, indicating direct involvement of opioid pathways [2,3].

- **Dopaminergic System-Dopamine release within reward-processing regions contributes to anticipation of therapeutic benefit and reinforcement of positive expectations** ⁽⁵⁾.
- **Endocannabinoid System-Conditioned placebo analgesia appears partly mediated by endocannabinoid pathways, which regulate nociceptive processing and emotional responses to pain** ⁽³⁾.
- **Oxytocin-Emerging evidence suggests that oxytocin may strengthen placebo responses by enhancing trust and therapeutic alliance between clinicians and patients** ⁽²⁾.
- **Nocebo Hyperalgesia-Nocebo effects involve activation of systems associated with anxiety and pain facilitation.**
- **Cholecystokinin (CCK)-CCK has been identified as a key mediator of nocebo hyperalgesia through its antagonistic effects on endogenous opioid activity** ⁽³⁾.
- **Anxiety and Stress Responses-Negative expectations increase activation of the hypothalamic-pituitary-adrenal axis and anxiety-related neural circuits, amplifying pain perception and symptom vigilance** ⁽⁶⁾.

Methodology:

This narrative review was conducted to summarize current evidence regarding placebo and nocebo effects in musculoskeletal pain and rehabilitation. A comprehensive literature search was performed using electronic databases including **PubMed/MEDLINE, Scopus, Google Scholar, Web of Science, and Cochrane Library**. The search included articles published from **2000 to 2024**, with priority given to recent systematic reviews, meta-analyses, randomized controlled trials, and high-quality narrative reviews.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms including **"placebo," "nocebo," "placebo analgesia," "nocebo hyperalgesia," "musculoskeletal pain," "low back pain," "neck pain," "osteoarthritis," "fibromyalgia," "manual therapy," "rehabilitation," "physiotherapy," "expectation,"** and **"contextual factors."** Boolean operators (AND/OR) were used to refine the search.

Studies were included if they:

- Examined placebo or nocebo mechanisms in musculoskeletal pain conditions.
- Investigated contextual or psychosocial influences on pain or rehabilitation outcomes.
- Included adult participants.
- Were published in English.
- Consisted of systematic reviews, meta-analyses, randomized controlled trials, clinical studies, or authoritative reviews.

Studies focusing exclusively on non-musculoskeletal conditions, animal models without clinical relevance, conference abstracts, editorials, and non-English publications were excluded.

Relevant articles were screened by reviewing titles and abstracts, followed by full-text evaluation. Reference lists of selected articles were also manually searched to identify additional eligible publications. The findings were synthesized narratively because of the heterogeneity of study designs, interventions, and outcome measures. Emphasis was placed on psychological mechanisms,

neurobiological pathways, contextual factors, and their clinical implications for musculoskeletal rehabilitation.

Evidence in Musculoskeletal Disorders:**Chronic Low Back Pain**

Clinical trials consistently demonstrate substantial placebo responses among individuals with chronic low back pain ⁽¹⁰⁾. Improvements are frequently observed in pain intensity, disability, and quality of life measures.

Positive expectations and reassurance may contribute to reductions in fear-avoidance behaviours and central sensitization mechanisms.

Osteoarthritis

Placebo effects are particularly prominent in osteoarthritis research. Meta-analyses indicate that contextual effects account for a substantial proportion of observed improvements following pharmacological, injection-based, and surgical interventions ⁽¹¹⁾.

Invasive procedures often produce larger placebo responses because of heightened expectations and perceived treatment credibility.

Neck and Shoulder Pain

Manual therapy and exercise interventions may derive part of their effectiveness from contextual factors such as clinician confidence, patient education, and therapeutic alliance ⁽¹²⁾.

Fibromyalgia

Patients with fibromyalgia exhibit altered central pain processing and appear particularly susceptible to expectation-driven modulation of symptoms. Both placebo analgesia and nocebo hyperalgesia have been demonstrated in experimental and clinical studies involving fibromyalgia populations ⁽³⁾.

Clinical Implications:**Harnessing Placebo Effects Ethically**

Healthcare professionals can ethically maximize placebo-related benefits without deception.

Recommended strategies include:

Establishing Therapeutic Alliance

Trust, empathy, and patient-centered communication strengthen positive treatment expectations.

Positive Framing

Information should be communicated honestly while emphasizing realistic opportunities for improvement.

For example:

Instead of stating that “the spine is severely degenerated,” clinicians may explain that “many spinal changes are common with age and do not necessarily prevent recovery.”

Enhancing Self-Efficacy

Encouraging active patient participation promotes confidence and adaptive coping behaviors.

Optimizing Treatment Context

Professional clinical environments and structured treatment experiences can reinforce therapeutic credibility and engagement.

Minimizing Nocebo Effects

Preventing nocebo responses is equally important in musculoskeletal rehabilitation.

Strategies include:

- Avoiding catastrophic language
- Providing balanced risk information
- Addressing misconceptions and fears
- Encouraging movement and activity
- Correcting maladaptive beliefs about pain and tissue damage

Research suggests that fear-inducing diagnostic labels may increase disability and worsen clinical outcomes independent of pathology severity ⁽⁷⁾.

Discussion:

The present review highlights that placebo and nocebo effects are not merely methodological artifacts in clinical research but represent genuine psychobiological mechanisms that substantially influence musculoskeletal pain outcomes. Contemporary evidence demonstrates that pain perception is shaped not only by tissue pathology but also by patients' expectations, previous experiences, emotional states, and the therapeutic context in which treatment is delivered. These observations strongly support the biopsychosocial model of pain and emphasize the importance of addressing contextual factors during rehabilitation.

One of the most consistent findings across the literature is the pivotal role of patient expectations. Positive expectations activate endogenous pain inhibitory pathways involving opioid, dopaminergic, and endocannabinoid systems, leading to measurable reductions in pain intensity and disability. Conversely, negative expectations may activate anxiety-related neural circuits and cholecystokinin-mediated pain facilitation, producing nocebo hyperalgesia. These findings suggest that clinicians influence treatment outcomes not only through the interventions they provide but also through the way those interventions are presented.

The therapeutic alliance emerged as another major determinant of placebo responsiveness. Empathetic communication, clinician confidence, active listening, and patient-centered care consistently improve patient satisfaction and rehabilitation outcomes. Positive communication enhances treatment credibility, increases adherence to rehabilitation programs, and promotes self-efficacy. In contrast, negative or overly biomedical explanations emphasizing structural damage or poor prognosis may unintentionally reinforce fear-avoidance behaviours, catastrophizing, and disability. Therefore, careful communication should be considered an essential therapeutic skill in musculoskeletal practice.

The review also demonstrates that contextual factors surrounding treatment—including the clinical environment, treatment rituals, frequency of visits, and perceived sophistication of interventions—can significantly modify patient outcomes. Although these factors do not replace evidence-based interventions, they can enhance or diminish their effectiveness. Ethical utilization of placebo mechanisms involves maximizing positive contextual influences while maintaining transparency and informed consent rather than deceiving patients.

Evidence from chronic low back pain, osteoarthritis, neck pain, shoulder disorders, and fibromyalgia indicates that placebo responses account for a considerable proportion of treatment improvement. This may partly explain why different therapeutic approaches often demonstrate similar clinical effectiveness despite differing mechanisms of action. Recognition of placebo mechanisms encourages clinicians to focus not only on selecting appropriate interventions but also on optimizing the context in which care is delivered.

An emerging area of interest is the use of open-label placebo interventions, where patients knowingly receive placebo treatment while being educated about placebo mechanisms. Early studies suggest that open-label placebos may still produce clinically meaningful improvements in chronic pain without deception, although additional high-quality research is needed before widespread implementation.

Despite growing evidence, several limitations remain. Much of the available literature consists of heterogeneous study designs with varying definitions of contextual factors and placebo responses, making direct comparisons challenging. Furthermore, individual differences in genetics, personality traits, psychological characteristics, and neurobiology likely contribute to variability in placebo responsiveness but remain incompletely understood. Standardized methods for measuring contextual influences are also lacking.

Future research should investigate biomarkers and psychological predictors of placebo responsiveness, evaluate strategies for reducing nocebo effects in routine clinical practice, and develop standardized educational programs for healthcare professionals. Greater understanding of these mechanisms may facilitate more personalized rehabilitation approaches that integrate biological treatment with optimized psychosocial care.

Overall, the available evidence indicates that placebo and nocebo effects are clinically meaningful components of musculoskeletal rehabilitation. Rather than being viewed as confounding variables, they should be recognized as modifiable contextual factors that can ethically enhance treatment outcomes. Incorporating effective communication, strong therapeutic relationships, positive expectation management, and patient-centered care into routine practice may improve pain relief, functional recovery, and patient satisfaction while minimizing adverse nocebo responses.

Future Directions:

Future research should focus on:

1. Identifying predictors of placebo responsiveness.
2. Understanding individual neurobiological differences.
3. Developing standardized methods for optimizing contextual factors.
4. Investigating open-label placebo interventions.
5. Integrating placebo and nocebo education into rehabilitation training programs.

Advances in placebo science may facilitate more personalized approaches to pain management and rehabilitation.

Conclusion:

Placebo and nocebo effects are powerful psychobiological phenomena that significantly influence musculoskeletal pain outcomes. Through mechanisms involving expectancy, conditioning, social learning, and neurochemical modulation, contextual factors can either enhance or undermine treatment effectiveness. Evidence demonstrates that positive therapeutic relationships, effective communication, and supportive clinical environments can augment pain relief and functional recovery, whereas negative expectations may exacerbate symptoms and disability. Recognition of these effects provides clinicians with opportunities to ethically optimize treatment outcomes by maximizing beneficial contextual influences while minimizing nocebo-inducing factors. As musculoskeletal care increasingly embraces the biopsychosocial model, understanding placebo and nocebo mechanisms has become essential for effective patient-centered practice.

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