Mechanisms of Placebo and Nocebo: Are We Counting Chickens Before They Hatch?

Senthil P Kumar.*

ABSTRACT

The role of psychosocial factors in patients' clinical presentations are being commonly evaluated and managed during physical therapy along a comprehensive biopsychosocial approach to care. Placebo is a positive therapeutic experience secondary to perceived beneficial outcome whereas nocebo is otherwise. The objective of this editorial was to provide an insight into mechanisms of placebo and nocebo, with implications for use in physical therapy.

Key words: biopsychosocial rehabilitation, placebo, nocebo, therapy responses, patient expectation.

1. Introduction:

The role of psychosocial factors in patients' clinical presentations are being commonly evaluated and managed during physical therapy along a comprehensive biopsychosocial approach to care. Patient-centered paradigm in a BPS model warrants informed choice-based shared decision making between the healthcare provider and patient.

The use of patient-specific tools as outcome measures patient understanding of therapeutic goals and methods, cooperation/participation during assessment, treatment and decision-making, satisfaction with treatment and adherence to prescribed home exercise program. Patient expectations determine their role in therapist-patient communication, scores of self-report measures, treatment compliance and adherence.

Placebo is a positive therapeutic experience secondary to perceived beneficial outcome whereas nocebo is otherwise. Placebo and nocebo are analogous to “two sides of the same coin”, and they powerfully influence the perception of pain both as a biophysical stimulus and as a psychosocial experience.

Both placebo and nocebo responses were influenced by learning, and involved both conscious and non-conscious cognitive processes.

“The placebo effect has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right”.

The objective of this editorial was to provide an insight into mechanisms of placebo and nocebo, with implications for use in physical therapy.

2. Placebo:

2.1. Definition of placebo:

The word ‘placebo’ was derived from the verb ‘placere’, meaning ‘to please’. “The nocebo effect is a phenomenon that is opposite to the placebo effect, whereby expectation of a negative outcome may lead to the worsening of a symptom”.

2.2. Theories of placebo:

Haour proposed two theories to explain the placebo effect: “the conditioning theory, which states that the placebo effect is a conditioned response, and the mentalistic theory, which sees the patient’s expectation as the primary cause of the placebo effect.”

2.3. Neurobiological mechanisms of placebo:

2.3.1. Functional Magnetic Resonance Imaging (f-MRI) studies:

Both placebo and reappraisal effect produced attenuated activity in the right amygdala and right insula and placebo effect activated the left subgenual cingulate.
whereas reappraisal activated the right dorsal prefrontal cortex (PFC) and the left inferior PFC, with both learning-based placebo effect and cognition-based reappraisal having common anxiety-relieving effects through direct and indirect pathways respectively. Placebo induced decreased activation of dorsolateral prefrontal cortex during anticipation and in somatosensory cortex, posterior cingulate cortex, and thalamus during pain in placebo-responders with chronic abdominal pain. Pollo et al in their comprehensive review found three neurotransmitter systems operated in placebo analgesia: the opioid system, cholecystokinin and dopamine. Placebo responses employed brain-body pathways leading to endocrine, immune and autonomic responses.

Opioid-receptor-rich rostral anterior cingulate cortex (rACC) was activated in both placebo and opioid analgesia, with lateral orbitofrontal cortex (lObfc) and ventrolateral prefrontal cortex (vlPFC) being involved in processing expectation and error signals. Correlation between rACC and vlPFC was reproduced during emotional placebo and correlated with the degree of the placebo effect, with a prefrontal top-down influence on rACC. Medicinal placebo administered in the form of sweetened capsules might operate at the level of nucleus tractus solitaries, by influencing production of endogenous opioids.

2.3.2. Positron-emission tomography studies:
Placebo-induced activation of opioid neurotransmission occurred in the rostral anterior cingulate, orbitofrontal and dorsolateral prefrontal cortex, anterior and posterior insula, nucleus accumbens, amygdala, thalamus, hypothalamus, and periaqueductal grey matter. Sustained activity primarily involved the temporal and parahippocampal cortices whereas transient activity involved linguistic centers in the left hemisphere and frontal regions of the right hemisphere generally associated with executive functioning.

Placebo effect in parkinson’s disease was powerfully mediated through the activation of the damaged nigrostriatal dopamine system with a substantial release of endogenous dopamine.

2.4. Population-specific placebo:
The placebo-induced psychosocially driven biochemical changes in a patient’s brain and body may in turn affect the course of a neurodegenerative disease and the elderly person’s response to a therapy. There was evidence for placebo responses in different neurological conditions, including pain, Parkinson’s disease, depression, sleep and immune-mediated disorders.

High placebo response rates in functional bowel disorders (functional dyspepsia, irritable bowel syndrome) are similar to those in non-intestinal diseases (depression, pain, Parkinson’s disease) and not too dissimilar to other organic gastrointestinal diseases (duodenal ulcer, inflammatory bowel diseases) and irritable bowel syndrome. The placebo responses had onset latencies of 15-60 min, developed slowly over the next 15-45 min and persisted for hours or several days in people with idiopathic chronic low back pain.

Mechanisms of placebo responses were studied through analysis of biological pathways and reported for its comparison with naloxone (an opioid antagonist that reverses analgesia and was used in experimental pain states) in populations of post-surgical pain and in dental extraction procedures.

2.5. Application of placebo mechanisms in therapy:
Application of the placebo effect to pharmacotherapy was seen in conditioning processes that aim at a placebo-controlled dose reduction of drugs while maintaining the efficacy of the medical treatment through pairing of a placebo and a pharmacological agent which might achieve satisfactory treatment outcomes in combination with a lower dose of medication.

2.6. Research on mechanisms of placebo:
Amongst numerous placebo-controlled trials, there were few placebo-controlled trials that investigated physiological and therapeutic mechanisms of action. Vase et al in their meta-analysis investigated the magnitude of placebo analgesia in mechanistic studies versus placebo-controlled studies, and they found that: “the magnitude of placebo analgesia in placebo
mechanism studies was large and about five times larger than placebo analgesia effects in placebo control studies; the magnitude of placebo effects was larger in studies that used long-term pain stimuli >20s as opposed to short-term stimuli; and, the largest placebo effects were found in studies wherein hyperalgesia was present.”

3. Nocebo:

3.1. Definition of nocebo:

"The nocebo effect refers to non-pharmacodynamic, harmful or undesirable effects occurring after inactive treatment, a phenomenon that also occurs in the context of active therapy." 42

“A nocebo response is a negative symptom induced by the patient's own negative expectations and/or by negative suggestions from clinical staff in the absence of any treatment.” 43 "The nocebo hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause sickness in the expectant". 44

3.2. Prevalence of nocebo:

The prevalence of nocebo ranges from 18% in migraine, to more than 74% in multiple sclerosis. 42 The frequency and severity of nocebo responses depended upon gender and population respectively. 45 Women responded stronger to conditioning while men responded to expectancies, but to a lesser degree of nocebo. 46 Women in 'waiting' also tend to perceive hurt and injury since they felt that they have no choice but to become patient waiters in a health system. 47

Subject's negative expectations of pain worsening induce anticipatory anxiety about the impending pain increase and this triggers the activation of cholecystokinin that, in turn, facilitates pain transmission. 48 Type-A personality and higher Bortner score were associated with reporting of nocebo response among healthy volunteers. 49

3.3. Nocebo in research:

Informed consent itself had the potential to elicit nocebo response among study participants due to the explicit disclosure of adverse events in therapy. 50 Wells and Kaptchuk 41 proposed a solution of "contextualized informed consent," which takes into account possible side effects, the patient being treated, and the particular diagnosis involved.

The nocebo responses were studied through patient perceptions and expectations in placebo-controlled trials where adverse events occurred, an example of such a study was the meta-analysis of trials on people with parkinson's disease which concluded that nocebo was associated with increased patient drop-outs. 52 Nocebo effects substantially accounted for adverse events in drug trials of fibromyalgia syndrome and diabetic peripheral neuropathy 53 and multiple sclerosis. 54

3.4. Neurobiological mechanisms of nocebo:

3.4.1. f-MRI studies:

A negative placebo effect or nocebo-induced signal increases were noticed in bilateral dorsal anterior cingulate cortex (ACC), insula, superior temporal gyrus; left frontal and parietal operculum, medial frontal gyrus, orbital prefrontal cortex, superior parietal lobule, and hippocampus; right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus. 55

3.4.2. Clinical studies:

Verbally induced nocebo hyperalgesia was associated to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, as assessed by means of adrenocorticotropic hormone and cortisol plasma concentrations. 56

4. Implications of placebo in Physical Therapy:

“Placebo effect is a real neurobiological phenomenon and is the brain’s 'inner pharmacy' that acts as a critical determinant for the occurrence of psychobiological and behavioural changes relevant to healing processes and well-being.”

Meissner et al 10 Pollo et al 57 emphasized the role of expectation in physical performance and the additive effects of pre-conditioning using placebo as a central governor of fatigue had unique therapeutic implications in sports injury rehabilitation.

Motivational concordance rather than response expectancy was an important therapeutic mechanism for real-life placebos. 58 Sustained activity primarily involved the temporal and parahippocampal cortices whereas transient activity included linguistic centers in the left hemisphere and frontal regions of the right hemisphere generally associated with executive functioning. 19

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It is essential to avoid negative verbal suggestions during therapist-patient communication so as to reduce anticipatory anxiety about the impending pain increase, and this verbally-induced anxiety triggers the activation of cholecystokinin (CCK) which, in turn, facilitates increased pain transmission.

Placebo effect represented one of the best situations where natural activation of endogenous opioid network occurs, where the biological mechanism mainly involved suppression of the acute-phase inflammatory response, together with activation of brain’s reward circuitry.

The physiological effects of placebo depend on the content of the patient's treatment-related imagery and hence it should be used intentionally together with treatments and therapies which have more direct physiological and therapeutic effects.

5. Implications of nocebo in physical therapy:

Clinically, minimization of the nocebo effect includes improving awareness and recognition, changing the manner of disclosure of potential therapy-related adverse effects, shaping patients' expectations and enhancing the treatment alliance. Physical performance in motor training depended upon expectation-induced nocebo more than a sham intervention. Thus a judicious use of nocebo would be useful in treating psychological dysfunction.

Patients with pending litigation after personal injury or disability claims, and those covered by workers' compensation programs present with poor outcomes in therapy. Most exaggerated illness behavior in compensation situations occurred because of a combination of suggestion, somatization, and rationalization secondary to nocebo.

Nocebo responses can be induced in suggestible patients when providers use language that tends to increase patients' stress and negative expectations.

Clinicians should avoid assigning a diagnosis without objective physical evidence and thus avoid creating the nocebo effect in patients.

The nocebo response was influenced by the content and the way information was presented to patients in clinical trials in treatment conditions. Nocebo effects adversely influence quality of life and therapy adherence, thus warranting the need for minimizing these responses to therapy.

Hauser et al listed the implications of nocebo in medicine as follows: "Physicians face an ethical dilemma, as they are required not just to inform patients of the potential complications of treatment, but also to minimize the likelihood of these complications, i.e., to avoid inducing them through the potential nocebo effect of thorough patient information. Possible ways out of the dilemma include emphasizing the fact that the proposed treatment is usually well tolerated, or else getting the patient's permission to inform less than fully about its possible side effects. Communication training in medical school, residency training, and continuing medical education would be desirable so that physicians can better exploit the power of words to patients' benefit, rather than their detriment."

The process of clinical focusing on pain may itself be a cause of pain, and hence, therapists should minimize the frequent emphasis on pain during history-taking, subjective and objective examination.

6. Conclusion:

"Placebo and nocebo responses are rooted in the complexity of mind/body interactions and that their underlying physiological mechanisms may be elucidated via methods that directly examine brain activity as the basis of subjective experience." - Kradin.

Spiegel concluded that, "The biopsychosocial concept provides a blueprint to bring the old-fashioned medical art of "humaneness" to modern scientific care. Identifying the interactions of the problem, the person, and the totality of resources permits a focus on therapeutic strategies to promote placebo effects and prevent the consequences of nocebo."

CONFLICTS OF INTEREST

None identified and/or declared.
References:


