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How do placebo effects and patient-clinician relationships influence behaviors and clinical outcomes?

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Placebo effects modulate clinical outcomes, result from the patient, proxy, and provider's expectancies, and depart from confounding factors such as regression to the mean, spontaneous remission, and symptoms' fluctuations. From a psychological perspective, placebo effects have been attributed to verbal suggestions and anticipation of therapeutic benefits, previous therapeutic experiences, observation and social learning, contextual cues, and interpersonal patient-clinician interactions.⁴

This theme issue covers both theoretical and original research articles exploring how often overlooked aspects of patient's medical encounters and experiences can influence health outcomes through the placebo and nocebo effects in pain medicine. Namely, the 5 articles and 3 reviews included in this special issue illustrate how a variety of factors, ranging from perception of competence and warmth before a surgical procedure¹ to psychological changes occurring as a result of treatment framing,⁹ alter pain experience and placebo effects. Other factors discussed include the role of expectations, desire for pain relief, and anxiety in pain-relieving intervention such as medial branch radiofrequency neurotomy low back pain patients,⁸ an online method of placebo manipulation,¹⁷ and operant conditioning with avoidance movements.¹⁰ The reviews describe the need for encouraging education about contextual and placebo effects in nursing,¹⁵ strategies to minimize nocebo effects,¹² and relevance of placebo effects for central nervous system (CNS) disorders.¹³ Together, this collection of innovative studies provides

a diverse snapshot of the clinical relevance of placebo and nocebo effects and, most importantly, how health practitioners might harness them to improve health outcomes.

Patient-clinician interactions can influence patients' perception of health pain outcomes through placebo and nocebo effects.⁴ However, it remained unknown how the patient's perception of warmth and competence of the clinician can affect clinical pain outcomes. Patients' feelings of surgeons' warmth and competence assessed immediately before wisdom tooth extraction surgery influenced the patients' postsurgical experiences of trust and acute pain; when patients perceived the surgeon as highly competent, but not warm, they experienced higher trust and lower pain during surgery.¹ Thus, a key aspect of the patient-clinician interactions is competence of health practitioners while interacting with their patients and the impression they create.

Another important feature of the clinical encounter is how treatments are presented to patients.² Disclosure and framing effects can eventually change treatment efficacy expectations, pain experience expectations, anxiety, positive and negative affect, and autonomic responses.⁹ To this end, Geers⁹ designed a study in which a standard analgesic message, an analgesic treatment with side-effect message, and a double-blind analgesic message along with a control treatment message were delivered. They found that treatment-specific expectations changed as a result of the way the information is framed compared with the other conditions and the control message. The fact that treatment messages can influence participants' expectations of treatment efficacy can be relevant for daily clinical practice.

Moreover, preintervention information acquired through websites is ubiquitously present in clinical settings. Investigating the impact of online delivery of information can have clinically relevant applications and can contribute to the development and improvement of both therapeutic strategies and tools to help patients alleviate their pain. In this issue, Pontén¹⁷ explored the occurrence of placebo effects when participants received the information about the nature of the study and related goals through online communication. Healthy participants were randomized to either empathetic or neutral online communication before completing an in-person placebo analgesia experiment. The online communication was designed to elicit significant placebo effects as compared to the control group, in which a sham analgesic device, without any previous communication was used. Significant placebo effects were induced by the online video clip as compared to the sham analgesic device without any previous communication that did not

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induce placebo effects in and of itself. Yet, exploratory analyses did not suggest any difference in placebo pain ratings between the empathetic and neutral communication groups, which further reinforces the idea that warmth and empathy may not be critical components of placebo effects.

Information conveyed online is relevant. However, participants' expectations are often shaped and even changed by both interactions with others and self-experiences.⁶ Along this line, Janssens¹⁰ measured the occurrence and persistence of placebo and nocebo effects when an operant avoidance learning task was used. In this study, participants performed movements with distinct levels of difficulty and intensities of painful stimulation including both a high cost of avoidance context, whereby pain stimulus intensity was reduced with increasing movement difficulty, and a low-cost avoidance context in which those contingencies were reversed. Movements were then tracked, and participants reported both their pain expectations and perceived pain intensity while making differential movement choices. Placebo and nocebo effects were tested using a medium-intensity pain stimulus, and in this phase, the differences in movement choices across contexts disappeared, despite pain expectations remaining stable. Placebo effects occurred within the low cost of avoidance context,¹⁵ suggesting that operant learning can shape pain-related avoidance behaviour with acquired pain beliefs that can be resistant to disconfirmation, despite self-initiated movements and contingencies.

The fact that expectations per se influence patients' pain ratings, regardless of the actual interventional experience, poses a challenge in situations in which placebos are (often incorrectly) used for diagnostic scopes.¹⁴ The occurrence of placebo effects in such an interventional setting has been carefully investigated by Finniss⁸ who conducted a clinical trial in which patients underwent denervation of the lumbar zygapophyseal joints by medial branch radiofrequency neurotomy to treat chronic low back pain. A control group with 2 local anaesthetic injections was also studied, and magnitude and frequency of placebo responses were assessed. Placebo injections resulted in both large response rate (78% placebo responders) and effect size (Cohens' $d = 1.85$). Expectation and anxiety were also important in modulating these therapeutic responses, indicating that pain-related surgical treatment outcomes may have a substantial placebo component.

Mechanisms of placebo analgesia may vary in chronic pain patients and patients suffering from CNS diseases as compared to healthy participants.⁴ Matthiesen¹³ focused on placebo analgesia in chronic pain conditions and diseases such as Alzheimer disease and Parkinson disease. They offer a clear and concise presentation of the strengths, weaknesses, and insights of the current understanding of placebo analgesia in chronic pain patients. Future mechanistic studies should explore placebo and pain in other neurological and psychiatric diseases including multiple sclerosis, autism, substance use disorders, and schizophrenia. Understanding how chronic pain patients respond to placebo treatments, as opposed to healthy controls, may help improve treatments among patients experiencing pain in relation to CNS diseases.

Efforts have been made to translate knowledge of nocebo mechanisms into helpful recommendations to prevent unintended nocebo effects in clinical practices. Manai expands upon concepts that have been reported in the literature^{3,5,7,11,16} by further emphasizing the needs for reframing information, reconsidering patient–physician communication and relationships, and providing education on coping skills to meet patient expectations.¹² These kinds of approaches should be introduced in the nursing discipline. Knowledge on placebo and nocebo effects can positively influence nursing education, administration, clinical practice, and research as outlined by Palese who

elucidated and debated the contextual factors that can trigger placebo and nocebo effects and their impact on nursing arena.¹⁵

Overall, this theme issue on Placebo and Pain Research presents new lines of research on framing effects and placebo analgesia as well as somewhat underestimated but highly relevant aspects of patient's clinical experiences and encounters. Contextual, nocebo, and placebo effects in clinical settings deserve increased attention because they offer avenues for simple, low-cost, and easy-to-implement improvements in pain-related patients' health outcomes.

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