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Placebo hypoalgesic effects in pain: Potential applications in dental and orofacial pain management

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Abstract

Placebo and nocebo effects are present within every treatment and intervention, and can be purposefully enhanced and reduced, respectively, in order to improve patients' clinical outcomes. A plethora of research has been conducted on the mechanisms of placebo hypoalgesia and nocebo hyperalgesia in experimental and clinical settings. However, its implications in particular clinical settings such as orthodontic pain management remain underexplored. We conducted a search of the literature regarding placebo analgesia, orthodontic pain management, and orofacial and dental pain. Articles were qualitatively assessed and selected based on the scope of this narrative review. Although no studies investigating the extent of the implications of the placebo and nocebo phenomena in the orthodontic clinical setting were found, we herein present a comprehensive review on the influences of placebo and nocebo effects in experimental and clinical pain management, as well as on the potential for engaging placebo-related endogenous pain modulation for orthodontic pain management. Ethical considerations for the clinical application of placebos are discussed, and future research directions are presented.

Background

The placebo effect is a fascinating phenomenon during which, likely, multiple endogenous neuropsychobiological mechanisms become synchronously engaged to produce a health or treatment benefit in the experiencer. With reports of placebo applications dating back to the 1500s,¹ placebo effects and responses have been an inherent part of both the science and art of health and medicine. *Placebos*, defined as inert substances or sham therapeutic interventions that lack a specific pharmacological or physiological effect for an outcome,² were adopted by scientific research in control groups as a mean to identify true treatment benefits from subjective and non-specific responses.³ *Placebo effects* and *placebo responses*, concepts that had been at times interchanged in the literature, have been clearly defined as differing concepts and phenomena.^{4–7} Placebo effects refer to bio-logically-measurable changes originating from patients' (and providers') expectancies, whereas placebo responses allude to observations that originate from other natural and non-specific factors such as time

effects due to disease or symptom variations, regression to the mean, as well as spontaneous remission.⁶ Within clinical trials, the addition of a placebo-control group does not suffice to identify placebo effects from placebo responses and other non-specific factors related to contextual effects. Rather, a no-treatment group is needed in order to determine the extent of true endogenous physiological modulation associated with placebo mechanisms.

Additionally, the concept of *expectancies* requires further consideration. Contrary to *expectations*, which are verbally and consciously identifiable predictions or anticipations regarding an event, intervention, or treatment that can usually be manipulated through verbal suggestions, expectancies are formed and dynamically shaped by both conscious and subconscious processes that may include a combination of classical or operant conditioning mechanisms, social observation, and partial reinforcement learning.^{8,9} A first-hand experience of a benefit through pharmacological and non-pharmacological conditioning can create conditioned responses and subsequently behavioral and neurobiological placebo and nocebo effects based on positive or negative effects.^{10,11} Moreover, the mere observation of other person plays a role in the formation of socially-induced placebo and nocebo effects.^{12,13}

The nocebo phenomenon

Nocebo effects have been defined as the negative counterpart of placebo effects, and can result from either the formation and potentiation of negative expectancies, or from the absence of positive expectancies through negative prior experiences and conditioning, social observational learning, and verbal suggestions, and can be further influenced by less controllable factors such as genetics and personality traits.¹⁴ Despite the fact that nocebo effects have been less researched than placebo effects, they are prevalent in both experimental and clinical settings.^{15,16} Adverse effects reported by participants in control groups of clinical trials have been usually attributed to the nocebo effect, as many studies have shown that these reported side effects are usually the same as the ones reported and experienced by individuals within groups receiving active treatments.^{17,18} Although similarities between some of the biological mechanisms of the placebo and nocebo effects exist, these pathways are not always bi-directional.¹⁴ Studies have shown that those individuals who respond to placebo interventions will not necessarily experience nocebo effects, and that those who are nocebo responders are not by default placebo responders.^{8,19–21}

Biopsychosocial mechanisms

It has been argued that placebo and nocebo effects innately exist in the organism as an evolutionary mechanism to help guide safety and appetitive behaviors, and to avoid dangerous events or behaviors, respectively.²² Many models^{2,23–27} have been developed to help characterize and understand the role of placebo effects within healthcare settings. Different drivers of expectancies, such as verbal suggestions, classical conditioning and social observational learning, have been shown to be primary players in engaging placebo and nocebo mechanisms.^{28,29} Following classical conditioning mechanisms as depicted by Pavlov,³⁰ associations of an unconditioned stimulus (e.g. a new treatment), occurring along or within a context or experience producing a positive or negative expectation (e.g.

conditioned stimulus), would then lead to a conditioned response that can either potentiate or antagonize the intended effects of the treatment that was initially delivered.²⁶ The patient-practitioner interaction also plays a key role in the development of both expectations and expectancies.^{2,25,31,32} More recently, the role of patients' *mindsets* in regards to health outcomes,^{33–35} physician competency and likeability,³¹ as well as individual power to change,³⁶ have been studied as additional factors that can lead to clinical and health outcome effects related to placebo mechanisms.

Pharmacodynamically, placebo effects have been observed to be associated to modulation arising from endogenous opioid,^{37,38} dopamine,^{29,38–40} cannabinoid,⁴¹ vasopressin,⁴² and oxytocin⁴³ release, whereas the nocebo effect is primarily modulated through the cholecystokinergic system, the latter being mainly involved in the modulation of anxiety and hyperalgesia.⁴⁴

Neural correlates of placebo and nocebo effects have been studied primarily through functional magnetic resonance imaging (fMRI), and areas of the brain such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), nucleus accumbens (NAc), hypothalamus, amygdala, thalamus and insula, as well as areas in the spinal cord such as the periaqueductal grey, and ipsilateral dorsal horn, have been correlated with changes in placebo-mediated sensory affective perceptions (for a full review, see refs^{14,28,29}). Other psychological factors, including personality factors and traits such as optimism, empathic concern, hypnotizability, somatic focus, pain catastrophizing, anxiety, and neuroticism, as well as factors associated to the function of the dopaminergic system, such as avoidance and reward responsiveness, have also been linked to changes in pain perception and placebo and nocebo responses.^{8,14,28}

Placebo effects in health and clinical outcomes

Research has demonstrated the vast influence of placebo responses and effects in multiple clinical and health outcomes for a variety of conditions and treatments. In one of the first pioneering scientific articles describing the extent of the effects of the placebo phenomenon, Beecher detailed that as much as $35.2 \pm 2.2\%$ of therapeutic effectiveness in subjective outcome measures collected from 15 different studies were related to placebo mechanisms.⁴⁵ Furthermore, studies on antidepressants have found considerable therapeutic impact in the placebo groups of such trials. For example, a study found that nearly as much as 30% of patients who were receiving placebos responded positively to the treatment, while the active drug group experienced a therapeutic improvement of about 50%.⁴⁶ A meta-analysis evaluating effect sizes related to the treatment of depression with antidepressants in a total of 2,318 patients in 19 double-blind clinical trials found that effect sizes of inactive placebos were comparable to those observed in patients receiving antidepressants and formed about 75% of drug responses.⁷ In this study, further analysis of no-treatment groups and waiting lists allowed for an identification of the estimates of true placebo effects versus non-specific factors, and revealed that drug effects consisted of approximately 51% placebo effects, 25% pharmacological effects, and 24% non-specific factors. The impact of placebo responses due to contextual and nonspecific factors is not limited to antidepressant treatments, as other

studies have estimated placebo responses to constitute as much as 50% of medication effects in the context of anxiety and pain.^{47–49}

Given the non-unanimity regarding the appropriate and ethical use and application of the placebo phenomenon in clinical settings, additional clinical research investigating the implications of placebo effects in different types of disorders and healthcare settings is needed before more conclusive guidelines can be defined. Considering the lack of data on placebo and nocebo effects in orthodontic pain management, this manuscript attempts to bridge the experimental and clinical knowledge of placebo-induced hypoalgesia and analgesia, and nocebo-induced algesia and hyperalgesia, in the context of general, orofacial and dental pain, along with evidence reported from trials in orthodontic pain management. Potential implications for placebo mechanisms acting within orthodontic pain management settings are discussed, and ethical considerations and general guidelines for improving placebo effects and preventing nocebo effects within the clinical setting are described. Future directions for research on the placebo and nocebo phenomenon within orthodontic settings are suggested.

Placebo effects in pain management

Experts in dental and orofacial pain have acknowledged that scientific and clinical research suggest that within every pain treatment, there is an inherent placebo effect that exerts benefits that, in some cases, can be equal to those observed with active treatments.⁵⁰ All treatments and interventions leading to any therapeutic response are intrinsically associated to the placebo phenomenon, and these placebo effects can work synergistically or additively to treatments and pharmacological drug actions based upon the condition being treated.²⁸ Conversely, nocebo effects can antagonize the action of interventions or pharmacological agents.¹⁴

In pain management, contextual effects and social factors play a significant role in eliciting placebo and nocebo effects. An open/hidden model of painkiller administration, where patients in a postoperative pain setting were given analgesics through either a computerized pump infusion or a sympathetic practitioner, demonstrated that patients' awareness of treatment delivery enhanced responses to the medication.^{51–53} These effects have also been observed in anxiety and Parkinson's disease.^{39,52,53}

Social and observational learning have been shown to extensively impact placebo hypoalgesic and nocebo algesic effects. Importantly, social induction of placebo effects in pain have been demonstrated to result in effects comparable to those attained through behavioral conditioning, and significantly more robust than verbally-induced analgesic effects.^{12,29,54} Socially-induced placebo and nocebo effects have been experimentally manipulated through video demonstrations⁵⁵ or in-person observations¹³ of confederates reporting low or high pain with treatments.

In a study evaluating the influences of positive and negative expectancies in pain outcomes, the analgesic action of remifentanyl was blocked in those participants within the negative-expectancy group, while those in the positive-expectancy group experienced a potentiation

of remifentanyl analgesia.⁵⁶ Expectancies play an incredibly significant role in the activation of descending modulatory pain pathways and response to an active treatment (e.g. painkillers given in perioperative settings). Prior experiences with interventions or the clinical setting can have important implications in treatment effectiveness. Colloca and Benedetti explored the magnitude and prevalence of placebo effects immediately and four-to-seven days after exposure to a manipulated intervention in which participants received painful stimulations with either an effective or ineffective treatment.¹⁰ It was found that participants in the effective treatment group experienced more robust placebo-induced hypoalgesia when compared to the ineffective treatment group after the intervention (49.3% versus 9.7% reduction, respectively), and that prior experience with the effective treatment group elicited larger placebo hypoalgesic responses after four-to-seven days when compared to the ineffective group (29% versus 18%, respectively).¹⁰ Other studies applying learning models to the investigation of placebo effects have also demonstrated positive correlations between the length and number of conditioned associations with effective treatments with increased persistence and decreased extinction of placebo effects.⁵⁷

Importantly, recent studies have shed light on mechanisms of placebo effects in clinical pain patients. For example, Klinger and colleagues have demonstrated that significant clinical benefits can be achieved through the engagement of conditioned and reinforced placebo mechanisms in chronic low back pain (CLBP) patients.⁵⁸ In this study, verbal instructions targeted to create either a negative or positive expectation, delivered along with conditioned reinforcers of those expectations through surreptitious exposure to manipulated pain reduction, were observed to influence both acute experimental pain intensity as well as preexisting clinical pain, functionality and back pain behaviors.⁵⁹ A recently published randomized controlled trial with CLBP patients demonstrated that open-label placebos (i.e. placebos administered in a non-deceptive manner) added to treatment-as-usual (TAU) produced superior pain reduction of moderate-to-large effect sizes when compared to TAU only.⁶⁰ The effects of this unusual and more recently adopted approach echo those observed by Kaptchuk et al, where open-label placebos were found to be significantly effective in managing symptom severity and promoting general improvement in a cohort of 80 patients with irritable bowel syndrome (IBS) when compared to a no-treatment group with matched patient-practitioner interactions.⁶¹ Thus, open-label placebos may offer an effective alternative that can address the ethical concerns that placebos have always been subject of (see *Ethical Considerations* below), while at the same time promoting substantial benefits in clinical outcomes.

Pharmacological conditioning through repeated administrations of active medication followed by surreptitious replacement with a placebo has also been shown to exert positive effects that mimic those observed with the active drugs. In a study, participants received morphine one-hour prior to beginning a pre-competition training, once for a period of two weeks. In the following week, morphine was covertly replaced with a saline solution (placebo) during the competition, and robust placebo responses were observed in the group who received the conditioning treatment with morphine when compared to no-treatment and placebo, and treatment and placebo and naloxone, the latter being a potent opioid μ -receptor blocker.⁶²

Similarly, so-called dose-extending placebos have been suggested to serve as potential enhancers of medical treatments.⁶⁴ While still in conceptual stages, dose-extending placebos may improve treatment outcomes through conditioning mechanisms and the development of positive expectations by unidentifiably intermixing active medications (e.g. painkillers) along with placebos in a same blister pack. Although this concept requires further investigation in terms of feasibility, safety, efficacy and effectiveness, it presents an option that could help reduce medication-related costs, risks, and side-effects.⁶⁴ As demonstrated by many investigations highlighting the importance of patient's expectancies, which can be shaped by prior experiences, conditioning, verbal suggestions, and social observation, as well as patient's state of anxiety, mindsets, and perception of meaning, placebo and nocebo effects can have important implications in various clinical contexts, including the management of both acute and chronic pain.

Placebo effects in orofacial and dental pain

Based on evidence provided by multiple clinical trials, patients suffering from temporomandibular disorders (TMD) are a group that may experience substantial treatment benefits due to placebo analgesia.⁵⁰ In a randomized, controlled, double-blind trial that examined the effectiveness of capsaicin in 30 patients with unilateral TMJ pain, capsaicin showed no statistically significant difference on pain measurements when compared to placebo, although both groups did demonstrate a statistically significant difference as an effect of time.⁶⁵ Although these results may indeed demonstrate effects related to expectancy-induced placebo analgesia, the lack of a no-treatment group makes it impossible to determine how much of the placebo response observed is an actual placebo effect, and how much of the treatment benefit is solely due to time effects related to natural progressions and variations of pain.⁶

A pioneering study conducted by Gracely et al. in 1985 compared postoperative pain after dental surgery between two groups that were administered either placebo or naloxone, or placebo, fentanyl or naloxone, respectively.⁶⁶ Pain reports in the placebo + fentanyl + naloxone group were significantly lower. Furthermore, the study suggested that subtle behaviors by the clinician providing the medications might have elicited such effects. Through physicians' interpersonal rapport with their patients, practitioners may still show their own personal expectancies and can thus influence patients' perceptions of the information in terms of treatment, health and disease outcomes, as well as the perceptions of the physician characteristics themselves. Authors concluded that "clinical analgesia depends not only on the physiological action of the treatment administered but also on the expectations of both the patient and clinician".⁶⁶ These potential influences were highlighted by a recent brain imaging study that found physicians' brain activation patterns during the patient-physician interaction.⁶⁷ The reciprocal understanding and interactions between practitioners and their patients elicited activation in neural systems underlying treatment's expectation, reward, empathy and attention.⁶⁷

Placebo responses and effects in orthodontic pain

Since no specific investigations have been conducted on placebo analgesia and orthodontic pain management, we reviewed multiple studies that have looked at pain management within the orthodontic setting. None of the studies were specifically directed towards the analysis of placebo-induced analgesia. Despite this gap in scientific knowledge and evidence, multiple investigations regarding non-pharmacological interventions for orthodontic pain management inclusive of placebo controlled and no-treatment groups were found.

A Cochrane review of pain management through non-pharmacological interventions during orthodontic treatment provided significant insight into potential placebo applications in orthodontics.⁶⁸ A total of 14 studies inclusive of 931 total randomized participants, and 860 analyzed participants, were evaluated for the effectiveness of four main non-pharmacological approaches, including: low-level laser therapy (LLLT), vibratory and chewing adjuncts, as well as psychosocial approaches including cognitive behavioral therapy (CBT), post-intervention text-messaging follow-up, and brain wave music.⁶⁸ From all of the studies, just one⁶⁹ was determined to have a low risk of bias, while six and seven were assessed as having an unclear and high risk of bias, respectively.⁶⁸ As reported, six studies included placebo-controlled groups involving the use of vitamin B6 pills⁷⁰, placebo irradiation of infrared light⁶⁹, inactive placebo laser irradiation⁷¹, light-emitting diode (LED) irradiation⁷², sham LLLT⁷³, and sham vibratory adjuncts.⁷⁴ Two studies included behavioral and dietary recommendations such as avoiding to chew gum^{75,76} and hard foods⁷⁵ while six studies^{77–82} made use of no-intervention groups.⁶⁸ Compared to placebo or no treatment, the evidence of effectiveness for LLLT was of low quality, although it was shown to have reduced self-reported pain levels on a visual analog scale (VAS) at 6 and 24 hours, as well as at 3 and 7 days following orthodontic appliance placement. Very-low quality evidence from one trial suggested a decreased perception of pain with brain wave music or CBT, and the same was observed in a high-risk-of-bias study evaluating post-intervention text messaging.⁶⁸ No definitive conclusions were able to be drawn in terms of the effectiveness of vibratory stimulation, as the evidence included was categorized as very-low quality and there was lack of evidence that this intervention produced analgesic effects when compared to placebo vibration or no vibration. However, the imprecision of results makes it difficult to reach any conclusion.⁶⁸ Inconsistent and non-conclusive results of very-low quality evidence were also found for chewing adjuncts.⁶⁸

Considering that no other systematic analyses have been conducted, authors suggested that there is a need for developing well-designed and comprehensive clinical trials that can appropriately evaluate the true impact of these therapies versus other non-specific context effects. Although contextual factors are indeed part of the overall placebo phenomenon, without high quality research knowledge about which specific factors, if any, are especially influential in pain perception and modulation in the context of orthodontic pain will remain undetermined.

Clinical and ethical considerations

In clinical practice, it is imperative to ethically manage and balance the risks and benefits of every intervention delivered to patients, as well as to offer acceptable and effective alternatives for those patients whose will is to not undergo pharmacological treatment, or those who are unable to take traditionally used medications due to allergic or other physiological and health complications.

Overall, the literature suggests that proper multidisciplinary pain management approaches would require a combination of careful baseline assessments of pain, patient's expectancies and psychological states, as well as cautious framing and management of contextual effects and interpersonal patient-practitioner interactions. Recently, suggested recommendations for preventing nocebo-induced algesia and hyperalgesia leading to worsening of outcomes in clinical pain have been published, and highlight five main concepts: (1) avoiding negative patient-practitioner communication and interaction; (2) allowing the patient to experience emotional relief when treating with analgesics; (3) avoiding excessive negative information regarding side-effects and/or limited information regarding benefits; (4) minimizing negative associations with outcomes and contextual factors or cues; and (5) preventing and avoiding intentional or unintentional "hidden" administration of analgesic treatments.⁸³

The use of placebos in clinical pain management is also a subject of much scrutiny. In fact, the use of deception has always been a concern surrounding the clinical application of placebos in consideration of the utmost importance of protecting and respecting patient autonomy and right-to-know. However, the traditional experimental and clinical application of placebos in a deceptive manner has been recently challenged. Some research has indicated that patients would be willing and open to use placebos if they could offer treatment and clinical benefits.⁸⁴ Furthermore, given that evidence has demonstrated that placebo analgesia persists despite the use of authorized deception during the informed consent process,^{42,85} as well as the evidence suggesting the effectiveness of open-label placebos in the clinical context of CLBP⁵⁹ and IBS,⁶¹ there is potential for further investigating the role, feasibility and safety of placebos utilized in non-deceptive manners. In addition to the promotion of dose-extending placebos as adjuvants to active painkillers to lengthen and improve the effects of pharmacological agents,⁶⁴ the potential for including placebos as part of the pharmacopeia to allow for practitioners to prescribe placebos as actual treatments has also been discussed.⁸⁶ Nonetheless, it is imperative to ascertain that strong ethical standards are followed, and that informed consent for nondisclosure is at all times provided by the patients.⁶⁴

Conclusion and future directions

Placebo and nocebo effects are pervasive in both experimental and clinical settings, and can be especially influential in pain management. A variety of conditions, including Parkinson's and anxiety,^{15,52} CLBP,^{59,60} migraine,⁸⁷ TMD,⁵⁰ IBS^{61,88} and postoperative pain,^{66,89,90} have shown a potential to be influenced through placebo and nocebo mechanisms. Many individual factors, such as personality traits,^{8,28} genetics,^{14,29} prior experiences,¹⁰ learning and conditioning,^{10,11,22,26,91–96} mindsets,^{33,34,36} and expectancies,^{8,27,42,56,92,93,96,97} in

addition to contextual,^{4,83,98,99} environmental factors (e.g. interpersonal interactions with the practitioner)^{2,25,31,32} and social observation,^{12,28} can drive experimental, clinical and health outcomes towards both positive and negative directions.

Overall, the literature suggests that proper multidisciplinary pain management approaches would require a combination of careful baseline assessments of pain, patient's expectancies and psychological states, as well as cautious framing and management of contextual effects and interpersonal patient-practitioner interactions. Recently, suggested guidelines for preventing nocebo-induced algia and hyperalgesia leading to worsening of outcomes in clinical pain have been published, and highlight five main concepts: (1) avoiding negative patient-practitioner communication and interaction; (2) allowing the patient to experience emotional relief when treating with analgesics; (3) avoiding excessive negative information regarding side-effects and/or limited information regarding benefits; (4) minimizing negative associations with outcomes and contextual factors or cues; and (5) preventing and avoiding intentional or unintentional "hidden" administration of analgesic treatments.⁸³

To our knowledge, there is limited research that has been specifically conducted on the impact of placebo effects (inclusion of a no-intervention arm) in the orthodontic clinical settings. Furthermore, a recent systematic review⁶⁸ found no high-quality evidence regarding the therapeutic efficaciousness of non-pharmacological strategies (e.g. vibratory devices; chewing adjuncts; brain wave music; cognitive behavioral therapy and post-treatment communication in the form of a text message) for managing orthodontic pain when compared to placebo or no-intervention. Given the widespread use of orthodontic appliances, as well as the lack of specific research on placebo analgesia/hypoalgesia as well as nocebo algia/hyperalgesia in this field, orthodontic pain management provides an opportunity for the development of novel strategies that can further explore and take advantage of endogenous pain modulatory systems.

Many of these unexplored aspects regarding pain experience and modulation within orthodontics offer fascinating as well as relevant potential research avenues that can help shape and enhance clinical guidelines. Can the discomfort of orthodontic appliances be clinically and significantly reduced by promoting placebo effects and preventing nocebo effects, whether through the use of dose-extending placebos or by carefully controlling the clinical environment and interaction? Could negative or painful experiences within orthodontic settings in adolescents and adults significantly affect subsequent expectancies and outcomes of future dental or orthodontic procedures in similar clinical settings? Considering the larger population of adolescents being exposed to orthodontic pain when compared to chronic pain disorders such as TMD, is there a potential for age-effects influencing placebo? Similarly, can the enhanced neuroplasticity present in adolescents when compared to adults be a significant factor in shaping placebo effects at the time of treatment as well as during further clinical interventions in practices both related and unrelated to dental settings? These questions will remain unanswered until further high-quality research is conducted on the precise role the placebo phenomenon in this particular setting, as well as on the comparative effectiveness between these and other traditionally utilized pain management methods.

Nonetheless, despite these scientific uncertainties, the extensive presence of the placebo and nocebo phenomena in both pain and other clinical settings suggest a substantial potential for positively and effectively engaging these mechanisms in the area of orthodontic pain management. Through these multidisciplinary approaches, not only clinical outcomes, but also quality of life and functionality could be significantly improved with the ultimate end of reducing patient harms and other health-related risks.

Uncited reference

[63].

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References

1. Kaptchuk TJ, Kerr CE, Zanger A. Placebo controls, exorcisms, and the devil. *Lancet*. 2009;374:1234–1235. [PubMed: 19839101]
2. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med*. 2009;52:518–539. [PubMed: 19855122]
3. Beldoch M. Is the placebo powerless? *N Engl J Med*. 2001;345:1278–1279.
4. Miller FG, Brody H. Understanding and harnessing placebo effects: clearing away the underbrush. *J Med Philos*. 2011;36:69–78. [PubMed: 21220523]
5. Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. *Philos Trans R Soc Lond B Biol Sci*. 2011;366:1922–1930. [PubMed: 21576150]
6. Colloca L. Treatment of pediatric migraine. *N Engl J Med*. 2017;376:1387–1388. [PubMed: 28382806]
7. Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. *Prevent Treat*. 1998;1.
8. Corsi N, Colloca L. Placebo and nocebo effects: the advantage of measuring expectations and psychological factors. *Front Psychol*. 2017;8:308. [PubMed: 28321201]
9. Colloca L, Flaten MA, Meissner K. Placebo and pain from bench to bedside 2013.
10. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain*. 2006;124:126–133. [PubMed: 16701952]
11. Colloca L, Sigauco M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain*. 2008;136:211–218. [PubMed: 18372113]
12. Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. *Pain*. 2009;144:28–34. [PubMed: 19278785]
13. Vogtle E, Barke A, Kroner-Herwig B. Nocebo hyperalgesia induced by social observational learning. *Pain*. 2013;154:1427–1433. [PubMed: 23707275]
14. Blasini M, Corsi N, Klinger R, Colloca L. Nocebo and pain: an overview of the psychoneurobiological mechanisms. *Pain Rep*. 2017;2(2):e585. [PubMed: 28971165]
15. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol*. 2007;20:435–439. [PubMed: 17873596]
16. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. *Psychosom Med*. 2011;73:598–603. [PubMed: 21862825]
17. Colloca L, Tinazzi M, Recchia S, et al. Learning potentiates neurophysiological and behavioral placebo analgesic responses. *Pain*. 2008;139:306–314. [PubMed: 18538928]
18. Doganci B, Breimhorst M, Hondrich M, Rodriguez-Raecke R, May A, Birklein F. Expectations modulate long-term heat pain habituation. *Eur J Pain*. 2011;15:384–388. [PubMed: 20951617]

19. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. *Pain*. 2010;151:430–439. [PubMed: 20817355]
20. Freeman S, Yu R, Egorova N, et al. Distinct neural representations of placebo and nocebo effects. *Neuroimage*. 2015;112:197–207. [PubMed: 25776211]
21. Jensen K, Kirsch I, Odmalm S, Kaptchuk TJ, Ingvar M. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. *Proc Natl Acad Sci USA*. 2015;112:7863–7867. [PubMed: 25979940]
22. Colloca L. Placebo, nocebo, and learning mechanisms. *Handb Exp Pharmacol*. 2014;225:17–35. [PubMed: 25304524]
23. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med*. 2002;136:471–476. [PubMed: 11900500]
24. Miller FG, Colloca L. Semiotics and the placebo effect. *Perspect Biol Med*. 2010;53:509–516. [PubMed: 21037405]
25. Adler HM. Toward a biopsychosocial understanding of the patient-physician relationship: an emerging dialogue. *J Gen Intern Med*. 2007;22:280–285. [PubMed: 17357001]
26. Wickramasekera I. A conditioned response model of the placebo effect predictions from the model. *Biofeedback Self Regul*. 1980;5:5–18. [PubMed: 7370359]
27. Kirsch I. Response expectancy theory and application: a decennial review. *Appl Prevent Psychol*. 1997;6:69–79.
28. Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. *Curr Pain Headache Rep*. 2014;18:419. [PubMed: 24771206]
29. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: from concepts to genes. *Neuroscience*. 2015;307:171–190. [PubMed: 26272535]
30. Pavlov IP. *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*. London: Oxford University Press; 1927.
31. Howe LC, Goyer JP, Crum AJ. Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response. *Health Psychol*. 2017.
32. Conboy LA, Macklin E, Kelley J, Kokkotou E, Lembo A, Kaptchuk T. Which patients improve: characteristics increasing sensitivity to a supportive patient-practitioner relationship. *Soc Sci Med*. 2010;70:479–484. [PubMed: 19900742]
33. Crum AJ, Langer EJ. Mind-set matters. *Psychol Sci*. 2007;18:165–171. [PubMed: 17425538]
34. Crum AJ, Leibowitz KA, Verghese A. Making mindset matter. *BMJ*. 2017;356:j674. [PubMed: 28202443]
35. Crum AJ, Salovey P, Achor S. Rethinking stress: the role of mindsets in determining the stress response. *J Pers Soc Psychol*. 2013;104:716–733. [PubMed: 23437923]
36. Crum A, Zuckerman B. Changing mindsets to enhance treatment effectiveness. *JAMA*. 2017;317:2063–2064. [PubMed: 28418538]
37. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*. 2009;63:533–543. [PubMed: 19709634]
38. Zubieta JK, Bueller JA, Jackson LR, et al. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci*. 2005;25:7754–7762. [PubMed: 16120776]
39. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science*. 2001;29:1164–1166.
40. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry*. 2008;65:220–231. [PubMed: 18250260]
41. Benedetti F, Amanzio M, Rosato R, Blanchard C. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. *Nat Med*. 2011;17:1228–1230. [PubMed: 21963514]
42. Colloca L, Pine DS, Ernst M, Miller FG, Grillon C. Vasopressin boosts placebo analgesic effects in women: a randomized trial. *Biol Psychiatry*. 2016;79:794–802. [PubMed: 26321018]
43. Kessner S, Sprenger C, Wrobel N, Wiech K, Bingel U. Effect of oxytocin on placebo analgesia: a randomized study. *JAMA*. 2013;310:1733–1735. [PubMed: 24150470]

44. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J Neurosci.* 2006;26:12014–12022. [PubMed: 17108175]
45. Beecher HK The powerful placebo. *J Am Med Assoc.* 1955;159:1602–1606. [PubMed: 13271123]
46. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA.* 2002;287:1840–1847. [PubMed: 11939870]
47. Shedden Mora M, Nestoriuc Y, Winfried R. Lessons learned from placebo groups in antidepressant trials. *Philos Trans R Soc Lond B Biol Sci.* 2011;366:1879–1888. [PubMed: 21576145]
48. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci* 2005;6:545–552. [PubMed: 15995725]
49. Andrews G. Placebo response in depression: bane of research, boon to therapy. *Br J Psychiatry.* 2001;178:192–194. [PubMed: 11230026]
50. Greene CS, Goddard G, Macaluso GM, Mauro G. Topical review: placebo responses and therapeutic responses. How are they related? *J Orofacial Pain.* 2009;23:93–107. [PubMed: 19492534]
51. Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain.* 2001;90:205–215. [PubMed: 11207392]
52. Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol.* 2004;3:679–684. [PubMed: 15488461]
53. Benedetti F, Maggi G, Lopiano L. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. *Prevent Treat.* 2003.
54. Schenk LA, Krimmel SR, Colloca L. Observe to get pain relief: current evidence and potential mechanisms of socially-learned pain modulation. *Pain.* 2017 In press.
55. Hunter T, Siess F, Colloca L. Socially induced placebo analgesia: a comparison of a pre-recorded versus live face-to-face observation. *Eur J Pain.* 2014;18:914–922. [PubMed: 24347563]
56. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Sci Transl Med.* 2011;3 70ra14.
57. Kessner S, Wiech K, Forkmann K, Ploner M, Bingel U. The effect of treatment history on therapeutic outcome: an experimental approach. *JAMA Intern Med.* 2013;173:1468–1469. [PubMed: 23780284]
58. Klinger R, Blasini M, Schmitz J, Colloca L. Nocebo effects in clinical studies: hints for pain therapy. *Pain Rep.* 2017;00:1–7.
59. Klinger R, Kothe R, Schmitz J, Kamping S, Flor H. Placebo effects of a sham opioid solution: a randomized controlled study in patients with chronic low back pain. *Pain.* 2017 In press.
60. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain.* 2016;157:2766–2772. [PubMed: 27755279]
61. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One.* 2010;5:e15591. [PubMed: 21203519]
62. Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions? *J Neurosci.* 2007;27:11934–11939. [PubMed: 17978033]
63. Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo response; boost pain endurance and physical performance: is it doping in sport competitions? *J Neurosci.* 2007;27:11934–11939. [PubMed: 17978033]
64. Colloca L, Enck P, DeGrazia D. Relieving pain using dose-extending placebos: a scoping review. *Pain.* 2016;157: 1590–1598. [PubMed: 27023425]
65. Winocur E, Gavish A, Halachmi M, Eli I, Gazit E. Topical application of capsaicin for the treatment of localized pain in the temporomandibular joint area. *J Orofacial Pain.* 2000;14:31–36. [PubMed: 11203735]
66. Gracely RH, Dubner R, Deeter WR, Wolskee PJ. Clinicians' expectations influence placebo analgesia In: Miller FG, editor. *The Placebo: A Reader*, 115. Baltimore, MD: The Johns Hopkins University Press; 1985.

67. Jensen KB, Petrovic P, Kerr CE, et al. Sharing pain and relief: neural correlates of physicians during treatment of patients. *Mol Psychiatry*. 2014;19:392–398. [PubMed: 23358155]
68. Fleming PS, Strydom H, Katsaros C, et al. Non-pharmacological interventions for alleviating pain during orthodontic treatment. *Cochrane Database Syst Rev*. 2016.
69. Nobrega C, da Silva EM, de Macedo CR. Low-level laser therapy for treatment of pain associated with orthodontic elastomeric separator placement: a placebo-controlled randomized double-blind clinical trial. *Photomed Laser Surg*. 2013;31:10–16. [PubMed: 23153291]
70. Farzanegan F, Zebarjad SM, Alizadeh S, Ahrari F. Pain reduction after initial archwire placement in orthodontic patients: a randomized clinical trial. *Am J Orthod Dentofacial Orthop*. 2012;141:169–173. [PubMed: 22284284]
71. Turhani D, Scheriau M, Kapral D, Benesch T, Jonke E, Bantleon HP. Pain relief by single low-level laser irradiation in orthodontic patients undergoing fixed appliance therapy. *Am J Orthod Dentofacial Orthop*. 2006;130:371–377. [PubMed: 16979496]
72. Kim WT, Bayome M, Park JB, Park JH, Baek SH, Kook YA. Effect of text message follow-up on patient's self-reported level of pain and anxiety. *Angle Orthod*. 2013;83:605–610. [PubMed: 23210546]
73. Harazaki M, Isshiki Y. Soft laser irradiation effects on pain reduction in orthodontic treatment. *Bull Tokyo Dent Coll*. 1997;38:291–295. [PubMed: 9566142]
74. Woodhouse NR, DiBiase AT, Papageorgiou SN, et al. Supplemental vibrational force does not reduce pain experience during initial alignment with fixed orthodontic appliances: a multicenter randomized clinical trial. *Sci Rep*. 2015.
75. Benson PE, Razi RM, Al-Bloushi RJ. The effect of chewing gum on the impact, pain and breakages associated with fixed orthodontic appliances: a randomized clinical trial. *Orthod Craniofac Res*. 2012;15:178–187.
76. Otasevic M, Naini FB, Gill DS, Lee RT. Prospective randomized clinical trial comparing the effects of a masticatory bite wafer and avoidance of hard food on pain associated with initial orthodontic tooth movement. *Am J Orthod Dentofacial Orthop*. 2006;130(6):e9–15.
77. Huang R, Wang J, Wu D, et al. The effects of customised brainwave music on orofacial pain induced by orthodontic tooth movement. *Oral Diseases*. 2016;22:766–774. [PubMed: 27417074]
78. Keith DJ, Rinchuse DJ, Kennedy M, Zullo T. Effect of text message follow-up on patient's self-reported level of pain and anxiety. *Angle Orthod*. 2013;83:605–610. [PubMed: 23210546]
79. Lobre WD, Callegari BJ, Gardner G, Marsh CM, Bush AC, Dunn WJ. Pain control in orthodontics using a micropulse vibration device: a randomized clinical trial. *Angle Orthod*. 2016;86:625–630. [PubMed: 26496680]
80. Marie SS, Powers M, Sheridan JJ. Vibratory stimulation as a method of reducing pain after orthodontic appliance adjustment. *J Clin Orthod*. 2003;37:205–208. [PubMed: 12747073]
81. Miles P, Fisher E. Assessment of the changes in arch perimeter and irregularity in the mandibular arch during initial alignment with the AcceleDent Aura appliance vs no appliance in adolescents: a single-blind randomized clinical trial. *Am J Orthod Dentofacial Orthop*. 2016;150: 928–936. [PubMed: 27894541]
82. Miles P, Smith H, Weyant R, Rinchuse DJ. The effects of a vibrational appliance on tooth movement and patient discomfort: a prospective randomised clinical trial. *Aust Orthod J*. 2012;28:213–218. [PubMed: 23304970]
83. Klinger R, Blasini M, Schmitz J, Colloca L. Nocebo effects in clinical studies: hints for pain therapy. *Pain Rep*. 2017;2:e586. [PubMed: 29034363]
84. Hull SC, Colloca L, Avins A, et al. Patients' attitudes about the use of placebo treatments: telephone survey. *BMJ*. 2013;347:f3757. [PubMed: 23819963]
85. Martin AL, Katz J. Inclusion of authorized deception in the informed consent process does not affect the magnitude of the placebo effect for experimentally induced pain. *Pain*. 2010;149:208–215. [PubMed: 20172652]
86. Colloca L. Sham opioids relieve multidimensional aspects of chronic back pain. *Pain*. 2017 In press.
87. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*. 2014;6 218ra215.

88. Kokkotou E, Conboy LA, Ziogas DC, et al. Serum correlates of the placebo effect in irritable bowel syndrome. *Neurogastroenterol Motil.* 2010;22:285–e281. [PubMed: 20028464]
89. Egbert LD, Battit GE, Welch CE, Bartlett MK Reduction of postoperative pain by encouragement and instruction of patients. A study of doctor-patient rapport. *N Engl J Med.* 1964;270:825–827. [PubMed: 14108087]
90. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain.* 2001;93:77–84. [PubMed: 11406341]
91. Martin-Pichora AL, Mankovsky-Arnold TD, Katz J. Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. *J Pain Res.* 2011;4:67–77. [PubMed: 21559352]
92. Kirsch I. Conditioning, expectancy, and the placebo effect: comment on Stewart-Williams and Podd (2004). *Psychol Bull.* 2004;130:341–343. [PubMed: 14979776]
93. Colagiuri B, Quinn VF, Colloca L. Nocebo hyperalgesia, partial reinforcement, and extinction. *J Pain.* 2015;16: 995–1004. [PubMed: 26168876]
94. Brody H, Miller FG. Lessons from recent research about the placebo effect—from art to science. *JAMA.* 2011;306:2612–2613. [PubMed: 22187283]
95. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci.* 2003;23:4315–4323. [PubMed: 12764120]
96. Bartels DJ, van Laarhoven AI, Haverkamp EA, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One.* 2014;9:e91727. [PubMed: 24646924]
97. Brody H. The placebo response. Recent research and implications for family medicine. *J Fam Pract.* 2000;49: 649–654. [PubMed: 10923577]
98. Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. *J R Soc Med.* 2008;101:222–225. [PubMed: 18463276]
99. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. *Lancet.* 2001;357:757–762. [PubMed: 11253970]