Placebo and Nocebo Effects on Itch: Methodological and Clinical Implications

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What Are Placebo and Nocebo Effects?

Placebo and nocebo effects can be described as positive or negative treatment effects respectively, after the administration of an inert or active treatment, that are not due to the treatment itself [1]. Both placebo and nocebo effects are most commonly observed on self-reported outcomes, such as pain, the most frequently investigated symptom in the field [2–4]. Extensive neurobiological research also indicates that placebo and nocebo effects are characterized by changes in brain processes, immunologic or neuroendocrine responses, and the autonomic nervous system [5, 6].

The core mechanism of placebo and nocebo effects is expectancy [1, 7–9]. The expectation that a treatment will be effective can predict and even cause positive treatment outcomes to occur, whereas the converse is true for expectations of harmful treatment effects. These expectations can be both conscious and automatically regulated [10] and are induced by learning processes. The main learning processes that have been found to underlie the induction of expectations in placebo and nocebo effects are verbal suggestion, conditioning, and social learning. Verbal suggestions are instructions regarding the expected or intended treatment outcomes that can, for example, be given by a clinician during a consult (e.g., "The agent that you have just received is known to powerfully reduce itch in some patients") [2, 3, 11–15]. Conditioning refers to the effects of prior treatment experiences on subsequent treatment outcomes. Research on the role of conditioning in placebo and nocebo effects involves the pairing of an originally neutral stimulus (e.g., inert pill) with an unconditioned stimulus (e.g., reduced pain stimulation) that triggers a reduced pain sensation. After successful pairing, the inert pill alone can elicit a pain reduction [11, 16–23]. Social, or observational, learning in placebo and nocebo

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_14

effects entails a patient observing that a treatment has positive or negative treatment outcomes for another person (either somebody present in real life or observed on video), causing the patient to experience similar treatment outcomes in response to an inert treatment [24–26]. In addition to learning, contextual factors largely influence placebo and nocebo effects. Most importantly, the quality of the doctor-patient relation plays a significant role. Research indicates that a warm and empathic attitude, as well as reassurance and validation of the patient's concerns can improve treatment outcomes and can interact with expectation inductions such as verbal suggestions [27–31]. Furthermore, treatment characteristics (e.g., pill or injection), characteristics of the patient and clinician (e.g., personality characteristics, professional status), and the health-care setting can also influence placebo and nocebo effects [7, 32, 33].

What Is the Evidence for Placebo and Nocebo Effects on Itch?

Placebo and nocebo effects on itch have been studied predominantly during the last decade, both in the clinical setting and in experiments. A recent meta-analysis of clinical trials underscores the potency of placebos in the treatment of itch [34]. In this meta-analysis, the placebo arms of clinical trials for systemic medications in patients with atopic dermatitis, psoriasis, and idiopathic urticaria were studied. The patients in the placebo arm of the clinical trials showed a 24 %-reduction in itch symptoms after systemic placebo treatment. Itch symptoms decreased on average by 1.3 (95 % confidence interval 1.0–1.6) on a scale from 0 to 10, which is in terms of effects size a moderate to large effect. Nocebo effects on itch in the clinical setting have, for example, been examined in studies investigating allergic reactions after (placebo) drug administration. Outpatients from allergology departments were blindly exposed to an oral challenge of placebo medication as part of routine medical practice [35, 36]. Patients had been selected on basis of previously experienced adverse drug reactions, i.e., generalized itch, urticaria, or respiratory symptoms, assuming that these patients were vulnerable to nocebo effects after adverse drug reactions. Results demonstrated that up to 27 % of the patients displayed nocebo responses, such as itch and skin lesions, after the placebo drug administration.

In experimental studies, patients' or healthy subjects' expectations regarding itch increase or decrease were induced by the main learning processes: verbal suggestion, conditioning, and social learning. In studies directed to verbal suggestion and conditioning, expectations were induced with regard to itch evoked by somatosensory stimuli, e.g., histamine [37–42]. Generally, results indicate that itch can be amplified by inducing nocebo expectations, and lowered by inducing placebo expectations [37–42]. Verbal suggestion seems to be sufficient to induce itch nocebo effects, while for the induction of placebo effects on itch the combination of verbal suggestion and conditioning seems to work best. These findings are comparable to other areas, such as pain research [1]. There is preliminary evidence that not only self-report of itch, but also physiological skin responses may be affected by placebo effects, particularly when using a conditioning procedure following histamine application [43, 44]. For example, in a conditioning study by Goebel and colleagues (2008), the repeated administration of an antihistaminic along with a novel tasting drink, resulted in a placebo effect on the skin responses after substituting the antihistaminic by similarly looking placebo medication offered together with the drink [44]. A phenomenon closely related to placebo and nocebo effects, i.e., contagious itch, involves social learning. Itch' contagiousness has originally been demonstrated by a study of Niemeier and colleagues [45], showing that people scratched more during a lecture about itch, including itch images, than during a neutral lecture. Since then, several studies have investigated contagious itch, for example by displaying videos depicting scratching people or by displaying pictures of insects or allergic reactions (e.g., [46–50]). The itch sensation induced by contagious itch is neurobiologically comparable to physically induced itch, e.g., by histamine [46]. These experimental studies on expectation inductions and contagious itch support the role of placebo and nocebo effects in itch.

Studies from placebo and nocebo effects in itch as well as contagious itch studies suggest that placebo and nocebo effects seem to play an even larger role in itch than in other sensations, such as pain (e.g., [41, 50]). The finding that itch is relatively easily induced by talking about itch or by displaying visual stimuli might be related to its underlying evolutionary function to protect against invaders of the skin, e.g., mosquitos. Apparently, when observing itch-related signals from the environment, the processing of itch is given high priority. In an early stage of information processing, attentional processes take care of filtering – mainly on an automatic level – which stimuli should be attended to, and thus more extensively processed. Due to its susceptibility to suggestion in combination with a high prioritization in the processing on an automatic level [41, 46–48], the sensation of itch may be particularly sensitive to placebo and nocebo effects.

How to Control for Placebo and Nocebo Effects?

In clinical research and practice, physicians are interested to know the "real" treatment effects in their patients, independently of possible placebo and nocebo effects. Also, clinical trials that usually consist of an intervention and a placebo arm without an additional condition with no treatment, cannot disentangle the "true" from placebo effects on itch. If physicians or researchers want to control placebo or nocebo effects in their patients or studies, additional procedures are required [1].

Since expectancies play a major role in the induction of placebo and nocebo effects, eliminating expectancies is the most effective way to control for placebo and nocebo effects. In open-hidden paradigms, the effects of openly administering a treatment, in full view of a patient by a clinician along with suggestions regarding treatment effects, is compared to treatment administration outside of the patient's awareness (hidden, e.g., infusion of drug regulated via a machine). Studies using this design demonstrate that the effects of active treatments such as morphine are significantly reduced when a patient is not aware of its administration [51–55]. Another possibility might be (after agreement of the patient about this procedure) not to disclose the moment at which the treatment is administered or expected to work. In clinical trials, it is necessary to add other control conditions to take the placebo and nocebo effects into account [1, 56]. At least, a condition without any treatment components should be added as a comparison group. When comparing the placebo condition to both the treatment and the control condition without treatment, relatively precise estimations of the intervention under investigation can be made. In addition, the information given in regular treatments and clinical trials strongly influences patients, such as the information that a patient has a 50 % or 100 % chance of receiving an active treatment. Ideally, trials consist of both blinded and non-blinded conditions (open-label designs) that vary in the amount of knowledge patients have about the treatment they receive. However, studies have hardly controlled for these placebo and nocebo effects in the area of itch.

How to Minimize or Alter Nocebo Effects?

Nocebo responses have a tremendous impact on clinical practice as they can initiate or worsen adverse treatment effects and reduce treatment efficacy. Particularly the doctor-patient communication about side effects of treatments appears to be an important trigger for nocebo effects in clinical practice, based on the main learning processes of verbal suggestion, conditioning, and social learning.

Whereas information regarding side effects or other information relevant for patient decision-making should in no case be withheld from patients, the way in which this is communicated is important, since it has the potential to induce unhelpful expectations and consequently nocebo effects. For example, a study on influenza vaccination showed that fewer adverse events were reported after influenza vaccination by patients who got information about the proportion of persons who tolerated the procedure well than by those who were informed about the proportion of persons who experienced adverse

events [57]. Studies on itch have still to be conducted to support this effect of positively framed information to patients rather than delivering detailed lists of specific adverse side effects. Additional suggestions to reduce nocebo effects are to provide percentages of occurrence of side effects instead of using a frequency format and to emphasize on patients ability to cope with possible mild side effects [58, 59]. In addition, experimental studies have shown that positive verbal information can minimize nocebo effects. For example, providing positive information as well as explaining how nocebo effects work to the patients can possibly reverse or dilute the effects of previously provided negative information as shown in studies regarding nocebo-like effects in wind turbine sound [60, 61]. The only study in the area of itch on this topic is a recent experimental study of our research group, which indicated that inducing positive expectations by conditioning and verbal suggestion can eliminate previously induced nocebo effects on itch [62], delivering further support for the role of positively framing information after induction of nocebo-effects. Finally, in the context of what is ethically desirable, procedures such as permitted non-information in which a patient agrees that no or less information about possible mild or temporary side effects is provided, can be considered for subgroups of highly anxious patients. For these groups, hidden-administration procedures for treatments with short-term unpleasant consequences might be possible when previously agreed upon by the patient [63].

For specific subgroups of patients with highly negative and inadequate expectations about a treatment (e.g., due to prior experiences of strong side effects or treatment failure), additional therapeutic psychological interventions, including techniques to reduce distress levels and anxiety (e.g., relaxation techniques), provided by a health professional can be an option. In addition, imagery of desired outcome, e.g., positive treatment outcomes, can induce positive expectations and enhance treatment outcomes [64, 65]. For example, brief imagery of reduced pain when immersing ones hand in cold water (by using an image of a glove) induced expectations of lowered pain and reduced actually experienced pain during a subsequent cold pressor task, especially when combined with a verbal suggestion regarding the effectiveness of the imagery exercise [66]. Comparable techniques for itch have still to be developed.

In addition to these psychological interventions in the area of doctor-patient communication, there are studies showing possible promising pharmacological or neurobiological pathways. For example, Benedetti and colleagues found that a nonspecific cholecystokinin (CCK) antagonist or benzodiazepine diazepam could block nocebo hyperalgesia [67, 68]. Possibly, similar interventions could be useful to prevent nocebo responses in itch. A more recent development in placebo research is transcranial magnetic stimulation (TMS) of the right dorsolateral prefrontal cortex (rDLPFC) aimed at reducing nocebo effects [69, 70]. However, much more research is warranted on the mechanisms, effects and the neurobiological and pharmacological pathways, also in the field of itch, before it can be used in clinical practice.

Can We Use Placebo Effects Therapeutically?

Placebo effects are largely influenced by the way in which a treatment is administered and prescribed by the physician. Different techniques can be used to optimize expectations and thereby make optimal use of placebo effects in the treatment of itch in an ethical way.

For the doctor-patient communication, it is important to inform the patient about intended and expected positive outcomes (and other aspects) of itch-reducing treatments in a realistic and easy to understand manner, without neglecting to mention possible side effects (i.e., harms). In addition to the face-to-face communication, written information (e.g., educational leaflets or online information about the treatment) or written or recorded testimonies of other patients who received successful treatment (e.g., leaflets by patient organizations) can be provided. For example, Tang and Colagiuri [71] found evidence that an educational leaflet about the efficacy of

analgesics can enhance the placebo analgesic effects of a verbal suggestion.

From the perspective of long-term conditioning processes, it is important to assess previous treatment experiences, since past treatment experiences can transfer to subsequent treatments, particularly if treatments are alike [72, 73]. Sticking to a route of administration that was previously experienced to be effective might enhance current treatment outcomes. Moreover, administering treatments in an open manner and emphasizing salient sensory aspects of the treatment (e.g., visual, tactile, or olfactory) to enhance awareness can establish a strong association between the treatment and its symptom relieving effects, and might thereby possibly enhance treatment effects. Also other contextual factors can facilitate these conditioning processes, e.g., administering treatment at a fixed time of the day in the same room [74].

Pharmacological treatment options to make optimal use of placebo effects are a promising new area of research. For example, by use of placebo-controlled drug reduction (PCDR) based on the principles of conditioning. PCDR provides the option of starting treatment with repeated full doses to establish associative learning and replacing medication by placebos later on. For example, psoriasis patients who received a full corticosteroid dose 25–50 % of the time displayed reductions in lesion severity that were equal to patients who continuously received a full dose and greater than patients who continuously received a dose that was reduced with 25–50 % [75]. Finally, recent experimental studies suggest that pharmacological treatments, such as oxytocin and vasopressin administration, can directly influence placebo effects [76, 77], however, this research is still in its infancy.

What Are the Implications for Research and Treatment of Itch?

Both clinical and experimental research increasingly support the role that placebo and nocebo effects play in itch, which appear comparable to other areas, such as pain. In view of the relatively limited research on placebo and nocebo effects on itch up to now, a major challenge remains whether experimental laboratory findings on placebo and nocebo effects on induced itch of short duration in healthy subjects can be generalized to patients in a clinical setting. The evidence from natural settings, such as studies from contagious itch, suggests a high relevance for clinical practice. Research focusing on both psychological and neurobiological mechanisms in healthy subjects and patients can further elucidate the specific mechanisms underlying placebo and nocebo effects on itch. This knowledge may help improve therapeutic interventions by enhancing favorable expectations and reducing unfavorable expectations in patients suffering from chronic itch conditions.

Acknowledgements Realization of this book chapter was supported by an ERC Consolidator Grant from the European Research Council (ERC) and an Innovation Scheme (Vidi) Grant from the Netherlands Organization for Scientific Research (NWO), awarded to AWM Evers. The authors declare no conflict of interest.

References

1. Benedetti F. Placebo effects. Understanding the mechanisms in health and disease. Oxford: Oxford University Press; 2008.
2. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, Vase L. The magnitude of nocebo effects in pain: a meta-analysis. Pain. 2014;155(8):1426–34.
3. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain. 2002;99(3):443–52.
4. Vase L, Petersen GL, Riley 3rd JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. Pain. 2009;145(1–2):36–44.
5. Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. In: Handbook of experimental pharmacology, Springer-Verlag, Berlin Heidelberg; vol 225. 2014. p. 37–69.
6. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. Pharmacol Rev. 2015;67(3):697–730.
7. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. Front Psychol. 2014;5:1079.
8. Kirsch I. Response expectancy as a determinant of experience and behavior. Am Psychol. 1985;40(11):1189–202.

9. Kirsch I. Response expectancy theory and application: a decennial review. Appl Prev Psychol. 1997;6(2):69–79.
10. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. Psychol Bull. 2004;130(2):324–40.
11. Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. Pain. 2007;128(1–2):31–9.
12. Schmid J, Theysohn N, Gass F, Benson S, Gramsch C, Forsting M, Gizewski ER, Elsenbruch S. Neural mechanisms mediating positive and negative treatment expectations in visceral pain: a functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. Pain. 2013;154(11):2372–80.
13. Vase L, Robinson ME, Verne GN, Price DD. Increased placebo analgesia over time in irritable bowel syndrome (ibs) patients is associated with desire and expectation but not endogenous opioid mechanisms. Pain. 2005;115(3):338–47.
14. Carlino E, Benedetti F, Pollo A. The effects of manipulating verbal suggestions on physical performance. Z Psychol. 2014;222(3):154–64.
15. Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, de la Fuente-Fernandez R, Phillips AG, Stoessl AJ. Effects of expectation on placebo-induced dopamine release in parkinson disease. Arch Gen Psychiatry. 2010;67(8):857–65.
16. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci. 1999;19(1):484–94.
17. 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(10):4315–23.
18. Lui F, Colloca L, Duzzi D, Anchisi D, Benedetti F, Porro CA. Neural bases of conditioned placebo analgesia. Pain. 2010;151(3):816–24.
19. Freeman S, Yu R, Egorova N, Chen X, Kirsch I, Claggett B, Kaptchuk TJ, Gollub RL, Kong J. Distinct neural representations of placebo and nocebo effects. Neuroimage. 2015;112:197–207.
20. 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 U S A. 2015;112(25):7863–7.
21. Kirsch I, Kong J, Sadler P, Spaeth R, Cook A, Kaptchuk T, Gollub R. Expectancy and conditioning in placebo analgesia: separate or connected processes? Psychol Conscious. 2014;1(1):51–9.
22. Klosterhalfen S, Kellermann S, Braun S, Kowalski A, Schrauth M, Zipfel S, Enck P. Gender and the nocebo response following conditioning and expectancy. J Psychosom Res. 2009;66(4):323–8.
23. Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. Pain. 1997;72(1–2):107–13.
24. Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. Pain. 2009;144(1–2):28–34.
25. 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(7):914–22.
26. Vogtle E, Barke A, Kroner-Herwig B. Nocebo hyperalgesia induced by social observational learning. Pain. 2013;154(8):1427–33.
27. Greville-Harris M, Dieppe P. Bad is more powerful than good: the nocebo response in medical consultations. Am J Med. 2015;128(2):126–9.
28. Jubb J, Bensing JM. The sweetest pill to swallow: how patient neurobiology can be harnessed to maximise placebo effects. Neurosci Biobehav Rev. 2013;37(10):2709–20.
29. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, Kirsch I, Schyner RN, Nam BH, Nguyen LT. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336(7651):999–1003.
30. Kelley JM, Kraft-Todd G, Schapira L, Kossowsky J, Riess H. The influence of the patient-clinician relationship on healthcare outcomes: a systematic review and metaanalysis of randomized controlled trials. Plos One. 2014;9(4):e94207.
31. Verheul W, Sanders A, Bensing J. The effects of physicians' affect-oriented communication style and raising expectations on analogue patients' anxiety, affect and expectancies. Patient Educ Couns. 2010;80(3):300–6.
32. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. Lancet. 2001;357(9258):757–62.
33. de Craen AJM, Tijssen JGP, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. J Neurol. 2000;247(3):183–8.
34. van Laarhoven AIM, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AWM. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol. 2015;135(5):1234–43.
35. Liccardi G, Senna G, Russo M, Bonadonna P, Crivellaro M, Dama A, D'Amato M, D'Amato G, Canonica GW, Passalacqua G. Evaluation of the nocebo effect during oral challenge in patients with adverse drug reactions. J Investig Allergol Clin Immunol. 2004;14(2):104–7.
36. Lombardi C, Gargioni S, Canonica GW, Passalacqua G. The nocebo effect during oral challenge in subjects with adverse drug reactions. Eur Ann Allergy Clin Immunol. 2008;40(4):138–41.
37. Bartels DJP, van Laarhoven AIM, Haverkamp EA, Wilder-Smith OH, Donders ART, van Middendorp H, van de Kerkhof PCM, Evers AWM. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. Plos One. 2014;9(3):e91727.

38. Darragh M, Chang JW, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: the influence of verbal suggestion on itch and weal size. J Psychosom Res. 2015;78(5):489–94.
39. Napadow V, Li A, Loggia ML, Kim J, Mawla I, Desbordes G, Schalock PC, Lerner EA, Tran TN, Ring J, Rosen BR, Kaptchuk TJ, & Pfab F. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. Allergy, 2015 ;70(11):1485–1492.
40. Scholz OB, Hermanns N. Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol. 1994;23(2):127–35.
41. van Laarhoven AIM, Vogelaar ML, Wilder-Smith OH, van Riel PLCM, van de Kerkhof PCM, Kraaimaat FW, Evers AWM. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152:1486–94.
42. Sölle AB, Bartholomäus T, Worm M, Klinger R. How to psychologically minimize scratching impulses: benefits of placebo effects on itch using classical conditioning and expectancy. Z Psychol. 2014;222(3):140–7.
43. Vits S, Cesko E, Benson S, Rueckert A, Hillen U, Schadendorf D, Schedlowski M. Cognitive factors mediate placebo responses in patients with house dust mite allergy. Plos One. 2013;8(11):e79576.
44. Goebel MU, Meykadeh N, Kou W, Schedlowski M, Hengge UR. Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychother Psychosom. 2008;77(4):227–34.
45. Niemeier V, Kupfer J, Gieler U. Observations during an itch-inducing lecture. Dermatol Psychosom. 2000;1:15–8.
46. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A. 2012;109(48):19816–21.
47. Lloyd DM, Hall E, Hall S, McGlone FP. Can itch-related visual stimuli alone provoke a scratch response in healthy individuals? Br J Dermatol. 2013;168(1):106–11.
48. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans. A study of visual "transmission" of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011;164(6):1299–303.
49. Schut C, Muhl S, Reinisch K, Classen A, Jager R, Gieler U, Kupfer J. Agreeableness and self-consciousness as predictors of induced scratching and itch in patients with psoriasis. Int J Behav Med. 2015;22(6):726–34.
50. Ward J, Burckhardt V, Holle H. Contagious scratching: shared feelings but not shared body locations. Front Hum Neurosci. 2013;7:122.
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(3):205–15.
52. Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. J Neurosci. 2012;32(23):8053–64.
53. Benedetti F, Maggi G, Lopiano L, Lanotte M, Rainero I, Vighetti S, Pollo A. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. Prev Treat. 2003;6:1a.
54. Petersen GL, Finnerup NB, Grosen K, Pilegaard HK, Tracey I, Benedetti F, Price DD, Jensen TS, Vase L. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. Pain. 2014;155(12):2687–98.
55. Schenk LA, Sprenger C, Geuter S, Buchel C. Expectation requires treatment to boost pain relief: an fmri study. Pain. 2014;155(1):150–7.
56. Vase L, Amanzio M, Price DD. Nocebo vs. placebo: the challenges of trial design in analgesia research. Clin Pharmacol Ther. 2015;97(2):143–50.
57. OConnor AM, Pennie RA, Dales RE. Framing effects on expectations, decisions, and side effects experienced: the case of influenza immunization. J Clin Epidemiol. 1996;49(11):1271–6.
58. Rief W, Bingel U, Schedlowski M, Enck P. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin Pharmacol Ther. 2011;90(5):722–6.
59. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012;307(6):567–8.
60. Crichton F, Petrie KJ. Accentuate the positive: counteracting psychogenic responses to media health messages in the age of the internet. J Psychosom Res. 2015;79(3):185–9.
61. Crichton F, Petrie KJ. Health complaints and wind turbines: the efficacy of explaining the nocebo response to reduce symptom reporting. Environ Res. 2015;140:449–55.
62. Bartels DJP, van Laarhoven AIM, Stroo M, Hijne K, Peerdeman KJ, Donders ART, van de Kerkhof PCM, Evers AWM. Reversing nocebo effects by conditioning with verbal suggestion. Submitted.
63. Hauser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int. 2012;109(26):459–65.
64. Kwekkeboom KL, Wanta B, Bumpus M. Individual difference variables and the effects of progressive muscle relaxation and analgesic imagery interventions on cancer pain. J Pain Symptom Manage. 2008;36(6):604–15.
65. Hanssen MM, Peters ML, Vlaeyen JWS, Meevissen YMC, Vancleef LMG. Optimism lowers pain: evidence of the causal status and underlying mechanisms. Pain. 2013;154(1):53–8.
66. Peerdeman KJ, van Laarhoven AIM, Bartels DJP, Peters ML, Evers AWM. Placebo analgesia via imagery. Submitted.
67. Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. Pain. 1997;71(2):135–40.

68. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J Neurosci. 2006;26(46):12014–22.
69. Krummenacher P, Candia V, Folkers G, Schedlowski M, Schonbachler G. Prefrontal cortex modulates placebo analgesia. Pain. 2010;148(3):368–74.
70. Egorova N, Yu R, Kaur N, Vangel M, Gollub RL, Dougherty DD, Kong J, Camprodon JA. Neuromodulation of conditioned placebo/nocebo in heat pain: anodal vs cathodal transcranial direct current stimulation to the right dorsolateral prefrontal cortex. Pain. 2015;156(7):1342–7.
71. Tang CW, Colagiuri B. Can an educational handout enhance placebo analgesia for experimentally-induced pain? Plos One. 2013;8(10):e77544.
72. Hofmann M, Wrobel N, Kessner S, Bingel U. Minimizing carry-over effects after treatment failure and maximizing therapeutic outcome can changing the route of administration mitigate the influence of treatment history? Z Psychol. 2014;222(3):171–8.
73. 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(15):1468–9.
74. Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov. 2013;12(3):191–204.
75. Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, Kimball AB, Fiorentino D. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med. 2010;72(2):192–7.
76. Kessner S, Sprenger C, Wrobel N, Wiech K, Bingel U. Effect of oxytocin on placebo analgesia: a randomized study. JAMA. 2013;310(16):1733–5.
77. Colloca L, Pine DS, Ernst M, Miller FG, Grillon C. Vasopressin boosts placebo analgesic effects in women: a randomized trial. Biol Psychiatry. 2015;79(10):794–802.