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VIEWPOINT

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Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments

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Abstract

The role of placebo and nocebo effects—that is positive or negative treatment effects that are entirely a consequence of the patient's expectations and beliefs about a treatment outcome in terms of efficacy, safety, usability or side effects—has been shown for almost all types of diseases and physiological response systems. Evidence for the relevance of placebo and nocebo effects in dermatology is also increasing, particularly for symptoms of itch and learned (conditioned) immune function. In addition, increasing knowledge is available about the neurobiological mechanisms of action, such as the role of the dopaminergic system. Studies on this topic offer innovative perspectives to unravel the multifactorial pathways of treatment effects and to use research designs for experimental research that provide full insight into the role of placebo and nocebo effects. Moreover, intervention strategies can be developed for dermatology practice that optimize regular treatments with innovative non-pharmacological treatment strategies (e.g. optimized doctor–patient communication and treatment adherence, or prevention of nocebo reactions with regard to adverse side effects). In addition, evidence on learned immune function offers new pathways to optimize pharmacological treatments (e.g. dosage adjustments and conditioning of physiological responses), the ultimate goal being to prevent individual treatment failures and maximize regular treatment effects.

KEYWORDS

conditioning, doctor–patient communication, expectation, learned immune function, placebo

1 | INTRODUCTION

A large proportion of the success or failure of dermatological treatment can be explained by factors other than the treatment mechanisms themselves. Placebo and nocebo effects, in particular, strongly contribute to treatment outcomes, with explained variances comparable to, for example, effects of analgesics or antidepressants (s1–s5).[1,2] Placebo and nocebo effects are positive or negative treatment effects that are a consequence not of the treatment itself, but exclusively of the patient's expectations and beliefs about a more or less beneficial treatment outcome in terms of efficacy, safety, usability or side effects.[1,2] The relevance of these placebo and nocebo effects has been demonstrated for almost all types of conditions and physiological response systems (e.g. immune and endocrine functioning) (s6–s12). The increasing evidence for placebo and nocebo effects in the field of dermatology has scientific and clinically relevant implications for experimental research designs as well as innovative (non-)pharmacological treatment strategies (s13–s15).

2 | WHAT IS THE EVIDENCE FOR PLACEBO AND NOCEBO EFFECTS IN DERMATOLOGY?

Indirect evidence for the role of placebo and nocebo effects in dermatology comes from contagious itch: itch sensations (in contrast to other physical sensations or noxious stimuli) are highly suggestible,

with both humans and animals starting to scratch themselves after viewing others scratching (s16–s18). Direct evidence for placebo and nocebo induction on itch has been delivered by experimental studies that support the role of both conscious and automatic learning processes, such as verbal suggestions and conditioning (s19–s22).[3–5] In one of the first experiments, negative suggestions about a histamine application resulted in higher itch scores (s19). In a study comparing itch and pain symptoms, nocebo effects were induced for both itch and pain after the verbal suggestion that the majority of subjects generally experienced high levels of itch or pain in response to the stimuli applied.[3] In line with research in other areas, such as pain, placebo and nocebo effects on itch can be induced most effectively by combining automatic and conscious processes, specifically conditioning and verbal suggestions (s20–s22).[4,5] These effects also play a role in dermatological research and practice, as is shown by a meta-analysis of clinical trials of oral systemic medication for psoriasis, atopic dermatitis and urticaria, showing moderate to large effects on itch of placebo medication (without any treatment ingredients).[6] These experimental and clinical studies clearly demonstrate the significance of placebo and nocebo effects in itch treatments and offers possible explanations for itch sensitization in patients suffering from chronic itch (s23). Preliminary evidence for the possible neurobiological pathways comes from a study examining nocebo effects in itch in patients with atopic dermatitis,[4] showing that when applying saline while patients expected a real allergen, similar brain responses were observed as with the previously applied real allergen, with greater activation in the striatum and the dorsolateral prefrontal cortex. These regions have previously also been linked to placebo- or nocebo-induced brain processes related to pain and its regulation (s24–s25).

Placebo and nocebo effects have also been shown to impact physiological pathways. Animal and human studies have shown that physiological reactions of histamine release, for example, can be the result of learning processes such as conditioning (s6–s10).[1] In conditioning trials, a pharmacological agent such as cyclosporine is combined with a neutral cue such as a specific beverage. When later exposed only to the beverage, as a conditioned stimulus, participants show comparable immune reactions as previously to the drug. Specific endocrine reactions, such as insulin reactions, have also been shown to be susceptible to conditioning (s10–s11). Particularly relevant for dermatology are the animal and human studies of conditioning anti-allergic reactions (s7, s9).[7,8] In the first study in humans, patients with allergies were given an antihistamine in combination with a distinct beverage for several days. When the patients were later exposed only to the beverage, they had less severe subjective symptoms and a reduced skin response (smaller wheal size and less basophil activation) to the skin prick test.[7] Results were replicated in part,[8] but much more evidence in this area is needed. Finally, placebo mechanisms with conditioning have also been applied in a clinical dermatological trial, showing comparable treatment effects and relapse rates when patients with psoriasis were treated in a conditioning design with about half of the doses of the topical corticosteroid treatments.[9]

Although results in the area of dermatology are relatively scarce and limited to the fields of itch (e.g. atopic eczema), allergic responses (e.g. house dust mite) or responses to topical corticosteroid treatments (e.g. psoriasis), these results strongly suggest that placebo and nocebo effects play a similar role as in other conditions (e.g. pain, Parkinson, depression) (s6–s12). Future research on the neurobiological effects and mechanisms in other dermatological conditions (e.g. acne, rosacea, lupus) as well as subgroups of patients (e.g. children with eczema) is clearly wanted.

3 | HOW PLACEBO AND NOCEBO EFFECTS WORK AND AFFECT BODILY FUNCTIONS

Research has evolved our understanding about the specific psychoneurobiological mechanisms through which placebo and nocebo effects work. Placebo effects influence treatments through mechanisms of expectancies; these include conscious learning processes, such as verbal suggestions and instructions by a doctor, and more automatic learning processes of conditioning (s2, s15).[1,2] The most effective strategy for reducing acute symptoms during a medical procedure appears to be verbal suggestions, for example by a medical doctor before surgery (s26). To obtain more stable placebo and nocebo effects, the combination of both conscious and automatic processes is most effective, as has been shown for a broad variety of symptoms and conditions, including itch (s2, s15).[1,2] For these longer-term placebo or nocebo effects, conditioning is a necessary learning mechanism, particularly when focusing on changes in the physiological response systems, such as immune and endocrine functioning (s6–s10). Conditioning as a learning mechanism can also explain the large role of individual and environmental influences—such as personality characteristics of patients and doctors' white coats or technical instruments—on the effectiveness of the placebo or nocebo effect for a specific treatment (s3-s5).[1,2] There is, for example, preliminary evidence that placebo effects vary with regard to the type of treatment (e.g. larger effects for intra-articular, subcutaneous and topical treatments than for oral treatments, and stimulant effects for red oral drugs (s27–s29), age groups (e.g. possibly stronger effects in children) (s30–s31), individual differences between patients (e.g. stronger placebo effects for more optimistic individuals and stronger nocebo effects for individuals with more worrying and negative attitudes towards medication)[5] (s5, s24, s32) and cultural differences (e.g. particular large placebo analgesic effects in US trials, possibly due to cultural differences in communication styles about expected drug effects) (s33).

Different neurobiological pathways have been established for these learning mechanisms of expectancies, with most research conducted in the field of pain (s1, s8).[1,2] The first neurobiological pathways were revealed by conditioning experiments that induced placebo responses of analgesic treatment; these placebo responses could be blocked when administering an opioid antagonist (e.g. naloxone).[1] Since then, several other possible physiological pathways have been shown in various symptoms and conditions (s34). For example, proglumide (a CCK-Cholecystokinin antagonist) has been shown to facilitate placebo analgesics and inhibit nocebo hyperalgesics (s34).[1] In addition, specific immune and endocrine responses are known to co-occur with placebo

and nocebo learning processes, as shown by immune and endocrine conditioning studies (e.g. IL-2, cortisol) (s6–s10). The related neurobiological processes of these learning mechanisms are also increasingly being disentangled, indicating for example specific areas of the prefrontal cortex and amygdala that are associated with learning processes of placebo and nocebo effects (s24–s25). These pathways seem at least partly dependent on the specific type of treatment (e.g. opioids for analgesic treatment), possibly due to specific conditioning effects of the drug (s34). However, possible affect-related pathways have also been identified that appear to be related to the reward or fear function of placebo and nocebo effects. For example, dysregulated dopaminergic and cortisol responses are involved in positive and negative expectation learning and memory processes of placebo and nocebo effects (s2, s35–s36).[1,2] Placebo and nocebo effects have finally shown to be also influenced by genotypes (e.g. specific *COMT* genotypes) (s35).[1,2]

4 | WHAT ARE THE IMPLICATIONS OF PLACEBO AND NOCEBO EFFECTS FOR DERMATOLOGICAL PRACTICE?

Particularly the neurobiological insights into how placebo and nocebo effects affect bodily functions contributed to the renewed research attention in this area. This may also have important implications for dermatological research and practice.

1. Dermatologists and their patients need to be aware that treatment outcomes in terms of efficacy and side effects can be partly attributed to their expectations about the treatments.

Although there are no precise effect sizes of placebo and nocebo effects in the area of dermatology yet, results suggest that effects on itch are at least similar as or even stronger than on pain.[3,6] This is possibly due to the high suggestibility of itch. Also, animal and human studies have yielded convincing evidence that learned (conditioned) immune functioning is possible (e.g. conditioning of antihistamines or cyclosporine) (s6–s10).[7] However, this knowledge has not yet been translated to implications for clinical practice. Once dermatologists and other health professionals are aware of the large impact of individual and environmental factors that enhance possible placebo and nocebo responses in their patients, they could pay more explicit attention to factors such as establishing a good doctor–patient relationship, improving the treatment adherence of the patient (e.g. by decreasing fear of side effects), or creating a health-stimulating environment, to optimize treatment effects.

A frequent concern and misunderstanding is that placebo only works when patients are not informed about the real mechanisms of an inert treatment. Open-label trials have demonstrated, however, that even knowing that one receives a placebo leads to beneficial treatments effects, such as fewer symptoms for patients with irritable bowel syndrome (s37–s39). From an ethical perspective, patients need to be informed about the multifactorial influences—including their own expectations—that play a role in treatment effects. This might at times lead to different treatment choices; for example, a regular treatment option might only be started when the patient believes in effects of this treatment or a less aggressive treatment strategy might be chosen for a patient with an elevated fear of side effects. However, the placebo responses and positive expectations of patients will only endure if they are based on trust in a long-term authentic relationship. Highly optimistic promises followed by limited effects will probably result in nocebo instead of placebo effects.

2. Researchers should maximally control for possible placebo effects in research designs.

Researchers are interested to know the actual effects of a specific new treatment, independently of possible placebo and nocebo effects. However, randomized controlled trials usually consist of an intervention and a placebo arm, without an additional condition without any treatment. In research designs, a condition without any treatment components should be preferably added as a comparison group to get relatively precise estimations of the treatment and placebo effects. Moreover, eliminating expectancies is the most effective way to control for placebo and nocebo effects. For example, in open-hidden paradigms, openly administering a treatment can be compared to treatment administration outside of the patient's awareness (e.g. hidden machine-regulated infusion of drug). An alternative procedure is—after agreement of the patient—not to disclose the moment that treatment is administered or expected to work. 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 (s4, s40).

3. Dermatologists can be trained to prevent unintended nocebo effects.

The large and relevant role of placebo and nocebo effects implies a central role of non-pharmacological factors, such as environmental influences and doctor–patient communication, that substantially contribute to treatment outcomes. Additional non-pharmacological treatment options could be considered for patients particularly at risk for nocebo effects, such as patients with numerous side effects due to heightened anxiety about possible adverse effects of regular treatments. To prevent nocebo effects, it is important to recognize that not all patients benefit from being informed in detail about all possible risks and side effects of a treatment. In view of ethical standards for informed consent procedures, future guidelines can focus more on the needs of the individual patient: information might be tailored to the patient's coping style, with information about risks and side effects available if needed, based on evidence-based guidelines on which informed consent procedure is most effective for specific subgroups of patients. In addition, general patient information material can be developed for all types of treatments to inform patients about unintended side effects, for example in the case of exaggerated fears about possible risks. In addition, communication trainings can support dermatologists in their communication about possible placebo and nocebo effects in regular dermatology practice. Moreover, specific nocebo-reducing treatments could be developed for patients who are, for example, particularly anxious and concerned about

possible side effects and risks of a standard treatment. All these factors emphasize non-pharmacological treatment components, such as the role of open and solid communication and the provision of psychological support for patients at risk, to decrease possible nocebo effects.

4. Insurance companies, the pharmaceutical industry and research foundations should realize that placebo responses can be used to optimize treatment outcomes in terms of increased effectiveness, fewer side effects and lower costs.

In view of the evidence for learned immune functioning based on conditioning principles, questions arise as to why these potential effects are not more systematically used to optimize our treatments. All pharmacological therapies make use of placebo effects, if perhaps unintentionally, when a patient starts a new treatment: they promise a better outcome. At the same time, the large heterogeneity in the long-term efficacy of many treatments might be at least partly a consequence of a lack of enduring placebo effects, as the conditioning effects are likely to be extinguished when subjects are not systematically re-exposed to the drug on the basis of conditioning principles (s41). The results of clinical studies (e.g. for pharmacological treatments in ADHD and hormonal ointments in psoriasis) that showed comparable treatment effects or fewer side effects when the dosage of regular treatment was reduced after a period of conditioning[9] (s38–s39) support the idea that the dosage of medication can be adjusted when making full use of possible conditioning effects. This also implies considerable possibilities for developing new treatments. Every drug or medication can be tested on its ability to enhance its effects by means of conditioning, to produce the same physiological reactions without the drug. This knowledge provides important opportunities for new treatment developments in terms of higher efficacy, fewer side effects and lower treatment costs. This has considerable relevance for research foundations, the pharmacological industry and insurance companies. The next challenging step will be to translate this knowledge into regular treatment options that make optimal use of a combination of regular drug therapy with conditioning principles of our physiological response systems, with the ultimate goal of preventing individual treatment failures and maximizing our treatments for all patients.

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CONFLICT OF INTEREST

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