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Placebo and nocebo effects on itch: a review of experimental methods

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Abstract

Itch is a commonly experienced symptom of acute and chronic dermatological and systemic conditions. Placebo and nocebo effects, positive and negative effects experienced after both real and sham interventions, putatively due to positive or negative outcome expectancies, can have a significant impact on the experience of itch and its treatment. Experimental methods to induce and study placebo and nocebo effects on itch have been developed, utilizing various combinations of expectancy-induction methods (eg, conditioning, verbal suggestions) and short-acting itch-evoking stimuli (eg, histamine, electrical, or mechanical stimulation). The aim of this review is to describe the current research methods used to induce placebo and nocebo effects on itch, and the results of these studies. The benefits and drawbacks of different expectancy-induction methods and itch-evoking stimuli are described, and future directions for research and clinical application are discussed.

Keywords: Placebo effect, Nocebo effect, Itch, Pruritus, Verbal suggestion, Conditioning, Expectancy

Itch is a commonly experienced and unpleasant bodily sensation that motivates scratching behavior. Pruritic sensations can occur as symptoms in acute and chronic dermatological conditions[1,2], in systemic diseases such as renal failure[3], and in response to cues in the environment[4]. There is evidence that expectancies, beliefs influenced by observation, contextual factors, and prior events, contribute to the experience of itch[5]. Expectancies are the putative core mechanism underlying placebo and nocebo effects. These effects describe the positive (placebo) or negative (nocebo) response to active and inert interventions, for example placebo or sham medication[6]. Understanding how expectancies affect outcomes for pruritus can improve its clinical treatment and expand our fundamental understanding of the factors which affect physical sensations such as itch.

Experimental studies of placebo and nocebo effects on itch typically combine expectancy-induction methods (eg, verbal suggestion) with the administration of a pruritic stimulus to induce a placebo or nocebo effect on the participants' experience of itch. The most frequently studied expectancy-induction methods used in placebo and nocebo studies can be generally grouped into 2 categories, verbal suggestions and conditioning. Verbal suggestions induce outcome expectancies through explicit instruction or suggestion (eg, instructions by the researcher or health care professional). Classical conditioning is a type of learning that forms and strengthens associations between stimuli and outcomes through repeated pairings of their presentation[7]. The most well-known example of this process comes from Pavlov's[8] observations on the salivary reflex of dogs. Giving a dog food naturally evokes a salivary response in anticipation of the meal. Pavlov observed that other stimuli repeatedly presented before the meal, such as the dog's food bowl, the approaching footsteps of the human bearing the food, or the sound of a bell, could evoke a similar salivary reflex as the meal itself. Associative learning through classical conditioning can occur both explicitly (with conscious awareness of the learner) and implicitly (without conscious awareness)[9]. The itch-evoking stimuli used so far in research on placebo and nocebo effects, which include histamine, electrical stimulation, mechanical stimulation, allergens, and audiovisual stimuli, are all typically capable of inducing acute, mild to moderate itch on a localized part of the body[10]. These stimuli may vary across other attributes, such as administration method, average duration of the itch response, or the resemblance of the model with underlying mechanisms of various clinical conditions. Consideration must be given to the attributes of the expectancy-induction method and accompanying pruritic stimulus when selecting the most suitable methods to address a given research question.

Previous reviews of placebo and nocebo effects on itch have addressed the mechanisms, predictors, and clinical relevance of these effects[11–13]. The current review aims to build on this work and fill a gap in the literature by providing an overview of the methods used to induce placebo and nocebo effects on itch. Common benefits and drawbacks of these methods will be

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described, and potential advances through future research in placebo-induction and nocebo-induction methods for itch will be discussed. First, we describe the expectancy-induction methods used to study placebo and nocebo effects, and the results of studies in this field. This is followed by an overview of the itch-evoking stimuli most frequently used in placebo and nocebo studies. Finally, we discuss the current literature and provide suggestions for future research.

Expectancy-induction methods

Studies of placebo and nocebo effects on itch typically pair an expectancy-induction method (ie, verbal suggestions, conditioning) with one or more itch-evoking stimuli (summarized in **Table 1**) to induce a placebo or nocebo effect on itch. In this section we review the findings of experiments that employed verbal suggestions, conditioning, and their combination, to study placebo and nocebo effects on itch.

Verbal suggestions

Verbal suggestions provide participants with information that can induce and modify their expectancies for future outcomes[34]. Studies of placebo and nocebo effects on itch, like those on pain[35], most frequently make use of verbal suggestion, as this method has proven effective at inducing expectancies and can be relatively easily incorporated into instructions given to participants in an experiment, or to patients in clinical practice.

Placebo effects

Research on the efficacy of verbal suggestions for inducing placebo effects on itch has yielded mixed results. Verbal suggestions for placebo effects on itch have been made for numerous placebo interventions. These include: a suggestion of the positive, itch-relieving effects of placebo lotions[36,37], a suggestion of the itch-relieving and pain-relieving effects of a nasal spray[38], a suggestion of the high likelihood of an effect of reduced physical sensitivity caused by a placebo pill[39], a suggestion of the reduction of itch caused by an electrode[19], and a suggestion of the effect of a (nonexistent) itch-reducing agent added to a histamine iontophoresis procedure[40]. These positive verbal suggestions were compared with conditions which received no verbal suggestion[19,36–38], a control verbal suggestion of a low likelihood of an effect of reduced physical sensitivity caused by a pill[39], or a control verbal suggestion of a high likelihood that participants will experience itch during a histamine iontophoresis procedure[40]. Following the verbal suggestion or control treatment in each experiment, itch of a similar intensity in both suggestion groups was then evoked with histamine skin prick[36,37], histamine iontophoresis[38–40], or electrical stimulation[19]. These studies compared participants' perceived itch intensity between the different verbal suggestion conditions during the itch-evoking procedure, providing a measure of the placebo effect. Only Darragh et al[37] were successful in reducing reported itch sensations during the subsequent histamine skin prick procedure. In this study, an extensive and detailed verbal suggestion regarding the effects of an inert placebo lotion was used. Other studies used verbal suggestions that were relatively short or broad (not specific to itch) and did not find a significant placebo effect on itch[19,36,39,40]. The mixed results of these experiments indicate that further study of factors like the length, specificity, and content of a suggestion is needed to understand the circumstances under which verbal suggestions alone can induce placebo effects on itch.

Nocebo effects

Several experiments have tested the efficacy of verbal suggestions to induce nocebo effects on itch[19,40–43]. The verbal suggestions used in these studies include a suggestion of a high likelihood that participants would experience itch during subsequent procedures[40], a suggestion of the itch-evoking effect of watching a video of someone scratching themselves[43], a suggestion of increased itch due to the activation of an electrode[19], or a suggestion that gave an exaggerated description of the itch participants were likely to experience[41,42]. The control treatments these verbal suggestion groups were compared with include no verbal suggestion[19], a verbal suggestion of a low chance of experiencing itch during subsequent procedures[40], or a verbal suggestion that forthcoming procedures would likely induce only a mild itch sensation[41–43]. Following the verbal suggestion or control treatment in each

Table 1

Attributes of the itch-evoking stimuli used in placebo and nocebo studies to date.

	Histamine	Electrical Stimulation	Mechanical Stimulation	Allergens	Audiovisual Stimuli
Methods of administration	Skin prick[14], iontophoresis[15], inert cowhage spicule, scrubbing or scratching of the skin[16,17]	Wire[18] or surface electrodes[19–21], connected to current generating device	Rubbing with wool fibers[22], von Frey monofilaments[23], vibration[24]	Skin prick[25]	Presenting itch-evoking images[5,26], videos[27–29], sounds of skin scratching[30]
Duration	1–4 min following termination of iontophoresis[15], other methods 5–15 min[14,22]	Dependent on length of stimulus Mild itch for up to 2 min past end of stimulus[18]	Dependent on length of stimulus Itch is typically felt for 1–2 s after von Frey stimulus[23]	5–15 min[25]	Variable, may depend on stimulus material
Stability	Stable response over repeated administration[31]	Initially stable response[32], efficacy declines with large number of trials[20]	Significant individual variability over repeated trials[23]	Requires further study	Requires further study
Multiple itch intensities	Intensity is dose dependent at certain concentrations[22] Intensity responds to thermal modulation[33]	Intensity can be modulated by varying the strength of the electric stimulus[18]	Limited by a low ceiling of intensity Requires further study	Intensity responds to thermal modulation[25]	Intensity from auditory scratching stimuli may be modulated by increasing high frequency noise[30]

This table briefly summarizes the attributes of the itch-evoking stimuli which have been used in currently published placebo and nocebo effect studies.

experiment, itch of similar intensity in both groups was then evoked with histamine skin prick[41,42], electrically evoked itch[19], and histamine iontophoresis, mechanical stimulation, and electrical stimulation in one study[40]. These studies measured the difference in participants' perceived itch intensity during the itch-evoking procedure after the different verbal suggestions, providing a measure of the nocebo effect. In each of these studies, participants receiving the increased itch verbal suggestions experienced a significantly higher itch intensity than the control participants who underwent the same itch-evoking procedures[19,40–43]. Aside from Bartels et al[19], the effects measured in these studies can be best described as nocebo-like effects rather than nocebo effects, as the verbal suggestions did not ascribe the increase in itch to an inert (nocebo) stimulus (eg, an electrode or a pill). These studies demonstrate that the experience of itch sensations can be influenced by verbal suggestions.

Conditioning and verbal suggestions

Placebo and nocebo effects can also be induced with conditioning, particularly in combination with verbal suggestions. Animal models of conditioning have demonstrated its ability to shape behavioral responses to pain[44], and human models of placebo and nocebo effects on pain have also been developed to investigate how these effects are learned through conditioning[45–49]. In studies of placebo and nocebo effects on itch, an association between an inert (placebo or nocebo) stimulus (conditioned stimulus, CS) and a stimulus that signals the evocation of itch (unconditioned stimulus, US, evoking an unconditioned response, UCR) is formed by repeatedly pairing the 2 stimuli during a training period (**Fig. 1**). After repeated trials, the placebo or nocebo stimulus (CS) is intended to induce changes in perceived itch intensity (conditioned response, CR) similar to the intensity of itch previously evoked by the US. This effect is measured during a test phase where the CS is presented with an itch stimulus of medium intensity, after having been associated with itch stimuli of lesser (placebo) or greater (nocebo) intensity. Some studies on itch have used only conditioning to induce placebo or nocebo effects, but most have combined verbal suggestions with conditioning. Combining verbal suggestions with conditioning provides the means to target both explicit and implicit learning processes, enhance the believability of a verbal suggestion, and the effectiveness of conditioning for inducing expectancies.

Placebo effects

Only few studies have induced placebo effects on itch using conditioning with verbal suggestions[19,20], as well as conditioning

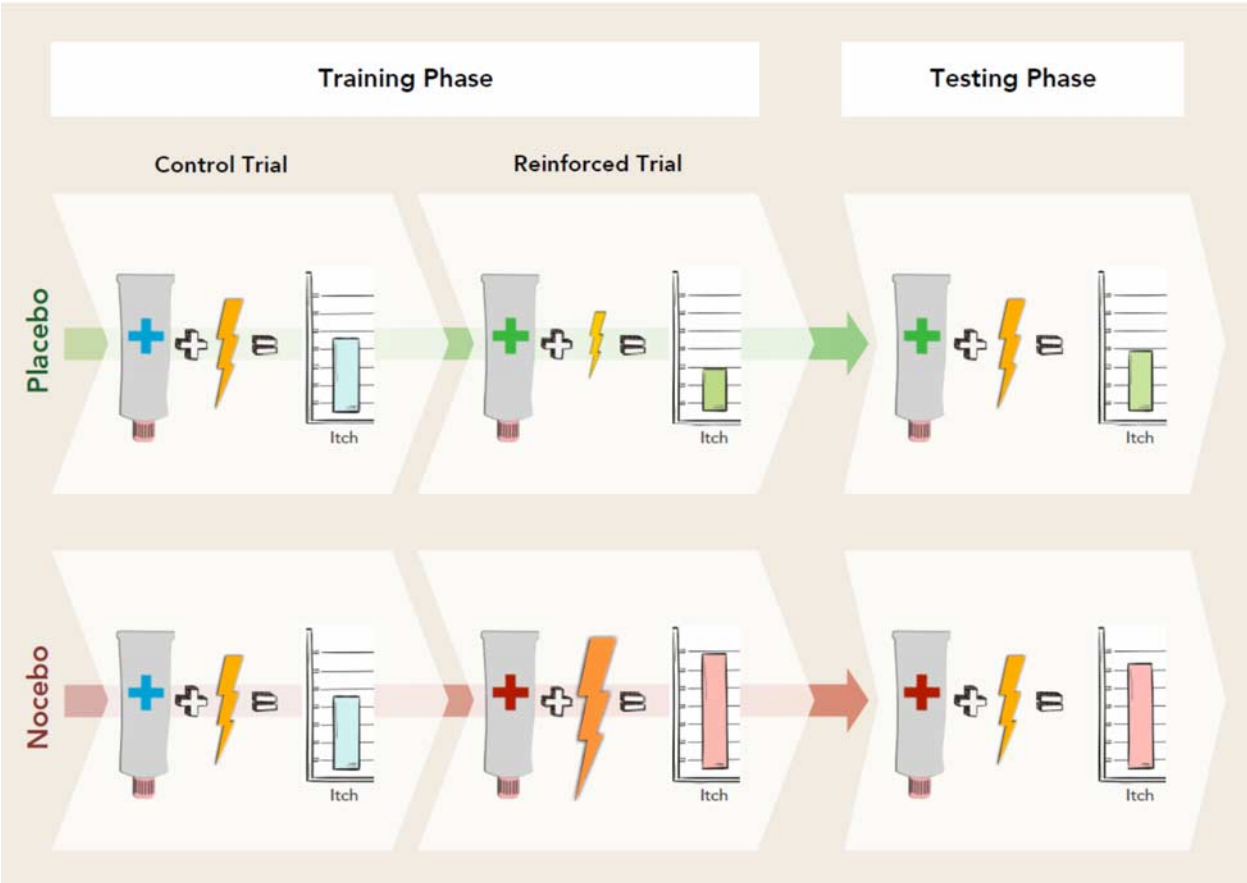

Figure 1. A typical conditioning experiment for placebo and nocebo effects on itch. Different inert stimuli (the differently colored lotion tubes) are repeatedly paired with itch stimuli of different intensities (the differently sized lightning bolts indicating different intensities of electrically evoked itch). During training, the associations between a neutral stimulus and medium intensity itch, and between a reinforced stimulus and decreased (placebo) or increased (nocebo) itch responses is conditioned through repeated exposure to the paired stimuli and itch responses. Verbal suggestions may also be used to strengthen the conditioned expectancies regarding the effects of the inert placebo or nocebo stimulus. The effect of conditioning is then measured during a test phase, when the reinforced stimulus is presented with medium intensity itch, and will be perceived as having lesser (placebo effect) or greater (nocebo effect) intensity.

without verbal suggestions[19]. In these experiments, participants in the verbal suggestion and conditioning group first received a verbal suggestion describing the associations between 3 differently colored stimuli which signaled the activation of a (sham) electrode, and changes in itch stimulus intensity. Itch was evoked with electrical stimulation (US), and one of the colored stimuli was paired with low-intensity itch to serve as the CS. This pairing was repeatedly presented to form an association between the colored stimulus and a low level of itch (UCR), and through verbal suggestion participants were led to believe that the reduction in itch was caused by the activation of an additional electrode[19,20]. Conditioning alone did not produce a significant placebo effect on perceived itch intensity, whereas combining conditioning with a verbal suggestion did produce a placebo effect, demonstrated by participants experiencing less itch (CR) during trials when the colored stimulus previously associated with a low level of itch was presented, relative to trials containing the neutral colored stimulus, during a test phase where the electrical stimulus intensity was identical for both trial types. Bartels et al[20] also used the combination of verbal suggestion and conditioning to counter-condition a previously induced nocebo effect on itch (forming a new association between decreased itch intensity and a colored stimulus previously associated with increased itch) and thereby turned the nocebo effect into a placebo effect. On the basis of these results, one can conclude that the combination of verbal suggestion with conditioning is more effective than conditioning alone for inducing a placebo effect on itch.

Nocebo effects

Three studies so far have used conditioning methods with verbal suggestions to induce nocebo effects on itch[19,25,33], one of which also tested conditioning without verbal suggestions[19]. Participants were conditioned to associate previously neutral stimuli such as a skin prick procedure[25], activation of a sham transcutaneous electrical nerve stimulation (TENS) device[33], or colored stimuli indicating the activation of a sham electrode[19], with the US of increased itch intensity. In these experiments, itch was evoked with an allergen skin prick[25], histamine[33], or electrical stimulation[19]. In Napadow et al[25], a single administration of allergen skin prick (US) to evoke itch (UCR) followed by thermal modulation was used to condition an association between thermal modulation after a skin prick procedure (CS) and the itch evoked by the allergen skin prick in patients with atopic dermatitis. When the skin prick was later performed with saline, a verbal suggestion telling the participants that the saline skin prick actually contained histamine was given. As a result, these participants experienced more itch (CR) compared with participants who were told that the second skin prick contained only saline. Van de Sand et al[33] conditioned a nocebo effect using thermal modulation of histamine-evoked itch (US) to repeatedly modulate itch intensity between a baseline temperature (low itch) and cool temperature (high itch, UCR). Participants were told that a TENS device (CS) was activated during the cooling phases of thermal modulation to form an association between activation of the TENS device and increased itch during cooling. A verbal suggestion explaining the role of the TENS device and its effects on itch was made to the participants prior to conditioning. During a subsequent test, the participants experienced increased itch on cooling trials when they were told the TENS device was active (CR), as compared with cooling trials when the participants were told the TENS device was not active. Bartels et al[19] used repeated trials of electrical stimulation (US) paired with 3 different colored light stimuli to form an association between one of the colored stimuli (CS) and the electrical stimulation, which was surreptitiously increased to evoke a high level of itch (UCR)[19]. In one condition, participants were additionally given a verbal suggestion that explained which colored stimulus signaled high and low levels of itch caused by activation or deactivation of a (sham) electrode. While conditioning without verbal suggestion did not induce a significant nocebo effect on itch, the combination of conditioning with verbal suggestion did induce a nocebo effect, demonstrated by participants experiencing increased itch during trials when the colored stimulus previously paired with the high level of itch was presented (CR), relative to trials in which the other colored stimuli were presented. This finding from Bartels et al[19] is in line with the other studies described in this section which induced nocebo effects on itch with a combination of verbal suggestion and conditioning[19,25,33]. Although it may be possible to induce nocebo effects with conditioning alone, the evidence so far suggests that nocebo effects on itch are most effectively induced with a combination of verbal suggestion and conditioning methods.

Itch-evoking methods

Several different substances have been used as pruritic stimuli in placebo and nocebo studies so far, and an overview of the most frequently used stimuli is provided in **Table 1**. Histamine is the most commonly administered itch-evoking stimulus in these studies, followed by electrical stimulation, mechanical stimulation, allergens, and audiovisual stimuli. Previous reviews offer an extensive description of a wide range of pruritogens[10,50]. Here we will focus specifically on the pruritic stimuli which have been used in placebo and nocebo studies, with special attention paid to the attributes of a pruritic stimulus most relevant to their utility in the context of a typical placebo or nocebo experiment. We consider 5 attributes. (1) The method of administration, as effective placebos and nocebos should have a plausible interaction with the method of evoking itch so that an individual can readily form an expectation regarding the effect of the placebo or nocebo on the experience of itch. (2) The typical duration of itch evoked by the pruritic stimulus, as this attribute affects how many times a pruritic stimulus can feasibly be administered in a given experiment. In general, a greater number of administrations is desirable when using conditioning methods. (3) The stability of the itch response over repeated administrations. A stable itch response to a pruritic stimulus across repeated administrations is beneficial to placebo and nocebo studies, where within-subject variability in the itch response creates noise in the data. (4) Whether multiple, distinct itch intensities can be evoked. To condition placebo and nocebo effects, evoking itch at 2 or more distinct intensities is necessary so that individuals associate the placebo-reinforced or nocebo-reinforced trials with experiencing lesser or greater itch, respectively. (5) Whether the model resembles the underlying mechanisms of a clinical condition. The clinical transferability of a pruritic stimulus to a given condition (eg, urticaria) is an important attribute to be considered when seeking to make comparisons from laboratory research to clinical practice.

Histamine

Histamine evokes a localized sensation of mild to moderate itch, along with a wheal (local edema) and axon reflex flare response (neurogenic inflammation) when administered to the epidermis[51]. Methods for efficient administration of histamine dihydrochloride or

diphosphate solutions into the epidermis include skin prick, iontophoresis, administration via inert cowhage spicules, and by scratching or scrubbing the skin. Histamine skin prick creates access to the epidermis by piercing the skin with a lancet where histamine has been administered[14]. Histamine iontophoresis utilizes a mild electric current to pass histamine through the dermis when histamine is applied onto the skin[15]. Cowhage spicules made inert through autoclaving and soaked in histamine can be administered by rubbing the spicules into the skin[52]. Scratching and scrubbing away the outermost layers of the dermis can be used to evoke itch with topical administration of histamine to the treated area[16,17]. In general, histamine-evoked itch lasts for ~5–15 minutes regardless of the administration method[31,33,53]. Repeated application of histamine is not known to cause habituation or reduced itch, and one study which reported on the test-retest reliability showed a strong positive correlation for the amount of itch evoked by 2 histamine administrations occurring a week apart[31]. Studies which investigated the effect of administering histamine in different concentrations have found that the amount of itch evoked by histamine is dose-dependent, with a higher concentration of histamine corresponding to increased itch[22], although there appears to be a ceiling effect for concentrations stronger than 1% histamine dihydrochloride[52,54]. One study demonstrated that an increased iontophoretic current was associated with an increase in itch[55]. Histamine-evoked itch intensity can also be manipulated with thermal modulation, in which cooling the skin at the site of histamine administration produces a brief, reversible increase in itch intensity[56–58]. Experimentally evoked histaminergic itch can be used as a model for urticaria.

Electrical stimulation

Administering a mild electric current through electrodes attached to the body (typically on the volar forearm) evokes itch in most participants[19,59,60]. Unlike histamine, electrical stimulation does not produce a visible wheal and flare reaction on the skin[18]. Several types of electrodes have been used in studies of electrically evoked itch, including wire electrodes[18] and various reusable and disposable surface electrodes[19–21]. Surface electrodes have been used more commonly than wire electrodes to evoke itch; however, a comparison of the itch evoked by different types of electrodes is required to conclude whether one is more effective for evoking itch. After receiving an electrical stimulus, a participant will typically experience mild to moderate itch sensations. The duration of the itch response is dependent upon the duration of the electrical stimulus, and itch typically dissipates within one to two minutes of the end of the stimulus. The stability of electrically evoked itch responses may depend on the number of stimuli used. Although nearly all participants initially experience itch in response to electrical stimulation[32], the evidence so far suggests that as many as 20% of participants may become desensitized to electrically evoked itch over many trials, as was the case in a study that administered 33 electrical stimuli[20]. The intensity of electrically evoked itch can be manipulated by varying the strength of the electric current used to evoke itch[18]. On the basis of our current knowledge of electrically evoked itch and clinical pruritic conditions, this method of itch-induction does not appear to resemble the underlying mechanisms of a clinical condition.

Mechanical stimulation

Low levels of itch can be evoked with mechanical stimulation of a participant's skin[23]. Methods of administering mechanically evoked itch include rubbing wool fibers on the skin[22], pressure from von Frey monofilaments[23], and applying vibration produced by a tuning fork[24]. Only mechanical stimulation by von Frey monofilaments have been used in placebo and nocebo studies. The duration of itching sensations evoked by mechanical stimulation is short, and abates within seconds of the stimulation. The stability of mechanically evoked itch is relatively poor. One study reported that across participants, ~40% of trials with von Frey monofilaments evoked no itch, indicating that there is a high degree of intravariability in participants' responses to mechanical stimulation[22]. Methods to modulate the intensity of mechanically evoked itch have not been reported to our knowledge, and such methods would likely be challenged by the low degree of stability in responses to mechanical-itch stimuli, and the low ceiling of itch intensity. The resemblance of mechanically evoked itch to the underlying mechanisms of clinical pruritic conditions requires further study.

Allergens

Allergens such as grass pollens and dust mites can be applied as itch-evoking stimuli to participants who are allergic to at least one of these compounds[61]. When administered via skin prick, such as in allergy testing, these compounds evoke an allergic itch response[62]. Allergic hypersensitivity to at least one allergen is believed to be prevalent in ~25% of the population in industrialized nations[63], and the use of allergens as a pruritic stimulus is limited to populations that test positive for an allergic response to a given allergen. In this subset of the population, allergens can evoke itch of a similar duration and intensity to that of histamine (ie, mild to moderate itch for 5–15 min)[25]. The stability of the itch response to allergens over repeated administrations has not been reported on to our knowledge. One study has shown that the intensity of allergen-evoked itch can be manipulated with thermal modulation, similar to histamine-evoked itch[25]. Allergens provide a clinical model of itch that may be used when researchers wish to study placebo and nocebo effects in allergic reactions.

Audiovisual stimuli

Contagious itch, the pruritic effect of viewing itch related stimuli such as videos of people scratching themselves, offers a purely psychological method of evoking itch. Researchers have demonstrated the pruritic effect of audiovisual stimuli with methods including images depicting scratching and skin conditions[5,26], videos of people scratching themselves[27–29], and auditory stimuli depicting the sounds of scratching skin[30]. Such audiovisual stimuli appear to evoke mild to moderate itch; however, a systematic comparison with a physiological itch-evoking stimulus (eg, histamine) has not been reported, which would help determine how much itch audiovisual stimuli evoke relative to other itch-evoking stimuli. The duration of itch evoked with audiovisual stimuli may vary with the length of the stimulus, and can persist after the stimulus has ended. The stability of the itch response to audiovisual stimuli has not been studied yet. The subjective intensity of audiovisual itch has been successfully modulated by manipulating the high frequency volume of scratching sounds, with increased high frequency volume contributing to increased itch intensity[30]. Itch evoked with audiovisual stimuli does not resemble a clinical model of itch; however, patients with atopic dermatitus (AD) are more sensitive to audiovisual itch stimuli than healthy controls[29]. For a thorough review of the research on contagious itch, see Schut et al[4].

Discussion

In this review, we have described the most commonly used methods of inducing expectancies and evoking itch to study placebo and nocebo effects. Several methods of evoking itch (**Table 1**) have been combined with expectancy-induction methods (**Fig. 1**) to induce placebo and nocebo effects on itch in both healthy and clinical samples. Here we discuss the most important conclusions, future research directions, and clinical implications for studies of placebo and nocebo effects on itch.

Expectancy-induction methods

Regarding expectancy-induction methods, it can be concluded that verbal suggestions are a simple and effective method of inducing nocebo effects on itch, whereas the findings for inducing placebo effects are mixed. However, both placebo and nocebo effects on itch appear to be weaker when induced with verbal suggestions alone compared to verbal suggestions with conditioning[19], a finding that also holds true for pain[47]. In the larger literature on placebo and nocebo effects on pain, verbal suggestions have been found to be an effective means of inducing placebo and nocebo effects (for review, see Koban et al)[35], whereas for itch verbal suggestions appear more effective for inducing nocebo effects than placebo effects. To use verbal suggestions most effectively, the content of the verbal suggestion should be believable, and contextual factors such as the laboratory environment and professional demeanor of the experimenter likely contribute to the effect[64]. A possible future direction for research with verbal suggestions is the investigation of open-label verbal suggestion. One recent study[65] employed an open-label verbal suggestion, wherein participants were explicitly told that the purpose of verbal suggestions was to induce expectations regarding itch intensity, and that verbal suggestions are effective even when participants are informed of this purpose. The open-label suggestion produced an effect on participant's expected itch intensity, but did not affect experienced itch during a histamine iontophoresis procedure. Future research on open-label suggestions could investigate how their effects on expectancies and perceived itch may differ from closed label suggestions, as this difference is not yet understood and may help to explain the factors which determine the efficacy of verbal suggestions. Whether the effects of open-label verbal suggestions can be reinforced with open-label conditioning also remains to be studied. Given the limited results for inducing placebo effects with verbal suggestion alone, more research is needed to understand the factors which make verbal suggestions effective, and why it may be more effective for inducing nocebo effects than placebo effects. However, the finding that learning for negative stimuli occurs more readily than for positive stimuli has been demonstrated across many domains of psychology and may be attributed to an evolutionary bias toward attending to negative, potentially threatening stimuli over positive, nonthreatening stimuli[66].

Conditioning, when combined with verbal suggestion, is an effective method for inducing placebo and nocebo effects on itch[19,20,25,33]. Many studies of placebo and nocebo effects on pain further support the efficacy of conditioning in placebo and nocebo inductions (for review, see Bräscher et al)[67]. However, given the small number of studies investigating placebo and nocebo effects on itch which used verbal suggestion with conditioning, many lines of research have yet to be explored. While Bartels et al[20] examined the unique and combined contributions of verbal suggestion and conditioning to placebo and nocebo effects on itch, it would be relevant to replicate these findings and to conduct a similar experiment using neuroimaging methods such as functional magnetic resonance imaging (fMRI) to compare the neural effects of verbal suggestion and conditioning. A detailed understanding of the interaction of verbal suggestion and conditioning on placebo and nocebo effects will be important for advancing effective treatments for itch in dermatological and systemic disorders. For example, a recent study[20] showed that counterconditioning may prove to be effective for treating nocebo effects on itch, and with further study we can understand its treatment potential and mechanisms of action.

Itch-evoking methods

Histamine application is a highly effective method of evoking itch and is the most frequently used itch-evoking stimulus in placebo and nocebo effect studies. Histamine may evoke a more stable itch response over repeated applications than the other itch-evoking methods commonly used in placebo and nocebo studies. However, disadvantages such as the duration of histamine-evoked itch, and the challenges of reliably modulating the intensity of histaminergic itch remain. The visible wheal and flare response associated with histaminergic itch may also act as a confounder to expectancy conditioning (eg, the severity of the skin response may confound expectancies for less intense itch). Methods to modulate histaminergic itch intensity, such as applying different concentrations of histamine, modulating the electric current of iontophoresis, and thermal modulation of histaminergic itch show some promise, although these methods are not without limitations. For example, different concentrations of histamine can induce different itch intensities in a dose-dependent relationship in concentrations ranging from 0%–1% histamine dihydrochloride[52], but the number of potential administrations is still limited by the time it takes for the previous histamine administration to wear off. Histamine is a useful model of pruritic symptoms in histaminergic itch conditions, such as urticaria. To further advance the practicality of studying placebo and nocebo effects with histamine-evoked itch, systematic analysis of the interaction between factors such as histamine concentration and administration method would be a useful line of future research.

Electrically and mechanically evoked itch have been used less frequently than histamine in placebo and nocebo research, and both warrant further investigation. Electrically evoked itch, although limited by a proportion of participants who may stop experiencing itch following repeated stimulation, is so far the most effective method of evoking multiple distinct levels of itch intensity repeatedly. The time needed for itch to dissipate between stimuli is also considerably shorter than that of histamine-evoked itch. These traits make it a potentially useful method for placebo or nocebo conditioning studies, though the risk of participants not experiencing itch from the electrical stimuli after repeated administrations must be considered. As for mechanically evoked itch, only von Frey monofilaments have been used in a single study of nocebo effects on itch[40]. Other means of mechanical stimulation, such as rubbing the skin with wool fibers[22] or applying vibration[24] have also been shown to evoke mild itch (although only on the chin in the case of vibration). These methods could be further explored in placebo and nocebo research as possible means of studying these effects with less burden placed on the participants. However, this method is not ideal for placebo effect studies because the low intensity of

mechanically evoked itch leaves little room for a placebo-induced reduction of itch. Mechanical stimulation may also be an interesting vehicle to study the generalization of placebo and nocebo effects from other, more intense itch-evoking stimuli, for example to investigate whether alloknesis and hyperknesis can be induced via nocebo inductions. While electrically and mechanically evoked itch possess useful attributes for laboratory research such as their relatively short duration, their potential resemblance to the mechanisms of clinical pruritic conditions requires further study. Neither histamine, nor electrical or mechanical stimulation are thought to evoke itch by acting on the class of peripheral C fibers affected in most chronic dermatological conditions like AD, thus limiting their use when making comparisons to such chronic pruritic conditions.

Cowhage spicules (*Mucuna pruriens*) which evoke itch when rubbed or pricked into the skin, may act via proteinase-activated receptor (PAR) 2 and 4, or Mas-related G protein-coupled receptors (MRGPRs)[68,69]. PAR receptors are believed to mediate itching sensations in AD given the increased levels of endogenous PAR2 agonist tryptase observed in AD patients[70], and MRGPRs have been linked to the experience of nonhistaminergic itch as well[71]. While the biological mechanisms underlying cowhage-evoked itch and AD both require further study, cowhage-evoked itch is believed to offer a model that more closely resembles itch experienced in AD than histamine, electrically, or mechanically evoked itch. Future placebo and nocebo effect experiments on cowhage-evoked itch could provide new insights in the possible underlying placebo and nocebo mechanisms that may differ between acute itch and chronic pruritic conditions, such as AD.

Whereas cowhage provides a more representative experimental model of AD than histamine, allergens can be used in samples with allergic hypersensitivity to experimentally model the pruritic symptoms observed in allergic responses, though histamine can be used in this role as well. Administering histamine may be a more practical alternative, due to the greater response rate and better documented itch response. Whereas administering allergens may require multiple, different allergic compounds based on an participant's allergy, administering histamine to all participants in a given experiment allows for a more homogenous sample.

Audiovisual methods of evoking itch provide a purely psychological method of evoking and studying itch experimentally. So far, one study has used itch-evoking videos paired with verbal suggestions to induce a nocebo-like effect on scratching behavior caused by the videos[43]. While nearly all placebo and nocebo itch studies conducted so far have used itch-evoking stimuli applied to the skin, future research could combine expectancy-induction methods with audiovisual stimuli to study how expectancies affect the perception of nonphysiological itch-evoking stimuli. Audiovisual stimuli may also be used to modulate perception of another itch-evoking stimulus such as mechanical stimulation or histamine[29].

All the itch-evoking stimuli described in this review, including cowhage, are known to be compatible with neuroimaging methods (eg, fMRI) when the appropriate equipment is used[58,72–76]. Although 2 studies have investigated nocebo effects on itch with fMRI, to date no neuroimaging studies of placebo effects on itch have been published. More research with neuroimaging of placebo and nocebo effects on itch with fMRI compatible itch-evocation methods is warranted. Such research would provide a better understanding of the neurobiological mechanisms of these effects, and of the neural correlates of the learning processes commonly involved in placebo and nocebo research.

Future research toward clinical applications

So far, we have described ideas for future research specific to itch-evoking and expectancy-inducing methods predominately from a methodological perspective. Here we describe the most important findings of this review in regards to suggestions for future research specifically aimed at advancing the clinical application of research on placebo and nocebo effects on itch. First, future research on placebo and nocebo effects on itch should move toward increased clinical relevance and transferability. At present, most studies of placebo and nocebo effects on itch use itch-evoking and expectancy-inducing methods tailored to study the existence and mechanisms of these effects, with less attention paid to the clinical transferability of these methods. While histamine or electrical stimulation have been used to evoke itch in placebo and nocebo studies of healthy participants, the use of a clinically transferable model of itch such as cowhage may advance both our mechanistic understanding of placebo and nocebo effects as well as advance the clinical relevance of research in this field. Studies using cowhage with clinical populations (eg, AD patients)[77] are also warranted for these reasons. A detailed understanding of the unique and shared effects of verbal suggestions and conditioning on placebo and nocebo effects will be important for advancing effective treatments for nocebo effects on itch in dermatological and systemic disorders. Verbal suggestions that more closely resemble the instructions given by health care providers in clinical practice, or written suggestions resembling the information patients my find about disorders through online resources could also be studied. Currently, the verbal suggestions used in laboratory research do not generally resemble the sort of verbal information which may be used in the clinic. This is particularly relevant for placebo studies, which typically used verbal suggestions (eg, stating that a pill reduces sensitivity to physical sensations in 95% of users)[39] to induce placebo effects on inert substances (eg, a sugar pill). Studying how verbal suggestions can enhance the efficacy of active treatments may provide more clinically applicable results. For example, Varelmann et al[78], examined the effect on pain resulting from different verbal suggestions preceding the injection of a local anesthetic for women in childbirth. Similarly, future research in this field could investigate how itch-relieving treatments are impacted by either neutral or positive remarks made by the experimenter or practitioner administering the treatment. Finally, observational learning could be studied as a learning process by which placebo and nocebo effects can be induced, in addition to instructional (ie, verbal suggestion) and associative (ie, conditioning) learning. For example, patients may learn by seeing and hearing about the treatment outcomes of fellow patients in doctors' waiting rooms and patient support groups. Results from several studies of placebo and nocebo effects on pain suggest that observational learning can yield effects of comparable strength to those of conditioning methods[79–81]; however, this process has not yet been studied in itch. Further research on these learning process that also addresses the current gap in clinical applications of placebo effects and detection or prevention of nocebo effects would help to advance the field.

Clinical transferability of our understanding of placebo and nocebo effects will benefit from further research on how to prevent

individuals from developing nocebo effects through learning processes. Methods to hinder or reverse the effects of conditioning could also be explored. These include *counterconditioning*, conditioning positive outcome associations with stimuli that were previously associated with negative outcomes (eg, pairing the administration of a cream that formerly preceded a high itch response with a low itch response)[19], and *latent inhibition*, exposing patients to treatment related stimuli (e.g. the treatment setting, medical devices) in the absence of a treatment to weaken the association with negative treatment-outcome expectancies (eg, fear of side effects)[82]. Evidence from a study on healthy participants indicates that counterconditioning can reduce experimentally induced nocebo effects and induce placebo effects on itch[20]. Future research could investigate the efficacy of counterconditioning on longstanding nocebo effects, as nocebo effects may pose the greatest risk in chronic conditions where the opportunity for learning and reinforcing negative expectancies is greatest. Latent inhibition methods have not yet been investigated as a means of preventing nocebo effects. Future research could first test latent inhibition as a means of blunting experimentally conditioned nocebo effects in healthy samples, by exposing participants to a nocebo stimulus (eg, inert cream) before it is paired with an itch response, and later in clinical settings, by providing patients with a chance to experience the treatment environment and learn about the treatment procedures before undergoing then. Especially when combined with verbal suggestions explaining the purpose of latent inhibition, such methods may be effective at preventing nocebo effects altogether. Experimental conditioning methods could also be extended to research on patients as a means of reducing reliance on medication by conditioning associations with the effects of a medication. Work on this line of research has already begun, such as in studies where an association was conditioned between antihistamine medication effects and a novel tasting drink, so that the drink could evoke a response similar to that of the medication after conditioning[83,84], and for the treatment of psoriasis with lower doses of medication following conditioning of the medication effects[85]. Future research on these topics offers a path toward translating scientific results into improvements in clinical practice.

Conclusions

In conclusion, research has only recently begun on placebo and nocebo effects on itch, and our understanding of these effects is growing rapidly. More research has been done on pain, and those findings can inform the research conducted on itch. Placebo and nocebo effects on itch have been induced with verbal suggestion, conditioning, and the combination of these methods for a variety of pruritic and inert compounds. Taken together, the results of these studies demonstrate that placebo and nocebo effects, induced by positive and negative outcome expectancies, can substantially affect the experience of itch. Future research examining effective expectancy inductions for itch and optimal methods and circumstances for itch-evoking stimuli will advance our understanding of the learning processes that underlie placebo and nocebo effects. More research should be conducted with clinical populations, preferably with condition-relevant itch stimuli, to advance basic understanding of placebo effects and treatments for nocebo effects in pruritic conditions. With a better understanding of how the learning processes underlying placebo and nocebo effects function in clinical settings, we can tailor treatments around promoting positive outcome expectancies and placebo effects, and minimize the risks of patients developing nocebo effects.

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Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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