Journal of Exploratory Research in Pharmacology **2023** vol. 8(4) | 286–294
DOI: 10.14218/JERP.2022.00090

Mini Review

A Narrative Review of Placebo and Nocebo Effects on Itch

Jessica A. Dietz[1*], Alisha Halver[2], Kimberly D. Hammer[1], Natasha J. Petry[2,3], Sara Westall[4] and Tze Shien Lo[1,4]

[1]Fargo VA Health Care System, Fargo, ND, USA; [2]School of Pharmacy, North Dakota State University, Fargo, ND, USA; [3]Sanford Health Imagenetics, Sioux Falls, SD, USA; [4]School of Medicine and Health Sciences, North Dakota State University, Fargo, ND, USA

Received: December 12, 2022 | **Revised:** March 03, 2023 | **Accepted:** March 10, 2023 | **Published online:** June 16, 2023

Abstract

There is limited information available on the evaluation of placebo or nocebo effects on itch. The present study developed a search strategy using PubMed to evaluate literature related to placebo and/or nocebo effects on itch. The search strategy identified 65 articles. After the independent review of each article, 10 studies were selected for inclusion. These studies varied, in terms of methods and outcome measures. Overall, verbal suggestion, conditioning, and/or placebo topical therapies led to placebo and/or nocebo effects on itch. Further understanding the mechanisms of placebo and nocebo effects on verbal suggestion and conditioning can open doors to the development of therapeutic strategies that could ameliorate or improve itch in patients.

Introduction

Have you ever had an itch you just can't scratch? Pruritus, or in layman's terms, itching, is essentially the miscommunication between sense of touch and the central nervous system. This can cause feelings of unease, irritation, or anxiety, often leading to an irresistible urge to quell this sensation. Recent studies have highlighted the importance of the emotional impact of itching, particularly in chronic cases. These studies demonstrated an association with higher rates of stress, anxiety, depression, and even suicidal ideation, leading to major deficits in quality of life.[1]

Although some itches may purely be due to physical or psychological causes, most pruritus occur due to the combination of these two. Thus, due to multifactorial causes, the treatment for pruritus may need to be tailored to target multiple causes. The use of the placebo effect to lessen itch has become a particular interest. This has become especially fascinating, because this has a potential for low risk of side effects and toxicities due to avoidance of pharmacologic therapy, and high rewards of effective itch relief for patients. This narrative review examined relevant studies for itching, especially for pruritus induced by physiological reasons, and treated using a psychological approach, placebo.

Keywords: Placebo; Nocebo; Itch; Pruritus.

***Correspondence to:** Jessica A. Dietz, Department of Pharmacy, Fargo VA Health Care System, 2101 N Elm St., Fargo ND 58104, USA. ORCID: https://orcid.org/0000-0002-1054-009X. Tel: +701-232-3241-4558, Fax: +701-451-7895, E-mail: jessica.dietz@va.gov

How to cite this article: Dietz JA, Halver A, Hammer KD, Petry NJ, Westall S, Lo TS. A Narrative Review of Placebo and Nocebo Effects on Itch. *J Explor Res Pharmacol* 2023;8(4):286–294. doi: 10.14218/JERP.2022.00090.

Methods

In order to identify relevant studies, the authors searched PubMed using a search strategy developed by the study team. The search strategy used a combination of keywords and controlled vocabulary words to capture the concepts of "itch", "pruritus", and "placebo" (refer to Table 1 for the details of the search strategy). The search was performed by S.W. in May 2022, and 65 articles were identified for review. Five reviewers independently checked the titles and abstracts. Then, the full articles of potential studies for inclusion were reviewed by the reviewers. For the inclusion of studies, the study was required to be specifically designed to evaluate the placebo or nocebo effect on itch. Among the reviewed studies, eight studies were identified for inclusion. Additional relevant studies were identified by checking the bibliographies of the relevant studies. Using this strategy, an additional two studies were identified for inclusion. Thus, a total of 10 studies were reviewed, and two additional studies were included, which provided additional statistical analysis related to the included studies.

Results

The results of the literature search resulted in a total of 10 studies (12 articles), and these were reviewed by the authors. One author (J.D.) reviewed the selected studies in detail, and compared the study methodology, size, interventions and findings. The details of the review are presented in Table 2. The study methodology varied among studies, and this often utilized verbal suggestion, conditioning, and/or the application of placebo topicals to elicit placebo responses. The sample sizes of all of the included studies

Table 1. Search strategy

Search strategy	Database	Article results	Excluded articles	Included articles
("placebos"[MeSH Terms] OR "placebo effect"[MeSH Terms] OR "placebo*"[Title/Abstract]) AND "open label"[Title/Abstract] AND ("pruritus"[MeSH Terms] OR "itch*"[All Fields])	PubMed	65	57	Eight studies were identified from the initial search for inclusion. Two additional studies were identified from the article references for inclusion. 10 studies in total (plus two additional articles that further analyzed the included studies).

Table 2. Review of manuscripts: placebo and nocebo effects on itch

Data source/ Location	Study methodology	Study size	Interventions	Findings	Author's conclusions
(1) A. Strumpf *et al*.,[2] 2016/ GERMANY	Closed-label; Randomized	*N* = 100; Healthy volunteers	1) Nocebo-like control I: a) NaCl Application; b) Noted: "does not cause itch in most people". 2) Nocebo-like control II: a) Histamine Application; b) Noted: "causes some itch in most people". 3) Nocebo-like effect II: a) Histamine Application; b) Noted: "causes an enormous itch in most people". 4) Nocebo-like effect I: c) NaCl Application; d) Noted: "causes an enormous itch in most people".	Larger wheal developed, significantly higher itch intensities, and increased unpleasantness under the nocebo-like condition I, when compared to under nocebo-like control condition I (received NaCl; $p = 0.001$, $p = 0.003$, $p = 0.003$). Larger flare size and itch intensity ratings differed between the nocebo-like experimental condition and nocebo-like control condition II (received histamine; $p = 0.02$, $p = 0.007$). The differences were not significantly different between males and females.	Itch and even skin reactions can be induced and intensified by suggestions and instructions, but these are not significantly impacted by gender.
(2) A. Van Laarhoven *et al*.,[3] 2011/ NETHERLANDS	Part 1: Verbal suggestions regarding various somatosensory stimuli that can evoke itch/pain. Part 2: Suggestions of a decrease or neutral response related to the application of histamine. Groups related to placebo impact on pain were also part of the study - outside the scope of the review.	Part 1: *N* = 56. Part 2: *N* = 36 (only those in the high expectation group from Part 1).	Part 1: 1) Itch Nocebo Condition (high expectation); 2) Itch Nocebo Control Condition (low expectation). Measured the effect of different somatosensory stimuli (mechanical, electrical, and chemical stimuli). Part 2: 1) Itch placebo; 2) Itch placebo control condition.	Part 1: Itch levels were significantly higher in the high expectation group, when compared to controls ($p < 0.001$). This was true for each type of stimulus. Higher expectations of itch were associated with higher levels of experienced itch. Part 2: The decrease in itch was larger in the itch placebo group, when compared to the controls ($p < 0.05$).	Nocebo effects can be indicated on itch by manipulating expectations through verbal suggestions. Verbal suggestions designed to induce a placebo effect resulted in a decrease in itch.

(continued)

Table 2. *(continued)*

Data source/ Location	Study methodology	Study size	Interventions	Findings	Author's conclusions
(3) D. Bartels *et al.*,[4] 2014/ NETHERLANDS	Multi-arm parallel group; Single-blind; Randomized	*N* = 95	1) Verbal Suggestion - noted that the third electrode would impact itch intensity based on the color on the screen (an actual sham electrode - all medium intensity stimuli); 2) Conditioning – noted that the color changes represent the change in intensity (low, medium, and high intensity stimuli were used); 3) Conditioning and verbal suggestion; 4) Control – the colors were not associated with change in stimuli intensity, no verbal suggestions were given.	Significant nocebo effect in the conditioning with verbal suggestion group (3), when compared to controls ($p = 0.02$). Borderline significant nocebo effect in the verbal suggestion group (1), when compared to controls ($p = 0.063$). No significant difference between the conditioning group (2) and controls. Significant placebo effect in the conditioning group (3), when compared to controls ($p = 0.009$). This was not observed in the other groups.	The combination of conditioning and verbal suggestion can induce significant nocebo and placebo effects on itch.
(4) D. Bartels, *et al.*,[5] 2017/ NETHERLANDS	Multi-arm parallel group; Single-blind; Randomized	*N* = 129	Part 1: negative verbal suggestions "receive a series of electrical itch stimuli with and without the activation of the third electrode that influenced intensity" third electrode = sham electrode = placebo, screen turned different color when third electrode was "activated". Part 2: Group 1: Positive expectation group "the third electrode will now decrease itch intensity". Group 2: Same procedure as Part 1; Group 3: Extinction Group - no instructions were given. Part 3: Same groups as Part 2, histamine iontophoresis was used	Part 1: Significantly higher itch score for the conditioned trials, when compared to that for the neutral trials ($p < 0.001$). Part 2: Change in itch score: group 1: −0.4 ± 1; Group 2: 0.5 ± 0.8; Group 3: 0.3 ± 0.9; ($p < 0.001$, $p < 0.01$). Part 3: Significantly lower itch scores in the positive versus negative expectation groups ($p < 0.01$).	The study demonstrates that nocebo effects can be effectively minimized by positive expectation induction, and that these may even result in placebo effects.
(5) D. Bartels *et al.*,[6] 2018/ NETHERLANDS	Additional analysis of D. Bartels, *et al.*, 2017/NETHERLANDS	*N* = 129	Refer to D. Bartels, *et al.*, 2017/NETHERLANDS	Part 1: Localized scratching with greater frequency and duration in the conditioned trials, when compared to the neutral trials ($p < 0.001$), total body scratching with greater frequency ($p = 0.056$) and duration ($p < 0.001$) in the conditioned trials. Part 2: No significant change in scratching episodes in the positive expectation group versus controls.	No conclusive evidence was identified for the generalization of nocebo effects on itch to scratching - further research is needed.

(continued)

DOI: 10.14218/JERP.2022.00090 | Volume 8 Issue 4, December 2023

Table 2. *(continued)*

Data source/ Location	Study methodology	Study size	Interventions	Findings	Author's conclusions
(6) M. Darrah *et al*.,[7] 2013/ NEW ZEALAND	Single blinded; Randomized	*N* = 58: Healthy college student volunteers	Written information was provided along with verbal explanation of skin reaction and antihistamine effect. Baseline administration: Aqueous cream applied (placebo). Histamine administered. Second administration: 1) Control group: Same as the baseline protocol; 2) Expectancy group: Verbal instructions were provided on the effectiveness expected from the antihistamine (placebo cream).	Expected wheal area: Significant between group difference in the change in expected wheal area with the expectancy group, expecting a greater reduction ($p = 0.005$). Wheal Area: No significant difference ($p = 0.64$). Heart rate (HR): A greater reduction in HR from baseline to second administration in the expectancy group, when compared to the control group ($p = 0.45$).	The wheal area was not impacted by the participants' expectation based on verbal instructions - participants in the expectancy group did expect greater reduction in wheal size, and experienced a greater reduction in heart rate.
(7) M. Darragh *et al*.,[8] 2015/ NEW ZEALAND	Closed label; Cross-over; Randomized	*N* = 50: Healthy volunteers	1) Group 1: Session 1 – Control; Session 2 – Treatment. 2) Group 2: Session 1 – Treatment; Session 2 – Control. For the treatment session - watched video explaining that an anti-histamine treatment cream would be applied to reduce itchiness and the size of the weal. In the control session - informed the subjects that the purpose was to get an indication of skin reactivity without treatment. The placebo cream was applied in all treatment sessions, followed by histamine.	Reduction of itch in the treatment group was noted after one minute ($p = 0.009$), three minutes ($p < 0.001$), and five minutes ($p < 0.05$). There was no difference in itch at seven minutes ($p = 0.23$), and no difference in weal size ($p = 0.39$).	Demonstrates the placebo effect in the context of inflammatory skin reactions using verbal suggestions alone.
(8) S. Meeuwis *et al*.,[9] 2018/ NETHERLANDS: *Study 1*	Open label; Randomized	*N* = 92: Healthy volunteers	1) Open-label positive VS; 2) Control no VS. VS = verbal suggestion.	The positive verbal suggestion group had significantly lower itch expectations, when compared to the control group ($p < 0.001$). No statistically significant difference between groups in mean self-reported itch during iontophoresis. ($p = 0.24$). The self-reported skin condition scores were lower in the experimental group ($p = 0.059$). No difference in physical parameters ($p > 0.14$)	The proof-of-principle study demonstrated that the open-label positive verbal suggestions were successful in reducing the level of itch the participants were expected to experience, but not in reducing the itch that was actually experienced.

(continued)

Table 2. *(continued)*

Data source/ Location	Study methodology	Study size	Interventions	Findings	Author's conclusions
(9) S. Meeuwis *et al*.,[10] June 2019/ NETHERLANDS: *Study 2*	Placebo controlled Crossover study. Open and closed label groups. Randomized	*N* = 92: Healthy volunteers	1) Open-label positive VS; 2) Closed-label positive VS; 3) Open-label negative VS; 4) Closed-label negative VS. VS = verbal suggestion. Positive VS = "tonic has an itch reducing effect". Negative VS = "tonic has an itch increasing effect". Open label = "tonic is a placebo, but people still have a response in their brain, impacting itch even if they know they received a placebo". Closed label = no additional information given.	The area under the curve (AUC) for itch during histamine iontophoresis: the combined positive VS groups and negative VS groups revealed a small sized non-significant difference ($p = 0.19$). The open and closed label analysis revealed similar findings. Maximum itch during iontophoresis: the combined and separate groups had no significant difference ($p > 0.24$). AUC for itch during the follow-up iontophoresis: significant and medium sized difference in changes for scores during the four-minute follow-up for the positive VS groups ($p = 0.16$), but not the negative VS groups ($p = 0.98$). No differences in subjective or physical skin response among the groups.	Both open-label and closed-label verbal suggestions were able to influence itch expectations, with closed label suggestions having more effect in reducing itch during follow-up. However, experienced itch during histamine iontophoresis was not influenced by suggestions.
(10) S. Meeuwis *et al*.,[11] Nov/ Dec 2019/ NETHERLANDS	Placebo controlled Crossover study. Open and closed label groups. Randomized	*N* = 92: Healthy volunteers	Two-phase conditioning paradigm: 1) Open-Label Conditioned Group: a) CS + UCS with explanation of conditioning and expected effects; b) CS + placebo. 2) Closed-label conditioned group: a) CS + UCS no explanation given; b) CS + placebo. 3) Conditioned not evoked control group: a) CS + UCS; b) water + placebo. 4) Non-conditioned control group: a) CS + placebo; b) CS + placebo. CS = conditioned stimulus - flavored beverage; UCS = unconditioned stimulus - H1 antihistamine	No differences in expected itch, remembered itch, or expected medication efficacy were identified ($p > 0.11$). No significant differences were found for mean self-reported itch, clinical skin response to histamine iontophoresis, spirometry, heart rate, or skin conductance level. When the groups were combined for comparison, conditioning was identified to be marginally effective in reducing itch ($p = 0.076$).	The study provides preliminary support for the behavioral conditioning of antipruritic effects. The findings suggest that this conditioning may be effective when it is known that a learning paradigm is being used. Further investigation in the open-label setting may help facilitate the utilization of placebos in clinical practice.

(continued)

Table 2. *(continued)*

Data source/ Location	Study methodology	Study size	Interventions	Findings	Author's conclusions
(11) S. Meeuwis *et al.*,[12] Jan 2021/ NETHERLANDS: *Study 3*	Closed and open label arms; Randomized	*N* = 112: Healthy volunteers	1) Open-label positive VS; 2) Closed-label positive VS; 3) Open-label negative VS; 4) Closed-label negative VS. VS = verbal suggestion, Positive VS = "caffeine-containing patch to shoulder, influence both cognitive abilities and sensitivity to stimuli such as itch". Negative VS = "caffeine-containing patch made the itch worse". Open Label = the participants noted that the patch does not contain caffeine, test effects of positive suggestions, studies have shown that this reduces itch, even if it is known that this is a placebo.	Expected itch/Expected patch efficacy: the expected itch in the positive VS groups was significantly lower, when compared to the negative VS groups ($p < 0.001$), larger effect size in the open-label group, the differences in expected patch efficacy were small ($p = 0.059$). Self-rated mean itch: Significantly lower in the positive VS groups ($p < 0.001$). Self-rated skin response: Reported as less severe in the positive VS group ($p < 0.001$). Clinical skin response: No difference between groups	Both open and closed label positive suggestions related to a sham transdermal patch were able to influence the expectations for itch, mean itch experienced, and self-reported skin response in the experimental setting, when compared to negative suggestions.
(12) S. Meeuwis *et al.*,[13] Dec 2021/ NETHERLANDS	Data used from previous studies (refer to the study details above). *Study 1: S. Meeuwis et al. 2018; Study 2: S. Meeuwis et al. June 2019; Study 3: S. Meeuwis et al. January 2021.*	*N* = 295 in total from three studies	Data used from previous studies (refer to the study details above). *Study 1: S. Meeuwis et al. 2018; Study 2: S. Meeuwis et al. June 2019; Study 3: S. Meeuwis et al. January 2021.*	Effects of VS on mean itch as mediated by expectations: For open-label participants: Positive VS indirectly reduced post-VS mean itch through mediation of expectation ($p < 0.001$). The lower pre-VS expected itch was significantly associated with lower post-VS expected itch ($p < 0.001$, $p = 0.032$). Closed label participants: Positive VS reduced expected itch, when compared to negative VS ($p < 0.001$). Post-VS expected that the itch was not associated with the post-VS mean itch ($p = 0.9$), while positive VS was directly associated with lower post-VS mean itch ($p = 0.014$). Post VS expected that the itch did not mediate the effects of CS on mean itch in the closed label context. Interindividual differences in the relationship between verbal suggestions, expectations, and itch: BAS (behavioral activation system) and body ignorance may play a role in the effect of VS. VS = verbal suggestion.	Innovative statistical methods were used to obtain detailed mechanistic information on the influence of interindividual differences on how placebo effects are formed. The effects of open-label positive and negative VS on itch may be more dependent on mediation by expectations, while closed-label suggestions directly influence itch. Low BAS sensitivity (sensitivity to rewards) was associated with increased impact of expectation on itch response. High ignorance of bodily signals is associated with increased placebo response to VS.

(continued)

were relatively low, which ranged within 14–129 subjects, with an average of 108 subjects.

A. Strumpf *et al*. (Study 1, Table 2) used histamine or saline application as the physical intervention.[2] Then, the subjects were verbally inquired whether they expected the application to cause itch.[2] Verbal suggestion for itch to occur in the placebo saline group led to greater wheal development, and significantly higher reported itch intensities.[2] Similar results were observed in groups that received histamine, indicating that itch, and in this case, even skin reactions, can be induced by verbal suggestion.[2]

A. Van Laarhoven *et al*. (Study 2, Table 2) reported similar results using various itch-causing stimuli, including mechanical, electrical, and chemical stimuli.[3] For all stimuli, higher expectations for itch were associated with the reported increase in itch experience.[3] Verbal suggestion was also effective in inducing a response in these subjects, resulting in a decrease in itch response.[3]

D. Bartels *et al*. completed several trials using both active and sham electrodes, in order to stimulate itch (Studies 3, 4 and 5; Table 2).[4–6] The authors combined the techniques of verbal suggestion and conditioning to elicit placebo responses, and reported that the combination of these techniques was more effective than using verbal suggestion alone.[4] Furthermore, it was reported that electrodes can decrease an itch, even though the intensity produced by the electrode does not change, significantly lowering the itch score.[5] The additional analysis did not reveal significant changes in scratching episodes in the subjects, indicating that the nocebo effect does not conclusively extend from subjects that reported a feeling of itchiness to the act of physically scratching.[6] More research is likely needed in this area, since this was the only analysis that addressed scratching episodes.

The use of a placebo cream, which was represented to the study participants as an antihistamine cream, in combination with verbal suggestion, was examined in several studies conducted by M. Darrah et. al. (Studies 6 and 7, Table 2).[7,8] Both studies revealed that when the placebo cream and verbal suggestion were utilized, there was no significant difference in wheal area, but there were improvements in itch at various time periods.[7,8] In addition, a reduction in heart rate from baseline was realized, when subjects were provided instructions on the effectiveness of the antihistamine (actually placebo) cream.[7]

In the Netherlands, S. Meeuwis *et al*. (Studies 8–12, Table 2) completed a number of studies related to placebo response and its impact on itch.[9–13] Three separate studies were completed using histamine iontophoresis as the itch inducing stimuli.[9–11] The use of this process enabled histamine to be introduced through the skin using current, creating an itch response. This process is commonly used in clinical research related to itch response and treatment. The group that initially conducted a study in 2018 reported that positive verbal suggestions can lead to significantly lower itch expectations, but there was no significant difference in mean self-reported itch during iontophoresis.[9] This result was in contrast to previous trials, which revealed improvement in experienced itch with verbal suggestion. Another study completed by the group of S. Meeuwis revealed similar results for both positive and negative verbal suggestion, resulting in changes in itch expectations, but without significantly impacting the experienced itch when looking at the area under the curve for the itch experienced during histamine iontophoresis and maximum itch intensity.[10] The subsequent study completed by a group of investigators used a two-phase conditioning paradigm to invoke a placebo response.[11] Various research groups used the combination of a conditioned stimulus (flavored water), an unconditioned stimulus (antihistamine), and placebo comparators, along with verbal suggestion.[11] However, no significant differences were identified for mean self-reported itch, clinical skin response to histamine iontophoresis, heart rate, or skin conductance level.[11] When the results of these groups were combined for analysis conditioning, these were identified to be marginally effective in reducing itch.[11]

An alternate approach of using a placebo patch was utilized by the group of S. Meeuwis in a study published in 2021.[12] In that trial, all subjects were given a placebo patch, that is, the subjects were given patches that contained caffeine (closed label group) or placebo (open label group).[12] These groups were further divided into the positive suggestion group (patches that would improve the itch) and negative suggestion group (patches that would worsen the itch).[12] No difference in clinical skin response was realized among the groups. However, the expected itch, self-rated skin response, and self-rated mean itch were significantly lower in the positive suggestion groups.[12]

An additional analysis of previous trials (Studies 8, 9 and 11; Table 2) was conducted by S. Meeuwis *et al*., and published in 2021.[13] Innovative statistical methods were applied to determine the interindividual differences on how placebo effects are formed.[13] The researchers reported that the effects of open-label positive and negative verbal suggestions on itch may be more dependent on its expectation, while the closed label approach would directly influence the itch.[13] Furthermore, the researchers determined that low sensitivity to rewards and high ignorance of bodily signals were associated with increased placebo response to verbal suggestion.[13]

Summary of available research and limitations

A review of 10 trials on placebo and nocebo effects on the perception of itch and skin reactions in young healthy individuals by verbal suggestion, learning process, expectancy, or conditioning, or other means in open-label and closed label trials was completed. The results slightly varied among the studies. However, overall, verbal suggestion, conditioning, and/or placebo topicals appeared to produce a beneficial placebo effect on itch.

Itch, such as pain, is a subjective sensation of a person, and the intensity depends on various factors, including the frame of mind, psychological state, underlying medical or mental illnesses, and external cues, such as verbal suggestions, conditioning, etc. Therefore, it remains challenging to have an objective measure of itch. Merely four of the reviewed studies (Studies 1, 5, 6 and 7; Table 2) used certain objective measures, such as the size of wheals, intensity of scratching, and heart rate, to gauge the placebo or nocebo effects on itch. However, these are not well-established accurate surrogates to measure itch intensity, due to the psychological component of the patient's itch experience. The use of subjective measures to evaluate the improvement or worsening of an itch remains difficult to some degree, given the interpatient variability. Furthermore, it remains difficult to directly compare the presently available literature, since the research methods and reported outcome measures are not standardized. Moreover, the placebo response varied in the studies, in which some studies reporting statistically and clinically significant improvements in itch, while other studies reported more modest placebo effects. Combining visual or tactile (i.e. patch or topical cream) with verbal suggestion appeared to improve the placebo response. These trials indicate that there is a psychological component to itch that can be influenced by inducing a placebo response, but the exact

mechanisms remain unknown.

Subjects who were recruited for the studies were healthy individuals, who had no acute or chronic skin diseases, psychiatric disorders, or other underlying medical diseases. Further studies on patients with medical conditions that cause itch, especially chronic itch, are warranted. The challenges of applying placebo, regardless of whether these are open-label or closed label, to patients with itch in real-world clinical practice would include moral, ethical, and patient-clinician trust relationship issues.

Compared to the field of pain, studies conducted for the placebo and nocebo effects on itch have been relatively new and few, and far between. The limitations of the present study include the following: a small number of studies were identified, the reviewed studies had small sample sizes, and the heterogeneous design of these studies made the comparison across studies difficult; merely studies published in the English language from 2011 to 2021 were reviewed, which may have caused relevant publications in other languages and publications outside of the search period to be missed; since the present study was a narrative review, and not a systematic review or meta-analysis, the quality of the included literature was not assessed.

The use of placebos with verbal suggestion, conditioning, and/or physical placebos can conceivably lower the risk of systemic or local toxicities, when compared to systemic or topical medications. It would be beneficial to invest more resources in elucidating the mechanisms of placebo effects, thereby opening doors to the development of therapeutic strategies that could ameliorate or improve itch in patients who do not respond to conventional modalities of treatment for itch.

Future directions

Research in the area of placebo and nocebo effects on itch remains limited. In order to further investigate the use of these techniques in the therapeutic setting, additional research is needed. The present studies appeared to support the use of verbal suggestion, conditioning, and/or topical placebos to elicit improvements in itch response. Future studies should focus on replicating these results in larger study populations, and in subjects with chronic itch conditions. These data would be necessary to move forward in the development of techniques that can be used in clinical settings, that is, using the placebo effect to improve patient outcomes. Before these interventions can be therapeutically used in real world applications, additional discussions on its ethics and impact on patient-provider relationship are necessary.

Conclusions

Studies, including those that investigate placebo or nocebo effects, are difficult to conduct and evaluate, due to multiple variables, subjectivity, and moral/ethical/trust concerns for various disease states, including itch. As anticipated, the standardized review approach resulted in the limited inclusion of articles. Although there were multiple limitations, the present study contributes to the literature by gathering small study data to present the potential positive impact of the use of placebo to treat itch, and identify future areas of study in this field, with the hope of advancing treatment options.

Acknowledgments

None.

Funding

No funding was received for the study.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

SW: research strategies; JD, AH, KH, NP and TL: review of articles for inclusion; JD, AH, KH, NP, TL and SW: drafting of the manuscript; JD: primary editing of the manuscript.

Disclaimer

The material is the result of work supported with resources, and the use of facilities at the Fargo VA Health Care System. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

References

[1] Silverberg JI. Selected comorbidities of atopic dermatitis: Atopy, neuropsychiatric, and musculoskeletal disorders. Clin Dermatol 2017;35(4):360–366. doi:10.1016/j.clindermatol.2017.03.008, PMID:28709566.

[2] Stumpf A, Zerey V, Heuft G, Ständer S, Pfleiderer B, Schneider G. Itch Perception and Skin Reactions as Modulated by Verbal Suggestions: Role of Participant's and Investigator's Sex. Acta Derm Venereol 2016;96(5):619–623. doi:10.2340/00015555-2336, PMID:26715067.

[3] van Laarhoven AIM, Vogelaar ML, Wilder-Smith OH, van Riel PLCM, van de Kerkhof PCM, Kraaimaat FW, *et al*. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 2011;152(7):1486–1494. doi:10.1016/j.pain.2011.01.043, PMID:21353388.

[4] Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Donders AR, van Middendorp H, *et al*. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One 2014;9(3):e91727. doi:10.1371/journal.pone.0091727, PMID:24646924.

[5] Bartels DJP, van Laarhoven AIM, Stroo M, Hijne K, Peerdeman KJ, Donders ART, *et al*. Minimizing nocebo effects by conditioning with verbal suggestion: A randomized clinical trial in healthy humans. PLoS One 2017;12(9):e0182959. doi:10.1371/journal.pone.0182959, PMID:28910291.

[6] Bartels DJP, van Laarhoven AIM, van de Kerkhof PCM, Evers AWM. Nocebo Effects and Scratching Behaviour on Itch. Acta Derm Venereol 2018;98(10):943–950. doi:10.2340/00015555-2979, PMID:29856465.

[7] Darragh M, Booth RJ, Koschwanez HE, Sollers J 3rd, Broadbent E. Expectation and the placebo effect in inflammatory skin reactions: a randomised-controlled trial. J Psychosom Res 2013;74(5):439–443. doi:10.1016/j.jpsychores.2012.12.010, PMID:23597333.

[8] 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):489–494. doi:10.1016/j.jpsychores.2015.01.011, PMID:25649275.

[9] Meeuwis SH, van Middendorp H, Veldhuijzen DS, van Laarhoven AIM, De Houwer J, Lavrijsen APM, *et al*. Placebo Effects of Open-label Verbal Suggestions on Itch. Acta Derm Venereol 2018;98(2):268–274. doi:10.2340/00015555-2823, PMID:29057429.

[10] Meeuwis SH, van Middendorp H, van Laarhoven AIM, Veldhuijzen DS, Lavrijsen APM, Evers AWM. Effects of Open- and Closed-Label Nocebo and Placebo Suggestions on Itch and Itch Expectations. Front Psychiatry 2019;10:436. doi:10.3389/fpsyt.2019.00436, PMID:31293458.

[11] Meeuwis SH, van Middendorp H, Pacheco-Lopez G, Ninaber MK, Lavrijsen APM, van der Wee N, *et al*. Antipruritic Placebo Effects by

Conditioning H1-antihistamine. Psychosom Med 2019;81(9):841–850. doi:10.1097/PSY.0000000000000743, PMID:31490841.
[12] Meeuwis SH, van Middendorp H, Lavrijsen APM, Veldhuijzen DS, Evers AWM. Open- and Closed-Label Placebo and Nocebo Suggestions About a Sham Transdermal Patch. Psychosom Med 2021;83(1):33–42. doi:10.1097/PSY.0000000000000862, PMID:32969962.
[13] Meeuwis SH, van Middendorp H, Veldhuijzen DS, Evers AWM. Associations Between Interindividual Differences, Expectations and Placebo and Nocebo Effects in Itch. Front Psychol 2021;12:781521. doi:10.3389/fpsyg.2021.781521, PMID:34966334.