Placebo and nocebo effects in itch : from conditioning to psychophysiological effects

Meeuwis, S.H.

Chapter 1

General introduction

Placebos are inert substances (e.g., sugar pills) or other types of inert treatment forms [1]. Particularly in the field of medicine, placebos are used as a tool to which active pharmacological substances can be compared [2]. The rule of thumb involved is as follows: you have two groups of people ('A' and 'B'), give 'A' the real medicine, and give 'B' placebos instead – any improvement of 'A' over 'B' is indicative of whether the real medicine is effective [2,3]. At first glance, this appears very straightforward indeed. However, while simply looking at the difference between groups 'A' and 'B' in a clinical trial paints a clear picture of the efficacy of a specific medicine, it is also somewhat limited: this difference does not tell a patient exactly how much improvement to expect after taking said medication. For that, comparisons to a 'starting point' or baseline value are needed, and here the previously clear picture becomes blurry. Studies show improvement of symptoms within the control groups of clinical trials – so for the people who are taking placebos – across a wide range of medical conditions [4]. This type of improvement is generally attributed to contextual or nonspecific treatment factors. Moreover, these factors impact outcomes within the treatment groups of clinical trials as well: so the total improvement following medication use would then be the sum of the specific effects of the medication and the nonspecific treatment factors [2,3,5]. In reality this may be even more complex however. Research has shown that nonspecific treatment factors can interact with the efficacy of medication – and that the efficacy of medication can likewise impact nonspecific treatment factors, such as placebo effects [2-4].

Placebo and nocebo effects: concepts and definitions

Placebo effects are part of the nonspecific treatment factors that can impact or interact with the efficacy of medication, and may make up a significant portion of what makes a treatment effective. They are defined as beneficial treatment outcomes that cannot be attributed to active treatment components [6]. Rather, these effects are attributed to expectations of beneficial or positive treatment outcomes [7-11]. It is important to emphasize the difference between placebos and placebo effects: where *placebos* refer to inert treatments (e.g., sugar pills) that can be given to a person, *placebo effects* refer to *positive reactions* a person can show in response to inert substances or as part of active treatments, with these reactions being elicited by expectations of benefit [1,6]. Unravelling the specific mechanisms that underlie placebo effects and investigating their impact is important for two reasons: 1) this knowledge may help to improve research on the efficacy

of (new) treatments, and 2) knowing how placebo effects can be elicited may help to develop strategies to maximize them in clinical practice, which could then lead towards enhanced treatment outcomes, optimized medication use, and reduced side effect occurrences [6]. Placebo effects are attributed to expectancy and can be elicited by a variety of factors, for example, but not limited to: information about a treatment, previous experiences with treatments or otherwise learned associations of treatment and improvement, general beliefs about medicine, aspects of the patient-provider relationship, and other social or contextual cues [7-11]. On the opposite side of the spectrum are nocebo effects: negative or adverse treatment outcomes that are attributed to non-active treatment components [12,13]. Researchers have spent the last decades unravelling the mechanisms behind placebo and nocebo effects, and have identified three main mechanisms through which these effects may be induced: associative learning (i.e., conditioning), instructional learning (e.g., through verbal suggestions), and social or observational learning (e.g., by social cues in the environment) [14-16]. These different types of learning are proposed to shape an individual's expectations about treatment either positively (in case of a placebo effect) or negatively (in case of a nocebo effect). Theoretical models of the placebo effect, for example the response expectancy model [17] and the learning model of placebo effects [18], state that these modulated expectations can then influence the experience of symptoms of disease [19].

Both placebo and nocebo effects have been found to significantly impact health-related outcomes. For example, placebo effects have been found to reduce itch and other somatic symptoms such as pain, dyspnea, fatigue and nausea [20], and research shows that they can impact physiological parameters as well, for example, immune or endocrine responses [21-23]. Nocebo effects in contrast have been found to increase the experience of somatic symptoms, to result in increased side effects, or to result in reduced treatment efficacy [12,13]. One area in which placebo and nocebo effects may be relevant is that of dermatology [24].

Placebo and nocebo effects in dermatology: effects on itch

Itch, or pruritus, is commonly described as an unpleasant sensation that evokes the urge to scratch, and is considered chronic if it lasts for over six weeks [25-28]. This symptom is a key marker of most cutaneous conditions, for example allergic disorders, atopic dermatitis or eczema, urticaria, psoriasis, and lichen simplex [29, 30]. Listed as the fourth leading

world-wide cause of non-fatal disease burden, skin diseases have a major social, societal and economic impact [31]. Especially in skin diseases, the burden of itch is high, with an estimated lifetime prevalence of itch set at 100 percent for patients (whereas in the general population, estimated prevalence ranges from 7-22%) [32]. Finding strategies to reduce this burden of disease therefore remains a priority for scientific research. In addition, itch is a common symptom for non-dermatological conditions. It has been often reported in systemic, uraemic, neurological, or endocrine diseases (for example, kidney failure, multiple sclerosis, or diabetes mellitus), and is also prevalent in some psychiatric conditions [28,33,34]. For these conditions, itch often also has a considerable impact on quality of life and wellbeing of patients [34].

Depending on the origin of the itch sensations, different classifications can be identified [33,35]. A common classification of itch is by the pathway through which it is evoked: histaminergic, or non-histaminergic [36,37]. Although several signaling chemicals are known to evoke itch, histamine is investigated most frequently [27,28]. Treatment of histaminergic itch often consists of systemic treatment with H_1-receptor antagonists, commonly referred to as antihistamines, or topical agents such as corticosteroids. However, these treatments usually have low efficacy or result in significant side effects [33,37], thus increasing the need for formal investigation into approaches by which the efficacy of existing treatments may be enhanced. Moreover, considering the broad range of conditions for which itch occurs and its debilitating nature, it is important to find ways to reduce this symptom and thereby positively impact patients' wellbeing. One of the ways to do this is by strategically using placebo effect mechanisms [24].

Strategies for inducing placebo and nocebo effects

Studies on the phenomenon of 'contagious itch' – itch that is induced by visual, auditory or other contextual cues – show that social and psychological factors can play an active role in determining the severity of itch that is experienced by patients [38-40]. Contagious itch therefore may indicate that placebo and nocebo effects could potentially play a large role in itch. Moreover, while most studies on placebo and nocebo effects focus on pain and pain-related conditions (for a review of placebo and nocebo effects in pain see, for example, [41]), there is also evidence that these effects occur in itch. A meta-analysis shows that in control arms of clinical trials with patients suffering from dermatological conditions, over 30 percent of itch reduction can be attributed to placebo effects [42]. In addition, several

studies have investigated whether placebo and nocebo effects for itch can be experimentally elicited by associative or instructional learning.

Associative learning: classical and pharmacological conditioning

Originally described by Pavlov, classical conditioning entails the learning process by which (new) associations between stimuli are formed [43,44]. In short, an association is made by presenting an initially neutral stimulus (thereafter the conditioned stimulus, CS) together with an unconditioned stimulus (UCS) that is known to elicit a certain response (unconditioned response, UR). After the CS and UCS have been presented together, the CS will then elicit a response that is similar to the UR by itself, even when the UCS is not presented (this is known as the conditioned response, CR; see **Figure 1**) [22,44]. Studies show that these classical conditioning procedures can be used to modify itch levels in healthy volunteers. To illustrate, one recent study investigated effects of conditioning on itch by combining visual cues (i.e., various colors) with high and low levels of itch. After these CS's and UCS's were repeatedly paired together in a learning phase, the visual cues were then found to influence the amount of itch that participants reported when they were presented together with a medium level of itch during a testing (evocation) phase [45]. Learned associations like these could be what drives the placebo effect: positive expectations trigger actual symptom reduction when certain visual cues are presented. The type of classical conditioning that was investigated in the study described above [45] has been found to occur mostly on a cognitive level however – in other words, the association between CS and UCS needs to be made consciously by participants and, more importantly, the UCS consists of changes in itch that are made by manipulating the experimental procedure (i.e., exogenous change). Placebo effects may also be learned by conditioning responses on a more endogenous level: through classical conditioning of pharmacological responses [46,47]. In studies investigating conditioned pharmacological effects, the UCS typically is a substance known to elicit a certain physiological response, such as an active medicine [23,24]. For example, patients can learn that treatment cues (e.g., the color of a pill; CS) belonging to a pharmacologically active substance (painkiller, UCS) are associated with certain treatment effects (pain reduction; UR). These treatment cues could then prompt the same response (CR), which is what we know as the placebo effect (i.e., itch or pain reduction after taking a colored pill, even when active pharmacological substances are absent; see **Figure 1**).

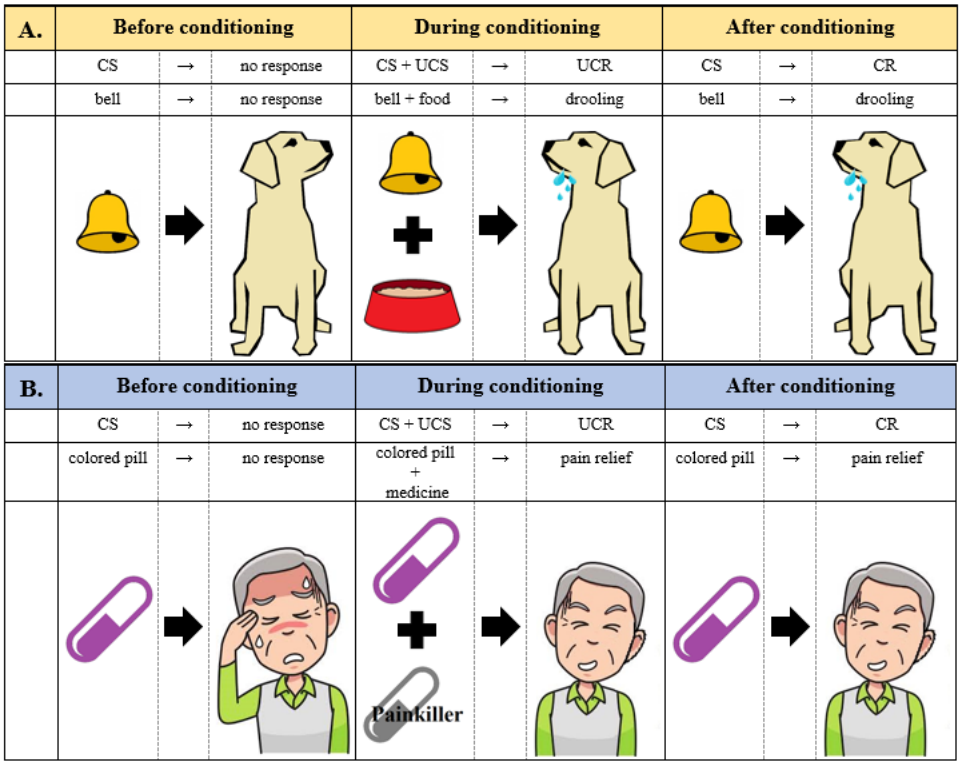

Figure 1. Schematic overview of (A) Pavlovian and (B) pharmacological conditioning: before conditioning, the (initially neutral) to-be conditioned stimulus (CS) causes no response. During conditioning, the CS is coupled with an unconditioned stimulus (UCS), that elicits an innate (unconditioned) response (UCR). After conditioning, the CS provokes a similar (conditioned) response (CR), even in the absence of the UCS.

Research demonstrates that it is possible to modulate immune functioning with pharmacological conditioning [47-50]. For example, studies show that, after having been conditioned with the immunosuppressive drug cyclosporine A as UCS, a saccharin solution can significantly reduce blood serum levels of interleukins, and thereby reduce the physiological response to immune challenges (e.g., viruses or allergens) in animal and human models of allergy [49,50]. Likewise, this type of conditioning can also increase immune responses, for example when a CS is coupled with a substance that challenges or sensitizes immune functioning, such as an allergen. Allergic responses were found to be sensitive to these conditioning effects [51-53]. For example, cases are known where patients who are allergic to roses have developed allergic asthma attack when presented

with artificial roses [54]. Such learned allergic responses to inert stimuli may exacerbate existing allergic disorders, which could be interpreted as a nocebo effect. There is also evidence that conditioned immunosuppression can be used to reduce allergic symptoms that are elicited through histaminergic pathways [55,56]. Goebel and colleagues [55] found that conditioning with the antihistamine desloratadine (UCS) could influence the basophil response to dust mite allergens on a level comparable to actual drug effects in humans, although they did show that effects of conditioning on self-reported allergic symptoms (including itch) and skin response to dust mite were less evident.

A second study complemented these findings by showing that allergic symptoms and physical responses to histamine reduced in both the conditioned and sham-conditioned (i.e., receiving a CS without UCS) groups compared to a natural history (i.e., no intervention) group [56]. Given that not only the conditioned group but also the sham-conditioned group showed reduced symptoms, it is likely that these reductions can be attributed to factors other than pharmacological conditioning [56]. Taken together, these two studies show mixed evidence for the efficacy of antipruritic conditioning of the effects of antihistamines for allergy [55,56]. However, as noted by the authors of both studies, a number of factors may have impacted study findings, such as elicitation of symptoms through non-histaminergic pathways, regression to the mean, receiving an intervention (regardless of this being a sham or active intervention), or potentially, participants' own previous experiences with antihistamines. More research is needed in order to unravel whether conditioning of antihistamines is possible in humans.

Instructional learning: the impact of positive and negative verbal suggestions

Where conditioning may largely rely on one's ability to associate one cue with another (which would then impact expectancy), another type of placebo and nocebo effect induction often used in laboratory settings is to alter expectancy by instructional learning. This type of learning does not rely on prior experience (as associative learning does) or on observations of others (as social learning does), but on communication of information or advice [57-61]. Placebo and nocebo effects can be elicited by instructional learning, for example when suggestive information is given about the effectiveness of a certain treatment (i.e., verbal suggestions) [14,16,22]. These suggestions can elicit positive or negative expectations, which would then in turn impact symptom perception [14]. Previous studies have shown that verbal suggestions can influence somatic symptoms, for example of pain,

fatigue, and nausea [20]. Evidence for the efficacy of verbal suggestions in itch varies: some studies show that placebo and nocebo effects in itch can be elicited by verbal suggestions [62-65], whereas others show mixed evidence, with suggestions eliciting nocebo but not placebo effects [66], or fail to show effects on itch of verbal suggestions alone [45,67,68]. Moreover, the methods used to elicit itch vary across studies and only a few have investigated histaminergic itch induction. A single study indicated that nocebo responses to verbal suggestions in physical responses to histamine (i.e., wheal or flare response) could be provoked [63], however, most studies report finding no significant changes in physical parameters following verbal suggestions [62,67,69]. Considering the mixed evidence, more research is needed to investigate whether placebo and nocebo effects could be induced for itch specifically through verbal suggestions.

Across studies variations in the type of verbal suggestions that are employed to elicit placebo and nocebo effects are found. For example, some studies give suggestions of high or low itch because of changes in the pain or itch induction method (also known as placebo- and nocebo-like responses) [45,66,70], whereas others give suggestions about a dummy treatment (e.g., an inert cream) provided alongside the pain or itch induction [62,67,69]. More research is needed in order to identify how and under which circumstances verbal suggestions may elicit placebo and nocebo effects. It should be clarified what type of information and which environmental cues can elicit placebo effects, as this knowledge could be used in clinical practice by health care providers, for instance to maximize positive expectations while informing patients who start new treatments. Knowing which manner of information provision may or may not be helpful could then be used to improve patient-provider communication, and by that enhance placebo effects and prevent nocebo effects in clinical practice.

Open-label placebo effects

Knowing how to best inform patients about treatments, and using this knowledge to improve patient-provider communication may be a potential strategy for utilizing placebo and nocebo effects mechanisms to improve healthcare. At a first glance it appears that this might in fact be the only way to use the knowledge on placebo and nocebo effects in clinical practice in an ethical and non-deceptive way [71,72]. After all, any use of inert substances or covert changes in medication dosages – which are common techniques used to study placebo and nocebo responses in laboratory experiments – would be considered

unethical in clinical practice as these involve deception [73]. Patients should be fully informed about which treatment they receive, and any attempt to circumvent this could harm a patient or challenge their autonomy. Because of this, the means by which placebo and nocebo effects are traditionally investigated in the laboratory (i.e. by providing inert substances under guise of an active treatment) cannot be immediately translated to clinical practice. In the last decade, however, research has shown that it may be possible to induce placebo effects in clinical practice without involving deception [74-76].

It has been found that providing inert pills to patients alongside a rationale that explains how subsequently elicited placebo effects could impact symptomatology can reduce self-reported symptoms for patients suffering from irritable bowel syndrome [77], chronic low back pain [78], attention deficit hyperactivity disorder [79], and allergic rhinitis [80,81]. Most of these aptly dubbed 'open-label' placebo effects are elicited on top of treatment as usual. Because of this it remains unclear by which aspects (or combinations thereof) open-label placebo effects are elicited [75]. For example, it may be possible that the effects of the open-label placebos are evoked by the provided explanation (instructional learning), or that the inert pills alone are enough to elicit improvements in symptomatology (through classical conditioning mechanisms). However, it may be equally likely that the open-label placebo could interact with treatment as usual and that this may enhance those pharmacological effects. For example, it may be possible that the open-label rationale (i.e. explaining the role of learning and expectations) interacts with expectations about or the pharmacological effects of treatment as usual, or that it impacts other components of treatment (e.g., patients' belief in treatment efficacy) and influences symptomatology through those components. Therefore more research into the specific mechanisms of open-label placebo effects is necessary. Likewise, the efficacy of open-label placebos for histamine-induced itch is unclear. Considering that placebo effects for itch appear to be substantial, it may be of interest to investigate them in an open-label (placebo) context as well. Finally, no study to date has investigated whether pharmacological conditioning of antihistamines for itch may be effective in an open-label context.

In short, placebo and nocebo effects can be elicited through various pathways, among which pharmacological conditioning and verbal suggestions. Previous literature indicates that placebo and nocebo effects may be relevant for the field of dermatology and itch. However, little is known about whether pharmacological conditioning with antihistamines may impact itch specifically, and evidence for the influence of verbal suggestions (providing either positive or negative information) on itch is oftentimes mixed. In addition,

placebo and nocebo effects for itch have not yet been investigated in an open-label context, either in case of placebo effects elicited through pharmacological conditioning, or placebo and nocebo effects elicited through verbal suggestions. Doing so may be a first step towards therapeutic application of placebo and nocebo effects and may help in improving existing treatments for itch.

The current dissertation

In this dissertation, placebo and nocebo effect inductions for histaminergic itch are investigated using multiple approaches in various randomized controlled studies, i.e., pharmacological conditioning and positive and negative verbal suggestions in both an open-label context as well as a closed-label context (i.e., concealed, with participants not knowing about the placebo or nocebo effect induction). Moreover, effects of these methods on other (psycho)physiological responses to histamine are addressed. An overview of the outline of this dissertation is provided in **Figure 2.**

In **Chapter 2**, studies using experimental placebo and nocebo effect induction methods within the field of dermatology are systematically reviewed. Evidence for placebo and nocebo effects elicited in cutaneous conditions, in symptoms of the skin and mucous membranes associated with itch, and in relevant experimental animal and human models is summarized. The impact of different placebo and nocebo effect induction methods on three broad categories of outcomes (self-reported, physiological, and behavioral) is reviewed and differential aspects of studies (i.e., different designs) are compared. Potential implications for clinical practice are discussed.

In **Chapter 3**, the design and results of a randomized controlled study are presented and discussed. In this study, the possibility of pharmacologically conditioning the antipruritic effects of antihistamines in healthy volunteers is assessed. Moreover, the potential of non-concealed, or open-label, use of conditioning for influencing itch is explored for the first time. Effects of (open-label) conditioning on other (psycho)physiological parameters are assessed, and the role of individual characteristics (e.g., expectations, personality) in eliciting placebo effects for itch is explored.

Chapter 4 describes the first in a series of three randomized controlled studies investigating the efficacy of open-label suggestions for itch. In this study, the effects of open-label positive verbal suggestions about the itch induction method are investigated for

itch and other responses to histamine in healthy volunteers and compared to neutral instructions.

In **Chapter 5**, a study is presented that was conducted as a follow-up study to the one described in Chapter 4. In this follow-up study, we assessed whether verbal suggestions about an inert substance (i.e., a sham tonic) can influence itch and other responses to histamine in healthy volunteers. Effects of positive verbal suggestions and negative verbal suggestions are compared. Moreover, the efficacy of verbal suggestions in influencing itch is assessed for both an open-label context and a closed-label (i.e., concealed) context.

The final of the three studies on the efficacy of open-label suggestions is described in **Chapter 6**. Here, it is investigated whether open-label and closed-label positive and negative suggestions can influence itch in healthy volunteers, when those suggestions are about side effects rather than treatment effects. As in the previous studies, the effects of the suggestions on itch and other responses to histamine are assessed.

Chapter 7 is the summary and main discussion of this dissertation. Here, the results of the conducted studies are summarized and discussed in light of other work in this field and possible clinical implications.

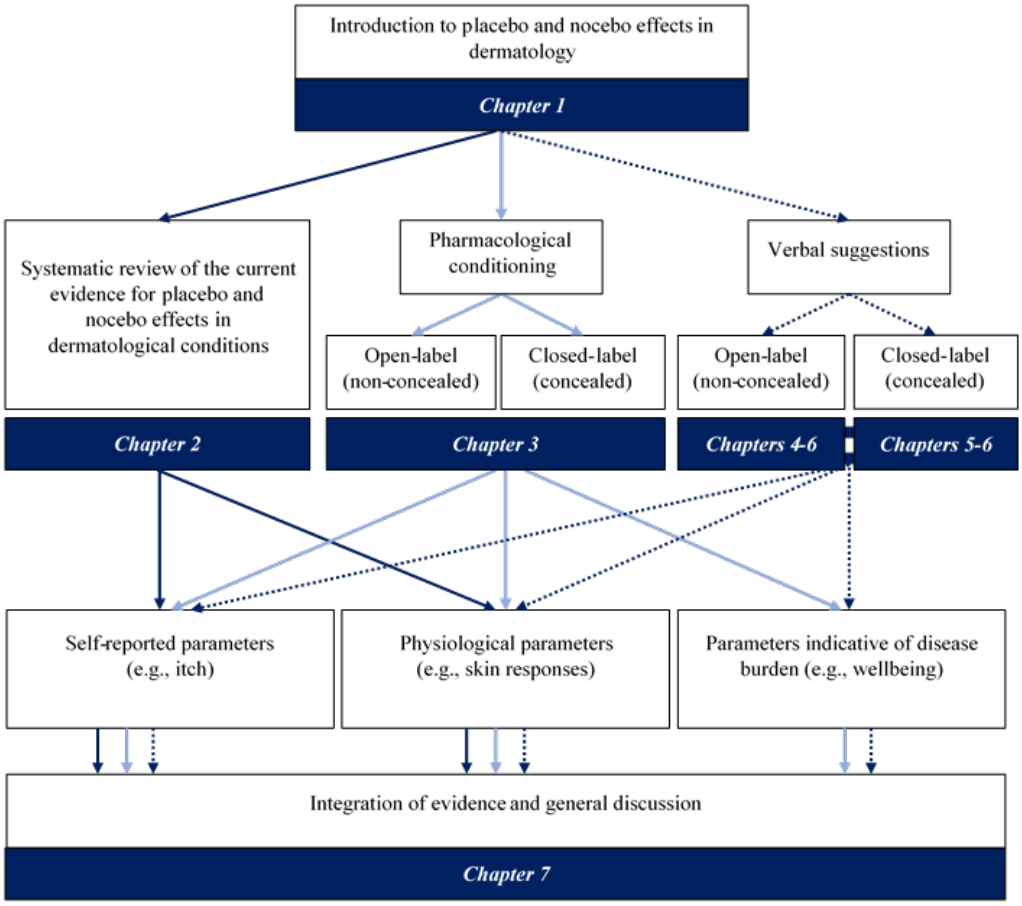

Figure 2. The outline of this dissertation and a brief overview of the topics within each chapter.

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