REVIEW

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Review of clinical studies on the nocebo effect

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Objective: To review clinical studies on the nocebo effect. PubMed was searched for relevant clinical studies as well as studies on the relationship between the nocebo effect and genes. *Data sources*: A total of 35 clinical studies on the nocebo effect and one study on its relationship with genes were selected for review. All were conducted outside Japan. *Results and conclusion*: An increasing number of clinical studies on the nocebo effect are being published. The 36 studies selected for review were grouped into the following five categories: (1) studies of how differences in participant characteristics such as personality affect susceptibility to the nocebo effect, (2) studies of how differences in provision of information about side effects affect susceptibility to the nocebo effect, (3) studies of how nocebo conditioning affects susceptibility to the nocebo effect, (4) studies of nocebo response mechanisms, and (5) studies of the nocebo effect and genetic polymorphisms. The first four categories comprised 5, 19, 8, and 3 studies, respectively, and the fifth comprised 1 study. Most of the studies investigated how differences in the provision of information affect susceptibility to the nocebo effect. Few studies investigated individual differences in the nocebo effect (differences between responders and non-responders) or mechanisms of the nocebo effect.

1. Introduction

The placebo effect is widely known to be a psychological factor that enhances response to treatment. It is a psychological phenomenon in which factors such as expectations that a treatment will be effective and past experiences of effective treatments produce an enhanced response to treatment (Finniss et al. 2010; Colloca and Benedetti 2006). Interest in placebo responsiveness has been growing. Studies on the placebo effect began appearing in the 1990s, and more than 100 have been published each year since the start of the 2000s (Weimer et al. 2015). Research on the so-called "placebome," which hypothetically differentiates people into placebo responders and non-responders based on polymorphisms related to brain neurotransmitters, has increased over the past 10 years (Hall et al. 2015) and includes research on expression mechanisms (Beneditti et al. 2005).

The phenomenon by which a placebo causes a negative effect in a patient is called the nocebo effect. The nocebo effect is also a side effect that can occur in placebo-controlled clinical studies. Like the placebo effect, the nocebo effect is prone to occur with drugs that act on the central nervous system and complicates the research and development of new drugs (Watanabe 2018).

In 1961, Kennedy defined the nocebo effect as experiencing unpleasant or harmful symptoms as a reaction to an inert substance (Kennedy 1961). The word nocebo means "I shall harm" in Latin and relates to side effects that influence response to treatment. Compared with clinical studies on the placebo effect, there are fewer studies on the nocebo effect. For this review, clinical studies on the nocebo effect were selected, and susceptibility to the nocebo effect and mechanisms of the nocebo effect were evaluated with a focus on differences in provision of information about side effects, conditioning, personality, and genotype.

2. Investigations, results and discussion

PubMed was used to search for clinical studies on the nocebo effect published between 1990 and 2018. The keyword used was "nocebo effect" and the "clinical trial" filter was applied. Another search was conducted for studies on the nocebo effect and genes. The keywords used were "nocebo effect" and "genotype" with the "AND" condition applied.

The first search yielded 67 clinical studies on the nocebo effect. The pool was narrowed down to 35 after excluding studies that primarily focused on the placebo effect (Table 1). The second search yielded only 1 study on the nocebo effect and genotype (Table 2). No studies were published between 1990 and 1994. With a few exceptions, one study per year was published between 1995 and 2011. One or two studies per year were published between 2012 and 2014, and four to seven studies per year were published between 2015 and 2018, which indicates an overall increasing trend. Although the progress of research continues overseas, few studies have been published in Japan.

Participants were healthy volunteers in 27 of the 35 clinical studies on the nocebo effect. Two studies were conducted in cancer patients, one in patients receiving hormone therapy for breast cancer, one in patients with depression, one in patients with a reliable history of drug-induced hypersensitivity reactions, one in patients with benign prostatic hyperplasia, one in outpatients with a history of side effects, and one in postoperative patients. The sample size was less than 100 in 22 studies, 100 to 199 in 7 studies, and 200 or higher in 6 studies. The intervention was administration of an inert substance (placebo) in 6 studies, an active drug in 8 studies, and pressure/thermal pain or another intervention in 19 studies. Effects were evaluated by means such as questionnaires about side effects (e.g., Generic Assessment of Side Effects in Clinical Trials), changes in itchiness (Itch Numeric Rating Scale), changes in pain (Pain Numeric Rating Scale), and visual analog scales. Psychological responses were self-evaluated by the State-Trait Anxiety Inventory (STAI) and objectively by electroencephalography and positron emission tomography (PET). Fifteen studies involved pain or itchiness and all showed that the nocebo effect produced the greatest pain or itchiness; one study showed that the nocebo effect was more pronounced with itchiness than with pain (Van Laarhoven et al. 2011). These studies illustrate

Table 1: Literature review on nocebo effects

Year	Author	Subject	Sample Size	Intervention	Category	Summary
1995	Drici et al.	Healthy volunteers	728	Inert substance	Personality	Subjects were phase I trial participants who received the placebo. Personality was assessed by Bortner score (BS) (behavior pattern). Subjects with a high BS were susceptible to the nocebo effect.
1997	Benedetti et al.	Postoperative patients	180	Proglumide	Mechanism	Injections had no effect when administered secretly, but did have an effect when administered visibly. When pain was induced, pain increased even with saline. In addition, pain disappeared with administration of the cholecystokinin receptor antagonist proglumide. Nocebo hyperalgesia may be caused by a cholecystokinin-dependent increase in anxiety.
1999	Flaten et al.	Healthy volunteers	66	Muscle relaxant/lactose	Provision of information	The group that received information experienced stronger effects compared with the group that did not.
2003	Johansen et al.	Healthy men	59	Inert substance	Provision of information	The blood concentration of cortisol (measure of stress level) increased the most in the nocebo group.
2004	Liccardi et al.	Outpatients	600	Inert substance	Conditioning	A diluted active substance was administered to outpatients who had previously experienced side effects to oral medication.
2006	Levine et al.	Healthy volunteers	75	Inert substance	Provision of information	Participants in the nocebo group who were told that nausea and motion sickness would worsen experienced worse symptoms. Symptoms were evaluated by electroencephalogram (gastric tachyarrhythmia is an accessory symptom of nausea and dizziness).
2007	Mondaini et al.	Benign prostatic hyperplasia	107	Finasteride	Provision of information	Subjects given information about side effects (n = 55) were compared with those not given information (n = 52). The group given information experienced stronger side effects.
2008	Scott et al.	Healthy volunteers	20	Painful stimulus	Mechanisms	Placebo responses were associated with opioid and dopaminergic activity. Nocebo responses were associated with deactivation of opioid release and dopaminergic activity. Placebo and nocebo produced opposite responses. These responses were confirmed on positron emission tomography. The brain areas involved in these phenomena correspond to the circuit for reward responses (expectations) and motivated behavior.
2010	Colloca et al.	Healthy volunteers	46	Light cues(pain)	Conditioning	The nocebo group was conditioned to believe the pain would be strong, the control group that it would be moderate, and the placebo group that it would be mild. Residual pain after conditioning in the placebo and nocebo groups was associated with the intensity and frequency of cues.
2011	Van Laarhoven et al.	Healthy women	105	Induction of pain and itchiness	Provision of information	The nocebo effect induced by verbal provision of information was more marked for itchiness than for pain. Effects were evaluated using a visual analog scale.
2012	Nir et al.	Healthy men	48	Thermal pain	Conditioning	Conditioned pain and perceived/modulated pain were evaluated by numerical pain score.
2012	Jensen et al.	Healthy women	40	Painful stimulus	Conditioning	Subjects rated their pain as a neural response score (NRS) from 0 = no pain to 100 = worst imaginable pain. Use of clearly visible pain cues produced a strong pain response (NRS = 63), which differed significantly from mild pain (NRS = 24). Pain decreased when masked cues were used, but there was still a significant difference. Conditioning was successful.
2013	Vogtle et al.	Female college students	85	Hyperalgesic ointment	Provision of information	Three groups were compared. One was told that the ointment would not affect their pain perception, one was told that the ointment would increase pain once applied, and one was shown a video depicting how the ointment would increase pain once applied.
2014	Van den Broeke et al.	Healthy volunteers	30	High-frequency electrical stimulation	Conditioning	Conditioning by high-frequency electrical stimulation (HFS) ⊠ pain response to pinprick stimulation was measured. Conditioning of the nocebo group by HFS caused pain to increase gradually with repeated pinprick stimulations
2014	Bottoms et al.	Healthy volunteers	12	drink	Provision of information	A three-group crossover study of a drink labeled as being for sports performance, a drink labeled as being fatigue-inducing, and water (control). The placebo effect increased sports performance, and the nocebo effect increased fatigue.
2015	Bavbek et al.	Patients with drug-induced hypersensitivity	137	Hypersensitivity reaction	Personality	Compared placebo and active drug forms of an antibiotic or analgesic. Nocebo responses were observed in 98 of 137 subjects.
2015	Aslaksen et al.	Healthy volunteers	142	Hyperalgesic cream	Provision of information	A thermal stimulus was applied (48°C for 15 s). The nocebo group, which was told the cream induced hyperalgesia, experienced the most pain.
2015a	Crichton and Petrie	Healthy students	64	Infrasound	Provision of information	This study investigated whether people exposed to online misinformation have a higher risk of nocebo response.
2015b	Crichton and Petrie	Healthy volunteers⊠	66	Infrasound	Provision of information	Single-blind study comparing a group who received an explanation about the nocebo effect with a group who received an explanation about its pathophysiological mechanisms.
2016	Pazzaglia et al.	Healthy volunteers	18	Hyperalgesic cream	Provision of information	Pain was induced by application of a chili pepper-based cream followed by laser pulses.
2016	Nestoriuc et al.	Breast cancer patients	88	Hormone therapy for breast cancer	Personality	Negative expectations increased treatment-specific side effects, nocebo-related side effects, and nonadherence risk.
2016	Albu and Meagher	Healthy volunteers	30	Hyperalgesic cream	Provision of information	Pain was induced thermally. The pain threshold decreased significantly in the nocebo group.

Year	Author	Subject	Sample Size	Intervention	Category	Summary
2016	Aslaksen et al.	Healthy volunteers	64	Hyperalgesic cream	Provision of information	Participants were exposed to heat pain (46°C–48°C) before and after application of the cream. Startle response was evaluated by electromyography. Four groups were compared. Group 1 received placebo, group 2 received no exposure, group 3 received nocebo plus an explanation, and group 4 received nocebo plus an explanation and sham heat. Pain and startle response increased with the nocebo. Verbal explanation induced a nocebo response. The nocebo response did not differ between sexes.
2017	Rheker et al.	Patients with depression	39	Antidepressants	Conditioning	Amitriptyline group (n = 19) and placebo group (n = 20); all received placebo after rest period.
2017	Piedimonte et al.	Healthy volunteers	34	Pain	Conditioning	Hyperalgesia was analyzed using contingent negative variation, also known as expectancy wave, on electroencephalography. Participants were conditioned to expect hypoalgesia after a green cue and hyperalgesia after a red cue. Placebo hypoalgesia and nocebo hyperalgesia differently affected pain perception and pain avoidance.
2017a	Bartels et al.	Healthy volunteers	95	Pain	Mechanisms	Placebo and nocebo effects were analyzed in participants whose cognitive schemas were evaluated and in participants in whom itch was induced electrically. The nocebo itch response had the same mechanism as the placebo response. Responsivity differed between sexes. A similar mechanism likely governs chronic pain as well.
2017	Hrust et al.	Healthy volunteers	712	Inert substance	Provision of information	Three groups were compared: one given a capsule they were told would improve performance (placebo; n = 288), one given a capsule they were told would reduce performance (nocebo; n = 232), and a group not told anything and not given a capsule (control; n = 192).
2017	Foster et al.	Cancer patients	446	Inert substance	Personality	There was no significant difference between patients 65 years or older compared with those under 65 years, and no difference in grade 2 or higher adverse events.
2017	Babel et al.	Healthy women	42	Painful stimulus	Conditioning	Participants received a moderately painful stimulus (control), a nonpainful stimulus (placebo), or a highly painful stimulus (nocebo) preceded by either orange or blue lights. The nocebo and placebo groups were conditioned by an electrical stimulus preceded by blue light. The placebo group experienced an analgesic effect, and the nocebo group a hyperalgesic effect.
2017b	Bartels et al.	Healthy volunteers	129	Painful stimulus	Provision of information	Three groups were compared: induction nocebo effect group (itch stimulus), an experimental group (nocebo-induced and placebo-induced), and reduction nocebo effect group (histamine-treated). The nocebo effect can be minimized by providing information in a positive way.
2018	Webster et al.	Healthy men	203	Non-prescription drug	Personality	Demographic and personality characteristics such as age, health worries, trust in medicine, and anxiety about symptoms were useful predictors.
2018	Milhelm et al.	Healthy men	80	Metoprolol	Provision of information	Dizziness as a side effect was evaluated by having participants exercise on a bicycle ergometer. The explanation format changed perception and conception.
2018	Quidde et al.	Gastrointestinal cancer patients	100	Study protocol	Provision of information	Educating patients about the nocebo effect, rather than explaining the nocebo effect, may attenuate side effects as well as reassure patients about the side effects.
2018	Verrender et al.	Healthy volunteers	44	Idiopathic Environmental Intolerance exposure	Provision of information	Study for idiopathic environmental intolerance attributed to electromagnetic fields (EMF). This study has provided further evidence that symptoms attributed to EMF exposure are likely the results of a nocebo response.
2018	Webster et al.	Healthy volunteers	203	Non-prescription drug(tablets)	Provision of information	Participants received “a well-known tablet” without a prescription together with one of two leaflets presenting standard side effect risk information. The only difference between the two leaflets was the “possible side effects” for common side effects. Positive framing of side effect information appears to be an effective intervention for reducing nocebo effects.

Table 2: Literature review on genetic polymorphisms

Year	Author	Enzyme name	SNP	Polymorphism	Summary
2014	Wendt et al.	Catechol-O-methyltransferase (COMT)	rs4680	Val 158 Met	In order of greatest nocebo effect: Val/Val > Val/Met > Met/Met.

that, analogously to the placebo effect, the nocebo effect is prone to eliciting pain and itchiness.
The 36 selected studies were grouped into six categories as discussed in the following sections.

2.1. Studies of how differences in participant characteristics such as personality affect susceptibility to the nocebo effect (labeled as "personality" in Table 1)

The oldest work in this review was a study on how personality affected susceptibility to side effects in participants who received the placebo in a phase I clinical study (Drici et al. 1995). Participants with a competitive and aggressive personality were more susceptible to the nocebo effect. Participants were also divided into four groups consisting of paramedical staff, medical students, science students, and non-science students, but there was no difference between groups. One study showed that high education level is associated with high susceptibility to the nocebo effect (Bavbek et al. 2015). In a 2-year cohort study, breast cancer patients were grouped by whether they had high or low negative expectations about treatment. Participants with more negative thought patterns were more prone to side effects, had lower quality of life, and had worse adherence (Nestoriuc et al. 2016). One study that examined susceptibility to the nocebo effect in participants aged 65 years or older compared with those under 65 years found no relationship with age (Foster et al. 2017). One study showed that women are more susceptible than men (Liccardi et al. 2004). Nakano (2013) found that placebo non-responders had high anxiety scores and scored low for extraversion and high for neuroticism on the Maudsley Personality Inventory (Nakano 2013). However, it is difficult to predict nocebo response based on personality (Webster et al. 2018), and further research is warranted to explore how personality and other participant characteristics influence the nocebo effect.

2.2. Studies of how differences in the provision of information about side effects affect susceptibility to the nocebo effect ("provision of information" in Table 1)

In one clinical study, participants were divided into three groups. The first group was told the drug they would receive relaxed the muscles (relaxant information group). The second group was told the drug they would receive increased muscle tension (stimulant information group). The third group was given no information. Half of the participants in each group were given a muscle relaxant, and the other half received a placebo (Flaten et al. 1999). Among the participants who received the active drug, those in the stimulant information group reported significantly greater muscle tension. The serum drug concentration was also significantly higher in the stimulant information group. Among the participants receiving placebo, those in the stimulant information group also reported significantly greater muscle tension. It is interesting to note that participants in the stimulant information group experienced muscle tension when given not only a placebo but also an actual muscle relaxant.
In another study, participants in whom nausea and motion sickness were induced using a rotating optokinetic drum were treated with an inert substance, and were told that the substance would reduce motion sickness, told that it would worsen motion sickness (nocebo), or not told anything at all (Levine et al. 2006). In yet another study, participants in whom pain was induced using a tourniquet were injected with an inert substance and were told that the substance would relieve the pain, told that it would increase the pain (nocebo), or not told anything at all. Subsequently, blood cortisol and β-endorphin levels were measured to assess stress (Johansen et al. 2003). Both worsening of symptoms and elevated levels of stress-related substances were most pronounced in the nocebo group.
Several studies selected for review investigated placebo and nocebo responses to an analgesic cream (Aslaksen et al. 2015; Pazzaglia et al. 2016; Albu and Meagher 2016; Vogtle et al. 2013). In all of these studies, pain was significantly greater in participants who were told the ointment would increase pain. A study that compared verbal and visual (video) suggestions showed that visual suggestion produced a stronger effect (Vogtle et al. 2013).
Other selected studies investigated how the nocebo response changes in people exposed to inaccurate online information about negative health effects and health scares (Crichton and Petrie 2015a, b). Participants were given positive or negative information about the health effects of infrasound inaudible to the human ear. The researchers concluded that access to and acceptance of positive health information reverses or attenuates negative expectations developed through exposure to negative information from the media. However, symptoms worsened (negative health effects appeared) in people given explanations about these pathophysiological mechanisms. This indicates that over-explanation can produce the opposite of the intended effect. In another study, participants were given antihypertensives and asked to perform an exercise test on a bicycle ergometer. Side effects decreased in participants who were told that people generally experience dizziness, but that the dizziness is a sign the drug is starting to work (Milhelm et al. 2018). Visual media are effective for counseling, but side effects actually increase when pathophysiological mechanisms are explained (Crichton and Petrie 2015a), illustrating that the opposite effect can occur depending on the type of explanation.
Many of the studies selected for review investigated both the placebo and nocebo effects. In one study, healthy volunteers were given an inert capsule and asked to perform 5 sets of 20-m all-out sprints (with 30 s of rest between sets). One group was not told anything (control group), one was told that the capsule would improve performance (placebo group), and one was told that the capsule would reduce performance (nocebo group). Performance dropped significantly in the nocebo group compared with the control group, but was comparable between the placebo and control groups (Hrust et al. 2017). Participants told that a substance will decrease an effect (nocebo group) are more susceptible to the suggestion than those told a substance will increase an effect (placebo group) (Vogtle et al. 2013; Hrust et al. 2017). This indicates that the element of anxiety is more influential than expectations about drugs.
A 2-year cohort study of breast cancer patients showed that those who had negative expectations about side effects went on to experience treatment-specific and non-specific (general) side effects, were at greater risk of non-adherence, and developed side effects sooner (Nestoriuc et al. 2016). In another study in gastrointestinal cancer patients, a specialist presented a case example of the nocebo effect to patients, explained the nocebo effect with a leaflet, and asked patients to consider how to apply the information to their treatment experience (nocebo education), with the aim of determining whether this education would reassure patients about side effects and reduce those side effects (Quidde et al. 2018).
The method of explaining side effects alters how the nocebo response manifests. Just as placebo research has shown that expectations that a drug will be effective increase hopefulness and enhance the drug's effect (Finniss et al 2010), it appears that explaining the nocebo effect similarly alters the perception of side effects. The results of these studies indicate that providing positive explanations about side effects to patients with negative expectations about treatment is effective in reducing side effects.

2.3. Studies of how nocebo conditioning affects susceptibility to the nocebo effect ("conditioning" in Table 1)

In one study, participants who had previously experienced side effects were administered a diluted active substance, and 27% experienced the nocebo effect (Liccardi et al. 2004). In a study on patients with depression, participants were first assigned to an amitriptyline group or placebo group, and then all participants received a placebo after a set period of time. Participants conditioned with amitriptyline experienced stronger side effects when receiving the placebo (Rheker et al. 2017). In a study of conditioned pain and perceived pain, a marked nocebo effect was observed for conditioned pain (Nir et al. 2012). In another study, high (nocebo group), low (placebo group), and moderate (control group) levels of pain were initially delivered in association with light cues, and when moderate pain was later

delivered to all groups, the nocebo group perceived significantly greater pain (Colloca et al. 2010). In yet another study in which participants were triggered with conscious cues for high and low pain levels, those conditioned to experience the nocebo effect later had pain triggered even with unconscious cues, indicating successful conditioning (Jensen et al. 2012).

These studies demonstrate that, just as conditioning by past treatment effectiveness enhances response to treatment through the placebo effect (Colloca and Beneditti 2006), past experience of side effects greatly contributes to how side effects will manifest in that person in the future through the nocebo effect.

2.4. Studies of nocebo response mechanisms ("mechanisms" in Table 1)

One selected study is a review of nocebo pain response mechanisms (Tracey 2010). The ability to switch to a positive mindset is called cognitive reappraisal, and this psychological process of switching from a negative mindset to a positive one influences activity in the right prefrontal area. Imaging research on the placebo and nocebo effects using modalities such as PET and functional magnetic resonance imaging has been flourishing, and findings support the involvement of the network between the prefrontal area, limbic system, and brainstem. Scientific understanding of the neurobiology of the placebo and nocebo effects is evolving. Neurotransmission of dopamine and endogenous opioids is said to increase with placebo analgesia and to decrease with nocebo (Scott et al. 2008; Tracey 2010). Cholecystokinin, which is considered to induce anxiety, is a neurotransmitter of the cranial nervous system that is co-localized with dopamine from dopaminergic neurons in the brainstem and may be involved in the nocebo effect (Benedetti et al.1997; Tracey 2010).

2.5. Study of the nocebo effect and genetic polymorphisms (Table 2)

One study on the nocebo effect and genetic polymorphisms in the dopamine pathway was selected for review (Wendt et al. 2014). It focused on catechol-O-methyltransferase (*COMT*), which encodes a neurotransmitter that degrades dopamine. *COMT* has a Val158Met polymorphism, and the Val form has a three- to four-fold higher enzyme activity compared with the Met form. When the relationship between subjective measures of the nocebo effect and *COMT* polymorphisms was analyzed, it was found that Val/Val homozygotes were highly likely to respond to a nocebo. The strongest nocebo effect was observed for Val/Val, followed by Val/Met, and lastly Met/Met. In contrast, the strongest placebo effect was observed for Val/Val, followed by Val/Met, and lastly Met/Met (Hall et al. 2012), which is the opposite order to the nocebo effect. Secretion of dopamine in the brain has been shown to increase with placebo, and decrease and even be reversed with nocebo (Scott et al. 2008), which are interesting findings when considered together. However, further research is warranted because this is the only study on the relationship of the nocebo effect with polymorphisms, and the results have not yet been sufficiently reproduced. In addition, *COMT* polymorphisms are known to differ between races, and their frequencies differ between Caucasian and Japanese populations (Palmatier et al. 1999). Consequently, research must also be conducted in Japanese participants.

Studies on the placebo effect have investigated the involvement of not only dopamine pathways (e.g., COMT and monoamine oxidase) but also serotonin pathways (e.g., serotonin transporters and tryptophan hydroxylase) and opioid pathways (opioid receptors) (Hall et al. 2015). Just as placebome research has been steadily increasing of late, research on the nocebo effect and related genes is likely the next frontier for the field.

3. Conclusion

Differences in the provision of information about side effects greatly affect susceptibility to the nocebo effect, and clinical studies have shown that counseling methods and quality are important; both of these findings should be considered in clinical practice. The nocebo effect is triggered by expectations and suggestions, and conditioning through means such as past experiences of actual side effects increases the frequency of side effects. There remains a need to investigate individual differences in the nocebo effect (differences between responders and non-responders) based on characteristics such as polymorphisms rather than just personality. It is clear that the treatment concept of maximizing treatment effects and minimizing side effects proposed by Colloca and Barsky (2020) is closely tied to the placebo and nocebo effects. Positive expectations reduce anxiety and attenuate the nocebo effect. Because this is an important element that influences response to treatment, research analyzing the mechanisms of the nocebo effect from pharmacological, psychological, and biological perspectives will likely continue to develop.

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