Review

The Placebo and Nocebo Phenomena: Their Clinical Management and Impact on Treatment Outcomes

Victor Chavarria, MD[1,*]; João Vian, MD[2,3,*]; Círia Pereira, MD[2,3]; João Data-Franco, MD[3,4]; Brisa S. Fernandes, MD, PhD[5,6]; Michael Berk, MBBCh, MMed(Psych), FF(Psych)SA, PhD, FRANZCP, FAAHMS[5,7,8,9,10]; and Seetal Dodd, MSc, PhD[5,7,8,9]

[1]Institut de Neuropsiquiatria i Adiccions (INAD), Parc de salut Mar (PSM), Barcelona, Spain; [2]Psychiatry and Mental Health Department, Centro Hospitalar Lisboa Norte, Lisbon, Portugal; [3]Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal; [4]Departamento de Psiquiatria e Saúde Mental, Hospital Beatriz Ângelo, Lisboa, Portugal; [5]IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia; [6]Laboratory of Calcium Binding Proteins in the Central Nervous System, Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; [7]University Hospital Geelong, Barwon Health, Geelong, VIC Australia; [8]Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia; [9]Centre for Youth Mental Health, Parkville, VIC, Australia; and [10]Florey Institute, University of Melbourne, Parkville, VIC, Australia

ABSTRACT

Purpose: This overview focuses on placebo and nocebo effects in clinical trials and routine care. Our goal was to propose strategies to improve outcomes in clinical practice, maximizing placebo effects and reducing nocebo effects, as well as managing these phenomena in clinical trials.

Methods: A narrative literature search of PubMed was conducted (January 1980–September 2016). Systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on placebo or nocebo effects in clinical practice were included in the qualitative synthesis. Search terms included: *placebo, nocebo, clinical, clinical trial, clinical setting, placebo effect, nocebo effect, adverse effects*, and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature.

Findings: Placebo and nocebo effects are psychobiological events imputable to the therapeutic context. Placebo is defined as an inert substance that provokes perceived benefits, whereas the term nocebo is used when an inert substance causes perceived harm. Their major mechanisms are expectancy and classical conditioning. Placebo is used in several fields of medicine, as a diagnostic tool or to reduce drug dosage. Placebo/nocebo effects are difficult to disentangle from the natural course of illness or the actual effects of a new drug in a clinical trial. There are known strategies to enhance clinical results by manipulating expectations and conditioning.

Implications: Placebo and nocebo effects occur frequently and are clinically significant but are underrecognized in clinical practice. Physicians should be able to recognize these phenomena and master tactics on how to manage these effects to enhance the quality of clinical

[*]These authors contributed equally to this work.

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Key words: adverse effects, clinical trial, nocebo, pharmacology, placebo, treatment.

INTRODUCTION

The placebo effect has been studied extensively throughout history.[1,2] The nocebo effect, also called "the evil brother of the placebo effect," has been less studied, but in recent years has become a subject of growing interest.[3–5] Both phenomena are composed of several intertwined biological and environmental mechanisms, displaying a complex interaction. Their operative mechanisms not only are affected by the characteristics of the individuals but also on the context in which they operate; thus, the search for a simple equation to predict the effect of placebo and nocebo has been met with limited success.

A precise definition of the placebo and nocebo phenomena is difficult to pinpoint, as different researchers have used different definitions, often depending on the context. A starting definition would be psychobiological events attributable to the overall therapeutic context[6]; herein, placebo effect would be the benefits provoked by an inert substance, and the nocebo effect is the induction of true or perceived harm after treatment with an inactive substance. Thus, a response to treatment, not attributable to the known mechanism of action of the treatment, is the core feature of both phenomena. This means that the definition can also be applied to an active substance treatment, then referring to the (extra) effects it elicits and that are not explained by its pharmacologic action. Many disorders have a natural course of illness in which symptoms fluctuate, making it difficult to differentiate between a placebo or nocebo response and the natural course of illness at an individual patient level. Similarly, many "side effects" occur commonly with or without pharmacotherapies (eg, headache), making it often difficult to disentangle, at an individual patient level, between a treatment-emergent adverse event that is a nocebo response or one that has occurred independently of treatment.

Paradigmatically, the placebo and nocebo phenomena have been most extensively studied in analgesia[7–10] and irritable bowel syndrome (IBS).[11] These phenomena have been studied more recently in the field of dermatology[12–14] and in psychiatry, particularly in depression.[15]

The underpinnings of placebo and nocebo are psychological and neurobiological. Psychological mechanisms include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning, and "placebo-by-proxy" induced by clinicians and family members.[16] Two principal mechanisms are well supported. The first aspect involves expectancy: the administration of placebo creates expectations in future responses by using simple verbal cues as modulators of expectations. Researchers can nudge a subject's expectations and boost the placebo effect. The second aspect involves classical conditioning: repeated associations between a neutral stimulus and an unconditioned stimulus (active drug) can result in the ability of the neutral stimulus by itself to provoke a response characteristic of the unconditioned stimulus.[4,17,18] In a study of placebo/nocebo in thermal pain, neither conditioning nor expectation alone seemed to be able to elicit placebo or nocebo effects; however, the combination of experience (conditioning) and expectation resulted in significant placebo (analgesia) or nocebo (hyperalgesia) effects.[19]

Misattribution is the inappropriate attribution of improvement or worsening to a treatment when it was actually caused by the disorder's natural fluctuation of symptoms or other causes.[20] Misattribution may have a more significant role in nocebo effects than in placebo effects, although this theory remains a focus of active debate.[21,22]

The neurobiology of the response to placebo and nocebo has been studied mostly in the paradigmatic field of analgesia and has been shown to be mainly related to the opioid and dopaminergic pathways.[6,23,24] A companion paper published in this issue of *Clinical Therapeutics* reviews the theoretical and biological underpinnings of the nocebo and placebo phenomena.[25]

It is important to note that placebo and nocebo responses are highly variable across individuals. Some individual differences have been associated with genetic polymorphisms or underlying neurologic impairments. For example, patients with frontal lobe impairment, especially prefrontal lobe, have decreased expectancy and learning, and thus they partially or totally lose their placebo response. In a study of Alzheimer's disease and pain, patients with reduced Frontal Assessment Battery scores exhibited a reduced placebo component of the analgesic treatment.[26] In intellectually disabled patients, a higher intelligence quotient was positively related with placebo response.[27]

Catechol-O-methyl transferase is involved in dopamine degradation, affecting the prefrontal lobe. The catechol-O-methyl transferase Val^{158}Met polymorphism

is a G to A mutation leading to amino acid substitution at codon 158 in the transmembrane form of the enzyme.[28] It was suggested as a biomarker of placebo response in IBS and a potential biomarker of placebo response in other conditions.[11] Thus, people who carry this polymorphism are more likely to experience the placebo effect.

The tryptophan hydroxylase-2 polymorphism (serotonin-related gene) seems a significant predictor of clinical placebo response in social anxiety disorder. Homozygosity for the G allele was associated with serotonergic modulation of amygdala activity and greater improvement in symptoms of anxiety.[29] People who experience anxiety disorder and carry this polymorphism are more likely to experience the placebo effect. Thus, psychological and neurobiological factors can predict individual differences in placebo and nocebo response.

The present review first focuses on the impact of placebo and nocebo effects in routine clinical settings as well as in clinical trials, and then offers strategies on how to use that knowledge to improve the quality of care and results in research.

MATERIALS AND METHODS

A literature search of PubMed was conducted for articles published between January 1980 and September 2016. Search terms included: *placebo, nocebo, clinical, clinical trial, clinical setting, placebo effect, nocebo effect, adverse effects,* and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature. Systematic reviews, randomized controlled trials (RCTs), observational studies, and case series were identified. Articles that had an emphasis on placebo or nocebo effects in clinical practice were selected for the qualitative synthesis.

CLINICAL APPLICATION

The clinical understanding of the placebo effect is a relevant issue. Placebo responses may be a major driver of clinical change after diverse therapies. Placebos are used in several fields of medicine (eg, neurology, psychiatry, rheumatology, pain management, ophthalmology), although ethical considerations limit their use in some areas. When surveyed, 45% of American physicians admitted to having used a placebo.[30] An English study found that only 12% of general practitioners use pure placebos (totally inert interventions) but the number was 97% for impure ones (interventions with clear efficacy for certain conditions but are prescribed for conditions in which their efficacy is unknown).[31] The most common reason to use a placebo was to tranquilize the patient (18%) and as a supplemental treatment (18%). Other reasons included "after 'unjustified' demand for medication" (15%), "for nonspecific complaints" (13%), "after all clinically indicated treatment possibilities were exhausted" (11%), "to control pain" (6%), "to get the patient to stop complaining" (6%), and "as a diagnostic tool" (4%).[30] It has been argued that the clinical benefits from many poorly evidence based complementary and alternative disciplines derive largely or even solely from cultivation of the factors that drive placebo effects.[32] Local regulations, however, preclude clinical use of placebos in some jurisdictions.

Patients need a greater dose of analgesic to achieve an equivalent outcome if their placebo response is impaired. When patients with postoperative pain were given intravenous saline (placebo), and buprenorphine was made available on request, the group told that the intravenous saline was a powerful painkiller took 33% less analgesia for the same pain compared with a control group (who were told they were receiving a rehydrating solution).[33]

CHALLENGES IN CLINICAL TRIALS

The placebo or nocebo response is related to common biochemical pathways that are activated both by social stimuli and therapeutic rituals on one hand and by drugs on the other. It has been shown that when an opioid agent is administered, it binds to μ-opioid receptors, but the very same μ-opioid receptors are activated by the patient's expectations about the drug.[34] This outcome is concordant with the finding that drugs without therapeutic rituals are less effective.[35] A suitable therapeutic setting can thus enhance the placebo response.[36]

The placebo effect has been well established in RCTs. In depression, its magnitude has been shown to vary depending on the investigators. Some propose that up to 75% of the drug effect is mediated by the placebo effect.[37,38] Others question these results, arguing that an unrepresentative subset of clinical trials (including many cases of mild to moderate depression) were analyzed, and therefore the data are not accurate.[39,40] This theory suggests that patients with less severe depression have a lower biological substrate and are more vulnerable to the

placebo effect. In 2002,[41] a meta-analysis was conducted with US Food and Drug Administration data containing RCTs that had not been published. This study revealed a small significant difference between antidepressant drug and placebo but not a clinical difference; the mean difference between drug and placebo was ~2 points on the Hamilton Depression Rating Scale. An alternative hypothesis to explain this difference in antidepressant trials is "breached blind." Because of the side effects of the drugs, the RCT patients may know if they are in the placebo or the active group.[42] Furthermore, when another active antidepressant is used as the comparator, instead of placebo, there is a significant increase in the effectiveness of the drug.[43]

It remains controversial whether the placebo effect is increasing across time in RCTs of depression. It has been proposed that the placebo effect has progressively increased over time[44] within the general population as a result of inflation of baseline severity to meet threshold inclusion criteria; that is, trials with less ill people, in which regression to the mean is more likely, and more comprehensive and frequent assessment procedures. Others have argued that pharmaceutical companies try to select only severely depressed patients because pharmacotherapy RCTs for mild and moderate depression often do not show statistically significant separation between the treatment and placebo trial arms,[45] thus downplaying the role of decreased baseline depression severity as an explanation. In contrast, a recent meta-analysis using published and unpublished data found stable placebo responses in the last 25 years,[46] implying the increase across time effect may be an artifact.

PLACEBO/NOCEBO AND SEPARATION FROM THE NATURAL COURSE OF ILLNESS

Understanding the natural course of illness is essential before commencing a clinical trial design or trying to separate drug from placebo effects. Given the fact that symptom severity does not stay frozen in time when no intervention is applied, the spontaneous progress or improvement of a pathological process can obviously confound or pose as a placebo or nocebo effect. These types of studies present numerous challenges, especially as modern medicine shifts its attention from infectious disorders to chronic or mental disorders (which wax and wane, where the natural history of illness extends greatly in time or has poor or no biomarkers available).[47]

Prospective nonintervention studies are increasingly ethically challenging as fewer diseases are lacking effective treatment. Therefore, in many cases, it is impossible to include a nontreatment arm in a clinical trial to guide our interpretation of results and discount the influence of natural progression. A loophole to this problem was found in studies of psychotherapy efficacy on major depressive disorder that use a wait-list as a control group. A meta-analysis[48] found that "wait-listers" experience ~33% of the symptomatic improvement of treated patients and 40% of the ones receiving placebo. An important caveat is that a wait-list is thus a very poor control group for clinical trials, despite being used often. Some studies even found that wait-list results in nocebo effects.[49]

STRATEGIES (USING PLACEBO TO IMPROVE RESULTS)

Maximizing Placebo

Patient expectations contribute toward the outcome of several disorders. This has been demonstrated for analgesia, treatment of myocardial infarction and Parkinson's disease, deep brain stimulation, orthopedic surgery, and antidepressant treatment.[22] Positively influencing patients' beliefs about therapeutic success is one way to maximize the placebo effect.[50] However, being too optimistic is also ethically problematic and can be construed as disingenuous if one is not cautious. Manipulating a patient's expectations may not necessarily require lying or deceiving. In a study of IBS, patients were informed they were being treated with placebo and still developed a positive clinical response.[51]

A partial reinforcement paradigm, placebo-controlled drug reduction (PCDR) (use of a full dose of medication for a set period of time [acquisition period] followed by a maintenance or evocation period with interposed placebo) has been shown to lower the dose needed to elicit a therapeutic response. This finding opens the door for a panoply of chronic disorders treated with medications with substantial side effects (Table I). PCDR allowed children with attention-deficit/hyperactivity disorder to be effectively treated with 50% of their optimal stimulant dose[52] and reduced the corticosteroid dose needed in psoriasis.[53]

Table I. Strategies to maximize the placebo effect.

Managing Expectations	Conditioning
Screen for patients with negative beliefs	Placebo-controlled drug reduction (PCDR)
Hidden applications when discontinuing a drug expected to cause withdrawal symptoms	Use salient stimuli and constant context when administering treatment including sensorial cues, same room and time of day when giving treatment
Promote social contact with other successful patients	Use effective pretreatments
Reduce anxiety	Avoid extinction in long-term treatments Motivation strategies, changes in situational cues Enhance physician–patient relationship Empathic style, more time of contact Describe the procedure before executing to improve attention

Adapted from Enck et al.[22]

It is usually assumed that more complex, time-consuming, and invasive interventions are more likely to be associated with placebo effects than other interventions. For instance, different colors and sizes of a pill seem to influence the clinical outcome.[54] However, to our knowledge, only 1 systematic review[55] has found mixed evidence of more invasive placebos having larger effects (7 of 12 studies with >1 placebo found no difference, 4 found single-outcome differences, and 1 found a large effect; 2 of 4 studies designed to differentiate placebo intensity were positive). The extant data may not be sufficient to discount its influence. To design studies directly comparing very different placebo interventions (ie, pill vs injection) while ensuring blinding for both patients and researchers ranges from very difficult to impossible. Also, to try to design studies controlling for context or for patient or clinician bias in expectancies might be a Sisyphean-like task, as the differences in context and expectancies themselves may be the cause of the placebo effect.

Although the placebo could be more powerful, deliberately administering a more invasive or intense placebo may be both ethically challenging (especially one with potential to cause harm) and lacking in evidence. Conversely, a meta-analysis of 41 RCTs assessing the effects of antidepressant agents on major depressive disorder showed that the more follow-up observations that occur, the more intense are the placebo effects elicited.[56] The number of medical visits in clinical trials contrasts with the shorter contact in community settings. This strategy is well established and can be useful because it is nonharmful. Profiling or choosing the right person to try a placebo might be more problematic. There was limited evidence for the role of age or sex, at least in psychiatric disorders.[57] A stronger correlation was found for low symptom severity and short duration of illness. There were 2 studies in children reporting a higher placebo effect in those of non-white ethnic origin.[58,59]

Managing Placebo in Clinical Trials

When comparing a drug versus a placebo, the first thing to bear in mind is that the effect of an active drug includes in itself a placebo component. Furthermore, issues are further complicated because the relation of the effects between the placebo and drug groups may not always be additive; that is, the measured effect in the active drug arm may be more (or less) than expected just by adding the placebo

Table II. Strategies to optimize drug–placebo differences in clinical trials.

Avoid enrichment/multidosing studies
Aim for a 50/50 probability of receiving placebo
Use treatment-naive patients
Randomized run-in and withdrawal periods
Use active placebos
Incorporate "no-treatment" groups
Avoid comparative effectiveness trials
Prioritize outcome evaluation in the following order:
1. Death
2. Biomarkers
3. Physician assessment
4. Patient-reported outcomes

effect to the actual active drug effect.[22,60] Therefore, perhaps "optimizing the drug–placebo difference" (vs minimizing placebo) is a preferable denomination.

Designing clinical trials is a specialized field in its own right. Separating a drug effect from a placebo effect always at the core of a clinical trial design, so that general quality guidelines for a clinical trial usually will work to optimize the drug–placebo difference: standardizing for symptom severity; avoiding physician's selection bias; controlling for center effects and patient adherence; and ensuring effective blinding.

However, sometimes these strategies are accompanied by other undesirable effects. For example, if we identify drug responders during a run-in phase or preselect patients who were previously exposed to a similar drug, we may increase the drug–placebo difference, but we also risk limiting a drug indication and overestimating benefits. If the population of previous responders comprised a specific group (eg, women), the trial will never generate approval for men. Some strategies involve deceit and thus have ethical concerns. Cost and feasibility are concerns as well (eg, when considering augmenting sample size). Therefore, it is up to the researcher to weigh the risks and benefits of each strategy.

Because the chance of being in a treatment group increases the magnitude of placebo responses,[61] a study design of equal likelihood of receiving placebo or treatment (ie, avoid enrichment or multidosing studies) should be preferred. Contrary to common belief, trying to exclude placebo responders using run-in phases early in the study was not able to prevent later placebo response.[62] Randomized run-in (ie, in a double-blind manner, patients first start receiving placebo and are then switched to the active drug after a few days) and withdrawal periods seem to hold more promise.[63] Crossover designs may promote conditioning[64] and may lead to unblinding of the study due to perceived side effects. Using active placebos (drugs that mimic the active treatment side effects) is a possible perfect placebo that rarely exists, mimicking all the side effects without any of the active mechanisms of the drug being tested. Controlling for the natural progression of the disease should also be a concern, even if in many situations it is ethically challenging and may motivate subjects to drop out. A way around this is using Zelen's design,[65] in which patients are randomly divided into an observational group and an interventional group comprising the active drug and placebo branches, allowing to control for the natural course of illness.

Comparative effectiveness trials are usually used when an efficacious treatment already exists for ethical standards. The new drug must then prove superiority, equivalence, or noninferiority. However, it has been shown that a drug tested against an active comparator performs better.[61,66] The placebo effect is also reportedly stronger when patients report the outcome than when the physician performs the assessment,[67] which is itself stronger than a biomarker-based evaluation.[68] The most objective outcome possible is death or survival rate, but this approach obviously cannot be used for many disorder endpoints (Table II).

Minimizing Nocebo

In the case of nocebo, no overt ethical dilemma is present. The intention of the physician is always to minimize its risk and effects. Also, we can expect the factors and strategies used to minimize the nocebo effect to be a mirror of the ones in placebo.

Of major importance would be to identify individuals more prone to develop nocebo effects. Several studies have been conducted to identify "risk factors" of the nocebo effect. A systematic review[4] found "learning/social observation," "perceived dose," "verbal suggestions of arousal and symptoms," and "baseline symptom expectations" to be the strongest predictors of nocebo effects. Interestingly, the type of administration again did not appear to be relevant, nor did self-awareness during exposure. Symptom severity at

Table III. Strategies to minimize nocebo.

Managing Expectations	Conditioning
Avoid informed consent overly focused on side effects	Low-dose initial regimen (when possible)
Framing of information	Hidden tapering in when feasible
Focus on the positive effects of treatment	
Conjoint plan	
Sense of control and ownership of the decision-making process (by the patient)	
Empathic attitude	

Adapted from Data-Franco and Berk.[73]

baseline (one of the strongest associations with placebo) also produced mixed results. Demographic factors such as sex, age, and literacy did not change the risk of a nocebo response. One study found that female investigator subjects report nocebo effects twice as frequently as male subjects after a social suggestion paradigm, but these data could have been confounded by the study design (the social cue was presented by a female).[69] In modern health systems in which access is good, participants who volunteer for trials may have presented with poor response or have not tolerated standard therapy. This earlier adverse experience increases the likelihood of these subjects being primed for nocebo responses.[70]

Managing patients' beliefs and experiences are at the core of possible strategies. Framing of information is an effective way to put the benefits and risks of treatment in perspective, focusing on the positive possibilities.[71] A caring and empathic relationship is beneficial.[72] When the medical problem allows for a small delay in the start of therapy, a lower initial dose might be helpful. Similarly, in RCTs, if a patient does not know when exactly he or she is getting exposed, nocebo effects are reduced (**Table III**). Nevertheless, this approach may be rarely feasible in outpatient settings or even time- and resource-consuming in a hospital setting.

CONCLUSIONS

Clinically, placebo and nocebo effects are of major importance, being present in daily medical practice. The overall effect of a drug stems from its pharmacodynamic actions plus the psychological effect derived from the act of its administration. Although both placebo and nocebo have been widely studied, the full complexity of their mechanisms needs further definition. Thus, when correctly applied, there are a number of strategies that can improve responses and patients' quality of life, maximizing placebo and reducing nocebo in clinical practice, and enhancing results in clinical trials. It underlines the impact of creating a good physician–patient relationship, increasing empathic attitudes, exposing information suitably, decreasing expectations of adverse effects, and promoting social contact between successfully treated patients.

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CONFLICTS OF INTEREST

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Address correspondence to: Seetal Dodd, MSc, PhD, University Hospital Geelong, Barwon Health, PO Box 281, Geelong, Victoria 3220, Australia. E-mail: seetald@barwonhealth.org.au

NEUROSCIENCE

Nocebo effects can make you feel pain

Negative expectancies derived from features of commercial drugs elicit nocebo effects

By **Luana Colloca**

The mysterious phenomenon known as the nocebo effect describes negative expectancies. This is in contrast to positive expectancies that trigger placebo effects (*1*). In evolutionary terms, nocebo and placebo effects coexist to favor perceptual mechanisms that anticipate threat and dangerous events (nocebo effects) and promote appetitive and safety behaviors (placebo effects). In randomized placebo-controlled clinical trials, patients that receive placebos often report side effects (nocebos) that are similar to those experienced by patients that receive the investigational treatment (*2*). Information provided during the informed consent process and divulgence of adverse effects contribute to nocebo effects in clinical trials (*1*). Nocebo (and placebo) effects engage a complex set of neural circuits in the central nervous system that modulate the perception of touch, pressure, pain, and temperature (*1, 3, 4*). Commercial features of drugs such as price and labeling influence placebos (*5, 6*). On page 105 of this issue, Tinnermann *et al.* (*7*) show that price also influences nocebo effects.

Tinnermann *et al.* evaluated the responses of healthy participants who received two placebo creams labeled with two distinct prices and presented in two boxes that had marketing characteristics of expensive or cheap medication. The creams were described as products that relieve itch but induce local pain sensitization (hyperalgesia). All creams, including controls, were identical and contained no active ingredients. Nocebo hyperalgesic effects were larger for the "more expensive" cream than for the "cheaper" cream. Combined corticospinal imaging revealed that the expensive price value increased activity in the prefrontal cortex. Furthermore, brain regions such as the rostral anterior cingulate cortex (rACC) and the periaqueductal gray (PAG) encoded the differential nocebo effects between the expensive and cheaper treatments. Expectancies of higher pain-related side effects associated with the expensive cream may have triggered a facilitation of nociception processes at early subcortical areas and the spinal cord [which are also involved in placebo-induced reduction of pain (*8*)]. The rACC showed a deactivation and favored a subsequent activation of the PAG and spinal cord, resulting in an increase of the nociceptive inputs. This suggests that the rACC–PAG–spinal cord axis may orchestrate the effects of pricing on nocebo hyperalgesia.

The anticipation of painful stimulation makes healthy study participants perceive nonpainful and low-painful stimulations as painful and high-painful, respectively (*9*). Verbally induced nocebo effects are as strong as those induced through actual exposure to high pain (*9*). Moreover, receiving a placebo after simulating an effective analgesic treatment, compared to receiving the same placebo intervention after a treatment perceived as ineffective, produces a 49.3% versus 9.7% placebo-induced pain reduction, respectively (*10*). The relationship between prior unsuccessful or successful pain relief interventions and placebo analgesic effects is linked to a higher activation of the bilateral posterior insula and reduced activation of the right dorsolateral prefrontal cortex (*11*).

Informing patients that a treatment has been stopped, compared to a covert treatment interruption, alters the response to morphine, diazepam, or deep-brain stimulation in postoperative acute pain, anxiety, or idiopathic Parkinson's disease, respectively (*12*). Patients openly informed about the interruption of each intervention experience a sudden increase of pain, anxiety, or bradykinesia (a manifestation of Parkinson's disease), whereas patients undergoing a hidden interruption do not (*12*). Neuroimaging approaches support the clinical observation. For example, the action of the analgesic remifentanil is overridden by activation of the hippocampus that occurs when healthy participants that receive heat pain stimulations are misleadingly told that the remifentanil administration was interrupted (*13*). These findings provide evidence that communication of treatment discontinuation might, at least in part, lead to nocebo effects with aggravation of symptoms.

In placebo-controlled clinical trials, nocebo effects can influence patients' clinical outcomes and treatment adherence. It was shown in a clinical trial that atorvastatin induced in the same individuals an excess rate of muscle-related adverse events in the nonblinded (i.e., patients knew they were taking atorvastatin), nonrandomized 3-year follow-up phase but not in the initial blinded 5-year phase when patients and physicians were unaware of the treatment allocation (atorvastatin or placebo) (*14*). Furthermore, misleading information about side effects for statins via public claims has led to treatment discontinuation and an increase in fatal strokes and heart attacks (*14*).

Given that nocebo effects contribute to perceived side effects and may influence clinical outcomes and patients' adherence to medication, we should consider how to avoid them in clinical trials and practices (*15*)—for example, by tailoring patient-clinician communication to balance truthful information about adverse events with expectancies of outcome improvement, exploring patients' treatment beliefs and negative therapeutic history, and paying attention to framing (i.e., treatment description) and contextual effects (i.e., price). Through an understanding of the physiological mechanisms, strategies could be developed to reduce nocebo effects. ■

University of Maryland, School of Nursing and School of Medicine, Baltimore, C655 West Lombard Street, Suite 729, Baltimore, MD 21201, USA. Email: colloca@umaryland.edu

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Science

Nocebo effects can make you feel pain

Luana Colloca

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Review

A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena

Seetal Dodd, PhD[1,2,3]; Olivia M. Dean, PhD[1,2,4]; João Vian, PhD[5,6]; and Michael Berk, PhD[1,2,3,4]

[1]Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Australia; [2]Department of Psychiatry, The University of Melbourne, Parkville, Victoria, Australia; [3]The Centre for Youth Mental Health, Parkville, Victoria, Australia; [4]The Florey Institute for Neuroscience and Mental Health, Parkville, Victoria, Australia; [5]Psychiatry and Mental Health Department, Centro Hospitalar Lisboa Norte, Lisbon, Portugal; and [6]Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

ABSTRACT

Purpose: Placebos are commonly used in experimental and patient populations and are known to influence treatment outcomes. The mechanism of action of placebos has been investigated by several researchers. This review investigates the current knowledge regarding the theoretical and biological underpinning of the nocebo and placebo phenomena.

Method: Literature was searched using PubMed using the following keywords: *nocebo*, *placebo*, *μ-opioid*, *dopamine*, *conditioning*, and *expectancy*. Relevant papers were selected for review by the authors.

Findings: The roles of conditioning and expectancy, and characteristics associated with nocebo and placebo responses, are discussed. These factors affect nocebo and placebo responses, although their effect sizes vary greatly, depending on inter-individual differences and different experimental paradigms. The neurobiology of the nocebo and placebo phenomena is also reviewed, emphasizing the involvement of reward pathways, such as the μ-opioid and dopamine pathways. Neurobiological pathways have been investigated in a limited range of experimental paradigms, with the greatest efforts on experimental models of placebo analgesia. The interconnectedness of psychological and physiological drivers of nocebo and placebo responses is a core feature of these phenomena.

Implications: Further research is needed to fully understand the underpinnings of the nocebo and placebo phenomena. Neurobiology pathways need to be investigated in experimental paradigms that model the placebo response to a broader range of pathologies. Similarly, although many psychological factors and inter-individual characteristics have been identified as significant mediators and moderators of nocebo and placebo responses, the factors identified to date are unlikely to be exhaustive. (*Clin Ther*. 2017;39:469–476) © 2017 Published by Elsevier HS Journals, Inc.

Key words: conditioning, dopamine, expectancy, μ-opioid, nocebo, pharmacology, placebo, treatment.

For the purpose of this review, a placebo response is an improvement in clinical symptoms when a person is administered an inert substance, whereas a nocebo response is a worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects. Typically, a placebo tablet is administered in control arms of

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0149-2918/$ - see front matter

clinical trials and is manufactured to look identical to the tablet in the active arm of a trial. Nocebo and placebo responses are also sometimes used to describe unexpected responses to active treatments that are not explained by the known mechanism of action of the treatment. It may not be possible to discern at an individual participant level between true placebo or nocebo responses and fluctuations in symptom severity due to the natural progression of the illness; however, insightful placebo and nocebo response data can often be obtained at a cohort level. While the importance of the placebo effect is widely understood, this is much less so for the nocebo effect. The biological bases of the nocebo and placebo effects are only now beginning to be unraveled. Attempts to understand the causes of the placebo effect have increased in the last 50 years, as placebo-controlled clinical trials have become the only accepted method for efficacy testing of new pharmaceuticals and the problems associated with placebos have become more apparent. Insights have been gained from exploring theoretical causes and influencing factors of the effect, which have probed the mechanisms underlying the phenomenon. This article reviews the theoretical and biological underpinning of the nocebo and placebo phenomena. A separate article also published in this issue reviews the clinical importance of the nocebo and placebo phenomena.

PSYCHOLOGICAL UNDERPINNINGS

There are a multitude of psychological elements that have been identified as the leading factors underpinning the placebo and nocebo effects.

The most well-known theories pertaining to the placebo and nocebo phenomena are the conditioning and expectancy hypotheses. Conditioning can occur when a person was pre-exposed to an active substance and had a reaction that imprints in memory. When they are then given an inert substance, they might respond to the inert substance in the same or similar way as they would to the active substance. A conditioned response is a triggering of a memory loop and, therefore, is driven by learning and adaptation.[1] The effect is mediated by many variables. The conditioning hypothesis alone is insufficient to explain the placebo and nocebo phenomena, for example, the extinction phenomenon in classic conditioning does not necessarily occur with placebos.[1]

Expectancy occurs where a pre-existing belief, or information received before being given an inert substance (or before reporting a response[2]), elicits a response to the inert substance predicated on what the person thinks will happen. It is not necessary to have ever been exposed to an active substance to have an expectation of response. This may be responding to a treatment that is not pharmacologically active because of a pre-existing belief that the treatment either works or might cause a specific reaction, and can be an important factor in alternative therapies in which pharmacologically active compounds are not included in the treatment.[3] Similarly, expectation can be a driver of inappropriate or over-prescription of some medications, including antibiotics, in a phenomenon that shares much in common with the placebo effect.[4] As with conditioning, expectancy also requires learning, which may come through direct receipt of information, suggestion, social cues, or the interaction of all these learning modalities.[5] Suggestion has also been used experimentally to extinguish a conditioned placebo response.[6] Extinction of a conditioned response requires learning, which in the case of a placebo response can be facilitated by suggestion, but may not necessarily occur solely through repeated administration of a placebo.

Hope for improvement has also been suggested as a driver of the placebo effect[1] and this has face validity; however, data have not been presented to support this theory. A corollary, where despair is suggested to drive the nocebo effect, has not been proposed in peer-reviewed literature. However, personality traits have been associated with placebo response,[7] leaving the possibility open to an association between personality traits, such as optimism and pessimism, being factors in the placebo and nocebo phenomena. However, considerable work needs to be done to unravel the relationship between personality and placebo response, including expanding the theoretic underpinnings of the association through hypothesis-driven research in addition to the current works that have focused on association between personality measures and placebo response.[8] State and trait variance are a limitation with personality measures[9] and may be relevant for the placebo response, for example, where there is variance in dependence.

The nature of the therapeutic alliance may also be a driver of the nocebo effect, with a hostile–dependent relationship being an exemplar. This relationship pattern occurs when one party is dependent on another, and the former is hostile or mistrusting of other people. This is a not uncommon but poorly recognized pattern in clinical practice, where people with insecure attachment styles are forced into trusting a clinician, and their interactional style makes this difficult Figure.

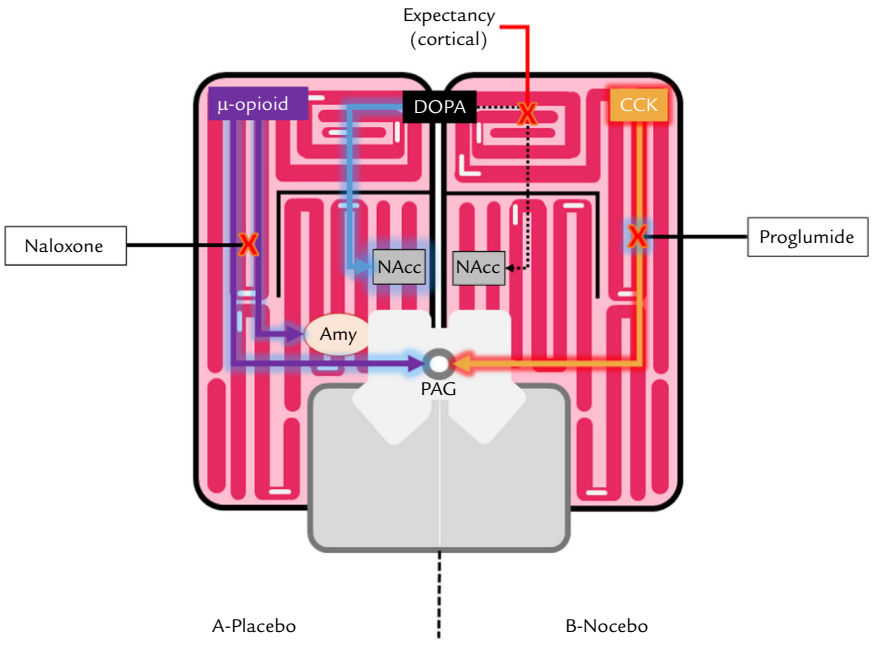

Figure. Summary of regions, circuits, and neurotransmitters implicated in placebo and nocebo. A-Placebo: Expectation activates cortical area signaling of dopamine to the nucleus accumbens and μ-opioid to the periaqueductal gray and elsewhere in the brain (the amygdala and other regions: not shown). The placebo effect is blocked by naloxone. B-Nocebo: Negative expectation has the opposite effect in the dopamine signaling and also activates cholecystokinin from the prefrontal cortex to the periaqueductal gray. The nocebo effect is blocked by proglumide. Amy = amygdala; CCK = cholecystokinin; DOPA = dopamine; NAcc = nucleus accumbens; PAG = periaqueductal gray.

In an open-labeled study, 80 women with irritable bowel syndrome were randomly assigned to placebo with a persuasive rationale but without deception, or to a control group with no treatment. Both groups received the same patient–provider relationship and contact time. Participants in the placebo-treated group had significantly higher global improvement scores.[10] In this study, the placebo effect occurred even though the participants were told they would be receiving an inert substance "like sugar pills." This may suggest that the placebo effect has multiple drivers, including expectancy, as participants were told that placebo "has been shown to produce significant improvement to [irritable bowel syndrome] symptoms," as well as the importance of the treatment rituals and therapeutic environment.

There is evidence that anxiety about the tolerability or efficacy of a treatment can be a driver of the nocebo effect. In a meta-analysis of placebo-treated participants in clinical trials of duloxetine versus placebo, treatment-emergent adverse events were reported more commonly in Phase II trials, then Phase III, and least in Phase IV.[11] This suggests that a nocebo response is more likely for a treatment that is more experimental and uncertain compared with one that is more established.

Choice of treatment and sense of control was found to influence both placebo and nocebo responses in an experiment where healthy participants (n = 61) were randomly assigned to choose between 2 equivalent β-blocker medications or be assigned to the medications. All study medications were actually placebos. There was an increased placebo response in the choice group and an increased nocebo response in the no-choice group.[12]

Neurobiological Findings

Numerous experiments have revealed insights into which regions of the brain are involved in the placebo response and which biochemical processes are occurring in association with placebo and nocebo events. Imaging studies have often used a placebo analgesia paradigm, as it is a reliable and convenient model.

Many variation of the analgesia paradigm exist. Placebos to replace psychotropic drugs are also a reliable and convenient paradigm, and a placebo antidepressant has been used for at least one imaging study. The placebo and nocebo phenomenon has been found in numerous medical conditions, across drug classes, and in non-pharmacologic contexts. It may be difficult to disentangle if a neurobiological response is applicable to the placebo and nocebo phenomena in general or only to a specific context or as treatment for a specific stimulus. The Figure summarizes brain regions, circuits, and neurotransmitters implicated in placebo and nocebo phenomena.

Neuroanatomic Regions

Studies using functional nuclear magnetic imaging (fMRI) and positron emission tomography (PET) have identified multiple brain regions involved in the placebo response. Several studies and a meta-analysis have identified the thalamus, primary and secondary somatosensory cortex, anterior cingulate cortex (ACC), amygdala, basal ganglia, and right lateral prefrontal cortex as brain regions; these were less activated when measured by fMRI, when placebo analgesia was used to modulate a response to a pain stimulus.[5] PET studies of placebo analgesia have identified the rostral ACC, prefrontal cortex, insula, thalamus, amygdala, nucleus accumbens and periaqueductal gray using a μ-opioid receptor radiotracers, and the basal ganglia using D2 and D3 receptor radiotracers as brain regions with neurotransmitter response to placebo analgesia.[13]

In a deceptive placebo analgesia paradigm fMRI study for visceral pain where participants are randomized to receive placebo and being told the substance is inert or placebo and being told that the substance is an analgesic, greater modulation by placebo analgesia of the posterior insula and dorsolateral prefrontal cortex was observed in women compared with men, although the efficacy of placebo analgesia in controlling expected or perceived pain did not differ between sexes.[14] A deceptive placebo analgesia paradigm fMRI study for noxious heat pain, where placebos were labeled as a popular branded original or a generic analgesic, original branded and generic labeled placebos were both associated with activation of the anterior insulae at baseline and activation of the dorsomedial prefrontal cortex after the interventions. Greater activation of the bilateral dorsolateral (as well as dorsomedial) prefrontal cortex (PFC) was observed for the placebo labeled as the original brand. The placebo labeled as the original brand was also associated with decreased pain intensity compared with the generic-labeled placebo.[15] A recent PET study using a μ-opioid receptor radiotracer, patients with major depressive disorder were treated with placebo in a crossover study in which one placebo was labeled "active" and the other "inactive," and told that the active treatment was a fast-acting antidepressant and the inactive treatment was a control. Active treatment was superior to inactive treatment for placebo-induced opioid release in brain regions subgenual ACC, nucleus accumbens, amygdala, thalamus, and hypothalamus.[16] Placebo activation of endogenous opioid neurotransmitters that bind to receptors in the pregenual and subgenual rostral ACC, the dorsolateral PFC, the insular cortex, and the nucleus accumbens, has also been observed in an analgesia paradigm using PET.[17] Substantial inter-individual variation has been reported for brain regions involved in placebo response to expectations of analgesia.[18]

An fMRI study of 24 healthy adults investigated neural activation in response to stimuli associated with different expectations. In 3 separate sessions (ie, training, conditioning, and scanning sessions) on different days, participants were subject to 12-second heat pain stimulus to their right forearm. At the conditioning and training sessions, participants skin was treated with an inert cream before the heat pain stimulus. One cream was labeled "lidocaine" (positive expectancy), one was labeled "neutral," and the third cream was labeled "capsaicin" (negative expectancy). Difference between positive and negative expectancy conditions were observed, either pre or post stimulus, in the dorsal ACC, right orbito-PFC, anterior insula, right dorsolateral PFC, left ventral striatum, orbitofrontal cortex, periaqueductal gray, and left operculum and putamen.[19] This experiment found that placebo and nocebo expectancies have effects on different brain networks in response to a pain stimulus.

There are limitations to using fMRI and PET to study models of the nocebo and placebo effects. Firstly, most experiments are conducted on health volunteers, so important drivers of the placebo response, such as hope and therapeutic alliance, are not included in the experimental construct. Secondly, study participants are inside a large piece of medical equipment, which is a specific experimental environment. Thirdly, the experimental environment limits the study design and duration.

Neurochemical Processes

The placebo response has been associated with the release of endorphins and dopamine, providing a neurochemical explanation of the efficacy of placebo analgesia.[13] Early evidence of the elevation of endogenous opioids in placebo analgesia was reported in 1978, when Levine et al[20] used placebo as an analgesic for dental postoperative pain and reversed the analgesic effects by administering the opiate antagonist naloxone. Endorphin and dopamine release and opioid and dopamine receptors are widely distributed, but are also clustered in specific brain regions that correspond with many of the regions identified by fMRI studies. There are 3 major types of opioid receptor, μ-opioid receptor, δ-opioid receptor, and κ-opioid receptor, which can be further divided into subtypes, and a fourth nociception or orphanin receptor.[21] These receptors are widely distributed through the brain and other organs, but with differences in expression and distribution.[21] Opioid receptors have a range of functions, including pain modulation and their association with analgesia, however, they are also associated with various functions, including mood regulation, homeostasis, cell proliferation, and neuroprotection.[21]

Much placebo neurobiological research has focused on analgesia, often investigating the μ-opioid receptor. Where major depressive disorder has been investigated[16] increased μ-opioid neurotransmission has been observed, similar to observations in analgesia research, which may suggest similarities to, or be a consequence of, using a similar research method. Inter-individual variation in μ-opioid neurotransmission has also been observed in a study of 50 healthy controls with and without placebo administration, where psychological trait scores measured with scales for altruism, straightforwardness, and angry hostility accounted for 25% of the variance in placebo analgesic response and also found that participants scoring above the median in a composite score of all 3 traits had increased μ-opioid neurotransmission in response to placebo administration.[22]

An experiment where hypertonic saline was injected into the masseter muscle of 20 healthy individuals to induce pain, with or without placebo analgesia, was investigated using PET to examine changes in dopamine and opioid neurotransmission. The study used [C^{11}]-labeled raclopride (selective for D_2 receptors) and carfentanil (selective for μ-opioid receptors). Participants were asked to rate the efficacy of the analgesic and describe adverse events. Effective placebo analgesia was associated with increased dopamine and opioid neurotransmission in multiple brain regions. A nocebo effect was identified in 5 participants who reported increased pain intensity during placebo administration. Nocebo responders showed decreased dopamine and opioid neurotransmission in the same brain regions where increased neurotransmission was observed in placebo responders.[23]

In a study where patients reporting mild perioperative pain were given saline solution and were told that the solution produced an increased pain (nocebo hyperanalgesia), pain was abolished when proglumide was added to the solution. Proglumide is a cholecystokinin antagonist, which blocks both the CCK_A and CCK_B receptor subtypes, suggesting that nocebo hyperanalgesia is mediated at least in part by cholecystokinin.[24]

PET studies have found that administration of a placebo to people with Parkinson's disease can induce dopamine release in the striatum.[25] Furthermore, in a study of 24 participants with Parkinson's disease undergoing deep brain stimulation, the firing rate of selected neurons was changed in participants who showed a clinical response to placebo, but not in nonresponders or partial responders to placebo. Mean firing frequency decreased in subthalamic and substantia nigra pars reticulata neurons and increased in ventral anterior and anterior ventral lateral thalamus neurons. The placebo effect had a duration of no more than 45 minutes. Other parts of the brain circuitry were not measured.[26] Another study found that placebo was enhanced with preconditioning by apomorphine exposure, with the greater number of exposures to apomorphine associated with a greater change in neuronal firing rates.[27]

Endocannabinoids have a role in placebo-induced analgesia, as reported in a study analogous to the 1978 naloxone experiment that reported on the role of endorphins.[20] Placebo was effective as an analgesic against tourniquet pain after preconditioning participants to analgesia with either the opioid morphine or the nonsteroidal anti-inflammatory drug ketorolac. In these preconditioned participants, the CB1 cannabinoid receptor antagonist rimonabant reversed placebo analgesia after preconditioning with ketorolac, but did not reverse placebo analgesia in participants preconditioned with morphine.[28]

Prostaglandin levels have also been found to change in response to placebo. In an experiment,

placebo was used to treat headache caused by high-altitude (3,500 m) hypobaric hypoxia, after preconditioning by treating headache with inhaled oxygen and later giving placebo (sham) oxygen, or by preconditioning with aspirin and later giving a placebo tablet. In both scenarios, the placebos were effective for reducing headache pain, but the analgesic effect of placebo oxygen was superior to placebo aspirin. Placebo oxygen was found to specifically reduce salivary prostaglandin E_2, mimicking the therapeutic pathway of oxygen therapy, whereas placebo aspirin had a more general effect on prostaglandin synthesis, mimicking the effect of cyclooxygenase inhibition.[29]

Interaction of Psychological and Physiological Factors

Placebo and nocebo responses occur within a psychological and physiological context. This context is critical for all aspects of the response, including the neurobiological elements. The context includes characteristics of the study or treatment in which the placebo or nocebo effect is observed and characteristics of the study participant or patient, as well as other characteristics, including the environment in which the study or treatment is being conducted. The doctor–patient relationship, for example, can include trust, where untrustworthiness has been associated with increased amygdala activity, and trustworthiness can be modulated by oxytocin.[30] Trust may be a characteristic not only of the active relationship, but is powerfully influenced by personality and developmental factors that set individuals levels of trust. Similarly, hope and hopelessness have been associated with serotonergic and noradrenergic systems,[30] showing the potential for variables relevant to placebo having a direct effect on neurotransmitter systems directly implicated in mood. Also relevant to the placebo response, admiration and compassion by a participant have been found through fMRI to result in a pattern of activation within the posteromedial cortice.[31] Learned helplessness has been found to effect serotonin regulation.[32] The relationship between pain and stress and anxiety with the hypothalamic–pituitary–adrenal axis and cortisol is well established.[33]

Negative and positive expectations, which are suggested to be major drivers of the placebo and nocebo responses, have been found to induce changes in reward circuitry in the nucleus accumbens, and similarly, conditioning may induce changes in learning mechanisms.[30]

DISCUSSION

The drivers of the placebo and nocebo phenomena may be a synergy of multiple biological and psychological variables, mediated by a further multitude of contextual and individual variables. There is clear evidence of physiological factors that underpin the phenomena, as well as a contribution by psychological factors. This is further complicated by considerable inter-individual differences. Although there is consistency in the literature in terms of which pathways are implicated in placebo and nocebo responses, neurotransmitter activation does not occur with all individuals experiencing the same stimulus. Factors such as conditioning, expectancy, hope and despair, wanting to please the experimenters, treatment setting, caring nature of the clinician, and personal beliefs about medications, all play a role.

Furthermore, while the placebo and nocebo effect has been observed for treatment for a broad range of medical conditions, it has only been carefully studied in experimental models of a narrow range of conditions, especially pain and analgesia. It is possible, or even likely, that the neural pathways involved in a placebo analgesia response are different, or only partly overlapping, from the neural pathways involved in a placebo response for a different treatment. The investigation of the biological and theoretical underpinning of the placebo and nocebo phenomena is at an early stage and much additional research is required.

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CONFLICTS OF INTEREST

SD has received grant support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier, speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis and conference travel support from Servier. OMD has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical

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Address correspondence to: Seetal Dodd, PhD, PO Box 281, Geelong, Victoria 3220, Australia. E-mail: seetald@barwonhealth.org.au

REVIEW ARTICLE

Nocebo Phenomena in Medicine

Their Relevance in Everyday Clinical Practice

Winfried Häuser, Ernil Hansen, Paul Enck

SUMMARY

Background: Nocebo phenomena are common in clinical practice and have recently become a popular topic of research and discussion among basic scientists, clinicians, and ethicists.

Methods: We selectively searched the PubMed database for articles published up to December 2011 that contained the key words "nocebo" or "nocebo effect."

Results: By definition, a nocebo effect is the induction of a symptom perceived as negative by sham treatment and/or by the suggestion of negative expectations. A nocebo response is a negative symptom induced by the patient's own negative expectations and/or by negative suggestions from clinical staff in the absence of any treatment. The underlying mechanisms include learning by Pavlovian conditioning and reaction to expectations induced by verbal information or suggestion. Nocebo responses may come about through unintentional negative suggestion on the part of physicians and nurses. Information about possible complications and negative expectations on the patient's part increases the likelihood of adverse effects. Adverse events under treatment with medications sometimes come about by a nocebo effect.

Conclusion: Physicians face an ethical dilemma, as they are required not just to inform patients of the potential complications of treatment, but also to minimize the likelihood of these complications, i.e., to avoid inducing them through the potential nocebo effect of thorough patient information. Possible ways out of the dilemma include emphasizing the fact that the proposed treatment is usually well tolerated, or else getting the patient's permission to inform less than fully about its possible side effects. Communication training in medical school, residency training, and continuing medical education would be desirable so that physicians can better exploit the power of words to patients' benefit, rather than their detriment.

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Department of Internal Medicine I, Klinikum Saarbrücken and Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München: PD Dr. med. Häuser

Department of Anesthesia, University Medical Center Regensburg: Prof. Dr. med. Dr. rer. nat. Hansen

Department of Psychosomatic Medicine and Psychotherapy, University Clinic Tuebingen (UKT): Prof. Dr. rer. nat. Dipl.-Psych. Enck

Words are the most powerful tool a doctor possesses, but words, like a two-edged sword, can maim as well as heal.", Bernard Lown (e1).

Doctor–patient communication and the patient's treatment expectations can have considerable consequences, both positive and negative, on the outcome of a course of medical therapy. The positive influence of doctor–patient communication, treatment expectations, and sham treatments, termed placebo effect, has been known for many years (e2) and extensively studied (1). The efficacy of placebo has been demonstrated for subjective symptoms such as pain and nausea (1). The Scientific Advisory Board of the German Medical Association published a statement on placebo in medicine in 2010 (2).

Method

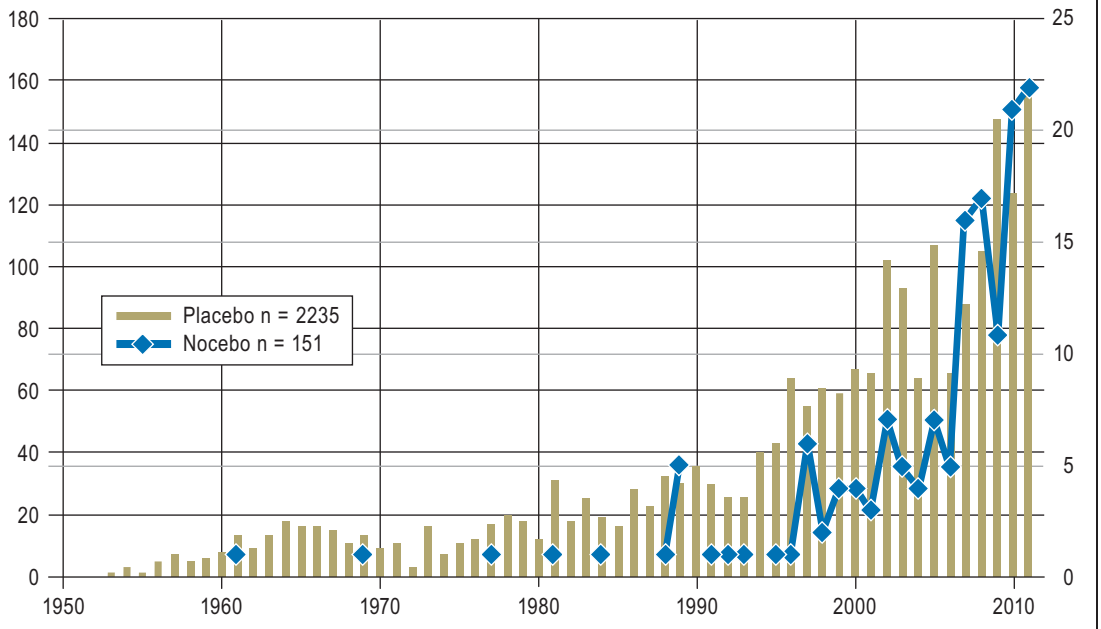
The opposite of the placebo phenomenon, namely nocebo phenomena, have only recently received wider attention from basic scientists and clinicians. A search of the PubMed database on 5 October 2011 revealed 151 publications on the topic of "nocebo," compared with over 150 000 on "placebo." Stripping away from the latter all articles in which "only" placebo-controlled drug trials were reported left around 2200 studies investigating current knowledge of the placebo effect. In comparison, the data on the nocebo effect are sparse. Of the 151 publications, only just over 20% were empirical studies: the rest were letters to the editor, commentaries, editorials, and reviews (*Figure*).

Our intention here is to portray the neurobiological mechanisms of nocebo phenomena. Furthermore, in order to sensitize clinicians to the nocebo phenomena in their daily work we present studies on nocebo phenomena in randomized placebo-controlled trials and in clinical practice (medicinal treatment and surgery). Finally, we discuss the ethical problems that arise from nocebo phenomena which may be induced by explanation of the proposed treatment in the course of the patient briefing and describe possible solutions.

Definition of nocebo phenomena

The term "nocebo" was originally coined to give a name to the negative equivalent of placebo phenomena and distinguish between desirable and undesirable effects of placebos (sham medications or other sham interventions, for instance simulated surgery). "Nocebo" was used to describe an inactive substance or

FIGURE



Number of studies on the placebo effect (olive-green bars, left ordinate) and the nocebo effect (blue diamonds, right ordinate) in PubMed between 1950 and 2011

ineffective procedure that was designed to arouse negative expectations (e.g., giving sham medication while verbally suggesting an increase in symptoms) (3).

"Placebo" and "nocebo" are meanwhile being used in another sense: The effects of every medical treatment, for example administration of drugs or psychotherapy, are divided into specific and non-specific. Specific effects are caused by the characteristic elements of the intervention. The non-specific effects of a treatment are called placebo effects when they are beneficial and nocebo effects when they are harmful.

Placebo and nocebo effects are seen as psychobiological phenomena that arise from the therapeutic context in its entirety, including sham treatments, the patients' treatment expectations and previous experience, verbal and non-verbal communications by the person administering the treatment, and the interaction between that person and the patient (4). The term "nocebo effect" covers new or worsening symptoms that occur during sham treatment e.g., in the placebo arm of a clinical trial or as a result of deliberate or unintended suggestion and/or negative expectations. "Nocebo response" is used to mean new and worsening symptoms that are caused only by negative expectations on the part of the patient and/or negative verbal and non-verbal communications on the part of the treating person, without any (sham) treatment (5).

Experimental nocebo research

Experimental nocebo research aims to answer three central questions:

- Are nocebo effects caused by the same psychological mechanisms as placebo effects, i.e., by learning (conditioning) and reaction to expectations?
- Are placebo and nocebo effects based on the same or different neurobiological events?
- Are the predictors of nocebo effects different from those of placebo effects?

Psychological mechanisms

The proven mechanisms of the placebo response include learning by Pavlovian conditioning and reaction to expectations aroused by verbal information or suggestion (6). Learning experiments with healthy probands have shown that worsening of symptoms of nausea (caused by spinning on a swivel chair) can be conditioned (7). Expectation-induced cutaneous hyperalgesia could be produced experimentally through verbal suggestion alone (8). Social learning by observation led to placebo analgesia on the same order as direct experience by conditioning (9).

Nocebo responses can also be demonstrated in patients. In an experimental study, 50 patients with chronic back pain were randomly divided into two groups before a leg flexion test: One group was informed that the test could lead to a slight increase in pain, while the other group was told that the test had no effect on pain level. The group with negative information reported stronger pain (pain intensity 48.1 [standard deviation (SD) 23.7] versus 30.2 [SD 19.6] on a 101-point scale) and performed fewer leg flexions (52.1 [SD 12.5] versus 59.7 [SD 5.9]) than the group with neutral instruction (10).

It can be concluded from these studies that both placebo and nocebo responses can be acquired via all kinds of learning. If such reactions occur in everyday clinical practice, one must assume that they arise from the patient's expectations or previous learning experiences (5).

Neurobiological correlates

A key part in the mediation of the placebo response is played by a number of central chemical messengers. Especially dopamine and endogenous opiates have been demonstrated to be central mediators of placebo analgesia. These two neurobiological substrates have also been shown to play a part in the nocebo response (hyperalgesia): While secretion of dopamine and endogenous opioids is increased in placebo analgesia, this reaction is decreased in hyperalgesia (11). Because worsening of symptoms e.g., increased sensitivity to pain is often associated with anxiety, other central processes play a part, e.g., the neurohormone cholecystokinin (CCK) in pain (12). To date, a genetic predisposition to placebo response has been demonstrated only for depression and social anxiety (e3); such a predisposition to nocebo response has so far not been shown (e4).

Interindividual variation

Sex is a proven predictor of the placebo response and also exerts some influence on the nocebo response. In the above-mentioned study on the aggravation of symptoms of nausea, women were more susceptible to conditioning and men to generated expectations (6).

Identification of predictors of nocebo responses is a central goal of ongoing investigations. The aim is to pinpoint groups at risk of nocebo responses, for example patients with high levels of anxiety, and optimize the therapeutic context accordingly (13).

Generation of nocebo responses by doctor–patient and nurse–patient communication

The verbal and non-verbal communications of physicians and nursing staff contain numerous unintentional negative suggestions that may trigger a nocebo response (14).

Patients are highly receptive to negative suggestion, particularly in situations perceived as existentially threatening, such as impending surgery, acute severe illness, or an accident. Persons in extreme situations are often in a natural trance state and thus highly suggestible (15, 16). This state of consciousness leaves those affected vulnerable to misunderstandings arising from literal interpretations, ambiguities, and negative suggestion *(Box)*.

In medical practice the assumption is that the patient's pain and anxiety are minimized when a painful manipulation is announced in advance and any expression of pain by the patient is met with sympathy. A study of patients receiving injections of radiographic substances showed that their anxiety and pain were heightened by the use of negative words such as "sting," "burn," "hurt," "bad," and "pain" when explaining the procedure or expressing sympathy (17). In another study, injection of local anesthetic preparatory to the induction of epidural anesthesia in women about to give birth was announced by saying either "We are going to give you a local anesthetic that will numb the area so that you will be comfortable during the procedure" or "You are going to feel a big bee sting; this is the worst part of the procedure." The perceived pain was significantly greater after the latter statement (median pain intensity 5 versus 3 on an 11-point scale) (18).

BOX

Unintended negative suggestion in everyday clinical practice (after 15, e5, e6)

- **Causing uncertainty**
  - "This medication may help."
  - "Let's try this drug."
  - "Try to take your meds regularly."
- **Jargon**
  - "We're wiring you up now." (connection to the monitoring device)
  - "Then we'll cut you into lots of thin slices." (computed tomography)
  - "Now we're hooking you up to the artificial nose." (attaching an oxygen mask)
  - "We looked for metastases—the result was negative."
- **Ambiguity**
  - "We'll just finish you off." (preparation for surgery)
  - "We're putting you to sleep now, it'll soon be all over." (induction of anesthesia)
  - "I'll just fetch something from the 'poison cabinet' (secure storage for anesthetics), then we can start."
- **Emphasizing the negative**
  - "You are a high-risk patient."
  - "That always hurts a lot."
  - "You must strictly avoid lifting heavy objects—you don't want to end up paralyzed."
  - "Your spinal canal is very narrow—the spinal cord is being compressed."
- **Focusing attention**
  - "Are you feeling nauseous?" (recovery room)
  - "Signal if you feel pain." (recovery room)
- **Ineffective negation and trivialization**
  - "You don't need to worry."
  - "It's just going to bleed a bit."

TABLE 1

Systematic reviews: discontinuation rates in placebo arms of randomized trials owing to adverse events

Reference	Verum	Number of studies	Discontinuation rate (%)
e9	Primary and secondary prevention of cardiovascular diseases: statins	20	4–26 *
e10	Multiple sclerosis: immune modulators	56	2.1 (95% CI: 1.6–2.7)
e10	Multiple sclerosis: symptomatic treatment	44	2.4 (95% CI: 1.5–3.3)
e11	Acute treatment of migraine	59	0.3 (95% CI: 0.2–0.5)
e11	Prevention of migraine	31	4.8 (95% CI: 3.3–6.5)
e11	Prevention of tension headache	4	5.4 (95% CI: 1.3–12.1)
22	Painful peripheral diabetic polyneuropathy	62	5.8 (95% CI: 5.1–6.6)
22	Fibromyalgia syndrome	58	9.5 (95% CI: 8.6–10.7)

CI = confidence interval; * no data on pooled discontinuation rates

The patient's expectations

Just as the announcement that a drug is going to be given can provoke its side effects even if it is not actually administered, telling headache patients that they are going to experience a mild electric current or an electromagnetic field (e.g., from cell phones) produces headaches (e7). The symptoms of Parkinson's disease patients undergoing deep brain stimulation are more pronounced if they know their brain pacemaker is going to be turned off than if they do not know (e8).

Nocebo phenomena in drug treatment

Researchers distinguish true placebo effects from perceived placebo effects. The true placebo effect is the whole effect in the placebo group minus non-specific factors such as natural disease course, regression to the mean, and unidentified parallel interventions. The true placebo effect can be quantified only by comparing a placebo group and an untreated group (19). The true nocebo effect in double-blind drug trials thus includes all negative effects in placebo groups minus non-specific factors such as symptoms from the treated disease or comorbid conditions and adverse events of accompanying medication (4). The nocebo effects in drug trials referred to below are perceived rather than "true" nocebo effects.

Adverse event profile and discontinuation rates in placebo groups of randomized trials

A systematic review showed that in randomized controlled trials (RCTs) of migraine (69 studies in total, 56 of them with triptans, 9 with anticonvulsants, and 8 with non-steroidal antirheumatic drugs), the side effect profile of placebo corresponded with that of the "true" drug being tested (20). A systematic review of RCTs of tricyclic antidepressants (TCAs; 21 studies) and selective serotonin reuptake inhibitors (SSRIs; 122 studies) revealed a significantly higher rate of adverse events in both the verum and placebo arms of the TCA trials compared to the verum and placebo arms of the SSRI trials. Patients given TCA placebos were significantly more likely to report dry mouth (19.2% versus 6.4%), vision problems (6.9% versus 1.2%), fatigue (17.3% versus 5.5%), and constipation (10.7% versus 4.2%) than patients taking SSRI placebos (21).

The side effects of medications therefore depend on what adverse events the patients and their treating physicians expect (20, 21). Rates of discontinuation owing to adverse effects of placebo in double-blind trials on patients with various diseases are presented in *Table 1*.

Problems in evaluating side effects of drugs

The methods used for recording adverse events influence the type and the frequency of effects reported: Patients specify more adverse events when checking off a standardized list of symptoms than when they report them spontaneously (21). In a large proportion of double-blind drug trials, the way in which subjective drug side effects were recorded is described inadequately or not at all (22). The robustness of the data on which summaries of product characteristics and package inserts are based must therefore be seen in a critical light.

The problems in evaluating side effects of drugs in RCTs also apply in everyday clinical practice. Is the symptom reported by the patient—nausea, for example—a side effect of medication, a symptom of the disease being treated, a symptom of another disease, or a (temporary) indisposition unconnected with either the drug or the disease?

Nocebo effects during drug treatment in everyday clinical practice

Nocebo effects have been described in *(Table 2)*:

- Drug exposure tests in the case of known drug allergy
- Perioperative administration of drugs
- Finasteride in benign prostate hyperplasia

TABLE 2

Nocebo effects in clinical studies

Reference	Diagnosis	Number of patients	Results
e12	Case series: exposure test in known drug allergy	600	27% reported adverse events (nausea, stomach pains, itching) on placebo
e13	Case series: exposure test in known drug allergy	435	32% reported adverse events (nausea, stomach pains, itching) on placebo
e14	Two RCTs: fatigue in advanced cancer	105	79% reported sleep problems, 53% loss of appetite, and 33% nausea on placebo*
e15	RCT: perioperative administration of drugs	360	Undesired effects were reported by 5–8% of patients in the sodium chloride group, 8% of patients in the midazolam-placebo group, and 3–8% of patients in the fentanyl-placebo group
e16	RCT: finasteride in benign prostate hyperplasia	107	Blinded administration of finasteride led to a significantly higher rate of sexual dysfunction (44%) in the group that was informed of this possible effect than in the group that was not informed (15%)
e17	RCT: 50 mg atenolol in coronary heart disease	96	Rates of sexual dysfunction: 3% in the group that received information on neither drug nor side effect, 16% in the group that was informed about the drug but not about the possibility of sexual dysfunction, 31% in the group that was told about both the drug and the possible sexual dysfunction
e18	RCT: 100 mg atenolol in coronary heart disease	114	Rates of sexual dysfunction: 8% in the group that received information on neither drug nor side effect, 13% in the group that was informed about the drug but not about the possibility of sexual dysfunction, 32% in the group that was told about both the drug and the possible sexual dysfunction
e19, e20	Acetylsalicylic acid versus sulfinpyrazone in unstable angina pectoris	555	Inclusion of gastrointestinal side effects in the patient briefing at two of the three study centers led to a six-fold rise in the rate of discontinuation owing to subjective gastrointestinal side effects. The study centers with and without briefing on gastrointestinal side effects showed no difference in the frequency of gastrointestinal bleeding or gastric or duodenal ulcers
23	Controlled study of lactose intolerance	126	44% of persons with known lactose intolerance and 26% of those without lactose intolerance complained of gastrointestinal symptoms after sham administration of lactose
e21	Case report from RCT of antidepressants	1	Severe hypotension requiring volume replacement after swallowing 26 placebo tablets with suicidal intent

*Worse ratings for sleep, appetite, and fatigue before the study were associated with a higher rate of reported adverse events; RCT = randomized controlled trial

- Beta-blocker treatment of cardiovascular diseases
- Symptomatic treatment of fatigue in cancer patients
- Lactose intolerance.

The lactose content of tablets varies between 0.03 g and 0.5 g. Small amounts of lactose (up to 10 g) are tolerated by almost all lactose-intolerant individuals. Therefore, complaints of gastrointestinal symptoms by lactose-intolerant patients who have been told by the physician or have found out for themselves that the tablets they are taking contain lactose may represent a nocebo effect (23).

In Germany, the *aut idem* ruling by which pharmacists may substitute a preparation with identical active ingredients for the product named on the prescription and discount agreements have led to complaints from patients and physicians of poor efficacy or increased adverse effects after switching to generic preparations. A cross-sectional survey conducted on behalf of the German Association of Pain Treatment (*Deutsche Gesellschaft für Schmerztherapie e.V.*) and the German Pain League (*Deutsche Schmerzliga e.V.*) questioned 600 patients who had been switched to an oxycodone-containing generic preparation. Ninety percent were less satisfied with the analgesic effect, and 61% reported increased pain intensity (German-language source: Überall M: *IQUISP Gutachten [Fokusgruppe Oxycodonhaltige WHOIII Opioide] Querschnittsbefragung zu den psychosozialen Folgen einer Umstellung von Originalpräparaten auf Generika bei chronisch schmerzkranken Menschen im Rahmen einer stabilen/zufriedenstellenden Behandlungssituation.* Überall M: IQUISP Expert Report [Focus Group Oxycodone-containing WHO III Opioids]: cross-sectional survey on the psychosocial consequences of substituting original preparations with generics for treatment of chronic pain in a stable/satisfactory treatment context [talk held on 8 March 2008 at a symposium sponsored by Mundipharma during the 19th German Interdisciplinary Pain Congress]).

A qualitative systematic review showed that patients with increased anxiety, depressivity, and somatization tendency are at greater risk of adverse events after switching to generic preparations (24). It must be discussed whether critical statements by medical opinion leaders (e22) and representatives of patients' self-help organizations (e23) on the substitution of powerful opioid preparations by generic equivalents might not be leading to nocebo effects. In the words of one such statement: "The consequences of substitution are always the same: more pain or more adverse events" (e23).

Expectations that a treatment will be poorly tolerated, whether based on experience or induced by information from the media or trusted third parties, may bring about nocebo effects. A systematic review and meta-analysis found a robust association between the expectation and the occurrence of nausea after chemotherapy (e24).

Ethical implications and the dilemma of the patient briefing

On one hand physicians are obliged to inform the patient about the possible adverse events of a proposed treatment so that he/she can make an informed decision (e25). On the other, it is the physician's duty to minimize the risks of a medical intervention for the patient, including those entailed by the briefing (25). However, the studies just cited show that the patient briefing can induce nocebo responses.

The following strategies are suggested to reduce this dilemma:

Focus on tolerability: Information about the frequency of possible adverse events can be formulated positively ("the great majority of patients tolerate this treatment very well") or negatively ("5% of patients report…") (4). A study on briefing in the context of influenza vaccination showed that fewer adverse events were reported after vaccination by the group told what proportion of persons tolerated the procedure well than by those informed what proportion experienced adverse events (e26).

Permitted non-information: Before the prescription of a drug, the patient is asked whether he/she agrees to receive no information about mild and/or transient side effects. The patient must, however, be briefed about severe and/or irreversible side effects (5). "A relatively small proportion of patients who take Drug X experience various side effects that they find bothersome but are not life threatening or severely impairing. Based on research, we know that patients who are told about these sorts of side effects are more likely to experience them than those who are not told. Do you want me to inform you about these side effects or not?" (5).

To respect patients' autonomy and preferences, they can be given a list of categories of possible adverse events for the medication/procedure in question. Each individual patient can then decide which categories of side effects he/she definitely wants to be briefed about and for which categories information can be dispensed with (e27).

Patient education: A systematic review (four studies, 400 patients) of patients with chronic pain showed that training from a pharmacist—e.g., general information on medicinal and non-medicinal pain treatment or on the recording of possible side effects of drugs and guidance in the case of their occurrence—reduced the number of side effects of medications from 4.6 to 1.6 (95% confidence interval of difference: 0.7–5.3) (e28).

Perspectives

Communication training with actor-patients or role-plays during medical studies or in curricula for psychosomatic basic care impart the ability to harness the "power" of the physician's utterances selectively for the patient's benefit (e29, e30). Skill in conveying positive suggestions and avoiding negative ones should also receive more attention in nurse training.

The German Medical Association's recommendations on patient briefing, published in 1990 (e25), urgently require updating. The points that need to be discussed include, for example, whether it is legitimate to express a right of the patient not to know about complications and side effects of medical procedures and whether this must be respected by the physician. Furthermore, it has to be debated whether some patients might not be left confused and uncertain by their inability to follow the legally mandatory comprehensive information on potential complications of medical treatments that is found, for example, on package inserts or multipage information and consent documents.

Conflict of interest statement
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KEY MESSAGES

- Every medical treatment (e.g., drug administration, psychotherapy) has specific and non-specific effects. Specific effects result from the characteristic elements of the intervention. The beneficial non-specific effects of a treatment are referred to as placebo effects, the harmful ones as nocebo effects.
- Placebo and nocebo effects are viewed as psychobiological phenomena that arise from the therapeutic context in its entirety (sham treatments, the patients' treatment expectations and previous experience, verbal and non-verbal communications by the person administering the treatment, and the interaction between that person and the patient).
- Nocebo responses may result from unintended negative suggestion by physicians or nurses.
- The frequency of adverse events is increased by briefing patients about the possible complications of treatment and by negative expectations on the part of the patient.
- Some of the subjective side effects of drugs can be attributed to nocebo effects.

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Corresponding author
PD Dr. med. Winfried Häuser
Klinik Innere Medizin 1, Klinikum Saarbrücken, Winterberg 1
66119 Saarbrücken, Germany
whaeuser@klinikum-saarbruecken.de

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REVIEW ARTICLE

Nocebo Phenomena in Medicine

Their Relevance in Everyday Clinical Practice

Winfried Häuser, Ernil Hansen, Paul Enck

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A Systematic Review of Factors That Contribute to Nocebo Effects

Rebecca K. Webster, John Weinman, and G. James Rubin
King's College London

Objectives: Medication side effects are common, often leading to reduced quality of life, nonadherence, and financial costs for health services. Many side effects are the result of a psychologically mediated "nocebo effect." This review identifies the risk factors involved in the development of nocebo effects. ***Method:*** Web of Science, Scopus, MEDLINE, PsycINFO, Journals@Ovid full text, and Global Health were searched using the terms "nocebo" and "placebo effect." To be included, studies must have exposed people to an inert substance and have assessed 1 or more baseline or experimental factor(s) on its ability to predict symptom development in response to the inert exposure. ***Results:*** Eighty-nine studies were included; 70 used an experimental design and 19 used a prospective design, identifying 14 different categories of risk factor. The strongest predictors of nocebo effects were a higher perceived dose of exposure, explicit suggestions that the exposure triggers arousal or symptoms, observing people experiencing symptoms from the exposure, and higher expectations of symptoms. ***Conclusions:*** To reduce nocebo induced symptoms associated with medication or other interventions clinicians could reduce expectations of symptoms, limit suggestions of symptoms, correct unrealistic dose perceptions, and reduce exposure to people experiencing side effects. There is some evidence that we should do this especially for persons with at-risk personality types, though exactly which personality types these are requires further research. These suggestions have a downside in terms of consent and paternalism, but there is scope to develop innovative ways to reduce nocebo effects without withholding information.

Keywords: inert exposure, nocebo effect, predictors, review, symptoms

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Adverse drug reactions (ADRs) are common (Davies et al., 2009), and can have serious implications in terms of patient well-being and adherence (Ammassari et al., 2001) as well as significant financial costs for health services (NICE, 2009; Rodríguez-Monguió, Otero, & Rovira, 2003). However, ADRs are not always related to the physiological action of the medication (Faasse & Petrie, 2013). Only 10.9% of reported ADRs to commonly prescribed drugs are clearly attributable to the medication (de Frutos Hernansanz et al., 1994). It is thought a nocebo effect may play a role in the formation of other apparent side effects (Barsky, Saintfort, Rogers, & Borus, 2002). As well as medication side effects, nocebo effects have been implicated in symptoms attributed to technological exposures such as electro-magnetic fields (EMF) from mobile phones and Wi-Fi (Baliatsas et al., 2012; Rubin, Cleare, & Wessely, 2008). A nocebo effect is the experience of negative symptoms following exposure to an inert substance, which are triggered or exacerbated by psychological mechanisms such as expectations (Kennedy, 1961). The name "nocebo" was created to distinguish between the desirable ("placebo") and undesirable effects of an inert exposure (Häuser, Hansen, & Enck, 2012), although in practice the distinction between undesirable and desirable is not always clear cut. For example increased alertness may be beneficial in some contexts (e.g., prior to an examination) and detrimental in others (e.g., prior to sleep).

Current literature suggests there are three main mechanisms for a nocebo effect; misattribution, expectation, and learning. Misattribution theory suggests that people misattribute preexisting symptoms to the effects of a new exposure (although some authors believe that misattribution does not technically constitute a nocebo effect, see Colloca & Miller, 2011 and Enck, Bingel, Schedlowski, & Rief, 2013). Symptoms are common in everyday life (Petrie, Faasse, Crichton, & Grey, 2014), and although often harmless and short-lived, when people are subjected to a new exposure, symptoms that were present before or occur coincidentally are available to be mistakenly attributed to it (Petrie et al., 2005; Petrie, Moss-Morris, Grey, & Shaw, 2004). Therefore factors such as high baseline symptoms or high self-awareness may serve as risk factors for nocebo effects resulting from this mechanism. Negative expectations can also mediate nocebo effects (Hahn, 1997), and may in turn arise through explicit suggestions about the effects of an exposure (Jaén & Dalton, 2014; Myers, Cairns, & Singer, 1987), or predisposing factors such as pessimism (Geers, Helfer,

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Rebecca K. Webster, Department of Psychological Medicine, King's College London; John Weinman, Institute of Pharmaceutical Science, King's College London; G. James Rubin, Department of Psychological Medicine, King's College London.

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Correspondence concerning this article should be addressed to Rebecca K. Webster, Department of Psychological Medicine, King's College London, Weston Education Centre, Cutcombe Road, London SE5 9RJ, United Kingdom. E-mail: rebecca.webster@kcl.ac.uk

Kosbab, Weiland, & Landry, 2005). These negative expectations can make the individual more likely to attend to new or current sensations, and attribute them to the exposure (Barsky et al., 2002). The response expectancy theory suggests that it is also possible for negative expectations to act more directly, with an expectation of, for example anxiety, being itself anxiety provoking thereby directly causing the negative effect that was expected (Kirsch, 1997a, 1997b). The last mechanism, learning, can elicit nocebo effects through association or social observation. For example, if an inert stimulus has been previously paired with a symptom-inducing stimulus (Barsky et al., 2002), which may occur through conscious or nonconscious mechanisms (Stewart-Williams, 2004), or through observing someone else experience symptoms to the same exposure (Vögtle, Barke, & Kroner-Herwig, 2013).

Given the significant costs nocebo effects can have on patient quality of life and health services it is important to develop interventions to minimize these effects from occurring. Many risk factors have been implicated, but no study has systematically reviewed these to identify those which are the strongest predictors of nocebo effects; something that would assist in the development of such interventions. Instead, previous systematic reviews have focused on the magnitude of nocebo effects for a specific symptom, for example, Petersen et al. (2014) or in clinical trials of experimental medical treatments (Häuser, Bartram, Bartram-Wunn, & Tolle, 2012). One review (Symon, Williams, Adelasoye, & Cheyne, 2015) has provided a preliminary assessment of some of the risk factors involved in nocebo effects. However this "scoping review" identified only 17 papers—a limited subset of the available literature. To address this gap our systematic review aimed to identify the risk factors involved in the reporting of any symptom in response to an inert exposure. This will allow the identification of factors which appear to be consistent predictors of nocebo effects and aid in the development of evidenced-based interventions to prevent them from occurring in the future.

Method

Identification of Studies

Searches were carried out on December 11, 2014, using the following databases: Web of Science, Scopus, MEDLINE, PsycINFO, Ovid, and Global Health. The search terms consisted of "nocebo" or "placebo effect," and where available, searches were limited to studies with a human sample, with review articles restricted. The reference sections of included studies were also examined as well as papers suggested through personal contacts. No gray literature was searched and no temporal constraints were used. The review followed a previously designed, unpublished protocol.

Selection Criteria

Studies were eligible for inclusion if they met the following criteria:

- Studied a human population (healthy volunteers, patients or children were allowed).
- Used an experimental or prospective design.
- Used an inert exposure, that is, containing no pharmacological or physiological active ingredient.
- Assessed factors on their ability to predict symptom reporting, and these factors could be baseline characteristics or experimentally induced.
- Included an outcome of symptom reporting after participants received an inert exposure. Reported symptoms must not have been attributable to an active exposure (e.g., studies where an inert exposure was applied after an active exposure such as heat stimulation were excluded, as in this case the symptoms would have resulted from the heat stimulation).
- Measured symptoms via self-report or inferred through objective measures (e.g., scratching behavior). Such symptoms could be somatic, a measure of arousal or mood. Because of the difficulty in defining when an outcome is aversive or beneficial we took an inclusive approach. For example measures of alertness (where an increase could be aversive in some instances) or contentedness (where decreases might be possible) were both included.
- Published in any language.

Data Extraction

For each study included in the review, details relating to 20 issues were extracted. In summary these related to: sample characteristics, methodological design, type of exposure, experimental conditions and/or baseline risk factors, symptom measurement, statistical analysis, and results. Any non-English articles were translated. We differentiated between studies that used an experimental or a prospective design to easily identify factors implicated in nocebo effects that can be manipulated and those that naturally occur at baseline. For a copy of the data extraction sheet used, see Appendix 1 in the supplemental materials.

Quality Assessment

Eligible studies using an experimental design were assessed using the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011). For prospective studies, the CASPin International (1998) critical appraisal tool was used and adapted to give a "high," "unclear," or "low" risk of bias score, which were color coded red, orange, and green, respectively. Originally the CASP is scored with yes/no answers but this was rescored to low risk (yes) and high risk (no) as well as including an unclear risk response for when enough information was not provided, similar to the Cochrane Risk of Bias tool. As these tools had no criteria assessing sample size we looked at this separately.

Review Process

Rebecca K. Webster conducted the database searches and screened the titles and abstracts of articles to assess their potential relevance. Guidance was obtained from G. James Rubin if there was any uncertainty as to including an article for full text review. Rebecca K. Webster obtained the full articles for those citations that appeared potentially relevant and checked them against the inclusion criteria. If it was unclear whether an article met the inclusion criteria, consensus was sought from G. James Rubin and John Weinman, Rebecca K. Webster then independently extracted data for each included study and carried out the quality assessment

with guidance from G. James Rubin Because of the expected heterogeneity in the studies we did not plan for any meta-analyses and instead we used a narrative synthesis. There is no general consensus on the best way to carry out a narrative synthesis for systematic reviews (Popay et al., 2006). As such we decided to use a weight of evidence approach. To do this, we identified the strength of evidence for each risk factor based on the number of studies investigating each risk factors and their respective quality.

Results

Search Results

The database search retrieved 12,582 citations. After removing duplicates 6,585 citations remained. After screening titles and abstracts, we reviewed the full text of 88 articles relating to 96 studies. Of these, 13 studies were excluded for not investigating any risk factors for the development of symptoms, nine were excluded for using an active exposure and seven were excluded for not measuring symptoms. Sixty-six articles met the inclusion criteria. Twenty-one additional articles were identified by reference checks of included articles and through personal contacts; resulting in a total of 87 articles. Two articles reported results on two separate studies each (Walach & Schneider, 2009; Winters et al., 2001) and are referred to as "Exp 1" or "Exp 2" where necessary, leaving 87 articles reporting on 89 studies. Of these, 70 were experimental (see Table 1) and 19 prospective (see Table 2). Figure 1 provides a flow diagram of the study selection according to the Preferred Reporting for Systematic Reviews and Meta-analyses statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

Quality Assessment

Experimental studies. The quality of experimental studies was poor (see Figure 2), with the main problem being a lack of clear reporting. Thirty-six studies neglected to mention how they carried out randomization, whereas 22 studies were at high risk of bias for failing to mention whether participants were randomized or for not using randomization at all. Because of the unclear reporting of random sequence generation, the risk for allocation concealment bias followed a similar pattern. For blinding of participants and personnel, studies often failed to state whether the experimenters were blind to the manipulation that accompanied the exposure, leaving the risk of bias unclear. Only six studies used adequate blinding procedures, with 12 not using blinding at all. Sixty-five studies used self-report measures, as such blinding of the outcome assessment was judged to be unlikely to influence these results. For 52 studies, drop outs were not addressed, or if they were, they typically failed to explain how this affected the results, leaving the risk of bias unclear. Only one study had lodged a protocol in a publically accessible registry before the start of recruitment, leaving us unable to assess the risk for selective reporting for the remaining studies. As well as this we looked for justification of sample size to assess if each study was adequately powered. Again this was poorly addressed, with only 9 of the 70 studies mentioning that they carried out an a priori sample size calculation.

Prospective studies. The prospective studies performed well against the quality check (see Figure 2). All studies addressed a clearly focused issue with a standardized exposure across all participants. Studies often lacked information about how participants were recruited. However, self-report measures were widely used to minimize bias from experimenters. The identification and control of confounding factors was only deemed an issue for six studies that neglected to control for demographic factors such as gender or age and past symptom reporting. The follow-up of participants was judged to be appropriate in 16 studies. Regarding the generalizability of the findings, it was often difficult to know whether the results could be applied to the population being studied because of the insufficient information about how participants were recruited. In addition, similarly to the experimental studies, justification for sample size was limited with only one study providing an a priori sample size calculation.

Experimentally Induced Risk Factors Categories

Seventy experimental studies were included that investigated risk factors which fell into 9 different categories as discussed below (further details in supplementary Tables 3–11).

Learning. Twenty-three studies manipulated different types of learning on symptom reporting finding some evidence for its role in nocebo effects. Four of these investigated prior experience of which two lower quality studies found no significant effects (Bayer, Coverdale, Chiang, & Bangs, 1998; Dinnerstein & Halm, 1970). However, André-Obadia, Magnin, and Garcia-Larrea (2011) showed that sham rTMS tended to worsen patients' pain when following an active yet unsuccessful rTMS treatment (however caution is required as no statistical test accompanied this finding), and a high-quality study by Stegen et al. (1998) found that participants reported significantly more arousal and respiratory symptoms when completing a breathing trial with room air before a breathing trial with carbon dioxide rather than afterward. As such there is some evidence that prior experience is involved in the development of nocebo effects. Two studies of mixed quality explored the impact of implicit association supporting its role in the nocebo effect, finding that drinking sham caffeine in a coffee solution resulted in significantly more alertness, contentedness, and arousal, than drinking sham caffeine in an orange juice solution (Flaten & Blumenthal, 1999; Mikalsen, Bertelsen, & Flaten, 2001). Three studies of high quality investigated learning through the manipulation of social observation, with two finding a significant effect, broadly supporting its role in the nocebo effect. Lorber, Mazzoni, and Kirsch (2007) failed to show any main effects of observing a confederate display symptom behaviors after inhaling a sham environmental toxin which they were also exposed to. However, in a similar study, participants who observed a confederate display symptoms had significantly higher symptom ratings after inhalation than participants who did not (Mazzoni, Foan, Hyland, & Kirsch, 2010). Similarly, patients who watched a video of people scratching compared to those who saw a video of people sitting idle had higher itch and scratching behavior rating after administration of sham histamine (Papoiu, Wang, Coghill, Chan, & Yosipovitch, 2011), no results were reported for the healthy volunteers in this study.

Of the remaining 14 studies, 13 investigated learning by using classical conditioning to pair inert exposures such as odors with CO2 inhalation before presenting the inert exposures on their own (De Peuter et al., 2005; Devriese, De Peuter, Van Diest, Van de

Table 1
Summary of the Methods Used in Experimental Studies

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
André-Obadia et al. (2011)[b,d]	RCT (B)	Chronic neuropathic pain patients (45, 55.0, 37.8)	Sham rTMS	1. Prior experience: a. Sham rTMS before active rTMS (20); b. Sham rTMS after successful active rTMS (12); c. Sham rTMS after ineffective active rTMS (13)	Pain
Angelucci and Pena (1997)[d]	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	1. Arousal suggestions: a. Given coffee with no expectations (37); b. Given coffee with low arousal expectations (37); c. Given coffee with high arousal expectations (37); d. no coffee and no expectations (37)	State and trait anxiety, Suggestibility, Expectations, Gender
Bayer et al. (1991)[d]	RCT (B + W)	Unemployed Men (100, U/K, 100.0)	Sham electrical shock	1. Symptom suggestions: a. Told they would receive a safe but often painful undetectable current (60); b. Were assured there would be no shocks (40) 2. Perceived dose: a. Within each group the stimulator setting increased from 0 to 80 mA	None
Bayer et al. (1998)[a,d]	RCT (B + W)	Job seekers (62, U/K, 82.0)	Sham electrical shock	1. Prior experience: a. Exposed to two physical pain induction procedures prior to sham stimulation (32); b. Warned of pain and received sham stimulation. They were not exposed to any prior pain induction (30) 2. Perceived dose: a. Within each group the stimulator setting increased in steps of 10 every 5 minutes till it reached 50	Expectations
Benedetti et al. (1997)[d]	RCT (B)	Video assisted thoracoscopy patients (36, 53.7, 66.1)	Sham treatment	1. Symptom suggestions: a. Open injection that it would increase pain (18); b. Hidden injection (18)	None
Brodeur (1965)[d]	RCT (B)	Healthy senior students (45, U/K, 91.1)	Sham arousal capsule	1. Arousal suggestions: a. Told it was a stimulant (15); b. Told it was a tranquilizer (15); c. No suggestion (15)	None
Colagiuri et al. (2012)[d]	RCT (B)	Students experiencing sleep difficulty (82, 20.2, 22.0)	Sham sleeping pill	1. Symptom suggestions: a. Treatment might cause one side effect (29); b. Treatment might cause four side effects (23); c. No warning about side effects (30)	None
Crichton et al. (2014)[d]	RCT (B)	Students (54, U/K, 37.0)	Sham infrasound	1. Symptom suggestions: a. TV footage detailing symptomatic experiences attributed to wind farms *(27)*; b. TV footage with experts stating wind farms would not cause symptoms *(27)*	None
Dalton (1999)[d]	RCT (B)	Healthy volunteers (180, 31.7, 49.4)	Odors	1. Odors: a. Pleasant smelling methyl salicylate (60); b. neutral smelling isobornyl acetate (60); c. Foul smelling butanol (60) 2. Symptom suggestions: a. Told they would have relaxing effects (60); b. Told they were industrial solvents (60); c. Told they were approved for olfactory research (60)	Odor reactivity, Olfactory sensitivity
De Peuter et al. (2005)[d]	RCT (W)	Asthma patients and healthy controls (40, *23.9*, 52.5)	Sham inhaler	1. Conditioning: a. one sham inhaler paired with CO2 challenge; b. one sham inhaler paired with O2	Expectations, Negative affect, Clinical condition
Devriese et al. (2000)[a,d]	Non RCT (B + W)	Healthy students (56, U/K, 41.1)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 3. Timing: a. Test phase immediately after conditioning trials (28); b. Test phase one week after conditioning trials (28) 4. Generalization: a. New foul smelling odor butyric acid; b. New foul smelling odor acetic acid; c. New pleasant smelling odor citric aroma	Negative affect

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Devriese et al. (2004)[a,d]	Non RCT (B + W)	Healthy students (53, U/K, U/K)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (28); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (25) 3. Symptom suggestions: a. Given information about possible health damaging effects of chemical pollution (U/K); b. No information (U/K)	Negative affect, Perceived cue odor
Devriese et al. (2006)	RCT (B + W)	Psychology students (40, U/K, .0)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling acetic acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, acetic acid paired with room air breathing task (20); b. Ammonia paired with room air breathing task, acetic acid paired with CO2 breathing task (20) 3. Symptom suggestions: a. Given information about possible health damaging effects of chemical pollution (20); b. No information (20)	None
Dinnerstein and Halm (1970)[c,d]	RCT (B)	Male students (80, U/K, 100.0)	Sham arousal liquid	1. Arousal suggestions: a. Told it was an energizer (40); b. Told it was a tranquilizer (40) 2. Prior experience: a. Received aspirin prior to sham (40); b. Received lactose prior to sham (40)	None
Faasse et al. (2013)[b,c,d]	RCT (B)	Healthy students (60, 19.4, 43.5)	Sham anti-anxiety tablet	1. Brand suggestions: a. Branded reformulation change (20); b. Generic reformulation change (20); c. No change (20)	None
Flaten (1998)[d]	RCT (B)	Healthy students (48, U/K, 35.4)	Sham arousal drink	1. Arousal suggestions: a. Told you will feel relaxed and sleepy (16); b. Told you will feel alert and a little stress (16); c. Told you will take an inactive drug (16)	None
Flaten and Blumenthal (1999)[d]	RCT (W)	Healthy coffee drinkers (21, 24.8, 61.9)	Decaffeinated solution	1. Association: a. Orange juice; b. Decaffeinated coffee	None
Flaten et al. (1999)[d]	RCT (B)	Healthy volunteers in non-health professions (34, U/K, 54.5)	Sham arousal capsule	1. Arousal suggestions: a. The drug will make you feel relaxed (11); b. The drug will make you feel alert (12); c. You will receive capsules that contain a prescription drug (11)	None
Flaten et al. (2003)[a,b,d]	W	Coffee drinkers (20, U/K, 50.0)	Sham coffee	1. Perceived dose: a. Participants were first given one cup and then a second	Symptoms, Expectations
Gavrylyuk et al. (2010)[d]	RCT (B)	Healthy volunteers (30, 24.9, 32.0)	Saline eye drops	1. Symptom suggestions: a. Informed of pupil dilation effects (10); b. Informed of pupil constriction effects (10); c. Informed of saline eye drops (10)	None
Geers et al. (2006)[d]	RCT (B)	Healthy students (54, U/K, 31.5)	Sham over-the-counter pill	1. Likelihood suggestions: a. Told the pill had unpleasant side effects (18); b. Told they may or may not receive the active drug (19); c. Told they would ingest an inactive drug (17) 2. Self-awareness: a. Told to closely monitor feelings/bodily sensations (27); b. Not given any such instructions (27)	None
Geers et al. (2011)[d]	RCT (B)	Healthy students (102, 20.5, 21.6)	Sham caffeine capsule	1. Likelihood suggestions: a. Told it contained 250mg of caffeine (34); b. Told they may or may not be ingesting 250mg of caffeine (34); c. Not given the capsule and received no caffeine expectation (34)	Gender, Age, Caffeine consumption

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Geers, Helfer, et al. (2005)[d]	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	1. Likelihood suggestions: a. Told the pill had unpleasant side effects *(18)*; b. Told the pill would make them feel either unpleasant or was an inactive substance *(18)*; c. Told they would ingest an inactive pill *(18)* 2. Self-awareness: a. Told to attend to any symptoms experienced (27); b. Not given any such instructions (27)	Age, Gender, Optimism
Geers, Weiland, et al. (2005)[d]	RCT (B)	Healthy students (57, U/K, 35.1)	Sham caffeine pill	1. Arousal suggestions: a. Told they were given caffeine (U/K); b. No mention of caffeine (U/K) 2. Cooperation prime: a. Given a scrambled sentence test with a cooperation prime (U/K); b. Given a scrambled sentence test with a neutral prime (U/K)	Caffeine consumption
Gibbons et al. (1979)[a,d]	RCT (B)	Female students (38, U/K, .0)	Sham drug	1. Symptom suggestions: a. Told they were taking Cavanol which would produce some noticeable side effects (19); b. Told they were taking baking soda (19) 2. Self-awareness: a. Mirror was facing participants (19); b. Mirror was not facing participants (19)	None
Goldman et al. (1965)[a,b,d]	Non RCT (B)	Male veterans with schizophrenia (64, 44.0, 100.0)	Sham arousal treatment	1. Type of administration: a. Received sugar pill (32); b. Received saline injection (32) 2. Arousal suggestions: a. Told it would heighten their ward activity (32); b. Told it would lower their ward activity (32)	Attitudes towards medication
Harrell and Juliano (2009)[c]	RCT (B)	Adult non-smoking coffee consumers *(30, 22.6, 22.0)*	Sham coffee	1. Performance suggestions: a. Told caffeine enhances performance *(15)*; b. Told caffeine impairs performance *(15)*	None
Harrell and Juliano (2012)[c,d]	RCT (B)	Adult smokers (43, 28.7, 67.4)	Sham cigarette	1. Performance suggestions: a. Told cigarette enhances performance (20); b. Told cigarette impairs performance (23)	Gender
Heatherton et al. (1989)[d]	RCT (B)	Female students (59, U/K, .0)	Sham vitamin pill	1. Symptom suggestions: a. Told vitamin has been reported to make people feel hungry (19); b. Told vitamin has been reported to make people feel full (20); c. Told no further information (20)	Participant restraint
Higuchi et al. (2002)[d]	RCT (B)	Healthy volunteers (30, 21.2, 40.0)	Fragrance (Jasmine or Lavendar)	1. Arousal suggestions: a. Told it was relaxing (10); b. Told it was stimulating (10); c. No information given (10)	None
Jaén and Dalton (2014)[a,b,d]	Non RCT (B)	Asthmatics (17, 38.5, 52.9)	Sham active odor	1. Symptom suggestions: a. Labelled the odor as therapeutic (9); b. Labelled the odor as asthmogenic (8)	None
Jensen and Karoly (1991)[d]	RCT (B + W)	Students (86, U/K, 45.3)	Sham sedative pill	1. Social desirability: a. Type B personality is more positive then type A. Type B have been shown to respond more to pills *(43)*: b. Relationship between type A and B personality and response to pills is very weak *(43)* 2. Perceived dose: a. Suggestions of a high dose or low dose were counterbalanced across each group	Gender
Kaptchuk et al. (2006)	RCT (B)	Adults with distal pain in the arms (266, 36.7, 45.9)	Sham treatment	1. Type of administration: a. Received sham acupuncture (133); b. Received placebo pill (133)	None
Kirsch and Weixel (1988)[d]	RCT (B)	Student coffee drinkers (U/K, *19.3, 31.0*)	Sham coffee	1. Likelihood suggestions: a. Told they would receive coffee (U/K); b. Told they may or may not receive caffeinated coffee (U/K); c. No beverage, waited for 20 minutes (U/K) 2. Perceived dose: a. 1 tsp (U/K); b. 2 tsps (U/K); c. 3 tsps (U/K); d. 5 tsps (U/K); e. 8 tsps (U/K)	None
Kuenzel et al. (2012)[d]	RCT (B)	English speaking students (148, 21.7, 18.2)	Herbal infusion tea	1. Arousal suggestions: a. Told it would make them feel relaxed (45); b. Told it would make them feel active (53); c. No information given (50)	None

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Lorber et al. (2007)[d]	RCT (B)	Students without upper respiratory conditions (86, U/K, 40.7)	Sham environmental toxin	1. Social observation: a. Told inhaled substance has been reported to produce symptoms and observed a female confederate inhale and display symptoms (U/K); b. As above but no observation of confederate (U/K); c. Did not inhale the substance and observed a female confederate inhale and display symptoms (U/K); d. As above but no observation of confederate (U/K)	Gender
Lotshaw et al. (1996)[d]	RCT (B)	Male student coffee drinkers (*50*, U/K, 100.0)	Sham coffee	1. Arousal suggestions: a. Told coffee received decaffeinated *(25)*; b. Told decaffeinated received decaffeinated *(25)*	None
Mazzoni et al. (2010)[d]	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Social observation: a. Observed a male/female confederate inhale the substance and display symptoms *(60)*; b. Did not observe a male or female confederate inhale the substance and display symptoms *(60)*	Personality, Gender, Gender of model
Meulders et al. (2010)[a,d]	Non RCT (B + W)	Healthy adults (58, 22.0, 48.3)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (29); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (29)	Ability to predict which odor produced the most symptoms
Mikalsen et al. (2001)[d]	RCT (W)	Student coffee drinkers (21, 25.9, 66.7)	Sham coffee	1. Arousal suggestions: a. Told it was caffeine; b. Told it was not caffeine 2. Association: a. Given in a juice solution; b. Given in a coffee solution	None
Mrňa and Skiřvánek (1985)[a,b,d]	W	Healthy volunteers (21, 17.0, 47.6)	Sham arousal drug	1. Arousal suggestions: a. Told it was a new doping drug undetectable by anti-doping tests; b. Told it was to relax pre-restart states	Prior placebo response
Neukirch and Colagiuri (2014)[a,d]	RCT (B)	Students with sleep difficulty (91, 21.3, 33.0)	Sham sleep medication	1. Symptom suggestions: a. Warned about an increase/decrease in appetite and received placebo treatment (24); b. Warned about the side effect but received no treatment (23); c. Not warned about the side effects and received placebo treatment (22); d. Not warned about the side effects and received no treatment (22)	None
Nevelsteen et al. (2007)[d]	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. Performance suggestions: a. Told magnetic fields enhance cognitive performance (15); b. Told magnetic fields impair cognitive performance (15); c. Told magnetic fields have no effect on cognitive performance (14); d. Not exposed to sham magnetic field and received no information (15)	State-trait anxiety, Depression, Positive and Negative affect, Sensitivity to anxiety, Vigilance, Comfort under helmet
Ossege et al. (2005)	RCT (B)	Healthy volunteers (60, *27.6*, 40.0)	Sham drug	1. Likelihood suggestions: a. Misleading information that is was an active medication (30); b. 50% chance that it was a placebo or active medication (30)	None
Papoiu et al. (2011)[d]	RCT (W)	Healthy volunteers and patients with atopic dermatitis (25, U/K, 44.0)	Sham histamine	1. Social observation: a. Watched a 5 minute video of people scratching their left forearm; b. Watched a 5 minute video of the same persons in the scratching video but sitting idle.	Gender
Penick and Fisher (1965)[a,b,c,d]	W	Healthy medical students (14, U/K, U/K)	Sham arousal drug	1. Arousal suggestions: a. Told they would receive a stimulant drug; b. Told they would receive a sedative drug	None

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Pennebaker and Skelton (1981)[d]	RCT (B)	Students (38, U/K, 31.6)	Ultrasonic noise	1. Symptom suggestions: a. Told it would increase skin temperature (13); b. Told it would decrease skin temperature (12); c. Told it would have no effect on skin temperature (13)	None
Put et al. (2004)[a,b,c,d]	W	Asthma patients (32, 40.0, 50.0)	Sham inhaler	1. Symptom suggestions: a. Told it would have no effect on breathing; b. Told it was a bronchoconstrictor; c. Told it was a bronchodilator	Negative affect, Social desirability
Read and Bohr (2014)[a,b,c,d]	Non RCT (B)	Volunteers without photosensitive epilepsy (177, 25.3, U/K)	Sham 3D TV	1. Symptom suggestions: a. Told it was 3D and wore passive 3D glasses (22); b. Told it was 3D and wore active no shuttering 3D glasses (33); c. Told it was 2D and did not wear glasses (122)	Gender
Schneider et al. (2006)[c,d]	RCT (B)	Healthy Adults (45, 31.0, 22.2)	Sham coffee	1. Arousal suggestions: a. Told they were to consume decaffeinated coffee (15); b. Told they were to consume regular coffee (15); c. Informed they would receive no beverage and no instructions (15)	None
Schweiger and Parducci (1981)[d]	RCT (B)	Students (34, U/K, 52.9)	Sham electric current	1. Symptom suggestions: a. Told a low current would be delivered, too mild to be felt but had produced mild headaches in the past (17); b. Told current would be too weak to be felt, but some people develop mild headaches as a side effect (17)	None
Slánská et al. (1974)[a,d]	Non RCT (B)	Medical students (33, U/K, U/K)	Salt solution	1. Arousal suggestions: a. Told it was a stimulant (17); b. Told it was a sedative (16)	Stability – instability, Activity – passivity, Submissive-dominance, Rationality-sensuousness, Introversion-extraversion
Stegen et al. (1998)[d]	RCT (W)	Healthy psychology students (72, U/K, 48.6)	Breathing trial with room air	1. Conditioning: a. Room air breathing trial before 7.5% CO2 challenge; b. Room air breathing trial after 7.5% CO2 challenge	Negative affect
Szemerszky et al. (2010)[a,b,c,d]	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. Perceived dose: a. Told it would be weak; b. Told it would be strong	Gender, Expectations, IEI-EMF scores, State anxiety, Dispositional optimism, Somatization, Somatosensory amplification, Motivation
Tippens et al. (2014)[d]	RCT (B)	Obese adults (79, 49.4, 10.4)	Sham weight loss supplement	1. Likelihood suggestions: a. Told they would be given an active weight loss supplement (27); b. Told they would be randomly assigned to either the active or placebo supplement (28); c. Only received lifestyle education (24)	None

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Van den Bergh et al. (1999)[a,d]	Non RCT (B + W)	Healthy students (64, U/K, 25.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (32); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (32)	None
Van den Bergh et al. (1995)[a,d]	Non RCT (B + W)	Healthy students (28, U/K, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14)	Negative affect
Van den Bergh et al. (1997)[a,d]	Non RCT (B + W)	Psychosomatic patients (28, 36.0, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14) 3. Generalization: a. New foul smelling odor Ichytol; b. New pleasant smelling odor Rose	Gender, State and trait anxiety, Blunting behavior
Van den Bergh et al. (1998)[d]	RCT (B + W)	Healthy adults (56, 42.5, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Self-awareness: a. Told to count lower tones and disregard higher tones (28); b. Told to ignore tones (28) 3. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 4. Generalization: a. New foul smelling odor Ichytol; b. New pleasant smelling odor Rose	Gender
Van Diest et al. (2006)[d]	RCT (B + W)	Students (28, U/K, 21.4)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling acetic acid 2. Conditioning: a. Ammonia paired with hypocapnic over breathing trial, acetic acid paired with normocapnic over breathing trial (13); b. Ammonia paired with normocapnic over breathing tria, acetic acid paired with hypocapnic over breathing trial (15) 3. Type of breathing: a. Test odors given with normocapnic breathing trial (U/K); b. Test odors given with spontaneous breathing (U/K)	None
Walach and Schneider (2009) Exp 1	RCT (B)	Healthy adult coffee drinkers (60, 32.3, 23.3)	Sham coffee	1. Likelihood suggestions: a. Told it was caffeine (15); b. Told it could be placebo or caffeine (15); c. Told it could be placebo or caffeine (15); d. Received no beverage (15)	Expectations
Walach and Schneider (2009) Exp 2	RCT (B)	Healthy adult coffee drinkers (*30, 29.9, 33.3*)	Sham coffee	1. Arousal suggestions: a. Told it was caffeine *(15)*; b. Received no beverage *(15)*	Expectations
Walach et al. (2001)	RCT (B)	Coffee drinkers (157, 28.1, 34.0)	Sham coffee	1. Likelihood suggestions: a. Told they would receive a placebo (41); b. Told they would receive coffee (39); c. Told they may receive real coffee or decaffeinated coffee (39); d. No substance or instruction given (38) 2. Experimenter expectations: a. Experimenter told the physiological effects from a caffeine placebo are real (proplacebo) (U/K); b. Experimenter told the effects of caffeine placebos are just due to artifacts (antiplacebo) (U/K)	Expectations

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Walach et al. (2002)	RCT (B)	Coffee drinkers (159, 25.5, 58.0)	Sham coffee	1. Symptom suggestions: a. Received an information leaflet describing the pharmacological effects of caffeine (U/K); b. Received no further information (U/K) 2. Likelihood suggestions: a. Told they would receive a placebo (39); b. Told they would receive coffee (40); c. Told they may receive real coffee or decaffeinated coffee (40); d. No substance or instruction given (40)	None
Winters et al. (2001) Exp 1[a,d]	Non RCT (B)	Psychology students (50, U/K,U/K)	Ammonia	1. Conditioning: a. Odor + CO2 trials and room air trials (10); b. Odor trials and CO2 trials (10); c. Odor trials, CO2 trials, odor + CO2 trials, room air trials (10); d. odor trials, room air trials (10); e. CO2 trials, room air trials (10)	None
Winters et al. (2001) Exp 2[a,d]	Non RCT (B)	18–30 year olds (40, U/K,U/K)	Odors	1. Odor: a. Foul smelling ammonia (20); b. Pleasant smelling niaouli (20) 2. Conditioning: a. Odor + CO2 trials and room air trials (20); b. Odor trials and CO2 trials (20)	None
Winters et al. (2003)[d]	Non RCT (B + W)	18–30 year olds (32, U/K,15.6)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (16); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (16) 3. Verbal suggestions of symptoms: a. Given leaflet describing widespread chemical pollution of the environment is a potential cause of multiple chemical sensitivity (16); b. No information given (16)	None
Wise et al. (2009)[c]	RCT (B)	Patients with poor asthma control (241, 39.0, *29.5*)	Sham asthma drug	1. Symptom suggestions: a. Emphasized benefit of treatment and described potential side effects (121); b. Expressed uncertainty about improvement following treatment and did not describe potential side effects (120)	None
Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	1. Symptom suggestions: a. Watched a documentary concerning the potential adverse health effects of Wi-Fi (76); b. Watched a BBC News report concerning the security of the internet and mobile phone data (71)	State anxiety, Age, Gender, Level of education, Personality
Zimmermann-Viehoff et al. (2013)[b,d]	RCT (B)	Healthy Caucasians (92, 24.5, 41.3)	Sham arousal oral spray	1. Symptom suggestions: a. Told it contained a drug to increase blood pressure (33); b. Told it contained a drug to decrease blood pressure (29); c. Told it was a placebo (30)	None

Note. RCT = randomized controlled trial; Non RCT = nonrandomized controlled trial; B = between subjects design; W = within subjects design; U/K = unknown; *italicized* = not directly given but has been extrapolated from the available data; rTMS = repetitive transcranial magnetic stimulation; EMF = electromagnetic field; tsp = teaspoon; IEI-EMF = idiopathic environmental intolerance attributed to electromagnetic fields; CO2 = carbon dioxide; O2 = oxygen.
[a] High-risk random sequence generation bias. [b] High-risk allocation concealment bias. [c] High-risk blinding of participants and personnel bias. [d] Did not mention an a priori sample size calculation.

Table 2
Summary of the Methods Used in Prospective Studies

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Baseline risk factor(s)
Bogaerts et al. (2010)[e]	P	Female patients with medically unexplained dyspnea and healthy controls (58, U/K, .0)	Breathing trial with room air	State anxiety, Negative affect, Clinical condition
Casper et al. (2001)[e]	P	Nonpsychotic major depressive patients (876, U/K, 42.8)	Sham fluoxetine treatment	Gender, Depression severity
Danker-Hopfe et al. (2010)	P	Villages in Germany with weak RF-EMF sources (397, U/K, 49.1)	Sham EMF	Bad sleep quality, General fear/anxiety towards risks of RF-EMF, Fear/anxiety towards base station, Preoccupation with EMF, Visibility of the base station
Davis et al. (1995)[a,d,e]	P	Healthy adults (27, U/K, 55.6)	Sham anti-depressant pill	Neuroticism, Somatosensory amplification
de la Cruz et al. (2010)[e]	P	Patients with cancer related fatigue (105, U/K, 40.0)	Sham treatment	Anxiety, Nausea, Sleep, General health, Well-being, Cognitive status, Age, Education level
De Peuter et al. (2007)[e]	P	Asthma patients (30, 38.0, 26.7)	Sham histamine inhalation	Negative affect
Drici et al. (1995)[b,e]	P	Healthy volunteers (52, 23.5, 50.0)	Sham paracetamol eye drop	Employment, Type A Personality, Type B Personality
Fillmore and Vogel-Sprott (1992)[e]	P	Male students (56, U/K, 100.0)	Sham coffee	Symptom expectations
Goetz et al. (2008)[e]	P	Parkinson's patients with dyskinesia (484, U/K, U/K)	Sham medication	Age, Gender, Dyskinesia severity, UPDRS motor score, Daily L-dopa dose, Dyskinesia duration, Adverse events, Severity of adverse events, Geographical site of enrolment, Study (1 or 2)
Köteles and Babulka (2014)[a,d,e]	P	Adult volunteers (33, 37.7,15.2)	3 types of Essential oils (Randomized to 1)	Expectations, Pleasantness of odor
Liccardi et al. (2004)[b,e]	P	Patients with ADRs (600, 42.0, 30.3)	Sham allergen pill	Gender, Hospital centre
Link et al. (2006)[a,b,c,d,e]	P	Students (36, 22.7, 44.0)	Sham herbal supplement	Expectations, State anxiety, Social desirability
Lombardi et al. (2008)[a,d,e]	P	Patients with ADRs (435, 39.7, 32.0)	Sham allergen pill	Gender, Age, Atopic status, Severity of previous reaction, Type of previous reaction
Molcăn, Heretik, Novotrý, Vajidičková, and Zucha (1982)[b,e]	P	Medical students (48, U/K, 52.1)	Sham arousal pill	Expectations, State anxiety, Trait anxiety
Stegen et al. (2000)[a,b,d,e]	P	Healthy psychology students (44, U/K, 27.3)	Breathing trial with room air	Negative affect, Social desirability
Strohle (2000)[e]	P	Healthy adults and patients with panic disorder (U/K, *33.5, 56.6*)	Sham panic disorder trigger	Gender, Clinical condition
Sullivan et al. (2008)[c,e]	P	Patients with neuropathic pain (24, 54.7, 62.5)	Sham cream treatment	Pain catastrophizing
Vase et al. (2013)[e]	P	Patient with pain due to tooth removal (U/K, *25.5, 47.5*)	Sham acupuncture	Expectations
Wendt et al. (2014)[e]	P	Healthy males (24, 25.0, 100.0)	Sham immunosuppressive capsule	Genes

Note. P = prospective design; U/K = unknown; *italicized* = not directly given but has been extrapolated from the available data; ns = nonsignificant; UPDRS = unified Parkinson's disease rating scale; RF-EMF = radio frequency electromagnetic fields; EMF = electromagnetic fields; ADRs = Adverse drug reactions.
[a] High-risk for selection bias. [b] High-risk for confounding factors. [c] High-risk for insufficient follow-up. [d] High-risk for low generalizability. [e] Did not mention an a priori sample size calculation.

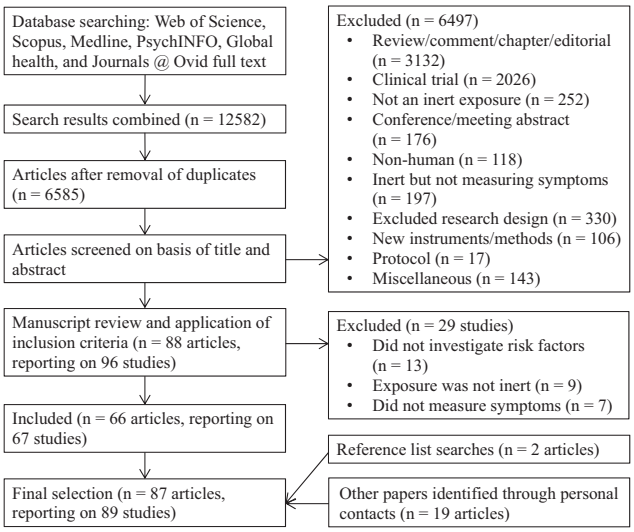

Figure 1. Flow diagram of the selection process of studies including the number of events and reasons for exclusion.

Woestijne, & Van den Bergh, 2006; Devriese et al., 2000; 2004; Meulders et al., 2010; Van den Bergh et al., 1999; Van den Bergh, Kempynck, van de Woestijne, Baeyens, & Eelen, 1995; Van den Bergh, Stegen, & Van de Woestijne, 1997, 1998; Van Diest et al., 2006; Winters et al., 2001 Exp 1 and 2; Winters et al., 2003). Six studies of mixed quality found significant effects of classical conditioning and although seven found no main effect of conditioning on symptom reporting, six of these were of lower quality. As such there is some evidence for the role of classical conditioning in nocebo effects, and that this learning effect can be generalized to new odors (Devriese et al., 2000; Van den Bergh et al., 1997, 1998). However, odor type alone without classical conditioning is not enough to elicit symptoms as demonstrated in this group of studies and the remaining study in this category (Dalton, 1999).

Perceived dose. Six studies manipulated participant perceptions of the dose of the exposure that they received. Four of these found significant effects with three being of higher quality, broadly supporting a link between higher perceived dose and nocebo effects. Only two studies found no significant effects of dose related to decaffeinated coffee consumption (Flaten, Aasli, & Blumenthal, 2003) or taking a sham sedative pill (Jensen & Karoly, 1991). The remaining four all demonstrated significant main effects: Increasing the setting on a sham shock generator increased pain intensity ratings in two studies (Bayer, Baer, & Early, 1991; Bayer et al., 1998), tension scores increased as a function of perceived dose following decaffeinated coffee consumption in one study (Kirsch & Weixel, 1988), and in a final study being told that a sham EMF exposure would be strong resulted in a higher overall symptom scores compared to being told the exposure would be weak (Szemerszky, Köteles, Lihi, & Bardos, 2010).

Self-awareness. Four studies manipulated self-awareness during exposure. Three higher quality studies found no significant effects with only one lower quality study reporting an effect. As such there is little evidence that self-awareness increases the likelihood of a nocebo effect. Both Geers, Helfer, et al. (2005) and Geers, Helfer, Weiland, and Kosbab (2006) showed no significant main effects of instructing participants to attend to any symptoms or sensations they experienced. Using a distraction task also did not have a significant effect on symptom reporting (Van den Bergh et al., 1998). Gibbons, Carver, Scheier, and Hormuth (1979), however, did find a significant main effect, with participants facing a mirror reporting less perceived arousal than participants not facing a mirror following ingestion of a sham drug.

Type of administration. Two studies of mixed quality tested whether type of administration affects symptom reporting, finding no evidence for a link with nocebo effects. There was no difference in symptom reporting between a sham pill and either a saline injection (Goldman, Witton, & Scherer, 1965) or sham acupuncture (Kaptchuk et al., 2006).

Verbal suggestions on performance. Three studies manipulated verbal suggestions about the effect an inert exposure would have on performance. Two higher quality studies found no significant effects with only one lower quality study reporting an effect. As such there is little evidence that suggesting an exposure impairs performance increases the likelihood of a nocebo effect. Both Harrell and Juliano (2009) and Nevelsteen, Legros, and Crasson (2007) found no significant main effects of suggesting sham coffee or sham EMF would enhance or impair performance on a task on any of their symptom measures, respectively. However, smokers told that a sham cigarette would impair performance had significantly more craving symptoms than those who were told it would enhance performance (Harrell & Juliano, 2012).

Verbal suggestions of likelihood of exposure. Nine studies manipulated suggestions about the likelihood that an exposure would occur. All studies were of higher quality with four finding

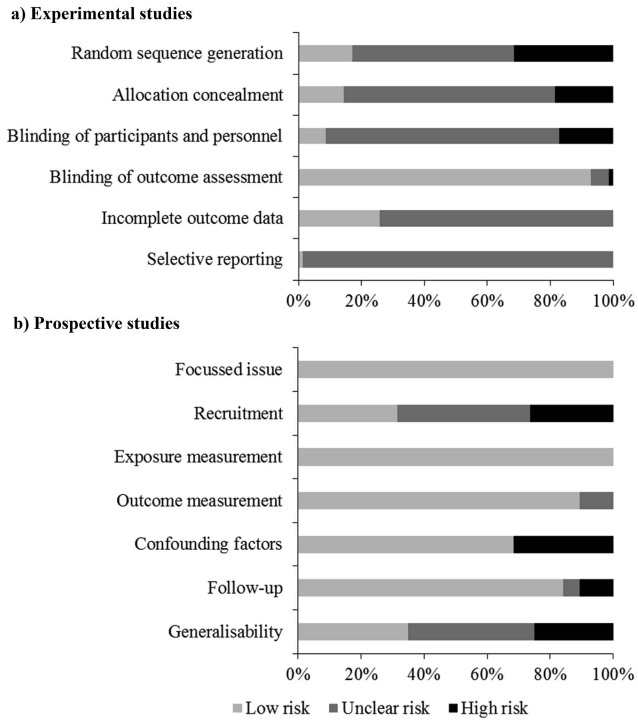

Figure 2. Quality assessment of experimental and prospective studies.

significant effects and five finding nonsignificant effects. In other words, there was mixed evidence for the role of likelihood suggestions in nocebo effects. The studies used a mixture of conditions in which participants were either told they would receive an active exposure (deception), might receive an active or inactive exposure (double-blind), would receive an inactive exposure (open) or nothing (control). Five of the studies found no significant main effects (Geers, Helfer, et al., 2005; Geers et al., 2006; Ossege et al., 2005; Walach, Schmidt, Dirhold, & Nosch, 2002; Walach & Schneider, 2009 Exp 1). Geers, Wellman, Fowler, Rasinski, and Helfer (2011), however, found that participants reported significantly more side effects in response to a sham pill when given deceptive information, compared with double-blind or control information. In addition, participants given deceptive or double-blind suggestions had a significantly higher increase in alertness following ingestion of sham coffee (Kirsch & Weixel, 1988) and a significantly higher number of adverse events following a sham weight loss supplement (Tippens et al., 2014) than participants in the control condition. For Walach, Schmidt, Bihr, and Wiesch (2001) participants told they would receive an inactive exposure scored higher on general wellbeing than those who received no substance or instruction.

Verbal suggestions of arousal. Sixteen studies manipulated suggestions about the effect an inert exposure would have on arousal. Thirteen studies showed a significant effect, with 10 of these being of higher quality. This strongly supports a link with nocebo effects. Only three studies revealed no main effects (Brodeur, 1965; Kuenzel, Blanchette, Zandstra, Thomas, & El-Deredy, 2012; Penick & Fisher, 1965). The remaining 13 all demonstrated significant effects. Participants given stimulant suggestions compared to sedative suggestions had higher tension scores and were more lively after administration of a sham drug (Flaten, Simonsen, & Olsen, 1999; Mrna & Skrivanek, 1985), and had higher scores of stress, arousal, alertness, friendliness and aggressiveness, and lower fatigue scores after ingestion of an inert drink (Dinnerstein & Halm, 1970; Flaten, 1998; Slánská, Tikal, Hvizdosova, & Benesova, 1974). Higuchi, Shoji, and Hatayama (2002) demonstrated lower stress and stimulant symptoms for participants given relaxing suggestions compared to no information for lavender and jasmine fragrances respectively. Goldman et al. (1965) found that more patients reported suggested drug effects in a sedative condition than in a stimulant condition. The remaining studies found a significant increase in caffeine related symptoms (Geers, Weiland, Kosbab, Landry, & Helfer, 2005; Lotshaw, Bradley, & Brooks, 1996), and alertness (Schneider et al., 2006; Walach & Schneider, 2009 Exp 2) and a significant decrease in calmness (Mikalsen et al., 2001) for participants told they would receive caffeine compared to participants who were told they would not receive caffeine or who received no beverage. Finally, Angelucci and Pena (1997) found that participants given coffee with low arousal expectations had significantly lower alertness compared to participants given coffee with no expectations, high arousal expectations, or no coffee at all.

Verbal suggestions of symptoms. Twenty-one studies manipulated suggestions about what symptoms to expect from an inert exposure. Thirteen found a significant effect, with 11 of these being of higher quality, broadly supporting a link with nocebo effects. Of the 21 studies, eight reported no significant main effects (Devriese et al., 2004, 2006; Heatherton, Polivy, & Herman, 1989; Jaén & Dalton, 2014; Schweiger & Parducci, 1981; Walach et al., 2002; Winters et al., 2003; Witthöft & Rubin, 2013). For the remaining 13 studies, Benedetti, Amanzio, Casadio, Oliaro, and Maggi (1997); Crichton, Dodd, Schmid, Gamble, and Petrie (2014); Wise et al. (2009) and Pennebaker and Skelton (1981) found significantly higher symptoms scores for those warned about side effects compared to those not warned after administration of sham treatment, infrasound, and ultrasonic noise, respectively. Dalton (1999), Neukirch and Colagiuri (2015), and Put et al. (2004) found that participants' symptoms were significantly consistent with the warning they received about an odor, sham sleep medication, and sham inhaler, respectively. Three studies demonstrated that participants experienced significantly more symptoms when informed about side effects to a sham drug (Gibbons et al., 1979; Zimmermann-Viehoff et al., 2013) or saline eye drops (Gavrylyuk, Ehrt, & Meissner, 2010) compared with being informed it was a placebo. Similarly both Bayer et al. (1991) and Read and Bohr (2014) established significantly higher symptoms scores for those informed they would receive an active compared to an inactive exposure. Colagiuri, McGuinness, Boakes, and Butow (2012), however, found the opposite; participants not warned about the side effects experienced more and a greater severity of side effects than those warned about one or four side effects.

Miscellaneous. Six studies looked at factors that did not fit into the above categories. There was no significant effect of manipulating participants to cooperate (Geers, Weiland, et al., 2005) or the experimenters' expectations of participants' symptoms (Walach et al., 2001). However, Faasse, Cundy, Gamble, and Petrie (2013) found that manipulating tablet brand to make participants think they had changed to a generic version resulted in a significantly higher number of symptoms compared with participants told that they were still taking the original branded tablet, although this study was of lower quality than the others in this group. Jensen and Karoly (1991) have shown that manipulating social desirability so that participants think responding to the pill is more socially desirable results in significantly higher symptom scores. Type of breathing has also been shown to affect symptom reporting with normocapnic overbreathing resulting in higher respiratory symptoms compared with spontaneous breathing (Van Diest et al., 2006). Lastly, a conditioned odor results in more symptoms if the odor is presented immediately rather than a week after conditioning trials (Devriese et al., 2000).

Baseline Risk Factors Categories

Nineteen prospective studies and also 33 experimental studies which assessed baseline risk factors were included which fell into six different categories as discussed below (further details in supplementary Tables 12–17).

Demographics. Twenty studies looked at the risk of demographic characteristics, finding no demonstrable evidence for their role in nocebo effects. Five of these investigated age and found it did not predict any symptom outcomes (de la Cruz, Hui, Parsons, & Bruera, 2010; Geers, Helfer, et al., 2005; Goetz et al., 2008; Lombardi, Gargioni, Canonica, & Passalacqua, 2008; Witthöft & Rubin, 2013). As four of these studies were of higher quality, this is good evidence that age is not linked with the development of nocebo effects. Eighteen studies (Angelucci & Pena, 1997; Casper,

Tollefson, & Nilsson, 2001; Geers, Helfer, et al., 2005; Geers et al., 2011; Goetz et al., 2008; Harrell & Juliano, 2012; Jensen & Karoly, 1991; Liccardi et al., 2004; Lombardi et al., 2008; Lorber et al., 2007; Mazzoni et al., 2010; Papoiu et al., 2011; Read & Bohr, 2014; Strohle, 2000; Van den Bergh et al., 1997, 1998; Witthöft & Rubin, 2013) looked at gender and only four reported significant results suggesting women are more susceptible to nocebo effects than men (Casper et al., 2001; Liccardi et al., 2004; Strohle, 2000; Szemerszky et al., 2010). Of the remaining 14 showing nonsignificant effects, 12 were of high quality, suggesting there is very little evidence for the role of gender in nocebo effects. The effects of level of education (de la Cruz et al., 2010; Witthöft & Rubin, 2013) were equivocal in two high quality studies, whereas employment (Drici, Raybaud, Delunardo, Iacono, & Gustovic, 1995) was not a significant predictor.

Clinical characteristics. Fourteen studies investigated clinical characteristics, finding mixed evidence for a link with nocebo effects. Six studies of high quality looked at the effect of baseline symptom scores, finding mixed evidence for a link with nocebo effects. Two found no significant effects (André-Obadia et al., 2011; Casper et al., 2001). For the other four, results were mixed. Danker-Hopfe, Dorn, Bornkessel, and Sauter (2010) and de la Cruz et al. (2010) found that higher symptom scores at baseline predicted higher symptom scores after exposure to sham EMF and treatment respectively, whereas Flaten et al. (2003) and Goetz et al. (2008) found the opposite after drinking decaffeinated coffee and taking sham medication for Parkinson's respectively. Six studies of high quality looked at the effect of type of clinical condition, with five finding a significant effect. They showed that suffering from a condition that is exacerbated by the suggested sham exposure significantly increased symptom reporting compared to healthy volunteers, strongly supporting a link with nocebo effects. Nevelsteen et al. (2007) found that depression did not predict symptoms in response to a sham magnetic field. However, De Peuter et al. (2005); Papoiu et al. (2011); Strohle (2000) and Bogaerts et al. (2010) showed that suffering from atopic dermatitis, panic disorder, asthma, or medically unexplained dyspnea resulted in significantly more symptoms in response to sham histamine, sham panic disorder trigger, sham inhaler, and breathing trials with room air, respectively, compared with healthy volunteers. In addition, Szemerszky et al. (2010) found that the level of perceived sensitivity to EMFs was positively correlated with symptom scores after sham EMF exposure. The remaining two studies looked at previous drug reactions finding weak evidence for a link with nocebo effects. Lombardi et al. (2008) found no significant effects of type or severity of previous drug reaction on symptoms in response to a sham allergen pill. However, a higher quality study by Mrňa and Skiřvánek (1985) found the reaction to another sham drug was significantly correlated with perceived drug effect.

Expectations. Thirteen studies looked at the effect of participant expectations on symptom reporting, broadly supporting a link with nocebo effects. Eleven of these studies looked at participants' symptom expectations, of which five higher quality studies revealed no significant effects (Angelucci & Pena, 1997; Molcăn et al., 1982; Walach et al., 2001; Walach & Schneider, 2009 Exp 1 and 2). The remaining six studies demonstrated that expectations of symptoms significantly predicted (Fillmore & Vogel-Sprott, 1992; Köteles & Babulka, 2014; Vase et al., 2013) or correlated (De Peuter et al., 2005; Flaten et al., 2003; Szemerszky et al., 2010) with symptom reporting. Five of these studies were of higher quality therefore broadly supporting a link with nocebo effects. Three studies also looked at expectations in terms of the substance taken finding weak evidence for its role in nocebo effects. Link, Haggard, Kelly, and Forrer (2006) found that participants who believed they had taken an active pill reported more symptoms than those who thought they had a taken a sham pill, however this was a low quality study. Higher quality studies by Bayer et al. (1998) and Walach et al. (2001) also investigated this but found no significant effects.

Anxiety. Nine studies looked at the influence of anxiety on symptom reporting, finding weak evidence for a link with nocebo effects. Six studies of mixed quality looked at state anxiety (Bogaerts et al., 2010; Link et al., 2006; Molcăn et al., 1982; Nevelsteen et al., 2007; Szemerszky et al., 2010; Witthöft & Rubin, 2013) but only Nevelsteen et al. (2007) found a significant effect, with state anxiety predicting physical symptom scores. Molcăn et al. (1982) and Nevelsteen et al. (2007) found no significant effects of trait anxiety. Angelucci and Pena (1997) found combined state and trait anxiety scores significantly predicted anxiety, but did not report results for state and trait anxiety separately. However, no such effect of combined state and trait anxiety was found on symptom reporting to an odor (Van den Bergh et al., 1997), although this was a lower quality study. Finally, a high quality study by Danker-Hopfe et al. (2010) found that anxiety toward a local base station predicted subjective sleep quality after sham EMF exposure.

Personality. Twenty-two studies looked at different aspects of personality as predictors of symptoms. Twelve studies showed significant effects of personality of which only three were of low quality as such finding evidence broadly supporting a link with nocebo effects. There were no significant effects of suggestibility (Angelucci & Pena, 1997), sensitivity to anxiety (Nevelsteen et al., 2007), restraint (Heatherton et al., 1989), or social desirability (Link et al., 2006; Put et al., 2004; Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2000). However, studies did show significant effects of the following on at least one symptom outcome: Type A personalities reported more side effects than Type B (Drici et al., 1995); pain catastrophizing positively correlated with side effect reports (Sullivan, Lynch, Clark, Mankovsky, & Sawynok, 2008); blunting behavior predicted symptom reporting (Van den Bergh et al., 1997); positive affect and vigilance predicted symptom scores (Nevelsteen et al., 2007); "frail and submissive" personality correlated with the exposures perceived effect (Slánská et al., 1974); somatization and motivation predicted symptom score (Szemerszky et al., 2010); and modern health worries and somatosensory amplification predicted symptom scores (Witthöft & Rubin, 2013). There was mixed evidence for the role of negative affect (Bogaerts et al., 2010; De Peuter et al., 2005, 2007; Devriese et al., 2000, 2004; Nevelsteen et al., 2007; Put et al., 2004; Stegen et al., 1998, 2000; Van den Bergh et al., 1995), neuroticism (Davis, Ralevski, Kennedy, & Neitzert, 1995; Mazzoni et al., 2010), and pessimism (Geers, Helfer, et al., 2005; Szemerszky et al., 2010).

Miscellaneous. Thirteen studies looked at baseline factors which did not fit into the above categories. These included caffeine consumption (Geers, Weiland, et al., 2005; Geers et al., 2011), olfactory sensitivity (Dalton, 1999), perceived cue odor (Devriese

et al., 2004), visibility of a mobile phone base station and preoccupation with EMF (Danker-Hopfe et al., 2010), geographical site of enrolment (Goetz et al., 2008), hospital center (Liccardi et al., 2004), stress experienced while wearing a helmet delivering sham EMF (Nevelsteen et al., 2007), ability to predict which odor produced the most symptoms (Meulders et al., 2010), and risk perception (Nevelsteen et al., 2007), which had no significant effects. Köteles and Babulka (2014), however, found that odor pleasantness predicted perceived change in alertness for eucalyptus oil. In addition, odor reactivity predicted symptom responding to odors (Dalton, 1999) and high regard for medications positively correlated with perceived drug effect (Goldman et al., 1965). Mazzoni et al. (2010) found that if the gender of the model matched the participant this predicted symptom development in social observation studies. Nevelsteen et al. (2007) found that less comfort under the helmet delivering the sham EMF predicted symptoms. Finally, Wendt et al. (2014) reported that significantly more symptoms were reported in val/val homozygous carriers compared to val 158/Met 18 and Met/Met 158 homozygous carriers after sham treatment.

Interactions Between Risk Factor Categories

As well as investigating the main effects of each risk factor, some studies assessed the interactions between risk factors, as displayed in the last column of Tables 3 through 17. Those risk factors which were implicated often in these interactions were factors such as "likelihood suggestion" which interacted with: "pessimism"—participants given deceptive suggestions report more symptoms compared to those told it was an inactive pill, if they were pessimists (Geers, Helfer, et al., 2005); "self-awareness"—participants given deceptive suggestions reported more symptoms when asked to monitor their bodily sensations (Geers et al., 2006); and "perceived dose"—tension increased with increasing coffee dose for those given deceptive suggestions, but decreased with increasing coffee dose when given double-blind suggestions (Kirsch & Weixel, 1988).

In addition, "classical conditioning" showed interactions with "odor"; pairing an odor with CO2 elicited symptoms to the odor alone, only if the odor was foul smelling (Devriese et al., 2000; Van den Bergh et al., 1995, 1997; Winters et al., 2003). This interaction between "classical conditioning" and "odor" was also found to more likely occur among people with high "negative affect" (Devriese et al., 2000) and those manipulated to have higher "self-awareness" (Van den Bergh et al., 1998). Negative affect also interacted with "symptom suggestions," with higher obstruction and dyspnea symptom scores after suggestions of bronchoconstriction compared to bronchodilation for a sham inhaler if participants had high negative affect (Put et al., 2004). An interaction was also found with "prior experience," with high negative affect participants reporting more arousal and symptoms on the whole to a room-air breathing trial when this preceded rather than followed a CO2 breathing trial (Stegen et al., 1998).

As well as interacting with negative affect, symptom suggestions interacted with other factors. These included the following: "self-awareness," participants reported more symptoms when told they were taking an active drug with side effects if they were not facing a mirror (Gibbons et al., 1979); "odors," more symptom reports following suggestion of symptoms if the odor was unpleasant (Dalton, 1999); "classical conditioning," higher total, respiratory, cardiac, and unclassified symptom scores following exposure to an odor previously paired with CO2 if participants received symptom suggestions (Winters et al., 2003); and "state anxiety," higher total and head/concentration symptoms following symptom suggestions if participants had high anxiety (Witthöft & Rubin, 2013).

Discussion

Summary of Main Results

From the 89 studies that met our inclusion criteria, 14 categories of risk factor for a nocebo effect were identified, including nine experimentally induced risk factor categories and six baseline risk factor categories (miscellaneous categories were present for both experimental and prospective studies). Of these categories, "learning/social observation," "perceived dose," "verbal suggestions of arousal and symptoms," and "baseline symptom expectations" appeared to be the strongest predictors of nocebo effects. There was some evidence for the role of "personality" in nocebo effects; however which facets of personality are more strongly linked with nocebo effects needs further research. In addition, although not strong predictors on their own, learning/classical conditioning, likelihood suggestion, self-awareness, and negative affect consistently interacted with other risk factors.

Given the proposed psychological mechanisms behind nocebo effects it is perhaps unsurprising that these factors have been consistently identified in the literature. Specifically looking at the expectation mechanism, it is intuitive that verbal suggestions of symptoms can generate expectations of these effects leading to symptom reporting. In support of this, participants' own baseline expectations can trigger symptoms, while perceived dose presumably affects symptom reports through a mediating effect of expectations, with a higher dose associated in a participant's mind with a stronger effect. This could also explain the significance of medication brand, with branded medication being generally expected by the public to be better quality than generic unbranded medication and therefore less likely to cause side effects (Faasse et al., 2013). Expectations could also explain why four studies which measured symptom reports both for prewarned and nonwarned symptoms found stronger effects for symptoms that had previously been suggested (Faasse et al., 2013; Gibbons et al., 1979; Lorber et al., 2007; Mazzoni et al., 2010). It also explains why no effect was found for performance suggestions, as this should not directly influence expectations of symptoms from the exposure.

It is important not to overemphasize the nature of our results with respect to expectation, however. In particular, it was striking that type of administration and verbal suggestions of the likelihood of exposure did not appear to be relevant despite both supposedly raising expectations of symptoms. Possibly, the influence of these factors on expectations is weaker than might be thought. Alternatively, methodological factors may account for the lack of effect. For example, both studies assessing type of administration used patient samples (Goldman et al., 1965; Kaptchuk et al., 2006). Given their greater experience with medical procedures, merely changing an intervention from a pill to an injection may not have triggered a substantial change in expectations. For three of the likelihood suggestion studies (Walach et al., 2001, 2002; Walach

& Schneider, 2009 Exp 1) it was suggested that the absence of an effect could have been because of cultural differences, with the caffeine effect stereotype not as strong in Germany as it is in the U.S.A.

The overall support for the role of expectations identified in our review still allows for at least two "submechanisms" to exist. The first is a role for attentional bias and symptom detection (Hahn, 1997). The second is a more direct effect, where-by expectations affect emotional state (Kirsch, 1997b; Stewart-Williams, 2004). For example, Kirsch (1997b) pointed out that the expectation of anxiety is likely to be anxiety provoking, thereby directly causing the outcome. This could explain the strong results seen for manipulating verbal suggestions of arousal on symptom reporting, as the expectation of arousal or relaxation is itself likely to be arousing or relaxing. However, there does need to be a degree of caution in interpreting these results on arousal as they could be interpreted as part of the placebo response.

With regard to misattribution as a mechanism, the evidence from the studies that investigated self-awareness as a risk factor did not support this, with the two most directly relevant studies that instructed participants to monitor for any sensations failing to find an effect. Equally, for the six studies investigating the effect of baseline symptoms on symptom reporting the results were mixed providing inconclusive support for misattribution. However, five studies (Bogaerts et al., 2010; De Peuter et al., 2005; Papoiu et al., 2011; Strohle, 2000; Szemerszky et al., 2010), showed that suffering from a condition with symptoms similar to those being induced was a predictor of symptom reporting. As such, although the mechanism remains plausible, further evidence is required to clarify its importance.

For the learning mechanism support was found from studies investigating the risk factor "association," with the taste of decaffeinated coffee being enough to elicit caffeine related symptoms (Flaten & Blumenthal, 1999; Mikalsen et al., 2001). For prior experience, the results were weak but this could have been attributable to a lack of experience as this manipulation was typically a one off event. However, there was evidence for the role of social observation, with two of three studies showing a significant effect. In addition, support for learning was seen in the studies using classical conditioning, which involved a number of trials. Almost half of the studies showed that conditioning CO2 inhalation with any odor is enough to elicit symptoms to the odor itself, and a reliable finding among the studies was that this was especially the case if the odor was unpleasant.

For baseline risk factors, we found no evidence of any effects of gender. However, since conducting the literature search, one additional study that would have met the inclusion criteria has become apparent and which is relevant here. This study by Faasse, Grey, Jordan, Garland, and Petrie (2015) investigated the risk factor of observing a female confederate display symptoms, demonstrating a significant effect on symptom reporting in females. It is interesting to note that Lorber et al. (2007), who also studied social observation, also only found a significant effect in females. One possibility is that it may be something inherent to social observation that makes females more vulnerable to nocebo effects. Other demographic factors such as age, employment status or level of education were also not risk factors. Interestingly, anxiety did not come out as a strong predictor despite the role it could play through misattribution (generating physical symptoms that are available to be misattributed) and expectations (apprehension of symptoms). One possible explanation for this advanced by Szemerszky et al. (2010) is that scores of anxiety could reach a ceiling effect due to advance information about the risks of taking part in the study. For other baseline risk factors, many different types of personality were implicated such as: Type A personality (Drici et al., 1995), lower positive affect, vigilance (Nevelsteen et al., 2007), pessimism, motivation to cooperate, somatization, somatosensory amplification, modern health worries (Szemerszky et al., 2010; Witthöft & Rubin, 2013), and neuroticism (Davis et al., 1995). A lack of consistency in the personality traits studied makes it difficult to interpret these findings, but many would seem to fit with expectation and/or misattribution mechanisms.

Nocebo effects have occasionally been referred to as the 'evil twin' of placebo effects. If true, one would expect the risk factors for a nocebo effect to be the inverse of the risk factors for a placebo effect. At a first look the mechanisms supported in our review do appear to be similar to those previously identified for placebo effects, albeit acting in the opposite direction. For example, the expectancy mechanism has been implicated for placebos through factors such as verbal suggestions, and participants' own baseline expectations which lead to positive expectations for pain or symptom relief (Benedetti et al., 2003; Kam-Hansen et al., 2014; Price et al., 1999; Vits et al., 2013). In addition, learning mechanisms such as prior experience of pain relief, social observation, or conditioning people to experience pain relief results in subsequent placebo responses (Colloca & Benedetti, 2006, 2009; Suchman & Ader, 1992). It also seems that opposite personality characteristics also predict placebo responding for example, optimism (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007) as opposed to pessimism. One notable exception, however, would be the misattribution of preexisting symptoms, as logically this can only be relevant for nocebo: one cannot misattribute the absence of preexisting symptoms to an exposure. However, it is possible one could misattribute and fixate on a coincidental decline in symptoms after taking a sham tablet, and misattribute their improved wellbeing to the tablet.

Quality of Original Research

It is possible that some of our conclusions may be attributable to differences in quality between those studies that found an effect and those that did not. We did not observe any clear trend for lower quality studies to report more or fewer significant results than higher quality studies. However, on the whole the quality of the studies included in this review was limited because of poor reporting of key issues in experimental research such as randomization, allocation concealment, blinding, and not registering a study protocol before initiating recruitment. Prospective studies had fewer quality concerns, however given that experimental studies allow the control of more variables the results of these have more weighting than those from the prospective studies. It is also worth noting that almost half of studies did not mention receiving ethical approval. In an area of research requiring deception, or at least withholding information to deliberately cause symptoms, this is surprising. There is scope for future researchers to improve the methodological rigor of this field. Another surprising limitation of many of the studies included in this review was the lack of a priori sample size calculations. Only 10 of 89 studies included in this

review mentioned carrying out a sample size calculation in order to make sure the sample was adequately powered to test their research question(s). As such, we could not assess the quality of studies based on their sample size in the large majority cases. Although it would have been useful to score each study for their strength of evidence, because of this lack of clear reporting and the heterogeneity across studies it was too hard to quantify the strength of each study using the same scale.

Quality of This Review

A strength of this review is that we did not include studies in which participants were exposed to an active exposure capable of eliciting symptoms through physiological mechanisms (e.g., experiments altering the information given to participants about a genuine medication). Such studies do not assess the pure nocebo effect, described as the undesirable effects experienced from an inert exposure (Kennedy, 1961) and can prove more difficult to interpret (Neukirch & Colagiuri, 2015).

Our search resulted in a large number of results. As the term 'nocebo' is still not widely used and may be preferentially used by those studies identifying a significant increase in symptoms in their participants, we deliberately adopted a broader search strategy than that used in previous reviews, for example, Petersen et al. (2014). Despite this, it is not certain that every study that met the inclusion criteria has been included, especially as nearly a quarter of included studies were identified through personal contacts. This inconsistent use of terminology makes the nocebo literature difficult to search and will continue to limit reviews in this area. We could have included terms such as 'adverse effects or negative outcome' in the search strategy but the number of results would be unmanageable as it would include many clinical trials that would not meet our inclusion criteria. On Medline alone, such search terms return over 97,000 results. This is also one of the reasons why we did not simply use 'placebo' as one of the search terms—every study which described itself as "placebo-controlled" would be returned.

In addition to limitations resulting from our search strategy, it is possible that some studies could have been falsely rejected after title and abstract screening (e.g., the main purpose of the study may have been on the placebo effect and therefore only placebo and not nocebo findings were reported in the abstract). We suspect that this is unlikely to have occurred often, however. In order to have been included such studies would have had to (a) manipulated factor(s) to affect nocebo responding or (b) looked at baseline measures as predictors of nocebo responding, which many do not do. Many studies which looked at the placebo effect passed through abstract screening as they mentioned participants experiencing negative symptoms or patients feeling worse after placebo exposure. However, going through the full manuscript the majority of these studies would not explore the possible reasons why, for example, baseline predictors. Therefore we feel this is not something to be too concerned about.

In addition studies published in non-European languages may have been less likely to have been identified as well as studies that were not reported in the conventional peer-reviewed literature.

Other limitations of the review reflect the way we grouped the results. We aggregated studies based on the independent variable. Because of this and because there are no direct replications each risk factor grouping contains several different outcomes. It is possible that an interaction exists between independent and dependent variables: for example, some outcomes may be more susceptible to the effects of changes in expectations than others. Unfortunately, we did not have enough data to explore this in depth.

Similarly as this review focused on identifying all the possible risk factors of nocebo effects that have been investigated in the literature, we included studies with different research populations, for example, students, healthy volunteers and patients. As such there could be differences between the groups in terms of which mechanisms are more likely to be at play. For example, it is likely the misattribution mechanism is more important for the development of nocebo effects in patient samples than healthy volunteers. However, looking at studies that had a patient sample we should interpret the results of those that just focused on baseline disease measures as support of the misattribution mechanism with caution. These studies did not measure actual baseline symptoms or emotions which are more likely to be subject to the misattribution mechanism, rather than disease status.

Finally, the interaction between the mechanisms, outcomes, and mode of delivery may also be important, but could not be explored in detail given the data available to us. For example, different forms of sham intervention for example, sham tablets versus sham caffeine versus sham EMF, may be more or less likely to trigger certain psychological mechanisms, and be more or less likely to affect certain outcomes, see Szemerszky, Dömötör, Berkes, and Köteles (2016).

Implications for Clinical Practice and Research

Our results suggest clinicians keen to reduce side effects induced by any nocebo effect associated with their interventions could (a) identify patient expectations of the adverse effects of an intervention and provide reassurance if these seem excessive, (b) avoid giving suggestions of side effects associated with the intervention, (c) down-play the dose that is being provided, and (d) reduce patient exposure to other patients experiencing side effects. Wells and Kaptchuk (2012) suggest the use of contextualized informed consent, whereby doctors should identify high-risk patients and tailor the medication side effect information so that these patients only receive drug specific side effect information, which is less susceptible to the nocebo response. Our review supports this and suggests that such tailoring may be especially required for those who have at-risk personality types. Clearly, these suggestions also have a downside, however, as they reduce informed consent and patient autonomy by restricting the information that is being provided. Alternative ways to reduce nocebo effects while maintaining the ability of a patient to give full informed consent are required. There is scope for researchers to develop innovative ways to reduce nocebo effects that does not require withholding of information. This has been shown by Crichton and Petrie (2015), who found that informing participants about nocebo effects effectively reduced symptoms to infrasound noise. In addition Bingel and the Placebo Competence Team (2014) provides some suggestions on how to avoid nocebo effects which are supported by this review such as improving the communication in patient information leaflets to make them more patient-orientated and reduce negative expectations of potential adverse effects.

Additional research should also aim to replicate risk factors which have so far received limited research, such as the more rarely investigated personality characteristics. It would also be advisable to look again at the risk factor 'type of administration' in a healthy volunteer sample and to assess this manipulation on expectations to explore possible mechanisms. It is also time for authors to use consistent terminology allowing easier identification of papers, and to enhance the quality of their research in this area. Simple acts such as being more explicit about randomization and blinding procedures and publishing protocols will enhance the transparency of the research in this area while also helping to alleviate some of the controversy surrounding nocebo research.

Conclusions

This review found that there is a mix of factors which predict whether someone will experience a nocebo effect. Given the implications nocebo effects have on patients' quality of life and the health costs they create, it is important for research to start developing interventions to prevent nocebo effects from occurring while still trying to uphold informed consent. This systematic review provides a useful starting point for researchers to develop evidenced based interventions designed to negate nocebo effects, while also highlighting areas that need further investigation and improvement.

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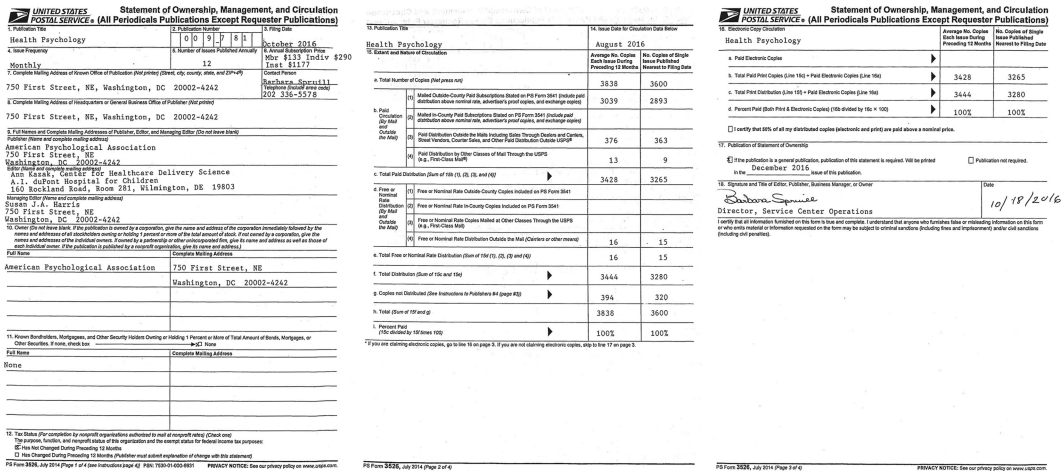

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