REVIEW

Nocebo as a source of bias in the assessment of treatment effect [version 1; peer review: 2 approved with reservations]

Karolina Wartolowska

Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, OX2 6GG, UK

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Abstract

The term nocebo refers to the worse outcomes or side effects experienced by patients as a result of their negative expectations regarding a treatment. It may distort estimates of treatment effectiveness and safety in both clinical trials and clinical practice; moreover, it may cause discontinuation of therapy or drop out from a trial.

Nocebo effect is evoked by the information given to patients during a clinical consultation or during enrolment into a study, but information available from the media or the Internet may also play an important role. In research settings, a trial design may introduce bias from the nocebo effect. For example, if the non-treatment group is unblinded and aware that they are not receiving any treatment, their treatment expectations are not met, which results in worse outcomes, and subsequently, the problems that the trial was supposed to investigate may be enhanced in the non-treatment arm.

Nocebo effect is common, and its magnitude may be large, but it receives less attention and research focus than the placebo effect. Unlike the placebo effect, which is usually taken into consideration while interpreting treatment results and controlled for in clinical trials, the nocebo effect is under-recognised by clinical researchers as well as clinicians.

It is important to recognise and any potential nocebo effect must be considered while assessing the effect of treatment and should be minimised through careful choice and phrasing of treatment-related information given to the patients.

Keywords

Review (article), Nocebo Effect, Placebo Group, Adverse Events in Clinical Trials, Randomised Clinical Trial (RCT)

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1 **Paul Dieppe**, University of Exeter, Exeter, UK

2 **Przemysław Bąbel**, Jagiellonian University, Kraków, Poland

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Karolina Wartolowska (karolina.wartolowska@phc.ox.ac.uk)

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Introduction

Nocebo is often described as placebo's evil twin, and it rarely gets discussed on its own. There is relatively little research on nocebo and this phenomenon is under-recognised in clinical practice or clinical trials, with many patients and healthcare professionals admitting that they are not aware of its existence (Berthelot *et al.*, 2001).

In research, nocebo effect is defined as the adverse effect of a placebo intervention, for example placebo hyperalgesia, whereas in clinical or trial settings the term is used to describe the negative outcomes caused by negative expectations, such as lack of efficacy or harm from a drug or other intervention (Benedetti *et al.*, 2007; Hahn, 1997; Häuser *et al.*, 2012).

Nocebo can be easily evoked by verbal suggestion, such as negative information about the properties of the drug (Benedetti *et al.*, 2007), or by conditioning (Klosterhalfen *et al.*, 2009). Moreover, the magnitude of the effect is larger when it is caused by verbal suggestion and conditioning than by the verbal suggestion alone (Petersen *et al.*, 2014).

Nocebo hyperalgesia is mediated by stress and anticipatory anxiety, which facilitate pain transmission (Bingel *et al.*, 2011; Keltner *et al.*, 2006). Nocebo is also associated with higher cortisol levels (Johansen *et al.*, 2003) and with the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which controls reactions to stress. In addition to that, nocebo and HPA hyperactivity are reduced by anxiolytic drugs (Benedetti *et al.*, 2006). Nocebo response is also associated with reduced activation of dopaminergic and opioidergic systems (Scott *et al.*, 2008; Svedman *et al.*, 2005) and with increased effects mediated by cholecystokinin (Benedetti *et al.*, 1995).

Nocebo effect in clinical practice

In clinical settings, the nocebo effect manifests as a reduced response to treatment or the development of adverse events, which often result in non-adherence or discontinuation of treatment (Blasini *et al.*, 2017).

Nocebo effect is caused by negative expectations about the outcomes of the treatment and negative emotions created during the patient-doctor communication (Häuser *et al.*, 2012). These negative expectations are most often created unintentionally by the description of the treatment effects and side effects; either verbally during a consultation or as information on a drug leaflet (Benedetti *et al.*, 2007; Tobert & Newman, 2016). Other sources of negative information include friends, family and other patients as well as news, internet, or social media (Crichton & Petrie, 2015). For example, patients in the countries where they are more likely to find websites about the side effects of statins are more likely to demonstrate statin intolerance (Khan *et al.*, 2018). Nocebo effect may also be created by observing the symptoms, side effects, and behaviour of other patients undergoing the treatment (Colloca & Benedetti, 2009; Hahn, 1997; Świder & Bąbel, 2013).

Nocebo effect may be caused by dissatisfaction with the current or past treatment (Kessner *et al.*, 2013). For example, patients often distrust generic drugs and believe they are less effective and more harmful than branded drugs (Al Ameri *et al.*, 2011; Himmel *et al.*, 2005). Switching to generic drugs may cause lower adherence (Labiner *et al.*, 2010), worse outcomes, and more frequent adverse events (Häuser *et al.*, 2012). Also, many doctors think that generic drugs are of lower quality (Heikkilä *et al.*, 2007) and unintentional cues given by the doctors may make patients' attitude even more negative and enhance the nocebo effect (Häuser *et al.*, 2012).

Not only the treatment but also a negative consultation may cause a nocebo effect. Patients expect a doctor to understand and recognise their problems (validation), give it a name (diagnosis), explain how it is going to progress (prognosis), and then to offer a treatment, usually in a form of a pill. If any of the elements of the consultation is negative, for example, a doctor dismisses patients' complaints as being "all in their head", patients may feel that their treatment needs were not met and their sickness was invalidated (Vangronsveld & Linton, 2012). This invalidation makes patients hopeless and angry (Häuser *et al.*, 2012) and increases the nocebo effect (Barsky *et al.*, 2002). Moreover, the negative effect of consultation may be stronger than the positive effects of consultation (Greville-Harris & Dieppe, 2015). It may persist for a long time (Blasini *et al.*, 2017); although clinicians positive suggestions may reduce the effect of these negative messages (Crichton & Petrie, 2015).

In clinical settings, the nocebo effect is highly undesirable. Negative expectation can make the therapeutic intervention more painful, for example, an injection of an epidural analgesic can be made more painful when patients are warned that it would feel like a bee sting rather than told only that it would create a numbing sensation (Varelmann *et al.*, 2010). Similarly, using the word "pain" rather than "cool sensation" in a description of a procedure may make this procedure painful (Lang *et al.*, 2005).

The information about treatment is so crucial that it can interfere with the pharmacological effects of a drug. For example, pain ratings after the suggestion of hyperalgesia were higher than after the suggestion of analgesia, regardless whether they were accompanied by an application of analgesic cream or placebo (Aslaksen *et al.*, 2015). Similarly, the efficacy of pharmacologically active drugs was greatly reduced when they were given with the contradictory information: bronchoconstrictors as reducing asthma and bronchodilators as provoking it (Luparello *et al.*, 1970). In another study, information that the injection of a powerful opioidergic analgesic was stopped, reversed its analgesic effects despite the continued delivery of the drug (Bingel *et al.*, 2011). Negative information may also evoke adverse events even after the delivery of an inert placebo substance. For example, nebulised saline evoked asthma attacks in patients with asthma if it was given with information that contained an irritant, while the same saline relieved these symptoms if it was presented as an active treatment (Luparello *et al.*, 1968).

Nocebo effect in clinical trials

In trial settings, nocebo manifests as reduced improvement or increased frequency of adverse events, especially if they are

subjective, not dose-dependent, and unrelated to the pharmacological properties of the drug; including adverse events after placebo. Patients' withdrawal from a trial due to these adverse events is also considered to be a nocebo effect (Barsky *et al.*, 2002; Blasini *et al.*, 2017; Tobert & Newman, 2016). Nocebo effect in clinical trials is undesired. It may distort the results of the trial, for example, if patients do not improve sufficiently, it may be concluded that the tested treatment is not effective. On the other hand, if patients report many adverse events, the conclusions may be that the treatment is harmful and a trial may be terminated early. Moreover, if these adverse events lead to the withdrawal of many participants, the missing data may further complicate interpretation of such a trial (Mitsikostas *et al.*, 2011).

Unlike the placebo, the nocebo effect is under-recognised; it is rarely discussed in the context of clinical trials, and it may be not taken into the account while interpreting the results of a trial. The magnitude of nocebo effect (Petersen *et al.*, 2014) and the percentage of patients in clinical trials who report adverse events as a result of the nocebo effect may be underestimated (Amanzio *et al.*, 2009; Mitsikostas *et al.*, 2011; Rief *et al.*, 2006). For example, a meta-analysis of clinical trials of pharmacological treatments for neuropathic pain found that about 52.0% (95% CI: 35.7-67.9) of placebo-treated patients reported adverse events and 6.0% (95% CI: 4.5-8.0) withdrew from a trial due to these side effects (Papadopoulos & Mitsikostas, 2012).

In a clinical trial, like in a clinic, nocebo may be introduced by the information about the effects and side effects of the tested treatment that are described in the information letter or during the informed consent process. This information may bias the subsequent reporting and affect the trial outcomes, especially if these outcomes are based on patients' report. For example, the frequency of reported gastrointestinal adverse events and the discontinuation rates due to these adverse events in a trial on aspirin were much lower in a centre that did not include information about possible gastrointestinal bleeds than in two centres that included this information (Cairns *et al.*, 1985; Myers *et al.*, 1987). These adverse events reported by trial participants but not caused by the pharmacological effects of the tested medication are referred to as the nocebo effect (Barsky *et al.*, 2002). These symptoms are typically generalised and unspecific for example nausea, headaches, fatigue, or irritability. These symptoms are often not associated with any disease and commonly occur to healthy people not taking any medication (Eriksen & Ursin, 2004). For example, 77% of students responded that they had experienced at least one such a symptom in the previous three days (Reidenberg & Lowenthal, 1968). Patients participating in a trial may focus on their symptoms and may interpret normal physiological sensations or benign symptoms, that may usually get little attention, as side effects of the treatment (Barsky & Borus, 1999; Gurwitz *et al.*, 2003; Rosenzweig *et al.*, 1993).

In trial settings, about a quarter of patients taking placebo spontaneously report at least one side effect, and this figure increases when they are actively asked about side effects (Barsky *et al.*, 2002; Rosenzweig *et al.*, 1993). Furthermore, patients with negative expectations, are more likely to expect adverse events and misattribute them as related to the treatment (Barsky *et al.*, 2002). Some of these symptoms are highly prevalent in populations in which the drug is prescribed, for example, headaches in women taking contraceptive pills (Grimes & Schulz, 2011) or muscle problems in older patients taking statins (Tobert & Newman, 2016). These "noise" symptoms may be misattributed to the treatment (Barsky *et al.*, 2002; Grimes & Schulz, 2011; Tobert & Newman, 2016).

Not all nocebo-related side events are "unspecific" (Rief *et al.*, 2009). Some complaints may be disease-specific as patients may mistake symptoms of an underlying illness for treatment side effects (Fine & Johnston, 1993). Many adverse events reported by patients in the placebo group are typical for the treatment in the active arm (Amanzio *et al.*, 2009; Barsky *et al.*, 2002; Blasini *et al.*, 2017; Rief *et al.*, 2009). For example in the meta-analysis of trials on anti-migraine treatment, anorexia and problems with memory, which often occur in patients taking anti-epileptic drugs, were reported only in patients in the placebo arm of trials on anti-epileptic drugs (Amanzio *et al.*, 2009). In another study, the rate of adverse events was much higher in the placebo arm of trials of tricyclic antidepressants than in trials on selective serotonin reuptake inhibitors, which reflects the side effect profile of these classes of drugs (Rief *et al.*, 2009). These examples demonstrate that information about adverse effects of different classes of drugs causes expectations that may influence the experience of side effects and may bias clinical trial outcomes (Rief *et al.*, 2009).

Some of the elements of a trial's design may evoke a nocebo effect. For example, random assignment to different treatment regimens means that patients are not given a choice, which may create a nocebo effect while having a choice increases the placebo effect (Bartley *et al.*, 2016). Moreover, if the control consists of the patients on a waiting list or in a non-interventional group, patients randomised to this group are being left without any treatment. A non-interventional arm does not represent a natural history of disease because there is a double bias: not only these patients are not blinded, but also their treatment expectations are not met, because they are left without any treatment, which leads to the nocebo effect and either worsening of their symptoms or slower recovery.

Nocebo may distort the results of open-label trials, because not only is there information about possible adverse events but even the knowledge about the received treatment may affect the incidence of reported side events. For example, in a group of patients who knew they were taking atenolol and that erectile dysfunction may a possible side effect, the incidence of this particular side event was 31.2%, while in a group that was informed about the drug but not about the side effects the incidence was 15.6%, and if the group that was blinded and not told explicitly about this potential effect the incidence was only 3.1%. In the patients who reported this side effect, both Sildenafil or placebo were equally effective at curing it (Silvestri *et al.*, 2003).

The bias caused by the nocebo effect is minimised in blinded randomised controlled trials (RCTs). In an RCT, bias is controlled by making the two compared groups differ only by the treatment allocation. Moreover, blinding of patients and assessors reduces placebo as well as nocebo bias, because the expectations are the same in both groups (Collins & MacMahon, 2007). An addition of a placebo control is useful not only to test whether the active treatment is more effective than placebo but also whether it is truly more harmful than placebo. Without a placebo control, all the side effects may be attributed to the active element of the treatment. For example, in a trial on statins, during the blinded and randomised phase, muscle-related symptoms were reported equally often in the active and the placebo arm, but during unblinded phase they were more frequent in patients receiving statins (Ganga *et al.*, 2014; Gupta *et al.*, 2017; Kashani *et al.*, 2006). Moreover, patients with well-documented statin intolerance due to muscle symptoms usually tolerate a statin under double-blind conditions (Brown *et al.*, 2016; Newman & Tobert, 2015).

Recommendations and future directions

Unlike improvement associated with placebo, there are no benefits related to nocebo and the nocebo effect so it has to be minimised by reducing the existing negative expectations or by preventing new ones (Tobert & Newman, 2016).

Nocebo effect can be prevented by careful phrasing of the information given to patients and by positive framing, for example, by focusing on chances of improvement, survival, being symptom-free, and of not developing side effects etc. (Crichton & Petrie, 2015). Similarly, some adverse events may not occur if they are not prompted; therefore, it may be beneficial not to inform the patients about potential adverse events that may be unrelated to the treatment or be of little clinical importance such as mild headaches or nausea (Tobert & Newman, 2016). However, it is crucial to warn patients about clinically important or potentially dangerous side effects caused by the pharmacological properties of a drug, for example, that, patients should not drive or operate heavy machinery after drugs that cause drowsiness. In a trial, it is also very important to record and include in the publication the exact content and phrasing of the information given to trial participants because it may have a substantial effect on the trial results.

Nocebo effect may be reduced by asking patients about their preconceptions and beliefs regarding a treatment. If patients beliefs are negative, for example, they think they are intolerant to the prescribed medicine, they will be more likely to report more side effects at the follow-up (Barsky *et al.*, 2002), especially when starting new medications (Nestoriuc *et al.*, 2010). Such patients will be also less likely to adhere to this treatment (Barsky *et al.*, 2002), and may be more likely to stop taking this medication altogether (Nestoriuc *et al.*, 2010). After a change of medication, patients with negative beliefs are likely to report even more adverse events than during the therapy with the original drug (Nestoriuc *et al.*, 2010). Therefore, it is important to change the patient's attitude before changing the medication. Moreover, it may be worth asking patients to agree to a re-challenge with a drug they claim they do not tolerate (Tobert & Newman, 2016) as having a choice is associated with better outcomes (Botti & Iyengar, 2004). It is also important not to leave the patient without treatment, as any type of treatment is better than staying on a waiting list (Khan *et al.*, 2012).

Conclusions

Nocebo effect is always negative and unwanted, and it can easily be evoked by a careless word or unfortunate phrasing. Recognising the nocebo effect is important because it may make the treatment look ineffective or harmful. It may seem that there is no improvement or much less improvement than there should be. It may also seem that the treatment has many side effects and is not tolerated by the patient and lead to a change of treatment; however, patients who reported those unspecific complaints after one treatment are likely to report even worse symptoms after a change of treatment. Nocebo effect is also responsible for non-adherence to treatment and for discontinuation. When patients expect to feel worse or not improve, they treat every negative sensation as caused by the treatment, so they do not take the treatment regularly or stop it altogether, which, in turn, results in a subtherapeutic dose of medication and actual pharmacological consequences. Therefore, any potential nocebo effect must be recognised and minimised in the clinic and in clinical trials.

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Version 1

Reviewer Report 04 February 2019

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Przemysław Bąbel
Pain Research Group, Institute of Psychology, Jagiellonian University, Kraków, Poland

This is a well-written short summary of the studies on a very important issue which deserves much more attention than it actually gets. I have only two major concerns. First, the paper is focused mainly on verbal information as a source of the nocebo. Although I do agree that it is the most common source of the nocebo effect in clinical practice and clinical trials, two other sources are also important and their role should be discussed, i.e. previous experience (classical conditioning) and observation of other patients/participants of clinical trials (see for example 1). Especially, the role of those two additional sources should be included in the recommendations and conclusions sections of the paper.

Second, through the paper the nocebo effect is discussed mainly in terms of negative expectations, however, it is only one of the explanatory mechanisms of the nocebo effect. Although nocebo effects induced by verbal information and observational learning are usually mediated by expectations, there is growing evidence that the nocebo effect induced by classical conditioning may not always be mediated by expectations (see references 2-8). Thus, I would rather avoid discussing the nocebo effect as the result of sole negative expectancies as well as I would avoid defining it in terms of negative expectations.

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Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Partly

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pain, memory of pain, placebo and nocebo effects, learning mechanisms of pain and placebo effects

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Mar 2019

Karolina Wartolowska, University of Oxford, Oxford, UK

I would like to thank the Reviewer for a very constructive review. I agree with the Reviewer that the nocebo effect should not be defined only in terms of negative expectations regarding a treatment, especially, if the expectations are defined, in the narrow sense, as a set of beliefs about the treatment. However, the literature on nocebo uses the term “expectations” in a broader sense, being the negative state (conscious or subconscious) accompanying a treatment/therapeutic intervention. It comprises negative beliefs about treatment efficacy, negative emotions such as stress and anxiety, and anticipation and expectation of failure, lack of improvement or adverse effects. This state may be caused by previous bad experiences (either as a failed treatment or experimental classical conditioning), knowledge gained through experiences or information about treatment obtained from doctors, drug leaflets, media, other patients, by observing other patients or by learning from family and peers. As suggested by the Reviewer, the importance of classical conditioning and learning by observing others have been highlighted in the revised version of the manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Report 30 January 2019

https://doi.org/10.5256/f1000research.19256.r43476

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Paul Dieppe
University of Exeter, Exeter, UK

This is a useful review of a subject that, as the author says, deserves more attention than it gets.
One of my concerns is that the abstract and opening sentences state that nocebo is a result of negative expectation, and yet, as mentioned later this is only one of a number of theories as to how the nocebo effect may be activated. Others include invalidation (mentioned briefly), conditioning (mentioned briefly) and activation of the fight or flight response (not mentioned at all).

Another issue for me is the contexts in which nocebo can be an issue. This article mentions clinical trials, experimental settings such as pain perception, and clinical practice. I would find it easier to navigate the article if there was a clearer differentiation between these very different contexts, perhaps with subheadings.

In relation to clinical practice, the article does not mention the fact that a consultation can make a patient's disease or symptoms worse as a result of nocebo mechanisms.

In the context of clinical trials I think that more attention should be given to the fact that the consent procedure can make symptoms worse, as well as resulting in a reduced response or adverse events.

I found the English a little clumsy in places.

Is the topic of the review discussed comprehensively in the context of the current literature?
Partly

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Partly

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Placebo, nocebo, wellbeing and healing research

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Mar 2019

Karolina Wartolowska, University of Oxford, Oxford, UK

I would like to thank the Reviewer for their useful comments. I fully agree that expectations are only one of the mechanisms responsible for nocebo effect, but they are the one that is mentioned most frequently in the literature. Other mechanisms that may cause the nocebo effect, including stress or the “fight or flight” response, have also been discussed in this manuscript.

I am grateful to the Reviewer for their comment on the lack of clarity regarding the subdivision of nocebo effect in clinical and trial contexts. In the revised version, additional subheadings have been added, and some paragraphs have been rearranged to follow the clinical/trial context subdivision followed by the possible causes and consequences of the nocebo effect. Hopefully, the new version of the manuscript is less clumsy and sufficiently highlights the role of conditioning, stress, consultation, and consent procedure in generating the nocebo effect.

Competing Interests: I have no competing interests.