Cancer and Metastasis Reviews (2019) 38:315–326
https://doi.org/10.1007/s10555-019-09800-w

CLINICAL

It is not just the drugs that matter: the nocebo effect

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Published online: 16 June 2019

Abstract

The role of psychological mechanisms in the treatment process cannot be underestimated, the well-known placebo effect unquestionably being a factor in treatment. However, there is also a dark side to the impact of mental processes on health/illness as exemplified by the nocebo effect. This phenomenon includes the emergence or exacerbation of negative symptoms associated with the therapy, but arising as a result of the patient's expectations, rather than being an actual complication of treatment. The exact biological mechanisms of this process are not known, but cholecystokinergic and dopaminergic systems, changes in the HPA axis, and the endogenous secretion of opioids are thought to be involved. The nocebo effect can affect a significant proportion of people undergoing treatment, including cancer patients, leading in some cases to the cessation of potentially effective therapy, because of adverse effects that are not actually part of the biological effect of treatment. In extreme cases, as a result of suggestions and expectations, a paradoxical effect, biologically opposite to the mechanism of the action of the drug, may occur. In addition, the nocebo effect may significantly interfere with the results of clinical trials, being the cause of a significant proportion of complications reported. Knowledge of the phenomenon is thus necessary in order to facilitate its minimalization and thus improve the quality of life of patients and the effectiveness of treatment.

Keywords Nocebo · Nocebo effect · Nocebo mechanism · Pharmacotherapy · Cancer · Psychobiology

While the existence of the *placebo* effect is widely known, its opposite in the form of the *nocebo* effect is less commonly recognized. The *nocebo* effect is defined as the effect which occurs when a harmless substance or treatment (*placebo*) is taken by, or administered to, a patient and is associated with harmful side effects or worsening of symptoms due to negative expectations or the psychological condition of the patient (https://www.merriam-webster.com/dictionary/nocebo). The term *nocebo*, which comes from Latin, meaning "I will do harm," was used for the first time by Walter Kennedy in 1961 [1]. The notion itself of a *nocebo* effect was introduced in order to make a distinction between the positive effect of a *placebo*, in contrast to the undesirable effects that may occur as a result of informing the patient about any possible adverse reactions or due to the negative expectations s/he may have with respect to a medication or treatment [2].

It has long been recognized that psychological factors may affect the appearance or disappearance of symptoms, as well as the results of treatment itself. William Steward Halsted, who lived at the turn of the nineteenth and twentieth centuries and is credited with being the father of American surgery, refused to carry out surgical procedures on those patients who were not totally convinced as to the likelihood of a positive outcome. He explained this on the basis of his observation that patients with a pessimistic attitude tended to deteriorate in spite of all biological indications for a full recovery. In the present day, the notion of a *nocebo* is used more widely to

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describe the appearance or exacerbation of symptoms connected with different types of therapy. Apart from the expectations of the patient her/himself, the *nocebo* effect may also be the result of previous experience or observation of other patients [3, 4].

The incidence of occurrence of the *nocebo* effect is surprisingly high. It has been estimated that at least 25% of people taking part in clinical trials and receiving a *placebo* report adverse effects [5]. The frequency of withdrawal from clinical trials attributed to the emergence of complications associated with treatment is similar in patients receiving the drug being tested and in those receiving *placebo* [6]. Furthermore, the profile of adverse effects reported in both groups of patients may be similar and in keeping with the mechanism of action of the tested drug [7]. This has far-reaching clinical implications, in terms of both basic and clinical research, and hence it is important to understand the neurobiological and psychological mechanisms giving rise to the *nocebo* effect, about which very little is still known.

1 Biochemical mechanisms of nocebo

It is not possible to explain the *nocebo* effect in terms of a single, universal neurobiological or psychological mechanism, because the process giving rise to this phenomenon is, without doubt, a complex one [8]. Even the process of attempting to examine this phenomenon is ethically somewhat ambiguous, because by definition it is a situation characterized by negative features and hence the number of available studies in this area is considerably limited. The fundamental psychological mechanisms giving rise to negative expectations, among these, the *nocebo* effect, are receiving information about possible negative effects and having the expectation that they will occur, earlier negative experiences of one's own, and the observation of such effects in other people [9]. Most research on the *nocebo* effect has been focused on the appearance of pain and changes in its intensity among healthy people, mainly because of the ease of controlling painful stimuli and observing the effects of these stimuli with the aid of advanced methods for imaging the central nervous system (CNS). An example of this is an experiment carried out at the beginning of the 1980s, in which a group of student volunteers agreed to participate in a study in which they received simulated electrical stimulation of the CNS, having been warned that a possible side-effect might be the induction of headache. As a result, almost two-thirds of the volunteers reported these adverse effects, even though they did not receive any kind of electrical stimulation [10]. Furthermore, the *nocebo* effect may modify the actions of positive stimuli or cause the occurrence of paradoxical reactions to a given treatment. In one study, healthy participants received nitric oxide, which is widely used in analgesia, while they were exposed to electrical stimulation of their tooth pulp. A proportion of the participants were informed that the application of the nitrous oxide may increase the experience of pain and in this group a significant decrease in pain threshold was observed, together with reported pain that was significantly more intense compared with those subjects who had not received the negative information at the outset [11]. This confirms that verbal information may change the perception of a typically neutral stimulus and generate a reaction that is as strong as that associated with an actual, negative stimulus. Interesting information concerning the potential mechanism for the *nocebo* effect was gained from a study in which volunteers were delivered a painful stimulus, while verbally induced hyperalgesia gave rise to an increase in activity in the hypothalamic-pituitary-adrenal axis (HPA axis), which was demonstrated by monitoring the levels of adrenocorticotrophic hormone and cortisol in blood plasma. Moreover, both hyperalgesia and the activation of the HPA axis were reduced after delivery of an anxiolytic—diazepam—which suggests that anxiety plays a significant role in the activation of the *nocebo* effect. In addition, the same volunteers were given an antagonist to the cholecystokinin receptor, which blocked the hyperalgesia, but did not have any effect on HPA axis activity [12]. This implies that there is a strong connection between anxiety and the occurrence of the *nocebo* effect. It may be that cholecystokinergic (CCK) systems mediate the appearance of the *nocebo* effect, without simultaneously affecting the anxiety component of the reaction. This is confirmed by research based on an animal experimental model in which hyperalgesia is evoked by anxiety. A significant increase in a substance similar to CCK was observed in the microdialysates of the frontal cortex in rats, while the use of a strong CCK receptor antagonist (CI-988) abolished the hyperalgesia [13]. The duration for which negative information continues to shape expectations and still has an influence on triggering the *nocebo* effect appears to be quite long, as demonstrated in the following experiment. Volunteers were subjected to painful heat stimulation on consecutive days. Some of them received a prior warning about the expected increase in the intensity of pain they might experience throughout the experiment. Among these participants, no increases in the intensity of pain were observed, in contrast to those who had not received the negative information and in whom the intensity of pain gradually decreased, as nociceptive habituation occurred over time. Both groups additionally underwent functional imaging of the CNS, which allowed differences in activation in the area of the right parietal operculum to be documented [14]. Brain activity during the *nocebo reaction* has also been assessed with the aid of electroencephalography. Healthy volunteers were subjected to local heat stimulation at one of two intensities: one innocuous and one evoking pain. Following this, an inert cream was applied to the area stimulated and the experiment was repeated, but this time some of the participants (experimental group)

were informed that the cream had the effect of accentuating pain. The *nocebo* effect was observed in the experimental group, and significant differences in the EEG were observed in the strength of alpha-1 waves during heat stimulation, before and after the manipulation [15]. In another study, the role of dopamine in giving rise to the *nocebo* reaction was investigated. Twenty healthy volunteers underwent a standardized evaluation following a pain challenge, before and after the intake of an inert substance, which was presented as having analgesic effects [16]. Changes in dopamine activity and endogenous opioids were monitored during the experiment with the aid of positron emission tomography using radioactively labeled raclopride and carfentanil, as were subjective affective state and expectancies concerning analgesia, using appropriate psychological tests. It was shown that dopamine deactivation occurring in the nucleus accumbens, part of the reward system of the brain, is associated with the *nocebo* effect. This reaction is the reverse of that occurring in the *placebo* effect, during which increases in dopamine activity are associated with a greater analgesic effect. Similar differences are observed in relation to the release of endogenous opioids, which are the main moderators of analgesia in the *placebo* reaction—increases in neurotransmission being associated with the *placebo* effect and decreases, in the case of *nocebo*. These results are indirectly confirmed by an experiment in which the administration of naloxone, an opioid receptor antagonist, did not affect the nocebo reaction [17]. The cholecystokinin-prostaglandin pathway represents another neurochemical system which may be modulated as part of the *nocebo* phenomenon. In an experimental model of headache evoked by hypobaric hypoxia, headache was exacerbated and an increase in prostaglandins was observed in the saliva of study participants who had been informed of the possibility that headache may arise, compared with those participants who did not receive this information (control group) [18]. Potential biological and psychological mechanisms underlying this phenomenon are presented in Fig. 1.

The *nocebo* effect should not be perceived exclusively as a negative reaction to biologically neutral interventions, such as those which occur in *placebo*-controlled experiments conducted in healthy volunteers. The effect can also disrupt the pharmacodynamics of drugs with established clinical effectiveness, which has been observed for example, by researchers who, during the process of infusion of the opiate remifentanil in a group of participants, gave false information to some of the subjects, stating that infusion of the drug had stopped. In this sub-group, no analgesic effects were observed, despite full therapeutic doses of the drug continuing to be applied [19]. Equally, in clinical practice, adverse effects which are in keeping with our knowledge of the pharmacodynamics of the drug are observed, although they are not always connected with the actual mechanism by which the drug takes effect. Informing the patient about the possible adverse effects of taking a particular medication may of itself induce the same effect, irrespective of the pharmacological properties of the medication [20].

It is possible that the immune system may also be involved in mediating the *nocebo* effect, as changes in its activity, associated with the phenomenon, have been observed in numerous studies. In one of them, a neutral stimulus (a blue liquid) was administered in association with an allergen, Japanese ivy, which elicited eczema in those study participants who were allergic to it. After some time, the blue liquid alone, without the active substance, was sufficient to induce an increase in the immunological reaction [21].

The occurrence of the *nocebo* effect may interfere with the results of clinical research, since a significant proportion of patients from the control group, receiving a *placebo*, often report undesirable effects, which are in keeping with the toxicity profile of the drugs under investigation. Confirmation of this may be found by reviewing the adverse effects reported in randomized clinical trials of anti-migraine drugs. A high proportion of complications has been observed among sufferers receiving placebo treatment, almost identical to the levels found in those receiving the medication being tested [7]. Further evidence comes from a meta-analysis of randomized clinical trials for anti-depressive medication, which demonstrated significantly greater tolerance for preparations from the group of selective serotonin reuptake inhibitors than for tricyclic antidepressants. Interestingly, identical differences in tolerance levels to drugs were also found for those patients receiving *placebo* treatment [22]. The association between the undesirable effects reported among the group of patients receiving *placebo* and the known adverse effects of the drug being tested suggests that the *nocebo* effect arises at the point at which the patient gives informed consent to participate in the treatment. Information concerning the possible harmful effects of treatment elicits negative expectations in the patient, which may affect the frequency of reported undesirable effects and, as a consequence, influence the results of the research. Moreover, recent analyses suggest that, of the adverse effects reported by patients participating in randomized clinical trials, only 20–30% result from the action of the drug being tested [23]. A clear clinical example of the influence of the *nocebo* effect in treatment is the frequent occurrence of muscular symptoms among patients receiving statins for cardiovascular conditions, and this is the most common reason for cessation of treatment with these drugs. The majority of studies have not reported any significant differences in the frequency of occurrence of these symptoms in patients treated with the active pharmaceutical preparation and those receiving placebo treatment [24]. Significant differences have only been observed in non-blind studies [25]. Population statistics from Denmark and the UK suggest that the increase in the number of patients who have ceased treatment with these preparations because of the adverse complications reported may be the result of

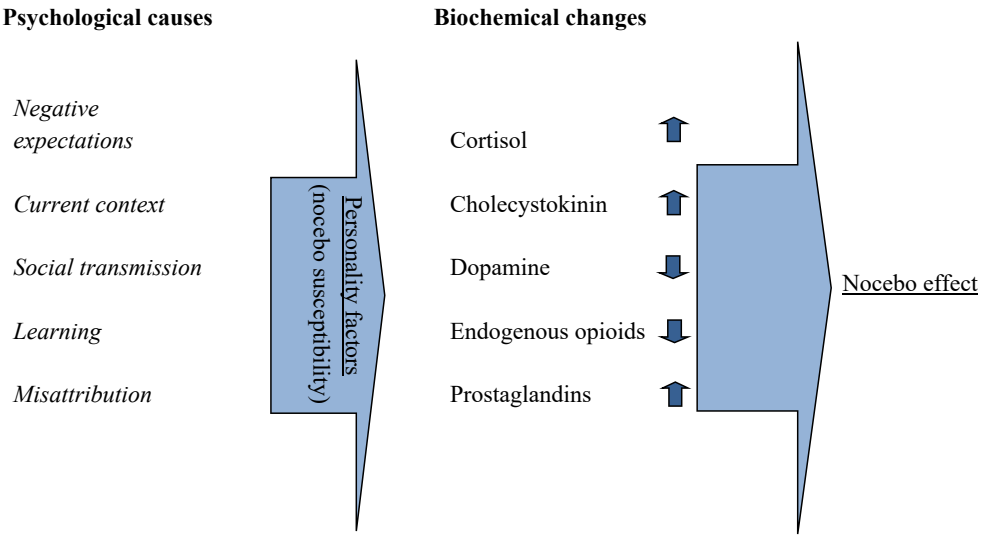

Fig. 1 Process for the development of the *nocebo effect*. Psychological mechanisms and their influence on biochemical changes in the CNS

negative media reports on the subject of statins. Significantly, this appears to have increased the risk of myocardial infarction and deaths due to cardiac failure [26, 27]. Similar findings come from an observation of the frequency with which information about the HPV vaccine (Gardasil) was the subject of internet searches and the correlation with the frequency of adverse reactions reported to the preparation [28].

These examples, however, concern retrospective analyses. Experiments have also been designed, whose aim has been to provide a prospective assessment of the association between providing detailed information to patients and the frequency with which undesirable events are recorded. In one of them, a group of patients with mild hypertrophy of the prostate gland, treated with finasteride, were told about the possibility of sexual dysfunctions as a result of treatment, while this information was not given to another matched group of patients. During a period of observation covering several months, sexual problems were reported in the experimental group (the group that had received the information) at a rate almost three times higher than that observed in the control group [29]. In another study, men treated with atenolol (β-blocker) reported erectile problems twice as frequently if they had been informed of the possible consequences before the onset of treatment, as compared with a situation in which this information was not given. The nocebo effect can also change the physiology of a healthy organism, as evidenced by the following experiment. Healthy volunteers with a mutation of the CREB1 gene, which is associated with diminished tolerance for aerobic exercise, as well as compromised cardiovascular capacity and increased body temperature during such exercise, were compared with volunteers with a protective genotype. Participants were assigned to one of three groups: those with a high, medium, or low risk/protective genotype. Within each group, participants were randomly divided into those who were informed of having a high-risk genotype and those who were told they had a low risk/protective genotype, irrespective of their actual genetic risk. They were all fully informed about the consequences of having a particular risk profile. The volunteers were twice subjected to controlled physical exercise: before being informed of their genetic profile and a week later, when they received this information before exercising. During the physical exercise, the following objective parameters were measured: the CO2:O2 exchange rate and the ventilatory flow rate, as well as subjective parameters such as the perceived heat and subjective experience of perceived exertion. The results of the experiment indicated that those who had received information about having a protective genotype exercised for longer and delayed reporting that they felt "hot" compared with baseline, while those informed of having a high-risk genotype did not differ on either of these parameters from baseline. Hence, the information received about genetic risk resulted in changes in cardiac and respiratory physiology, perceived exertion, and endurance during physical exercise, and the impact of perceived risk on perceived exertion was greater than that of the actual genetic risk [30].

Oncological treatment is universally associated with significant burden and the occurrence of a large number of adverse reactions. This frequently occurring profile of negative expectations may be a cofactor in determining the occurrence of real complications in the *nocebo* mechanism. In a prospective study which included over 100 patients receiving surgical treatment for hormone-sensitive breast cancer, the association between expectations concerning a supplementary course of hormone therapy and the occurrence of undesirable side effects was examined. High levels of negative expectations before treatment significantly correlated with the occurrence of complications as assessed in the third month and second year

of therapy and were, in addition, associated with lower levels of compliance with medical recommendations [31]. A meta-analysis of 14 studies of patients with malignant tumors receiving chemotherapy demonstrated a significant association between the expectation of adverse effects such as pain, fatigue, nausea, and vomiting, and actually experiencing them [32]. Moreover, patients with advanced neoplastic disease may experience a range of symptoms and often require supportive treatment, which paradoxically may have a deleterious effect on their quality of life, resulting in a *nocebo* effect. Conclusions of this kind can be drawn on the basis of results of a combined analysis of two randomized clinical trials of drugs used to reduce the symptoms of cancer-associated fatigue syndrome (CRF). Only subjects receiving *placebo* were included in the analysis. The occurrence of the *nocebo* effect, defined as the presentation of at least two adverse side effects, was observed in 71% of patients. It is also worth adding that patients who were initially in a worse overall condition were more likely to report side effects, and the occurrence of a specific symptom before treatment (e.g., insomnia, dizziness) correlated with a greater likelihood that such symptoms would be more frequently reported as a complication of the drug [16]. The tendency to report nocebo effects does not depend on age, a finding confirmed by the joint analysis of clinical trials on two anticancer drugs, in which there were no differences in the nocebo effect in control groups among patients over 65 years of age compared with younger patients [33].

The *nocebo* effect has also been observed among patients in whom a change in treatment occurred, from the original drug to a chemically equivalent generic drug [34, 35]. A separate clinical problem lies in the clearly evident occurrence of this phenomenon in patients receiving biological therapies at the time of changing to a biologically similar product, which nonetheless is not chemically identical in every respect to the original drug. In patients with rheumatoid arthritis receiving treatment with CT-P13, which is biosimilar to infliximab, used in the treatment of this condition, in around 16–28% of patients treatment with the biosimilar preparation ceased within three months of starting treatment. In comparison with historical data, this proportion was significantly higher than that in cases of treatment with the original drug, despite there being no evidence of any differences in the actual effectiveness, immunogenicity, and safety of treatment. These discrepancies were explained mainly in terms of the way in which the effectiveness of the treatment was perceived and the occurrence of side effects such as general lethargy, fatigue, and headaches [36].

More recently, investigations have focused on assessing the possibility of interventions which might reduce the frequency of occurrence of the *nocebo* effect. A very interesting option was proposed in a German study to which patients about to start adjunctive hormonal therapy for breast cancer were recruited. Patients were assigned to one of three groups. Patients in the first group received standardized medical care. Those in the second group received cognitive-behavioral training in order to prevent the undesirable effects of treatment, while the third group received a neutral psychological intervention in order to control for any non-specific effects of contact with the psychologist. The cognitive-behavioral training consisted of three therapeutic sessions and three "top-up" sessions during which the patients received education and were encouraged to visualize the positive effects of therapy, relaxation training, etc. The central outcome measure in this study was the number of negative side effects of the hormonal therapy reported in each of the three groups, with the expectation that the group receiving cognitive-behavioral training would report the fewest. In addition, assessment included a quality of life measure, the patients' capacity to cope with stress, and the degree to which they complied with medical advice. The results of the study will be available in 2020 [37].

2 Psychological mechanisms of nocebo

Two fundamental psychological mechanisms have been invoked to explain nocebo effects. These include learning and negative expectancies in relation to treatment; the former is underpinned by a behavioral mechanism and is usually unconscious, and the latter is essentially cognitive in nature, relating to the person's thinking and beliefs, of which they are aware. Many of the factors that have been consistently associated with nocebo responding can be attributed to these basic mechanisms, which need not be mutually exclusive because both can play a role in its emergence under different circumstances [38, 39]. These include personality factors, in particular pessimism [40], an unsatisfactory relationship with the care provider [41], heightened awareness of somatosensory stimulation [42, 43], previous and current experience of symptoms [44], anxiety [45], and depression [46, 47].

The learning explanation for the occurrence of nocebo effects is in terms of associative learning, otherwise known as Pavlovian or classical conditioning. As the result of previous experience, in which a noxious event occurred simultaneously alongside a neutral one, an association is formed and with repeated exposure; the neutral event itself is sufficient to elicit an adverse reaction similar to that consequent upon the noxious stimulus. There are many examples of this effect reported in the literature, both in experimental and clinical settings. For example, the treatment setting itself may become a conditioned stimulus, having previously been the scene in which a specific form of therapy (unconditioned stimulus) was administered, giving rise to specific treatment response (unconditioned response). The association of the therapeutic procedure with the environment in which it took place eventually leads to the environment itself (conditioned stimulus) being

sufficient to elicit the treatment response (conditioned response) [48]. Thus, classical conditioning is held to account for the phenomenon of anticipatory nausea which is commonly seen among patients receiving chemotherapy in oncology clinics. The mere sight, smell, taste, or other reminder of something they associate with their treatment, such as the clinic personnel or physical surroundings, is sufficient to give rise to the unpleasant side effects, which commonly occur as a result of chemotherapy [49, 50]. Moreover, if the adverse reaction is particularly unpleasant, such as severe headache, nausea, or vomiting, then fewer exposures to the association between the noxious and neutral stimuli are necessary to induce the adverse reaction in the form of a nocebo response [51]. The number of conditioning sessions though is strongly related to the persistence of both placebo and nocebo responses, with greater levels of exposure increasing the resistance to extinction of the ensuing nocebo response [4]. Conditioning effects may also be generalized, so that patients who have experienced side effects to drugs in the past are more likely to manifest them to medication that they have not previously been prescribed [52]. Furthermore, a previous history of adverse drug reactions also makes it more likely that similar responses will occur to the administration of inert substances [53]. A controlled study using a sample of healthy controls in which both active treatment and the use of a neutral substance were combined demonstrated that the learning effect driving the nocebo reaction can be generalized. Participants initially received 50 mg of amitriptyline for four days after which the antidepressant was substituted with an inert pill, and this also provoked the side effects specific to amitriptyline [54]. Since negative side effects cannot be related to the pharmacokinetics of new or inert treatments, it is most likely that they arise from the generalized effects of learning, leading to the nocebo response. The nocebo response may be widespread, since those patients whose previous responses to treatment become generalized are at greater risk of experiencing undesirable side effects in future treatments, even if the new drugs have pharmacological actions unrelated to those used in the past [8].

Social learning processes such as observational learning (otherwise known as modeling) also appear to be an important mechanism leading to nocebo responding. While this kind of learning depends on social exchange rather than firsthand experiential learning, observing that another person becomes ill as a result of a particular treatment or exposure to such information either personally or through the news and social media is a powerful way of generating nocebo effects in observers [35, 55]. An example of this comes from a video study in which participants observed a model who displayed a heightened pressure pain response with prior application of an ointment than without. The resultant nocebo hyperalgesia reported by the observers is a socially induced response [56, 57]. Indeed, such interactions appear to be even more potent than warnings from doctors about the potentially negative side effects of specific treatments [56]. In addition, however, the application of the ointment, whether or not it had been modeled as exacerbating pain, was found to increase pain ratings, a finding that cannot be attributed to observational learning alone [57]. A possible interpretation is that expectations concerning the ointment may have been triggered by its mere application, in keeping with the general belief that ointments are used for the relief of pain, so "this is going to be painful." The laboratory context (white coats, gloves, medical supplies) may also have given rise to expectations that something unpleasant was about to happen. A familiar example of this is the phenomenon of white coat hypertension, in which a patient's blood pressure is raised above the normal range in a clinical setting, but not elsewhere. This is attributed to anxiety having been conditioned as the result of previous clinical experiences. The effect is higher with doctors than that with nurses [58], and these effects are greater for women and with increasing age and in cognitively compromised states such as dementia [59]. Similarly, generalized expectations arising from previous conditioning have been shown to affect reactions to different colored pills. A popular perception is that blue and green tablets have sedative effects, while red, yellow, and orange tablets are stimulants [60]. In keeping with these expectations, volunteers taking blue placebos reported being less alert and more drowsy than those taking pink ones [61].

Expectations themselves may be shaped by previous learning in the form of classical and social conditioning. An example of the former is the white coat hypertension effect referred to above [58], while a demonstration of the latter comes from the previously described study, concerning the potential hazards of developing hypoxia-induced headache under hypobaric conditions [18]. This demonstrated that just one participant who had been informed of the risks was the source of information for the other participants who developed negative expectations and the majority of whom subsequently developed headache. This proportion was significantly higher than that for the control group in whom the negative expectations had not been raised. In the experimental group, the greater the number of social contacts, the more likely that the nocebo response was generated.

However, unconscious conditioning mechanisms alone are insufficient to explain nocebo effects, as they are known to vary widely among individuals in both experimental and clinical studies. Moreover, the associational learning effects should, in theory, extinguish over a period of time after cessation of treatment (e.g., chemotherapy), as it is unlikely that the pairing of the noxious and neutral events are sustained indefinitely. However, as mentioned above, nocebo effects appear particularly resistant to extinction [4, 51] and so questions arise as to how they are maintained. Stronger conditioning occurs when particularly averse responses are generated and this is usually in the context of unpleasant stimuli (e.g.,

odors), but may also be evoked by anxiety-provoking thoughts or mental images (e.g., being stuck in an elevator) [51]. Thus, pre-existing expectations about a stimulus may be activated from previously established mindsets or cognitive schema which help to intensify the effects of conditioning [62] and maintain conditioned responses in the form of nocebo reactions. Support for this idea was provided by a meta-analysis showing that nocebo effects were largest when they were induced by a combination of conditioning and expectations [63].

Both conditioning and cognitive factors are thus believed to be involved in placebo and nocebo responses; the former being associated with unconscious physiological functions such as hormone secretion, and the latter with conscious physiological processes such as pain and motor performance [64]. Expectations represent characteristic patterns of thinking and processing information which arise from cognitive schema (underlying mental structures) and may be biased as a result of previous experience and hence become dysfunctional for the patient. These specific beliefs or expectations, especially negative ones, have been implicated in the nocebo response [3, 65] in the form of increasing awareness and reporting of adverse outcomes. Negative expectations can be raised by external sources, such as verbal warnings from doctors and others [66, 67], written information [68], or cultural beliefs [3]. As mentioned above, it has been observed that simply informing people about the possible side effects of treatment increases the likelihood that they will develop them, as negative expectations focus attention on monitoring bodily sensations and increase the tendency to interpret any changes catastrophically and attribute them to the intervention [52]. For example, manipulating expectations in patients following surgery by informing them that an injection of saline would increase their experience of pain resulted in reports of significantly more pain than in patients who received the same injection through an intravenous line but were unaware that it had been administered [17].

Cognitive factors determining expectancies include both perceptual and response biases, as well as systematic biases in the way in which information is interpreted. Perceptual biases refer to the way in which, as humans, our perceptions are not necessarily accurate reflections of the world but are filtered through prior expectancies that are based on our knowledge of the environment [69]. For example, widely held convictions about the harmful effects of some drugs may be sufficient to generate nocebo effects. Some 10% of hospitalized patients report an allergy to penicillin, but it has been shown that 97% of those declared "penicillin allergic" in one study did not actually demonstrate any adverse reactions to oral penicillin [52]. Perceptual biases which create negative expectations may focus attention on internal sensations, heightening awareness of them and resulting in their identification and confirmation as expected side effects [35, 70]. Similarly, perceived sensitivity to medicines may result from excessive monitoring of internal body state resulting from pre-established expectancies [71].

Response biases result from assumptions about the consequences of human behavior, and in order to serve damage limitation purposes, may have been tuned to respond to a false alarm, rather than to miss a signal for potential danger [69]. Thus, a response bias may be responsible for greater symptom reporting, as when expectations lower the criterion for labeling an experience as painful without actually altering the recipient's pain threshold and therefore their experience of pain [72]. Other examples include situations in which patients' preoperative expectations are associated with acute post-surgical pain and post-surgery quality of life [73]. Moreover, negative expectations can change the perceived action of drugs, as in the study referred to above concerning the opioid remifentanil, where false information, warning of its hyperalgesic effects, abolished the analgesic effect of the drug [19].

Whether such expectancies arise or not is somewhat variable, and individual differences in responsiveness as seen in nocebo effects might suggest that personality variables have a role to play in generating the response. Little is known about whether stable (trait) variables or situation-specific (state) variables have a more significant role, but there is no reason to believe that one or the other is more or less likely to be implicated. The personality trait most frequently reported as influencing expectancy is optimism (or as regards nocebo, its opposite state, pessimism), defined as a generalized and relatively stable expectancy regarding positive or negative future outcomes [40, 74–80].

State personality variables are derived from the psychosocial context in which the patient finds her/himself and include environmental clues, the nature of the relationship with the healthcare provider, information provided verbally and in written form (pamphlets regarding medication and treatment), availability of support from others, and a host of other contextual factors which may affect the patient's state of mind at a particular time during the receipt of healthcare. These factors may temporarily evoke a negative mindset in the patient which is situationally dependent. For example, if aspects of the doctor-patient relationship are unsatisfactory, affecting the patient's mood and generating anger and resentment or feelings of helplessness, the likelihood of the nocebo response may be increased [52]. So situational factors of the kind described may evoke responses that are typical for the individual when under pressure and these may be of a kind more likely to elicit a nocebo response.

A recent review, however, concluded that dispositional factors of this kind are somewhat inconclusive in their ability to predict nocebo effects [34]. Other factors such as female gender [53] have proven equally elusive, but together with measures allegedly indicative of nocebo responding, such as the number of symptoms at baseline

[44], previous symptom experience [81], modern health worries [82–84], anxiety [12, 45, 71, 76], and depression [46, 47], may reflect attitudes and beliefs, supporting a cognitive explanation of the nocebo phenomenon. Indeed, where females appear more susceptible to modeling nocebo effects than males, variations in levels of empathy (which is conceptualized in terms of both affective and cognitive components) seem to underlie the difference [85]. This has been confirmed by a study demonstrating that baseline levels of empathy predict increases in side effects as a result of social modeling [86]. Patients with fears surrounding previous illness experience and modern health worries including negative beliefs about medication appear more likely to misattribute symptoms to medications and hence decide to terminate treatment [87]. Fears of this kind are supported by negative medicine-related *beliefs*, which influence not only the use of treatment, but also the extent to which side effects are reported [88]. These beliefs include expectancies concerning the need to use medicines and the potential harm of doing so, perceptions of one's own sensitivity to medicines, concerns about the safety and effectiveness of generic drugs, and more general worries about the way in which aspects of modern life (e.g., radiation from mobile phones, food additives, environmental pollution) may be detrimental to health. Such beliefs serve to fuel *expectations* that the allegedly "toxic" exposure is likely to produce adverse side effects [35] and this mechanism is considered to play a substantial role in the creation of nocebo effects [34]. Finally, people who are anxious or depressed are more likely to have negative thinking patterns arising from underlying cognitive schema characteristic of the disorders. Cognitive schemas (mindsets) are stable and enduring patterns of thinking, which exist in the form of memories, emotions, cognitions, and bodily sensations giving rise to beliefs about oneself and the world. These core beliefs arise during childhood and may be distorted by negative, noxious, or traumatic experiences; they are reinforced and remain stable throughout life. They are problematic in that they predispose individuals to the development and maintenance of psychological disorders [89]. It is not difficult to see how such negative thinking patterns could shape the expectancies giving rise to nocebo effects. A promising line of investigation therefore is the use of a cognitive-behavioral therapy approach aimed at modifying dysfunctional thinking styles in order to remediate nocebo effects, as described above [37].

From a more experimental perspective, an interesting line of enquiry lies in the prediction that in people with a limited ability to form expectations as a result of impairment to the prefrontal lobes, such as that what frequently occurs in Alzheimer's disease, the placebo/nocebo effect should be diminished, if not entirely abolished. This is a reasonable assumption to make as expectations are known to modulate activity in the frontal cortex [90]. Evidence from a study of patients with impaired cognition as shown by reduced scores on a series of neuropsychological tests assessing frontal lobe function demonstrated that the effect of placebo on pain was reduced in these patients and loss of these placebo-related mechanisms reduced treatment efficacy such that a higher dose of the real drug was necessary in order to produce adequate analgesic effects. These findings demonstrate the role of cognition in contributing to the therapeutic outcome [91]. In an analogous fashion, it might be expected that nocebo effects should equally be reduced, but this does not appear to be the case [92], suggesting perhaps that negative expectations are at least partially mediated by different mechanisms. There may be reasons to support this proposition. The placebo component of analgesic therapy has been found to correlate with both cognitive status and functional connectivity among different brain regions such that reduced connectivity predicted

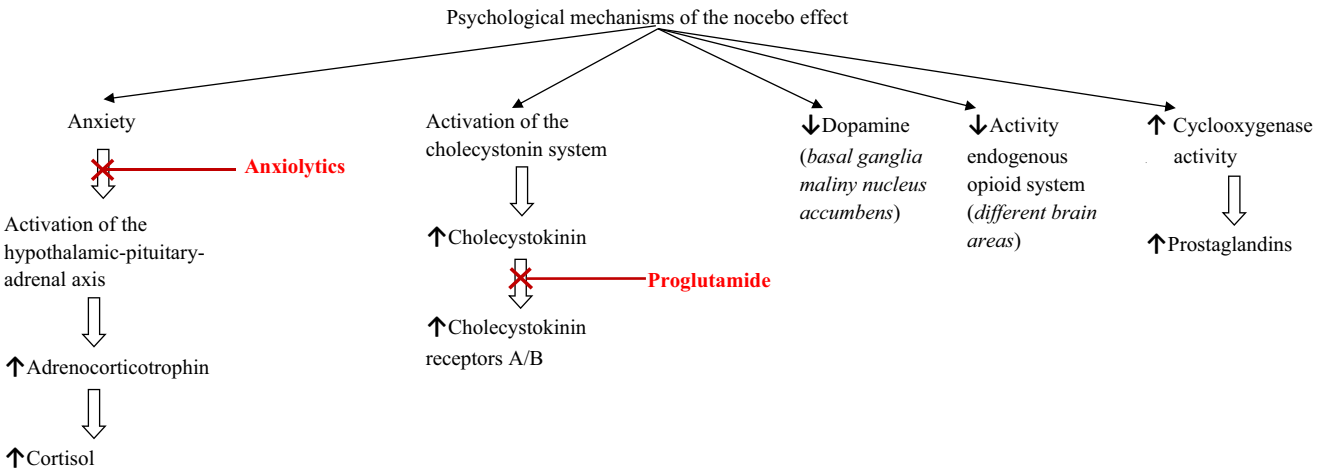

Fig. 2 Changes in the activity of biochemical systems participating in the nocebo effect. Points for possible intervention (marked in red) with substances known to reduce the phenomenon

impaired cognition [91] and this may be enough to disrupt the positive expectancies mediating the placebo effect, leading to its reduction. Although cognitive deficits would equally be expected to temper the effects of negative expectations, nocebo effects actually appear to be heightened in patients with Alzheimer's disease and other neurological disorders [92]. A plausible explanation may be that in the context of the confusion and general disorientation arising against a background of cognitive loss, patients are likely to feel threatened and anxious. As described above [12, 45], anxiety and anticipation are known to exacerbate the pain/nocebo experience; these effects being reflected in increased activity within the parahippocampal, entorhinal, and brainstem network [93]. Fewer investigations have been carried out into nocebo effects compared with placebo, but the significant role of cholecystokinin in nocebo hyperalgesia is thought to depend on its anxiogenic effects in the CNS [17]. Evidence from an fMRI study has shown that nocebo effects are mediated by the hippocampus and regions involved with anticipatory anxiety, while those activated in association with placebo effects are quite distinct, involving a frontal-limbic-brainstem network [93]. The mechanism by which negative expectations or anxiety activate the cholecystokinin system to generate nocebo effects is, as yet, unknown. However, it is clear that nocebo effects may be generated and modulated by both cognitive and affective mechanisms.

3 Summary

An increase in the occurrence of adverse side effects reported by patients who appear to be connected with the *nocebo* effect may lead to the diminished effectiveness of treatment and, as a result, give rise to premature decisions regarding the modification of treatment or to its complete withdrawal. While our understanding of the nocebo effect is still in its infancy, a number of preliminary conclusions may be drawn from our current understanding of the research, in order to limit its undesirable consequences for clinical practice. The first of these is recognizing that certain types of patients, as well as specific situations, may be particularly susceptible to the *nocebo* effect. These include people with dementia, those with anxious or pessimistic personality traits, and those with so-called type A personality, which is characterized by high levels of stress and the drive for achievement, in the form of competitiveness, aggression, and hostility [94]. Situations leading to greater vulnerability include contexts associated with particularly aversive reactions (e.g., chemotherapy, pain) and unsatisfactory doctor-patient relationships. Secondly, measurable results in attempting to minimalize the nocebo effect in the context of pharmacological treatment may be achieved by integrating patients' beliefs and expectations into drug treatment regimes in order to optimize treatment outcomes. This could be achieved by avoiding the provision of informed consent to treatment by focusing excessively on adverse effects and re-establishing focus on positive treatment effects, strengthening the patient's sense of control over the decision-making process, modifying dysfunctional beliefs about treatment, and bearing in mind that empathic and supportive communication with the patient is the cornerstone of such action [95]. There are also sporadic data on the possibility of manipulating the reduction of the nocebo effect using a latent inhibition mechanism [96]. Latent inhibition refers to the observation in classical conditioning that a familiar stimulus takes longer to acquire the characteristics of a conditioned stimulus than an entirely new one. Thus, pre-exposure to neutral cues likely to be conditioned in clinical settings may help to reduce aversive reactions by means of a latent inhibition effect. It is equally important to understand the biochemical mechanism of the *nocebo* phenomenon; however, the data in this regard are scarce (Fig. 2). An attempt to simply translate the better-understood processes that occur during a placebo reaction to *nocebo* seems excessively simplistic, because the same person can experience the *nocebo* effect while simultaneously benefiting from the *placebo*. Furthermore, *nocebo* effects can be interpreted as an indication of the strong action of the drug, strengthening the *placebo* effect [97, 98].

Finally, due to the wide impact of the *nocebo* effect on the effectiveness of treatment, the quality of life of patients, the results of clinical trials, etc., as described above, it is necessary to increase awareness of this phenomenon among clinicians as well as those designing and conducting clinical trials. The possibilities for its further reduction or elimination require continuation of both basic and clinical research.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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