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The nocebo effect of drugs

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Abstract

While the placebo effect has been studied for a long time, much less is known about its negative counterpart, named the nocebo effect. However, it may be of particular importance because of its impact on the treatment outcomes and public health. We conducted a review on the nocebo effect using PubMed and other databases up to July 2014. The nocebo effect refers by definition to the induction or the worsening of symptoms induced by sham or active therapies. Examples are numerous and concerns both clinical trials and daily practice. The underlying mechanisms are, on one hand, psychological (conditioning and negative expectations) and, on the other hand, neurobiological (role of cholecystokinin, endogenous opioids and dopamine). Nocebo effects can modulate the outcome of a given therapy in a negative way, as do placebo effects in a positive way. The verbal and nonverbal communications of physicians contain numerous unintentional negative suggestions that may trigger a nocebo response. This raises the important issue of how physicians can at the same time obtain informed consent and minimize nocebo-related risks. Every physician has to deal with this apparent contradiction between *primum non nocere* and to deliver truthful information about risks. Meticulous identification of patients at risk, information techniques such as positive framing, contextualized informed consent, and even noninformation, is valuable.

Abbreviations

ACC, anterior cingulate cortex; CCK, cholecystokinin; fMRI, functional magnetic resonance imaging; HPA, hypothalamic–pituitary–adrenal axis; PAG, periaqueductal gray; SPC, summary of product characteristic.

Introduction

Any pharmacological or nonpharmacological treatment has two components, one related to the specific effects of the treatment itself and the other, nonspecific, related to the perception that the therapy is being administered (Colloca and Benedetti 2005). The nonspecific effects of a treatment are called placebo effects when they are beneficial and nocebo effects when they are harmful (Häuser et al. 2012a).

As a positive psychosocial context may induce a placebo effect, a negative context, including information about adverse effects, may lead to opposite expectations and outcomes, called the nocebo effect (Colloca and Miller 2011a).

Compared to the placebo effect, much less is known about the nocebo effect, since clinical trials investigating the nocebo effect are generally considered unethical because they trigger negative outcomes and do not provide any benefit to the patient (Enck et al. 2008).

However, some recent studies on healthy volunteers and some others on animals have shed new light on this phenomenon (Benedetti et al. 2007). The nocebo effect increasingly interests the scientific community because of its particular importance in treatment compliance and therefore treatment outcome. This obviously has consequences at the individual level, but this is also important to understand because it can have consequences in terms of public health and health costs and influence the results of clinical trials. This is a problem that should be taken into account by the health authorities.

This review aims to describe the current knowledge on the nocebo effect, the mechanisms involved, the

implications in clinical practice, and the perspectives related to the ethical issues it raises. It also takes stock of the various ideas proposed to prevent the occurrence of nocebo effect in patients, and one the other hand manage if it occurs.

Methods

We conducted a review of articles relevant to the nature, mechanisms, medical management, and ethical issues of nocebo effect.

The PubMed, Pascal, Embase, Web of Science, and International Pharmaceutical Abstract databases were searched for English and French language articles published from 2003 to July 2014, using the following terms: "nocebo," "nocebo effect," and "nocebo effects."

The search was extended by a manual search of the references cited in pertinent recent articles and reviews. Articles were screened for relevance based on the title, abstracts, and keywords.

Eighty-six articles were selected and reviewed. Among them, 23 relate concrete examples of nocebo effect, 34 are about the mechanisms of the nocebo effect, 11 about the implications of nocebo effect, and 6 are considering solutions to manage it.

Results

Definition

Already in the V–IV century BC Hippocrates said that patients should not be harmed. This was later synthesized in the famous Latin phrase *primum non nocere* ("first do no harm") (Conti 2010).

The term "nocebo" derives from the verb *nocere* ("I shall harm"). Furthermore, this effect was empirically used in witchcraft and voodoo activities (Edwards et al. 2010).

This term was recently introduced in medicine by Walter P. Kennedy in 1961 to designate noxious effects produced by a placebo (Kennedy 1961). These included effects resulting from the true nocebo effect, from the natural evolution of the disease, or due to mere coincidence.

Later, the nocebo effect was considered as the nonspecific negative symptoms occurring in clinical trials with both placebo and the active drug. Nonspecific adverse effects are generally nonserious symptoms that are idiosyncratic, not clearly attributable to the pharmacological action of the drug involved, and not dose dependent. These types of symptoms include difficulty in concentrating, drowsiness, nausea, dizziness, fatigue, headache, and insomnia (Wells and Kaptchuk 2012).

Now, the nocebo effect refers to the symptoms related to the patient's negative expectations not only in a clinical trial setting, but also in a routine care setting (Benedetti and Amanzio 2011). This can mean new and worsening symptoms that are caused by negative verbal and nonverbal communications on the part of the treating person, without any (sham) treatment (Häuser et al. 2012a).

Hahn (1997a) has distinguished two forms:

- a specific form: subjects expect a particular negative outcome and it occurs.
- a generic form: subjects have vague negative expectations and bad things happen. Negative outcomes might be different from those expected.

Consequently, the nocebo effect can lead to distrust in healthcare professionals or lack of confidence in a treatment (Teixeira et al. 2010).

Examples

Table 1 presents some examples of nocebo effects described in the literature in various fields. The largest number of available studies concerns the fields of pain and drug side effects.

Negative treatment expectations may reduce also drug effectiveness. In a recent study of the opioid analgesic remifentanil, expectations of a positive treatment outcome doubled the analgesic effect of the drug, while expectations of a negative outcome eliminated the analgesic effect (Bingel et al. 2011).

An interesting hypothesis is made by Meynen and Swaab (2011): in psychiatry, involuntary treatments are often used. But patient expectations in settings of involuntary medication tend to be less positive than in voluntary settings. As a consequence, placebo effects are likely to be diminished in coercive treatment, while nocebo effects are probably increased. This may result in an overall decreased effectiveness of medication in coercive settings.

Mechanisms

Nocebo effects are a result of the complex interactions between the patient, his surrounding general psychosocial context, the healthcare provider, and the way the information is delivered and received (Colloca and Miller 2011b).

Patient-related factors

Sex

Nocebo seems to be stronger in women than in men: women demonstrated more nocebo nausea after a condi-

Table 1. Examples of nocebo effect described in the literature.

Area of study	Method/effect	Conclusion	Reference
Pain: migraine and tension-type headache	Meta-analysis of reported side effects after placebo treatment in headaches Frequency of nocebo in migraine treatment, migraine prevention, and tension-type headache prevention was 18.5%, 42.8%, and 23.9%, and dropout frequency was 0.3%, 4.8%, and 5.4%, respectively	Nocebo is prevalent in clinical trials for primary headaches, particularly in preventive treatment studies. Dropouts due to nocebo effect may confound the interpretation of many clinical trials	Mitsikostas et al. (2011)
Pain: neuropathic pain	Meta-analysis of the frequency of nocebo responses in clinical trials of pharmacological treatments for neuropathic pain Nocebo responses were 52.0% and nocebo severity (dropout due to drug-related adverse events) was 6.0%	A strong nocebo effect may be adversely affecting adherence and efficacy of current treatments for neuropathic pain in clinical practice	Papadopoulos and Mitsikostas (2012)
Pain	Analysis of the database ClinicalTrials.gov about interventional trials in various kind of pain Withdrawals due to adverse effect in the placebo arm were 8.0% in fibromyalgia trials, 5.0% in neuropathic pain trials, and 0.5% in migraine trials	Migraine studies had the lowest withdrawal rate. Perhaps subjects who are experiencing pain relief are more tolerant of the adverse events. On the contrary fibromyalgia subjects showed a low placebo response and a high frequency of nocebo effect	Cepeda et al. (2013)
Pain: fibromyalgia/DPN	Systematic review of the adverse events in drug trials in fibromyalgia and diabetic peripheral neuropathy (DPN) Dropout rate due to adverse events in placebo groups was 9.6% in fibromyalgia trials and 5.8% in diabetic peripheral neuropathy trials	Nocebo effects substantially accounted for adverse events in drug trials of fibromyalgia and diabetic peripheral neuropathy. Strategies to minimize nocebo effects in clinical trials should be developed	Häuser et al. (2012b)
Pain	Randomized study about pain in women at term gestation requesting labor epidural analgesia Women informed to expect pain comparable to a bee sting during the injection (nocebo group) scored pain higher than those receiving the procedure along with gentle positive words	The positive framing for the description of the procedure induced significantly lower pain compared with neutral information deprived of positive words and encouragement	Varelmann et al. (2010)
Pain	Analysis of the effects of positive and negative expectations on rectal pain perception, rectal pain thresholds, state anxiety, and cortisol responses Whereas perceived pain intensity was significantly decreased in the placebo group, the nocebo group revealed significantly increased pain intensity ratings, along with significantly greater anticipatory anxiety on the test day	The experience of abdominal pain can be experimentally increased or decreased by inducing positive or negative expectations. Nocebo effects involve a psychological stress response, characterized by increased anticipatory anxiety	Elsenbruch et al. (2012)
Drug: vaccines	Analysis of Sanofi Pasteur pharmacovigilance database on nonlive vaccines • Signal of trismus and pain jaw with tetanus vaccine • Signal of breast and genital adverse effects with HVP vaccine • Signal of hepatobiliary disorders and hepatitis B vaccine	Patients and healthcare professionals tend to preferentially report the symptoms of the disease or symptoms of the organs affected by the disease. This bias could generate false safety signals	Okaïs et al. (2011)

Table 1. Continued.

Area of study	Method/effect	Conclusion	Reference
Drug: allergology	Oral challenge with alternative drugs with different chemical structure (to exclude any cross-reaction) in patients who probably presented initially a nonallergic reaction • 27% presented a new reaction (subjective symptoms) • 1/3 of them presented identical symptoms	Oral provocation test can be biased by the nocebo effect Frequency comparable to the frequency of the placebo effect	Liccardi et al. (2004)
Drug: generic substitution	Review about patients' adherence to generic substitution and the extent of the nocebo effect 36.7% of all patients consider that inexpensive products are inferior to or different from the brandname drugs. 13.2% of patients who already had experience with a generic substitute reported adverse effects that had not been observed with the brand drug	Generic drugs may be associated with more side effects because of negative expectations. The general public and medical practitioners alike often hold negative views of generic medicines	Weissenfeld et al. (2010), Faasse and Petrie (2013)
Drug: information	120 patients were randomized to receive finasteride Blinded administration of finasteride was associated with a significantly higher proportion of sexual dysfunction in patients informed on sexual side effects (43.6%) as compared to those in which the same information was omitted (15.3%)	The physician relationship with his or her patients is fundamental for an excellent result in terms of a low incidence of sexual side effects	Mondaini et al. (2007)
Other: lactose intolerance	Realization of a sham breath test to patients reporting symptoms of lactose intolerance in spite of a negative H2 breath test With a sham breath test, 44% of patients report abdominal symptoms	Symptoms reported by patients during a negative breath test cannot be attributed to a false-negative test. Nocebo effect is likely implicated	Vernia et al. (2010)
Other: acupuncture	Randomized controlled trial comparing sham acupuncture and placebo pills in arm pain 25% patients reported one or more adverse events with sham acupuncture that mirrored the disclosure information specific to needling technique	Adverse events and nocebo effects are linked to the information provided to patients	Kaptchuk (2006)
Other: cardiovascular disease	The Framingham Heart Study regarded 45- to 64-year-old female participants. Women subjectively believing to be likely to have heart attacks actually had a 3.7 times higher probability of dying because of coronary disease than women not considering themselves prone to cardiovascular pathology	Negative expectations can really have an impact on morbidity	Voelker (1996)
Other: posttraumatic stress disorder	Meta-analysis of studies concerning critical incident stress debriefing In the acute period following an intense trauma, physiological arousal may make trauma victims particularly susceptible to suggestion	Learning what symptoms to expect may lead to an increase in self-directed focus of attention that may cause more of those symptoms to appear	Bootzin and Bailey (2005)

Table 1. Continued.

Area of study	Method/effect	Conclusion	Reference
Other: pharmacogenetic testing	Study about pharmacogenetic (PGx) testing and the potential impact of pharmacogenetic test results on drug response PGx information could adversely affect drug response through negative expectations that a drug will be less than optimally effective or cause an adverse response	Physicians should be sensitive to the potential impact of PGx results, regardless of whether they are considered as positive or negative on their patients' drug response and give special consideration to how best to deliver these test results to minimize adverse responses	Haga et al. (2009)
Other: Parkinson's disease	The velocity of movements was analyzed in Parkinson patients who had been implanted with electrodes in the subthalamic nuclei for deep brain stimulation. They expected either a good motor performance or a bad motor performance The hand movement was faster when the patients expected a good motor performance than when they expected bad performance	Motor performance can be modulated in two opposite directions by placebos and nocebos, and this modulation occurs on the basis of positive and negative expectations about motor performance	Pollo et al. (2002)
Other: "vibroacoustic disease"	Studies about "vibroacoustic disease" and "idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF)" These studies cannot find any robust evidence to support the existence of electromagnetic hypersensitivity as a biological entity or any link between wind turbines and vibroacoustic disease	Nocebo seems to explain in part "vibroacoustic disease" and "IEI-EMF"	Röösli (2008), Rubin et al. (2010), Szemerszky et al. (2010), Chapman (2013)
Other: water	Article about the barriers to public acceptance of waste water reuse with its ultimate culmination in direct reuse for drinking Contamination of drinking water can lead to consumer distrust in municipal water supplies and catalyze public rejection of water recycling programs	The nocebo effect could play a key role in the development of adverse health consequences from exposure even to trace levels of contaminants simply by the power of suggestion	Daughton (2004)

tioning procedure than after verbal suggestion alone, whereas men showed stronger responses to the verbal suggestion than to the conditioning procedure, but to a lesser degree (Klosterhalfen et al. 2009).

Casper et al. (2001) had the same result in patients with major depressive disorder, where more women than men reported symptoms with placebo.

Psychiatric illness

Individuals with pathologies such as anxiety and depression, and those with a tendency toward somatization have been found to be more likely to develop the nocebo response (Wells and Kaptchuk 2012).

Not so surprisingly, the definition of anxiety, as found in various dictionaries, carries some features of the nocebo effect such as anticipation and neurovegetative signs.

Clinicians have noted that the side effects reported by highly anxious patients are often the somatic concomitants of anxiety itself (tachycardia, dyspnea, or sweating). A tendency toward somatization, symptom amplification, and a heightened awareness of bodily sensation has also been associated with nonspecific side effects (Barsky et al. 2002). For example, anxious individuals are more likely to have pseudoresistant hypertension due to white-coat effect (Terracciano et al. 2014).

Personality

Aggressive/competitive/hostile personalities. According to Drici et al. (1995), more subjects with behavior pattern A

described subjective side effects of the placebo than type B. Based on the Bortner Rating scale, type A subjects are aggressive, competitive, have a sustained drive for achievement and a sense of urgency, and are hostile. They lead more stressful working lives than type B people, and it has been suggested that type A people are more likely to report side effects than type B subjects. This could explain the prevalence of type A among the subjects describing side effects under placebo.

Pessimistic personalities. Pessimism may predispose to negative expectations and to the nocebo phenomenon (Hahn 1997a; Geers et al. 2005; Data-Franco and Berk 2013). On the contrary, optimists are more likely to be persuaded by positively framed arguments and less likely to be persuaded by negatively framed arguments. But Geers et al. (2005) showed that it can be more complex: negative outcome is only increased in pessimistic patients when they are informed that they could take a medication with a bad safety profile; if they are informed that they will receive the unsafe active medication or a placebo, they present the same rate of negative outcome as optimistic patients.

Environment

Studies in social psychology have consistently revealed that the effects of basic personality are influenced by situational or contextual factors (Geers et al. 2005). This explains why a nocebo effect in patients with a normal psychological pattern can be observed in particular situations.

Hahn (1997b) presents nocebo as a social illness: local cultures present traditional ideas of what sickness is and of what to expect. Because expectations are largely learned from the cultural environment, nocebo effects are likely to vary from place to place.

In addition, the environment can be a powerful stressor and lead persons who find their social positions intolerable or otherwise unavoidable to experiment nocebo effects (Hahn 1997b).

The nature of the physician–patient relationship may also be a factor, and the way in which a medication is presented can have a significant effect on safety (Rogers 2003).

A slightly different form could be likened to a negative Hawthorne effect: if asked, some patients overestimate their symptoms to express their concerns about the treatment or to prove to the doctor they do not tolerate it.

Information

Nocebo effects are also influenced by the patient's perception of the medication and the context in which it is given (Reeves et al. 2007).

Information can be presented to patients in various ways during the informed consent process, each of which has different effects on their attitudes, judgments, and decision making (Williams et al. 2013). Medical professionals can transmit their expectations to patients directly by expressing their views of a medication to a patient and providing information about possible side effects (Faasse and Petrie 2013).

The verbal and nonverbal communications of physicians and nursing staff contain numerous unintentional negative suggestions that may trigger a nocebo response: body posture, tone of voice, shrug of shoulders, frown, or furrowed brow (Häuser et al. 2012a). These signs can be perceived unconsciously. But keep in mind that anxious or pessimistic patients can also actively find negative information by themselves (pairs, Internet, and leaflets of drugs). So that healthcare professionals are not always the culprit.

Psychological mechanisms

Conditioning

The same mechanism as described by Pavlov can be applied and the placebo/nocebo effects can be considered as an example of classical conditioning. It can be triggered by external factors such as color, taste, shape, perceived strength (based on milligram dosage), and even the name of a pill. For example, red, orange, and yellow tablets are associated with stimulant effects, and blue and green suggest sedative effects. Thus, volunteers taking blue placebos report more drowsiness than those taking pink placebos (De Craen et al. 1996).

The therapeutic environment can also act as a conditioned stimulus, eliciting a therapeutic response in the absence of an active principle, just because it has been paired with it in the past (Benedetti and Amanzio 2011). For example, nausea can be triggered by the sight or the smell of the hospital or in a room painted in the same color as the room where the chemotherapy was administered (Benedetti 2012). In the later example, the nocebo effect would be a consequence of an unconscious conditioning to a previous negative therapeutic experiences (Geers et al. 2006).

Patients may manifest side effects to a prescribed medication not because of its specific pharmacological actions, but rather because they have experienced side effects to other drugs in the past (Barsky et al. 2002).

Another well-known example is the white-coat hypertension phenomenon, and the effect is even higher with doctors than with nurses (Clark et al. 2014). A study (Colloca et al. 2010) suggests that there is a causal relation between the number of conditioning trials and the

resistance to extinction of the ensuing placebo and nocebo responses. The persistence of placebo and nocebo responses was firmly connected to the number of exposures to effective treatments (one vs. four sessions of conditioning). In fact, a long-lasting positive or negative conditioning paradigm resulted in the formation of sustained nocebo and placebo responses.

Negative expectations and suggestibility

Humans have a tendency to perceive what they expect to perceive (Pennebaker and Skelton 1981; Barsky and Borus 1999; Geers et al. 2010). The placebo effect is the result of positive expectations, whereas the nocebo effect is the result of negative ones (Benedetti 2012).

These expectations depend on the patient himself, the most important personality trait influencing on expectancy being optimism or pessimism, defined as a generalized and relatively stable expectancy for positive or negative future outcomes (Nes and Segerstrom 2006) and the most important illness being anxiety–depressive disorders.

These expectations also depend on the complex psychosocial context surrounding the patient such as verbal and written instructions, environmental clues, and the interaction with care providers.

Because of their historical reputation, some medications may be more likely to have adverse effects ascribed to them. For example, penicillin allergy is widely recognized by the public and up to 10% of hospitalized patients report being affected by it, whereas, on careful investigation, 97% of adults labeled as "penicillin allergic" were found to tolerate oral penicillin (Barsky et al. 2002).

Expectation of drug side effects can focus attention on these symptoms, resulting in greater detection and reporting of expected side effects. Greater self-focus on internal sensations is associated with increased levels of symptom reporting (Faasse and Petrie 2013).

A recent study (Vögtle et al. 2013) has assumed that observing others might be one way in which pain-related beliefs and attitudes are acquired. Participants in an observational learning condition watched a video in which a model displayed more pain when an ointment was applied. And as hypothesized, they rated the pain stimuli with ointment as more painful than those without. Seeing another person become ill after taking a medication or receiving an injection or hearing about their symptoms or side effects personally or through news or social media coverage can increase a person's expectation that he too will become unwell, resulting in the spread of nocebo-type symptoms to a wider group of people (Faasse and Petrie 2013).

A suggestion phenomenon has been identified through various episodes of mass psychogenic illness also called "mass hysteria" or "assembly line hysteria" (Hahn 1997b). Those sociogenic outbreaks are commonly associated with a source believed to be related to the symptoms, for example, a strange odor or gas, new solvent, or an insect bite (Colligan and Murphy 1979). For example, the June Bug outbreak in 1962 in Montana as described by Hahn (1997b) clearly showed that even if symptoms initially occurred in workers with social stress risk factors, secondary spreading occurred by contiguity in workers without such risk factors. Communicating powerfully shapes attention and perception, suggesting particular experience to be expected.

The belief that a treatment will cause pain can lead to an increase in pain, the so-called nocebo hyperalgesia (Atlas and Wager 2012). Indeed, the expectation that pain is about to occur or that pain will increase induces negative emotions like nervousness and fear, which in turn increase pain (Flaten et al. 2011). For example, informing patients about interruption of treatment, such as an infusion of morphine for postoperative pain, is associated with a significant increase in pain compared with when treatment is stopped without informing the patient. In the study by Colloca et al. (2004), patients in one group were aware that the infusion would eventually cease, but not the exact time. In the other group, the cessation of therapy was made obvious through negative instructions from the clinician. The negative verbal instructions and manner in which the therapy was stopped altered clinical outcomes, not just in terms of pain, but also motor performance and anxiety.

In addition, the specific information told to patients directly shapes the specific side effects experienced. Information can be self-fulfilling. A trial comparing two placebo groups, placebo acupuncture versus a placebo pill, revealed that the types of side effects patients experienced were completely different in the two study groups and entirely mirrored the information provided to participants (Kaptchuk 2006). Patients who received placebo acupuncture and were told they had a 50–50 chance of receiving genuine or placebo acupuncture experienced side effects typical of acupuncture (pain during treatment, increased pain after "removing" the needle, and local redness or swelling), while those who were administered placebo pills and were told they could be receiving either placebo pill or amitriptyline complained of the usual side effects of this medication (drowsiness, dry mouth, restlessness, dizziness, and headache).

Misattribution of negative symptoms

Misattribution of symptoms as being the result of medications is most likely to occur when patients expect to experience a side effect, have been conditioned to

experience a side effect by previous adverse events, or in those with specific psychological predispositions, particularly anxiety, depression, or somatization. Misattribution must be particularly relevant in patients with advanced cancer, pain, and many comorbidities that are being treated with multiple medications that have potentially significant toxicities (Sanderson et al. 2013).

Somatic symptoms caused by pre-existing medical illnesses or by anxiety and depression, which are simply endemic to daily life, can be misattributed to a newly instituted medication (Barsky et al. 2002). This phenomenon is strongly linked to the patient's negative expectations.

Neurobiological mechanisms

Much less research has been done on nocebo than on placebo effects. But several endogenous substances have been identified, especially using the model of nocebo hyperalgesia (Benedetti 2012).

Cholecystokinin

Cholecystokinin 2 (CCK2) receptor agonists are known to have anxiogenic properties. In humans, especially those with a predisposition to panic, intravenous injection of CCK receptor agonists produces panic-like anxiety, which can be prevented by prior administration of CCK2 receptor antagonists (Lovick 2008).

The mixed CCK type A/B receptor antagonist proglumide has a placebo-potentiating role. In the study of Benedetti et al. (1997), patients were subjected to a nocebo procedure and then received either open or hidden infusion of proglumide, and some received an infusion of naloxone. The nocebo hyperalgesic response was blocked by relatively large doses (0.5 and 5 mg) of proglumide compared to the low dose (0.05 mg), which is ineffective. When the injections of proglumide were hidden, it had no effect on pain perception, indicating that proglumide itself had no analgesic effect.

The anticipatory anxiety about imminent pain, suggested by verbal suggestions, triggers the activation of CCK, which facilitates pain transmission and leads to hyperalgesia.

The periaqueductal gray matter (PAG) is a critical site for the anxiogenic actions of CCK as well as for its pronociceptive effects, suggesting that CCK-driven activation of proalgesic pathways from the PAG could be central to anxiety-related pain. Under certain stressful circumstances, hyperalgesia is evoked by the pronociceptive actions of CCK in the PAG, perhaps facilitated by CCK-driven activation of descending pathways to the PAG from prefrontal regions (Lovick 2008).

Corticoids

Another study (Benedetti et al. 2006) showed that verbally induced nocebo hyperalgesia was associated to hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, as assessed by means of adrenocorticotropic hormone and cortisol plasma concentrations.

Opioids

Endogenous opioids secretion in the brain is the main event in placebo pain modulation. Placebo analgesia is abolished when patients are given the opioid antagonist naloxone (Levine et al. 1978). But, as shown by Benedetti, the blocking of the nocebo response is not mediated by endogenous opiates since the infusion of naloxone did not prevent the effects of proglumide (Benedetti et al. 1997).

The opioidergic and the CCKergic systems may be activated by opposite expectations of either analgesia or hyperalgesia, respectively. Verbal suggestions of a positive outcome (pain decrease) activate endogenous μ-opioid neurotransmission, while suggestions of a negative outcome (pain increase) activate CCK-A and/or CCK-B receptors (Benedetti et al. 2007).

Dopamine

Placebo and nocebo effects are associated with opposite responses of dopaminergic system and endogenous opioid neurotransmission in various brain areas. Scott et al. (2008) showed that high placebo responses are associated with greater dopaminergic and opioid activity in the nucleus accumbens (significant decrease of the μ-receptors' binding potential), whereas nocebo responses are associated with a deactivation of dopamine.

Importance of anxiety. Both nocebo hyperalgesia and HPA hyperactivity were antagonized by the benzodiazepine diazepam, suggesting that anxiety played a major role in these effects (Benedetti et al. 2006). These data indicate a close relationship between anxiety and nocebo hyperalgesia, in which the CCKergic systems play a key role in anxiety-induced hyperalgesia.

Proglumide does not act on the nocebo-induced anxiety but rather on anxiety-induced hyperalgesia. It suggests two independent biochemical pathways activated by nocebo suggestions and anxiety. CCK appears to play a pivotal role in the psychological modulation of pain, antagonizing placebo-induced opioid release on one hand and mediating nocebo-induced facilitation of pain on the other hand (Enck et al. 2008).

In neuroimaging studies, it appears that the circuitry underlying nocebo hyperalgesia largely involves, with the

opposite modulation, the same areas as those engaged by placebo analgesia.

Studies of functional magnetic resonance imaging (fMRI) have been used to investigate the area involved in nocebo hyperalgesia. For example, in Kong et al. (2008), the nocebo response to an expectation of hyperalgesia showed signal increases in brain regions including bilateral dorsal anterior cingulate cortex (ACC), insula, superior temporal gyrus; left frontal and parietal operculum, medial frontal gyrus, orbital prefrontal cortex, superior parietal lobule, and hippocampus; right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus. Nocebo hyperalgesia is predominantly produced through the affective-cognitive pain pathway.

These elements are summarized in Figure 1.

Management of the nocebo effect

Nocebo effects can modulate the outcome of a given therapy in a negative way, as do placebo effects in a positive way. The way in which adverse events are presented affects not only risk perception, but, more importantly, also clinical outcomes.

How much information should doctors provide to their patients about medication side effects? This question raises an ethical issue: on one hand they have to inform the patient about the possible adverse events, and on the other hand they have to minimize the risks of a medical intervention for the patient (Häuser et al. 2012a).

How, then, can physicians simultaneously obtain informed consent and minimize nocebo-related risks (Wells and Kaptchuk 2012)?

Identification of patients at risk

Some patients may be more susceptible than others to the nocebo response. Individuals who have experienced prior adverse reactions are also more likely to experience future ones, due to the effects of prior conditioning (Liccardi et al. 2004). Patients experiencing nonspecific symptoms at baseline are more likely to report them as side effects of a new medication. Furthermore, individuals with psychological symptoms (such as anxiety and depression), and those with a tendency toward somatization have been found to be more likely to develop the nocebo response (Wells and Kaptchuk 2012). Depression is associated with negative and pessimistic perception of self or events and in the context of receiving a new drug, the expectation is that the medication is not likely to do anything positive and it will make things worse. An anxious person is hypervigilant for harmful dangerous situations and may anticipate harm from a pill, as will a person who tends to somatize (Rogers 2003).

In order to provide clinically meaningful information to medical professionals, clinical assessment tools which enable the standardized assessment of patient's expectations may be used (Faasse and Petrie 2013); there are a number of such tools like the Revised Illness Perceptions

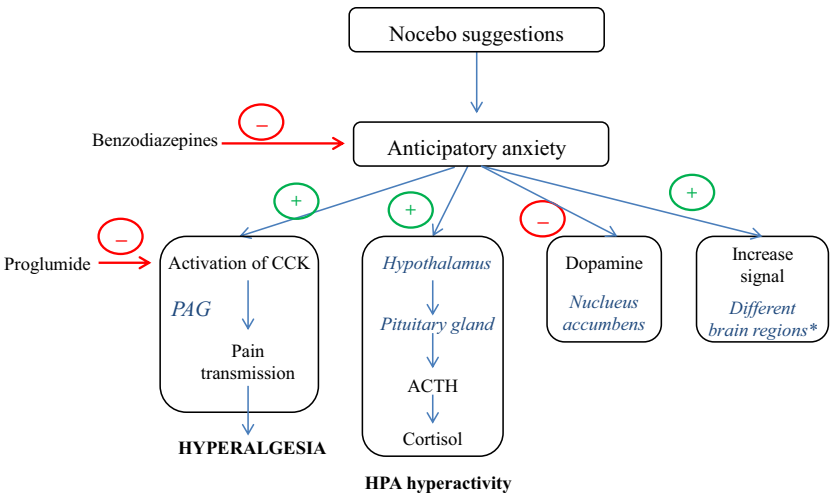

Figure 1. Neurobiological mechanisms of nocebo effect. Nocebo suggestions induce anticipatory anxiety, which activates two independent pathways, a CCKergic pronociceptive system on one hand and the hypothalamus–pituitary–adrenal (HPA) axis on the other hand. Benzodiazepines act on anxiety, thus blocking both the HPA hyperactivity and the CCK pronociceptive system. CCK antagonists act on the pronociceptive system only, thus preventing nocebo hyperalgesia but not HPA hyperactivity. *Bilateral dorsal anterior cingulate cortex, insula, superior temporal gyrus, left frontal and parietal operculum, medial frontal gyrus, orbital prefrontal cortex, superior parietal lobule, and hippocampus, right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus. +: activation or stimulation; −: inhibition or deactivation.

Questionnaire (Moss-Morris et al. 2002), the Beliefs about Medicines Questionnaire (Horne et al. 1999), the Perceived Sensitivity to Medicines Scale (Horne et al. 2013).

Physicians can ask patients whether they consider themselves "especially sensitive" to drugs (Barsky et al. 2002; Rogers 2003). It is also possible to use a two-step strategy: therapy is initiated at doses that may be subtherapeutic, with the objective of allowing the patient to get used to the idea of taking a medication. In the second phase, the dose is gradually increased into the therapeutic range (Rogers 2003).

A little test could be interesting to better convince patients that their "side effects" are possibly just linked to nocebo effects: when a "fake" treatment is available, patients are told that at the beginning of the test, only an inactive substance will be given, but that at hidden moment (hours or days after the start), the real drug will be given. This type of test could be useful for three reasons:

- if the patients experience the side effects when still only on placebo, they will be more easily convinced that their fear was irrelevant.
- if they do not experience any side effects, whereas the drug had already been given for several days or weeks, a nocebo effect is not likely to appear once they are told that the real drug was already administered.
- if the side effects are described just after the real drug introduction, it might help physicians not to overrate some patients as nocebo responders when they do experience idiosyncratic reactions.

Information techniques

Truthful information relating to adverse effects of treatments can be presented in various ways, and here are some options:

Positive framing

The probability of experiencing adverse effects can be communicated qualitatively or statistically. And this information can be conveyed "negatively" (by focusing on the minority of patients who experience a particular side effect: "5% of patients report...") or "positively" (by focusing on the majority of patients who do not experience the side effect: "the great majority of patients tolerate this treatment very well"). Clinicians could incorporate in their communication positive framing and percentage formats as opposed to negative framing and frequency format, thus possibly reducing nocebo effects by minimizing attention on the negative aspects of medication (Colloca and Finniss 2012). Presenting a percentage score is less worrying for the patient than telling "x people in 1000 had an adverse effect," because he will focus on the x patients, forgetting that the denominator is 1000 (Williams et al. 2013).

A study on briefing in the context of influenza vaccination showed that fewer adverse events were reported after vaccination by the group that was told what proportion of persons tolerated the procedure well than by those informed what proportion experienced adverse events (O'Connor et al. 1996).

Tailored information

Wells and Kaptchuk (2012) propose to use what they call "contextualized informed consent" instead of the full detailed disclosure of all medication side effects. It consists in tailoring the information about medication side effects to provide the most transparency with the least potential harm, focusing on three main elements:

- the potential side effects involved: the type of side effect should help a physician determine how much information to reveal. A physician may consider not labeling the subjective nonspecific effects when dispensing a new medication, but rather explain to the patient that he should contact the physician with "any new or unusual symptoms." Drug-specific side effects are on the contrary critical to reveal because they may result in more debilitating symptoms/conditions and thus may be more important for the patient's full informed consent.
- the patient: a physician should identify high-risk patients and tailor the amount of information about medication side effects to these patients such that only the drug-specific side effects are described. He has to be attentive to the expectations of the patient, positive and negative (Rogers 2003).
- the pathology treated: if the pathology is mild or if there are other treatment options (e.g., nonpharmacological approaches), then any side effect might not be worth the patient starting a medicine and an expanded full disclosure is important. However, in critical, life-threatening conditions, minor side effects of a medication may be of less concern and less important to inform about.

Furthermore, the process of tailoring information should account for what the patient wants to know and what the patient has already learned about his or her condition given the widespread access to information about treatments and their adverse effects (Colloca and Finniss 2012).

Permitted noninformation

Before the prescription of a drug, the patient is asked whether he 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. 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 definitely wants to be briefed about and for which categories information can be dispensed with (O'Connor et al. 1996). A physician who is recommending a given drug to a patient might communicate in the following way: "A relatively small proportion of patients who take this drug 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?" (Colloca and Miller 2011b).

Miller proposes to adopt an "authorized concealment approach." A patient's voluntary waiver of side effect information does not constitute informed consent, but arguably, it can be valid consent that respects autonomy (Miller and Colloca 2011).

Patient education

More than three quarters of patients are unaware of or do not believe in the nocebo effect (Berthelot et al. 2001; Berthelot 2011). It might be of interest to better educate people about nocebo effects including examples (Faasse and Petrie 2013) and pointing out that the anticipation or fear of an adverse reaction can become a self-fulfilling prophecy may in itself help to obviate some nonspecific side effects. It may also be helpful to discuss the nocebo phenomenon explicitly with such patients. It may help to explain how somatic symptoms caused by pre-existing medical illnesses or by anxiety and depression, and those that are simply endemic to daily life, can be misattributed to a newly instituted medication (Barsky et al. 2002).

Guiding the patient in the knowledge process and discussing valuable examples of nocebo effects engage him in the decision-making process and potentially averts negative outcomes (Colloca and Finniss 2012).

If a side effect does occur, physician can try to reframe the nocebo response into something positive. It may be helpful to point out that a side effect indicates that the medicine is "in their system" and begin to exert an effect rather than presenting a danger (Rogers 2003).

Healthcare providers' education

All healthcare providers should be aware that their own words and gestures can have a negative impact and should be educated in techniques of communication, in order to minimize nocebo responses (Colloca and Miller 2011a).

They should also provide explanation and reassurance, if needed (Barsky et al. 2002).

Finally, a balance must exist between communicating important clinical information and ensuring that every attempt is made to minimize negative instructions and a negative therapeutic context. This fine balance must take into consideration the patient's autonomy to make a decision based on all relevant information, with attempts to reframe how information may be delivered in a nondeceptive, yet reassuring way (Colloca and Finniss 2012).

Discussion

Drug-related adverse effects contribute to patient nonadherence, illness burden, and psychological distress. This leads to more physician visits and an overall increase in the cost of medical care (Wells and Kaptchuk 2012). This may lead the physician to stop a treatment that really works or treat the side effect with additional drugs (Barsky et al. 2002). Frequent medication changes can result in suboptimal care and complications. For example, adverse effects that result in stopping or changing antihypertensive medications have been shown to be associated with worse blood pressure control (Davies et al. 2003) and an increased incidence of cardiovascular disease (Psaty et al. 1990).

In addition to the burden on individual patients, the nocebo response has significant public health ramifications and other less direct negative consequences.

Nocebo burden is presumed to be important and must be minimized through good clinical, informational, and educational practices.

Perspective for clinical trials

The difference in the rates of a particular side effect between the active medication and placebo in clinical trials involving the treatment would represent the true frequency of that pharmacological side effect for the medication (Rogers 2003). But this is not as simple as that.

Nocebo responses are common and can produce discontinuation of trial participation, alteration of treatment schedules, and lack of adherence (Colloca and Miller 2011a). Between 4% and 26% of patients in trials ran-

domized to the placebo group discontinued the placebo because of perceived adverse events (Rief et al. 2006, 2009b; Amanzio et al. 2009). Moreover, dropouts due to nocebo effect may call into question the interpretation of many clinical trials (Mitsikostas et al. 2011), and a high frequency of placebo-related side effects could impair the evaluation of a new drug and prevent its further clinical development (Drici et al. 1995).

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 (Rief et al. 2009a).

Feys et al. (2012) hypothesize that randomized controlled trials with inadequate blinding report enhanced placebo effects for intervention groups and nocebo effects for placebo groups, compared with adequately blinded studies.

Furthermore, some have speculated that the rates of the nocebo effect seen in clinical trials may be an underestimate of the true prevalence, as patients who are reluctant to receive novel medical treatments due to anxiety or mistrust (and may be more susceptible to the nocebo response) might avoid participation in a clinical trial (Mitsikostas et al. 2011).

The nocebo effect generates an interpretation bias that is almost never discussed in the published clinical trials. The information provided to subjects in trials produced the side effects that mimicked the information given. A systematic review of adverse events in placebo groups of antimigraine clinical trials showed that the adverse events in the placebo arms corresponded to those of the antimigraine medication against which the placebo was compared (Amanzio et al. 2009). A systematic review from 143 placebo-controlled trials of antidepressant medications (with data from over 12,000 subjects) also showed that the adverse effects reported in those receiving placebo closely related to the corresponding drug in the trial (Rief et al. 2009b). This means differences in adverse reaction profile between both arms are erased, in favor of the active drug. There is clearly a need to attempt to disentangle not only adverse effects associated with placebo from those associated with active medications, but also nocebo-related effects, in order to describe a more accurate safety profile of the active medication (Antonaci et al. 2007).

Perspectives for health authorities

The current European Guideline of Summary of Product Characteristics (SPC) of drugs is silent about the nocebo effect: "This section should include all adverse reactions from clinical trials, postauthorization safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC." The problem is that nocebo-related effects are not adverse events but have a truthful causality link with the considered drug and should therefore appear in the SPC.

The reading of SPC of many drugs has become a very hard exercise for healthcare practitioners. What is hiding behind a mention of minor symptoms such as abdominal pain, insomnia, or tinnitus? Is it pharmacologically related? Is it a mention resulting from a protective policy of the marketing authorization holder and clemency from health authorities? or Is it a nocebo effect?

Nocebo-related adverse effects should not reasonably appear in SPCs and patient's information leaflets because they do not provide specific information about the drug itself and they can generate in turn nocebo effect in some other patients.

The next regulatory step would be the evaluation of nocebo effect liability by investigators during clinical trials, in addition to the causal relationship assessment.

The media have a significant responsibility for the maintenance of a nocebo effect in the population, as shown in the study of Witthöft and Rubin (2013). He says media reports about the adverse effects of supposedly hazardous substances can increase the likelihood of experiencing symptoms and developing an apparent sensitivity to it. Greater engagement between journalists and scientists is required to counter these negative effects.

Conclusion

Nocebo effects are adverse events produced by negative expectations. Nocebo effects can be observed not only in everyday clinical practice, but also in clinical trials. These nonspecific side effects distress patients, add to the burden of their illness, and increase the costs of their care. They may lead to nonadherence, cause physicians to discontinue what is otherwise an appropriate therapy, or prompt attempts to treat these side effects with additional drugs.

But recognition of the nocebo-related adverse effects is challenging, because of their nonspecific nature or their similarity to known adverse reaction profile. They must be recognized as true adverse reactions and not neglected.

Nocebo-related adverse effects would remain a diagnosis of last resort when all other etiologies or confounding factors have been ruled out. But as this procedure can be very expensive, the doubt persists and the patient cannot

be totally reassured, thus generating new negative expectations.

The informed consent process involving the explicit mention of medication adverse effects is a key step and must be considered as potentially harmful.

Clinical management of the nocebo effect therefore includes awareness and recognition, changing the manner of disclosure of potential drug-related adverse effects, shaping patients' expectations, and enhancing the treatment alliance. All healthcare professionals should be familiar with proper information and communication techniques to better face the ethical challenge of minimizing the nocebo response and at the same time of delivering truthful information about risks.

Disclosures

None declared.

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