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Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects

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Abstract

Placebo effects constitute a major part of treatment success in medical interventions. The nocebo effect also has a major impact, as it accounts for a significant proportion of the reported side effects for many treatments. Historically, clinical trials have aimed to reduce placebo effects; however, currently, there is interest in optimizing placebo effects to improve existing treatments and in examining ways to minimize nocebo effects to improve clinical outcome. To achieve these aims, a better understanding of the psychological and neurobiological mechanisms of the placebo and nocebo response is required. This review discusses the impact of the placebo and nocebo response in health care. We also examine the mechanisms involved in the placebo and nocebo effects, including the central mechanism of expectations. Finally, we examine ways to enhance placebo effects and reduce the impact of the nocebo response in clinical practice and suggest areas for future research.

Contents

> The mind is its own place, and in itself can make a heaven of hell, a hell of heaven.
>
> John Milton, *Paradise Lost*

INTRODUCTION

Expectations have a strong influence on health outcomes. The power of expectations is clearly illustrated in research investigating how different types of information can influence pain reduction (Bingel et al. 2011). In this study, participants were provided with a uniform dose of a short-acting powerful opioid drug (Remifentanil) and then subjected to a painful heat stimulus. When no expectancy was given to participants, the drug still reduced pain significantly (see **Figure 1**). However, when the positive expectation that the drug would help to reduce pain was given, the effect of the drug was doubled. In contrast, creating negative expectations by telling participants that, after withdrawal of the drug, they would become more sensitive to pain completely wiped out the analgesic effect of the powerful opioid.

This review focuses on positive and negative expectations as important drivers of the placebo response across a wide range of medical treatments. The positive effects of placebo interventions have been demonstrated in many medical and psychological conditions. These include Parkinson's disease (Benedetti et al. 2004, de la Fuente-Fernandez et al. 2001), hypertension (Wilhelm et al. 2016), fatigue in cancer patients (de la Cruz et al. 2010), and neuropathic pain (Quessy & Rowbotham 2008), as well as depression (Rief et al. 2009a, Walsh et al. 2002) and many other psychological disorders (Khan et al. 2005). When placebo-controlled designs are used to investigate surgical procedures, impressive improvements are typically found in the sham surgery conditions (for a review, see Wartolowska et al. 2014).

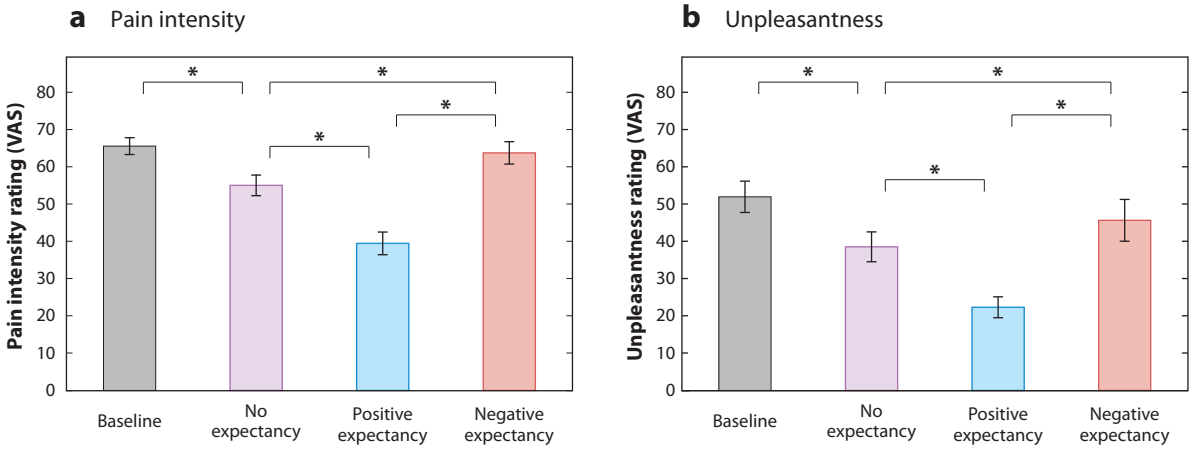

Figure 1

The effect of positive and negative expectations on the reporting of (*a*) pain intensity and (*b*) unpleasantness after administration of Remifentanil, a powerful short-acting opioid. * denotes differences between groups ($p < 0.05$); error bars are standard error of the mean. Abbreviation: VAS, visual analog scale. Adapted with permission from Bingel et al. (2011).

Placebo effects are not limited to patient-reported outcomes, but also affect physiological parameters. In students, positive expectations can help to reduce heart rate and blood pressure reactions in test anxiety situations (Faasse et al. 2013). In patients with Parkinson's disease, placebo-induced dopamine release has been demonstrated (Lidstone et al. 2010). Placebo treatment also partly normalizes polysomnographic variables in patients with sleep disorders (Winkler & Rief 2014). Expectations can also affect immune responses, especially when they are developed through classical conditioning procedures (Goebel et al. 2008, Kirchhof et al. 2018).

Patients do not always have positive expectations about treatment, and studies have shown that, when patients hold negative expectations, these expectations can lead to lower treatment efficacy (as illustrated in **Figure 1**), as well as greater numbers of side effects and other negative outcomes. This is known as the nocebo effect and is an important but relatively neglected phenomenon compared to the placebo effect. However, we know that the act of informing patients about the possible side effects of a treatment alone can significantly increase the numbers of patients who report those side effects (Cocco 2009) and intensify worry and concern (Barsky 2017).

In this review, we summarize how these powerful expectation effects on medical outcomes develop and how they contribute both to positive placebo effects and to the development of negative nocebo experiences. We examine the mechanisms involved in these effects and how these mechanisms can be used to boost and minimize placebo and nocebo effects. The power of placebo and nocebo effects indicates not only that we should control these effects in clinical studies, but also that the opportunity exists to use them to make current treatments more effective. We discuss this possibility in the section titled Conclusions and Future Directions, before summarizing our perspectives on how to further develop this field.

THE PLACEBO EFFECT

The placebo effect was first described as the set of positive changes that occur following placebo treatments (treatments without active ingredients). However, some of these positive changes can

occur for other reasons, such as the natural course of the condition, regression to the mean, and simply the effect of repeated assessment. In this section, we focus on a better understanding of placebo mechanisms that contribute to improvements beyond these statistical confounders. As placebo effects are not limited to placebo treatments, but are also a component of any treatment, including active medical interventions, our emphasis is on the psychological and contextual factors that directly cause improvements in treatment outcome.

Unfortunately, few clinical studies have compared placebo interventions with natural course groups to demonstrate the benefit of a placebo intervention. Due to the lack of such studies, some authors have expressed doubts about the power of placebo mechanisms in clinical trials (Hróbjartsson & Gotzsche 2001). One of the few randomized controlled trials (RCTs) that directly compared the changes in an active antidepressant arm and a placebo pill arm with a supportive care–only (natural course) group was able to show only minor differences between the active pill and placebo pill group, but it showed significant advantages of both pills compared to supportive care only (Leuchter et al. 2014). More such clinical trials are needed. Furthermore, experimental studies that are designed to directly investigate placebo mechanisms, compared to those that try to disentangle placebo effects from drug effects in clinical trials, are more likely to enhance our understanding of the impact and limitations of the placebo effect.

Mechanisms Involved in the Placebo Response

It is widely agreed that expectations are among the most important factors contributing to placebo responses. Expectations about treatment can develop through personal experiences (learning), observational learning, instructions or information from doctors and other clinical staff, information from other sources such as the Internet, or personal beliefs. Expectations can also be triggered by cues from within the clinical setting. These cues could be symptoms from the patient's illness or current mental state, but could also be stimuli like the white coat of the physician, the syringe, the friendly face of the nurse, the shape of a pill, or the act of swallowing a drug.

Some experts in placebo research discriminate expectation from conditioning, with the former being used as a synonym for a form of instructional learning (Benedetti et al. 2003). However, according to learning theory, expectancies or expectations are higher-level terms that encompass conditioning effects, instructional learning, and other types of learning (Lopez et al. 2016). The significant aspect is that an individual has learned that specific cues will be followed by specific consequences, but how this association was learned is only of secondary importance.

What Are Expectations?

In contrast to cognitions in general, expectations are defined as specific cognitions about the likelihood of future events (Rief et al. 2015). In the context of clinical interventions, different types of expectations can be relevant. These could include the patient's expectations about the course of their illness, their response to the treatment, the likelihood of side effects, and their ability to influence these outcomes. Most authors use the terms expectancy and expectations interchangeably, while others limit expectations to specific conscious or verbalized cognitions about future events. Kirsch (1985, 1997) distinguishes between stimulus expectancies, or the anticipation of external events, such as the pain that will occur when a dressing is removed, and response expectancy, which is the prediction of nonvolitional responses, such as the expectation of a reduction of pain after an aspirin is taken. Kirsch (2018) emphasizes that response expectancies tend to be self-confirming, stable and more resistant to extinction than stimulus expectancies.

Crum and colleagues (Crum & Leibowitz 2017, Zion & Crum 2018) have also proposed a wider set of expectations and beliefs that may orient an individual to particular general associations that have health consequences. These mindsets are broader sets of beliefs that shape attention and motivational behavior and seem to have important influences on health. For example, the benefits of exercise are related to the degree to which an individual sees a particular physical activity as good exercise (Crum & Langer 2007), and the belief about whether stress negatively affects health seems to be important in the relationship between stress and health outcomes (Crum et al. 2013).

Verbal Instructions

Many studies use verbal information and instructions to create placebo effects from inert pills, plasters, or lotions (Carlino & Benedetti 2016, Roderigo et al. 2017). While it is clear that verbal instructions are able to induce placebo responses in patient-reported outcomes, their potential to affect biological and emotional responses is less well established. A recent study (J.A. Glombiewski, J. Rheker, J. Wittkowski, L. Rebstock, and W. Rief, unpublished manuscript) extended this approach to affective disorders, using a paradigm to induce sadness. Participants received a placebo nasal spray and were told either that the spray was just a placebo without any active ingredient or that the spray contained citalopram, a medication that blocks emotional reactions to emotional stimuli. After watching a sadness-inducing movie clip, the participants who believed that they had received an emotion-blocking spray reported less sadness than participants in the control condition, even though both sprays were inert. These types of paradigms can help to extend experimental placebo research to the field of affective disorders and thus help researchers understand the large placebo effects that are found in trials investigating antidepressants (Kirsch 2016, Kirsch et al. 2008, Rief et al. 2009a, Walsh et al. 2002).

Open–Hidden Designs

Another approach used to investigate expectation effects is the open–hidden experimental paradigm. The principle is similar to the instructional induction of expectations, but the roles of visual and time cues are much more pronounced. This technique has been used to investigate placebo effects in the context of both placebos and active drug treatments. The open application represents the typical clinical situation, where a doctor or nurse gives a drug (such as an analgesic) and the patient can clearly identify when the drug is administered and also when to expect that the drug will start working. In hidden conditions, drugs are typically administered electronically by infusion at a predetermined point without the patient's knowledge. Studies show that the hidden application can substantially decrease the effectiveness of analgesics. Typical nonsteroidal anti-inflammatory drugs (NSAIDs) are only half as efficacious in a hidden application compared to an openly administered pain treatment (Amanzio et al. 2001), and even powerful opioids lose at least 30% of their efficacy if administered in a hidden paradigm (Bingel et al. 2011). Such studies show that placebo mechanisms are not limited to placebo treatments, but are also applicable to active treatments. Studies using open–hidden designs also demonstrate that clinicians can amplify the efficacy of a treatment by making the application of the therapy highly visible and salient to the patient.

Changing Patients' Expectations

In the clinical realm, it is likely that changing specific dysfunctional expectations will be more useful than establishing a new set of expectations. Therefore, we need to better understand not

only how expectations develop and act, but also how dysfunctional expectations can be changed in clinical encounters.

The typical way to change expectations is to induce expectation-violating experiences, either by using information or through direct experiences. To offer a framework for these processes, Rief & Petrie (2016) developed the ViolEx model to explain not only why expectations change, but also why expectations are maintained despite expectation-violating information. When expectation violations occur, as when the clinician provides new information that the treatment is likely to lead to better outcomes than the patient expects, many patients activate cognitive reappraisals or strategies to invalidate the expectation-violating experience. Examples of these cognitive immunization strategies can be thoughts such as: "While the clinician's information might be true for most other people, I am the exception to the rule;" "Research results are typically wrong, a fact that is confirmed in most journals and newspapers;" or perhaps even "The doctor wants to hide threatening information." These are strategies to avoid the modification of expectations despite expectation-violating experiences; we have labeled these strategies cognitive immunization.

Considering this dynamic, the challenge of changing expectations is, first, to optimize the power of the expectation-violating experience and, second, to minimize potential cognitive immunization strategies. Successful methods to reduce cognitive immunization and to make expectation violations more powerful include addressing the potential role of the immunization processes directly and a priori, verbalizing expectations and potential immunization strategies before expectation violations occur, formulating expectations as specifically as possible (the more generally expectations are formulated, the more difficult it is to violate them), focusing attention on the identification of expectation-violating experiences, and focusing attention on the identification of cognitive immunization processes.

Learning

Expectancies typically develop by associative learning or Pavlovian conditioning. The effects of expectation on outcome can be relatively variable depending on the individual's prior experience with the cues and outcome. The associative strength between cues and outcome depends on how frequently an association between the stimuli and the positive or negative outcome has been experienced, how intense the positive effects or aversive consequences of prior treatments were, and the saliency of relevant cues. A typical experiment to induce placebo mechanisms via associative learning paradigms (Pavlovian conditioning) exposes participants to a standardized painful prestimulation. Afterward, the participant receives a placebo treatment and is then re-exposed to pain stimulations. However, during the second exposure period, the intensity of the pain stimuli is reduced without the participant's knowledge. In this deceptive design, participants come to learn that the placebo treatment works like an active analgesic. After this learning phase, participants are re-exposed to the original pain stimuli with the placebo treatment and typically report lower pain experiences than before. This conditioning paradigm to induce placebo analgesia can be used either alone or in combination with placebo instructions. These classical conditioning paradigms to induce placebo analgesia have been used for decades (see Babel et al. 2017, Klinger et al. 2017). Conditioning has recently been extended to improving the efficacy of immunosuppressive drug responses in renal transplant patients (Kirchhof et al. 2018) and has the potential to be used more widely in other medical treatments, either to increase drug response or perhaps even as a dose reduction strategy, as has been done with sleep medication (Perlis et al. 2015) (see **Figure 2**).

While the classical conditioning paradigm uses the same placebo treatment during acquisition and evocation of the conditioned response, such a paradigm can also be used to investigate the role of different prior experiences with other treatments. In these cases, for example, participants are

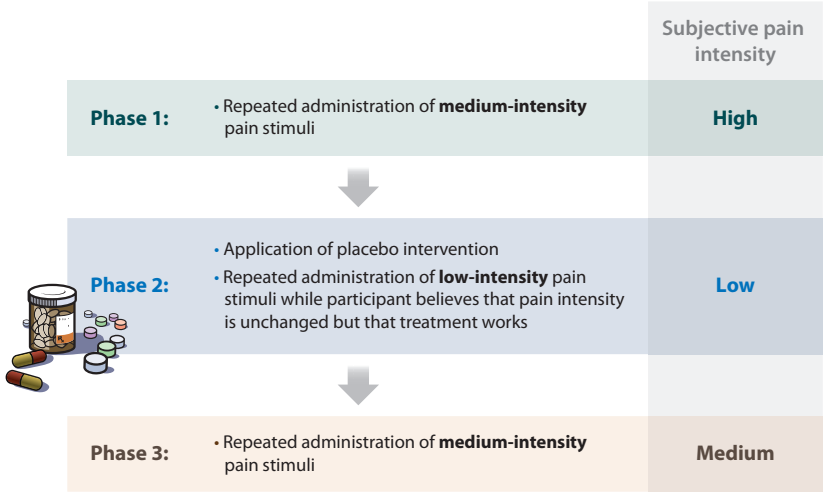

Figure 2

Establishing placebo reactions by conditioning. Participants experience that a pain stimulus elicits less pain if a (placebo) pill is applied (phase 2). If the original pain intensity from phase 1 is applied in phase 3 (together with a placebo pill), it typically elicits less pain than during phase 1.

given a positive experience with one placebo treatment, such as an ointment. Afterward, they are exposed to another placebo treatment, such as placebo plasters. Using such a paradigm, Kessner and colleagues (2013) were able to show that the success of prior treatments amplifies the placebo effects of subsequent treatments and, conversely, that prior treatment failures carry over and make future treatments less effective (Zunhammer et al. 2017). This is valuable evidence for the role of learning in influencing treatment outcomes. Such data show that some patients can learn to become treatment responders through the success of prior treatments, while other patients can learn to become treatment failures because of a history of unsuccessful treatments.

Another way to induce placebo responses is through observational learning. If participants see others receiving an effective pain treatment, their own subsequent pain experience will be reduced when using a similar treatment (Colloca & Benedetti 2009, Colloca et al. 2008). This is an example of how treatment success (and treatment failure) can become contagious in clinical settings when there is opportunity for patients to talk to each other and share their treatment experiences. This aspect is discussed further in the section titled The Nocebo Effect.

Clinician–Patient Interaction

The empathy of the treatment provider and other factors that enhance or reduce the quality of the clinician–patient interaction also influence the placebo response. Kaptchuk and colleagues (2008) have investigated how empathy influences placebo responding. The researchers instructed one group of clinicians to interact with participants suffering from irritable bowel syndrome (IBS) in a very empathetic way (by asking questions and using a warm and supportive interaction style) while administering a placebo treatment. The control clinicians administered the same placebo treatment but were asked to act formally and without expressing warmth toward the participant. While both groups improved more than a wait-list control group, the patients who had an enhanced empathetic relationships with their clinicians showed the greatest improvement, demonstrating that positive aspects of the clinician–patient relationship can increase placebo effects.

Other studies have confirmed the importance of the clinician–patient relationship in other areas. One of the few studies that experimentally manipulated doctor's behavior, using standardized actor protocols, was able to show that a clinician interaction style that built rapport and increased the patient's faith in the treatment led to an increase in pain threshold and pain tolerance (Czerniak et al. 2016). The presence of an empathetic other appears to increase an individual's ability to cope with pain and activates brain regions that are involved in pain management (Edwards et al. 2017, Eisenberger et al. 2011).

Other studies have shown that empathy is not the only characteristic of the clinician's behavior that may determine a positive outcome. In an elegant study design using a histamine skin prick test to induce allergic reactions, Howe and colleagues (2017) varied the provider's behavior in terms of both warmth and perceived clinical competence. Both features were found to independently influence a positive placebo response. The largest improvements were evident when the provider showed both warmth and competence. Depending on the particular clinical problem (e.g., chronic pain management versus surgery), patients may prioritize competence over empathy (Ashton-James & Levordashka 2013).

Using Other Factors to Boost the Placebo Response

Studies suggest that side effects in RCTs can enhance the drug response and reduce differences between the drug and placebo groups by giving participants cues that they are receiving the active medication (Rief et al. 2011). There is evidence to show that adding substances to placebos that enhance the belief that they are active medicines can increase their effectiveness (Berna et al. 2017, Rief & Glombiewski 2012). Placebo responses also tend to be greater with other physical characteristics of treatment. Capsules (rather than tablets), larger pills, and strong- or foul-tasting medicines seem to have more powerful placebo effects (Buckalew & Coffield 1982).

The brand name and even the sound of the name may also be important in adding to the perceived therapeutic effect of a drug, although this is an area with very little published work. Certain letters of a brand name can be used to produce a link between a sound and a meaning. Drug companies have increased their use of X and Z in drug names dramatically over recent years (Stepney 2010). These letters have the advantage of being visually distinct and modern and are unlikely to have the negative associations of other medications. The letter Z has connotations of efficacy, while the letters T and S have been shown to be associated with ideas of smaller, lighter, faster, and more tolerable treatments (Abel & Glinert 2008). These are only a few examples highlighting the fact that we are just beginning to discover the different mechanisms that contribute to the overall outcome of clinical interventions (see the sidebar titled Are Improvements from Antidepressants Mainly Due to Placebo Effects?).

To summarize, while the importance of the clinician–patient relationship in influencing clinical outcomes has been discussed for decades, it is only recently that new research designs have allowed investigators to study this area using experimental methodologies. These investigations have provided important information on how the placebo effect is influenced by the quality of the clinician–patient relationship and how other aspects of the interaction and of the treatment can also influence the placebo response.

Neurobiological Mechanisms

The neurobiological mechanisms of the placebo response have most frequently been investigated in the field of placebo analgesia. Various brain imaging studies have shown that the expectation of improvement induced by placebo applications leads to reductions of most pain-associated brain

ARE IMPROVEMENTS FROM ANTIDEPRESSANTS MAINLY DUE TO PLACEBO EFFECTS?

Kirsch and colleagues' (2002, 2008) analysis of US Food and Drug Administration data on antidepressants suggests that most of the effect of antidepressants may come from placebo mechanisms. This is supported by a meta-analysis that showed that the efficacy of the placebo arms of antidepressant trials is 65% that of the antidepressant arms and that this proportion is higher when nonpublished trials are included (Rief et al. 2009b). A recent review including 522 trials comprising 116,477 patients with depression revealed an average advantage of antidepressants over placebos in a low range (effect size of 0.3 standardized mean difference) (Cipriani et al. 2018). However, the small difference between drug groups and placebo groups is only one part of the story. Most antidepressant studies are not really blinded because patients experience onset symptoms and side effects in the drug arms. These drug-associated side effects trigger positive expectations that have been shown to boost response (Rief & Glombiewski 2012). The few studies comparing antidepressants with active placebos (placebos that induce some side effects) have not shown a significant advantage of antidepressants over active placebos (Moncrieff et al. 2004) and suggest that a reconsideration of the effectiveness of antidepressants is needed (Rief et al. 2016).

activities (Price et al. 2006; Wager et al. 2004, 2007). Even the activity of primary somatosensory fields that directly reflects the perception of pain is reduced if positive placebo effects are expected in experimental pain stimulation paradigms.

Placebo analgesia offers elegant paradigms to demonstrate not only the bottom-up pathways of pain perception, but also the top-down pathways that reflect pain control. Several studies have confirmed the crucial role of the rostral anterior cingulate cortex as a center to control pain perception (Bingel et al. 2006). Moreover, as predicted by pain control models, the activity of the prefrontal cortex can also contribute to the top-down processes of pain control (Wager et al. 2004). Research has demonstrated that the expectation of pain reduction triggered by placebo instructions can lead to lower neural activity even at the level of the upper spinal cord pathways (Eippert et al. 2009). In other words, clinician's instructions can initiate top-down inhibition processes that lead to variations of neurophysiological activities, even at the level of the spinal cord. The studies on placebo analgesia have confirmed that pain perception is a product of bottom-up activation and top-down inhibition in neural activities and that expectation contributes specifically to the top-down inhibition process of pain control.

How do these neural top-down inhibition processes of pain control affect placebo analgesia? Benedetti (2013) has evaluated the hypothesis that placebo analgesia is based mainly on biological pain control strategies that have been experienced during past analgesic treatments. If participants have a history of opioid use, placebo analgesia could be based mainly on the activation of endogenous opioids. This has been confirmed in several studies (Benedetti et al. 2006a, Wager et al. 2007). If participants have prior experiences with other analgesics, such as NSAIDs, subsequent pain analgesia could be based mainly on cannabinoid pathways of the neural system (Benedetti 2013). This again shows that, on a neurophysiological level, learning mechanisms play a crucial role in developing placebo mechanisms.

The neurobiology of placebo analgesia confirms that placebo effects are not based on abnormal processes, but rather are the result of healthy brain activity. Indeed, only people with highly functioning brains are able to develop robust placebo responses. Individuals with serious brain dysfunctions show no or reduced placebo response (Benedetti et al. 2006c). Therefore, not surprisingly, placebo mechanisms are based on healthy brain connectivity, as has been confirmed by recent studies (Sinke et al. 2016).

Considering the crucial role of expectations for the development of placebo responses, an improved understanding of the neurobiology of expectations and expectation changes offers an important link between the psychology and neurobiology of placebo mechanisms. This is even more relevant when conceptualizing the brain as a prediction machine. According to these new concepts of brain activation, the brain is not considered as a passive organ waiting for external stimulation, but rather as a continuously predictive system that only activates further higher processing if predictions are violated by external stimulation. Schwarz et al. (2016) conclude that predictive coding accounts for placebo effects and integrates prior experiences at the neurophysiological levels via recurrent systems in the ascending and descending pathways. The fact that the dopamine system and the nucleus accumbens are both strongly implicated in the processing of reward has led to the formulation of the placebo–reward hypothesis: Expecting a positive treatment effect could be considered a reward, and this expectation therefore relies on typical structures of reward processing (de la Fuente-Fernandez et al. 2001, Lidstone et al. 2010).

While the role of brain mechanisms that contribute to placebo analgesia has been extensively investigated, much less is known about the neurobiological pathways of other placebo effects. Investigating patients with Parkinson's disease who have taken dopamine-active drugs confirmed that, in many (but not all) patients, placebo applications can even trigger dopamine release (de la Fuente-Fernandez et al. 2001, Lidstone et al. 2010). Peripheral psychophysiological placebo reactions can also result from Pavlovian conditioning, as has been confirmed in studies by Meissner (2008) and others. Typically, expectations are associated with psychobiological anticipatory reactions that can either represent or facilitate placebo reactions (e.g., heart rate increases when expecting stress). However, the neurobiological trajectories of nonpain placebo effects need further investigation.

In contrast to the placebo response, neurophysiological correlates of the nocebo response seem to involve more pathways related to negative expectations and anxiety. An imaging study of nocebo hyperalgesia highlighted the role of the affective cognitive pain pathway (Kong et al. 2008). Nocebo hyperalgesia has also been shown to be related to hyperactivity of the hypothalamic-pituitary-adrenal axis (Benedetti et al. 2006b), and cholecystokinin, a peptide hormone of the gastrointestinal system that is involved in anxiety states, also plays a role in the nocebo response (Benedetti et al. 2007) (see the sidebar titled Do Genes Underlie the Variability of the Placebo Response?).

DO GENES UNDERLIE THE VARIABILITY OF THE PLACEBO RESPONSE?

Advances in genomics have enabled a closer examination of pharmacogenetic effects in active or inert treatments. Recent work by Hall et al. (2018) at Harvard Medical School has investigated whether there may be some genetic basis for the placebo response and why some people respond to a placebo and others do not. Multiple genes associated with the placebo response are related to neurotransmitter pathways. One such gene is *catechol-O-methyltransferase* (*COMT*), which encodes an enzyme that metabolizes catecholamines like dopamine and epinephrine. Hall's group has shown that polymorphisms in this gene are related to a stronger placebo response in three large trials (Hall et al. 2012, 2014, 2016). Interestingly, the same gene seems to be involved in the development of nocebo responses, as well (Wendt et al. 2014). By mapping *COMT*, and other genes reported in the literature to be associated with the placebo response, to the constellation of all known human protein–protein interactions, Hall's group has expanded the set of genes putatively involved in the placebo response, creating the placebome (Wang et al. 2017). The placebome is now being used to examine genetic correlates of the placebo response across a wide cross-section of clinical trials.

EXPLOITING THE PLACEBO EFFECT

Maximizing Expectations: The PSY-HEART Trial

While the role of expectations as a predictor of clinical outcomes has been frequently investigated, experimental approaches to optimizing patients' expectations as a way of improving clinical outcomes are rare. One successful demonstration of the value of these approaches is a recent study on patients recovering from heart surgery (Rief et al. 2017). Other studies have shown that patients' expectations before undergoing heart surgery are a powerful predictor of disability three months after surgery (Juergens et al. 2010), but expectations have not been specifically manipulated in this context. To investigate this further, Rief et al. (2017) randomized 124 patients that were scheduled for coronary artery bypass graft surgery to three intervention arms: (*a*) Expect, in which expectations on how life will develop after a successful heart surgery were optimized; (*b*) Support, in which, using a similar format, patients received emotional support only, without directly targeting expectations; and (*c*) standard medical care. In the Expect condition, patients were encouraged to develop very clear expectations of how daily life would change after successful surgery, such as what kind of positive activities they would be able to perform, how they would be able to cope with potential symptoms and problems during the recovery process, and how they could actively contribute to a positive recovery. The two psychological interventions were highly focused and involved relatively minimal levels of contact. The week before surgery, patients received two in-person sessions and two phone calls, and a third phone call took place six weeks after surgery as a booster session to refresh the contents of the presurgery interventions (see **Figure 3**).

Six months after surgery, patients in the Expect condition showed the best outcomes in terms of subjective working ability and psychological quality of life. A postcard from a patient in the Expect group illustrates how these interventions can have real-life impact. It is most striking that

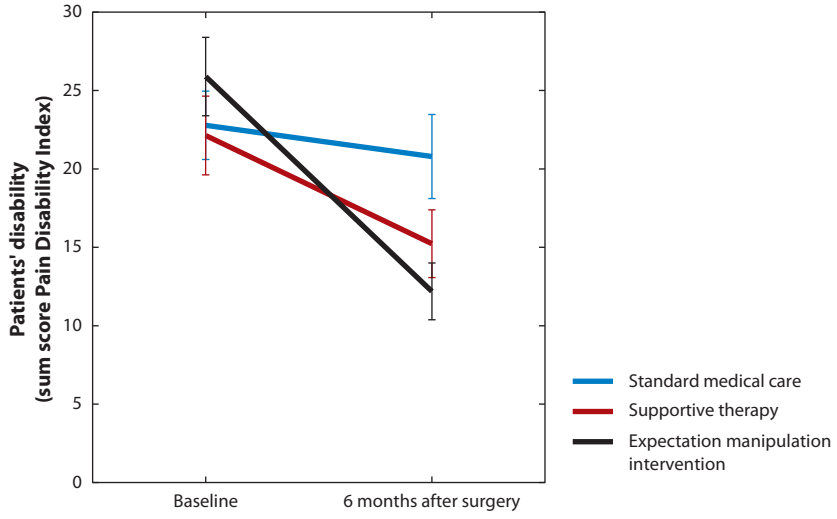

Figure 3

PSY-HEART study (Rief et al. 2017): optimization of expectations prior to heart surgery. If heart surgery patients receive a pre-operative intervention to optimize outcome expectations (Expect condition), their disability at a 6-month follow-up is significantly lower than after heart surgery with standard medical care. Patients receiving a psychological attention intervention (emotional support; Support condition) report disability scores at follow-up that fall between those of the Expect and standard medical care groups.

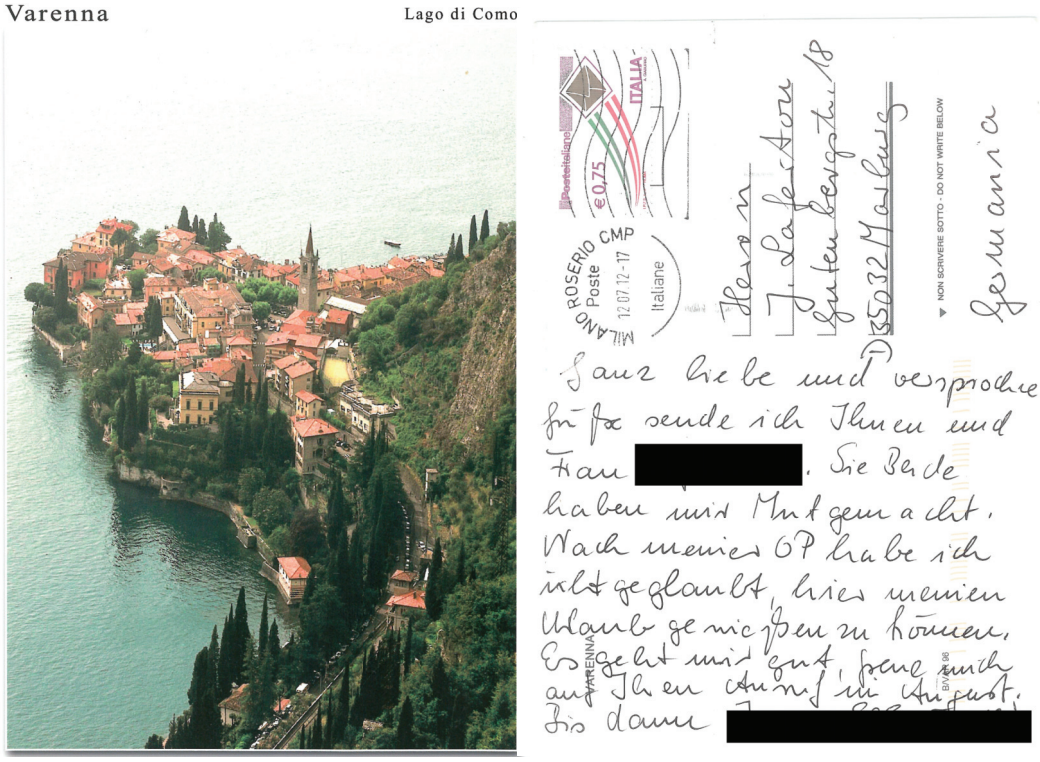

Figure 4

Expect group patient's postcard. "As promised, I send you and your friendly colleague best greetings from Italy. You were so encouraging! Before surgery, I did not expect to be able to spend my holidays here at this wonderful place. I feel quite well, and I am looking forward to your anticipated phone call in August. Yours."

this relatively low-intensity intervention led to significant differences in clinical outcomes. Some of the benefits of the psychological interventions were even associated with endocrine changes (Salzmann et al. 2017). While these results are promising, they require replication and extensions to other clinical conditions (see **Figure 4**).

Open-Label Placebos

There has been recent interest in the use of open-label placebos, i.e., placebos that patients take knowing that they do not contain active medicine. Open-label placebos avoid the ethical issues involved in the deceptive prescription of placebos, which violates informed consent and may compromise the clinician–patient relationship. In the studies that have used open-label placebos, positive expectations are typically established by describing the power of the placebo effect as being established through conditioning and expectations and working through mind–body processes to improve health. The patient is informed that, even though they are not taking any active medicine, a placebo may still help improve health.

An initial RCT of 80 patients with IBS assigned patients to open-label placebo pills described as being "made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvements in IBS symptoms through mind-body self-healing processes" (Kaptchuk et al. 2010, p. 1) or to a no-treatment control group with the same amount of provider

contact. Findings revealed significant improvements in symptoms at the 3-week follow-up. The study demonstrated that open-label placebos delivered with a convincing rationale can improve subjective symptom reports in IBS. This prompted other researchers to investigate whether open-label placebos could improve outcomes in other conditions. Positive effects from open-label placebos have now been demonstrated in low-back pain (Carvalho et al. 2016), allergic rhinitis (Schaefer et al. 2016), and cancer-related fatigue (Hoenemeyer et al. 2018). A review of five open-label placebo studies found a positive medium effect size on subjective symptoms (Charlesworth et al. 2017).

While the initial results of studies of open-label placebos have been positive, there are some reasons to be cautious about the findings. A recent study evaluated the effect of open-label placebos on an objective, measurable physiological outcome, wound healing, and found no effect (Mathur et al. 2018), suggesting that the main benefit from open-label placebos could be restricted to subjective symptoms. The participants recruited into the initial studies for a mind–body treatment are also more likely to be receptive to open-label placebos than individuals with a preference for more traditional medical treatments. A further question at this stage is whether open-label placebo treatment will be acceptable to doctors and therefore more widely adopted.

To summarize, initial attempts to make use of placebo mechanisms to improve treatment outcomes indicate that this strategy could have enormous potential to improve clinical care. A number of the factors that have been found to improve placebo response could be easily incorporated into current treatments to maximize outcomes. These include optimizing patient's expectations prior to treatment, using a positive role model to demonstrate treatment effectiveness, and inducing positive pretreatment experiences with similar drug treatments. Improving aspects of the clinical interaction, such as empathy, shared decision making, and patient perceptions of physician competence, is also likely to lead to improved outcomes, although future research in this area is needed. It is likely that open-label placebos will also play a role in treatment in the future as an adjunct to standard therapies, either to reduce side effects or to maximize response to treatment, but the exact niche of open-label placebos has yet to be established.

THE NOCEBO EFFECT

The nocebo effect was originally defined as an adverse effect from an inert treatment (Kennedy 1961). The nocebo effect was seen as complementary to the placebo effect, the beneficial health effect that occurs following an inactive treatment. Although its better-known and more glamorous counterpart, the placebo effect, has attracted more research interest, the nocebo effect has an arguably more important impact on medical care. The high rates of nocebo effects attached to medical treatments result in impaired quality of life for many patients and can cause significant issues in adherence and persistence with medical therapy that lead to increased medical costs (Kardas et al. 2013). There is also evidence that negative effects of treatment transfer to reduce the effectiveness of future therapies (Kessner et al. 2013).

Much of the nocebo literature has focused on side effects reported in the placebo arms of drug trials; however, over time, the use of the term nocebo has widened. The term nocebo is now used to refer to the adverse effects of active treatments that cannot be attributed to the pharmacological or other active ingredients of the therapy (Barsky et al. 2002). A recent analysis of the side effects reported in the active treatment groups in RCTs suggested that approximately 70–80% were probably not attributable to the effects of the drug (Mahr et al. 2017). Furthermore, approximately 25% of patients randomized to take a placebo in clinical trials report side effects (Clark & Leaverton 1994), and this incidence rises substantially when participants are asked about specific side effects (Barsky et al. 2002).

A recent example of the importance of the nocebo response is illustrated in the side effects reported for statin drugs for preventing and treating cardiovascular disease. Complaints of muscle pain are a common cause of discontinuation among patients prescribed statins (Cohen et al. 2012), even though RCTs show that the rates of muscle symptoms do not significantly differ between drug and placebo groups (Finegold et al. 2014, Kashani et al. 2006). In fact, an analysis of a large statin trial of over 10,000 patients found an excess of muscle-related adverse events reported when patients and doctors knew that statin therapy was being used but not when the treatment was blinded (Gupta et al. 2017). Interestingly, large population studies in Denmark (Nielsen & Nordestgaard 2016) and the United Kingdom (Matthews et al. 2016) found early discontinuation from taking statins was associated with negative statin-related news stories in the media and, importantly, also increased the risk of heart attack and death from cardiac disease.

The term nocebo has also been extended from the purely medical arena to describe reported adverse effects following exposure to benign new technology, environmental agents, or stimuli that the individual believes are likely to cause symptoms or have other negative health effects (Petrie & Wessely 2002, Petrie et al. 2001, Rief et al. 2012). Electrosensitivity is an example of such a condition; sufferers complain of symptoms after they believe that they have been exposed to weak electromagnetic fields, such as Wi-Fi or cell phone signals, even though double-blind studies do not support a link between such exposure and symptoms or physiological effects (Rubin et al. 2011). Similar concerns have been raised about infrasound generated by wind turbines. Many individuals have reported symptoms when wind turbines are constructed nearby, and an impressive number and range of symptoms and diseases have been attributed to the effects of wind turbines (Chapman 2016). However, the distribution and pattern of complaints suggest that a nocebo response is the most likely cause of these symptoms (Chapman et al. 2013, Crichton et al. 2014a).

A more pervasive illustration of the nocebo effect is the current popularity of gluten-free diets. Many individuals now believe that they are gluten sensitive and report symptoms such as abdominal discomfort and bloating, as well as headache, lethargy and other symptoms, following ingestion of products containing gluten. The gluten-free food manufacturing industry has grown rapidly to accommodate the popularity of this new diet, but double-blind provocation trials with either placebo or gluten have failed to support this sensitivity in individuals without celiac disease; a more likely explanation for the reported symptoms is the anticipation of intolerance and a misattribution of normal symptoms (Lionetti et al. 2017).

Mechanisms

Several factors have been proposed as causing the nocebo effect. These include an individual's negative expectations, symptom misattribution, and prior learning. Contextual factors and the characteristics of the treatment have also been identified as important mechanisms, along with transmission of the nocebo response from others in the individual's social environment.

Negative expectations. In the placebo response, positive expectations about a treatment cause patients to focus on and report improvements in symptoms and health outcomes. Conversely, in the nocebo response, negative expectations increase the awareness and reporting of negative or adverse outcomes (Kirsch 1985). Negative expectations can be generated by external sources, such as explicit warnings of specific side effects that may occur from a treatment, or even by increases in general awareness about the potential of a treatment or environmental stimuli to cause health problems.

The creation of expectations by an external source was clearly illustrated by a treatment trial for unstable angina (Myers et al. 1987), where the patient consent form in two research centers

specifically listed gastrointestinal side effects as a possible adverse effect of the drug, while the consent form in another center did not. The centers that listed gastrointestinal side effects had six times the withdrawals for gastrointestinal symptoms than the center that did not list this side effect. Similarly, among patients who were being treated with beta blockers, those warned of sexual dysfunction side effects reported these side effects three to four times more frequently than a control group who did not receive this information (Cocco 2009).

The power of information to frame expectations and symptom experiences was also clearly demonstrated by a study of infrasound (Crichton et al. 2014b), a low-frequency sound below the threshold of hearing that is claimed to be the cause of health complaints in residents living near wind turbines. In this study, participants were randomized to receive either positive expectations (infrasound has health and therapeutic benefits) or negative expectations (infrasound causes health problems) before being exposed to the same infrasound stimulus. The results revealed that participants who received negative expectations showed a significant increase in the number and intensity of symptoms, while those who received positive expectations showed the opposite pattern, with a significant decrease in number of symptoms and symptom intensity following exposure to infrasound.

Expectations can be generated by the individual when concerns about a particular medicine or their own personal sensitivity to medicine are activated after they receive a prescription for a new treatment. A longitudinal study of patients with rheumatoid arthritis found that patients with more concerns about their medication at baseline were more likely to report side effects six months after beginning treatment (Nestoriuc et al. 2010). Similarly, in women taking endocrine therapy for breast cancer, higher expectations of side effects at baseline predicted later side effect reporting and drug nonadherence (Nestoriuc et al. 2016).

The belief that an individual is especially sensitive to the actions and side effects of medicine is a relatively common belief, with around one in five individuals in a general population sample agreeing with the statement "My body is very sensitive to medicines" (Faasse et al. 2015). A recent study looking at symptoms attributed to medicine after the ingestion of a placebo described to participants as "a well-known tablet" found that beliefs that medicines cause harm and greater perceived sensitivity to medicine were associated with increased odds of attributing symptoms to the medicine (Webster et al. 2018). A study of adults receiving travel vaccines found that perceived sensitivity to medicine was associated with the number of symptoms attributed to the vaccination immediately following the injection (Petrie et al. 2004). A later study found that parents were more likely to report side effects in their children following influenza vaccination if they held beliefs that the vaccine can cause short- or long-term health problems (Smith et al. 2017). Clearly, perceived sensitivity to medicines is important in generating negative expectations about the effects of a medicine, and consistent with this finding, patients with high levels of perceived sensitivity to medicine are more likely to seek out information about medicines from the Internet or drug information sheets and to report symptoms when taking prescription medicine (Faasse et al. 2015) (see the sidebar titled Items from the Perceived Sensitivity to Medicines Scale).

Concerns about personal sensitivity to an environmental agent can also trigger a nocebo effect and even cause the individual to believe that others have experienced symptoms if they have been similarly exposed. In a longitudinal study of a community sprayed by a pesticide from fixed wing planes and helicopters, individuals who had high levels of concern before the spraying about aspects of modern life and technology affecting health (modern health worries) reported more symptoms in response to the spray (Petrie et al. 2005). They also reported that the health of their children and pets had been negatively affected by the spray. Modern health worries have also been associated with higher levels of symptom reporting in a general population sample (Rief et al. 2012).

ITEMS FROM THE PERCEIVED SENSITIVITY TO MEDICINES SCALE

The perceived sensitivity to medicines scale, developed by Horne and colleagues (2013), includes:

1. My body is very sensitive to medicines.
2. My body overreacts to medicines.
3. I usually have stronger reactions to medicines than most people.
4. I have had a bad reaction to medicines in the past.
5. Even small amounts of medicines can upset my body.

Contextual factors. Systematic reviews of RCTs for different classes of drugs have shown that the side effects reported by patients in the placebo groups are similar to the type of side effects reported in the active medication group. For example, patients in the placebo group in tricyclic antidepressant studies are significantly more likely to report dry mouth, constipation, vision problems, sexual difficulties, and fatigue than patients in the placebo arms of selective serotonin reuptake inhibitor trials (Rief et al. 2009b). Similar results are reported for different classes of drugs used to treat migraine headaches (Amanzio et al. 2009). These findings illustrate that the side effects reported in placebo groups in randomized trials closely match the expectations created as part of the informed consent process for that type of medication. Importantly, this highlights the difficulties of determining the true side effect profile of drugs by simply comparing the treatment and placebo groups, as this comparison alone is likely to seriously underestimate the true rate of adverse effects.

The nocebo response can also be created by more subtle branding cues when patients are switched from a branded to a generic medicine. Approximately 20–30% of patients, and a similar percentage of pharmacists and physicians, have negative views of generic drugs, seeing them as being less effective and having poorer quality than their branded equivalents (Colgan et al. 2015). Laboratory research shows that, even when drugs are placebos, the change in label from branded to generic can result in increased side effect reporting and reduced effectiveness (Faasse et al. 2013). Drug switches from branded to generic can result in increased reports of side effects and complaints that the new drug is less effective (Boone et al. 2018, Weissenfeld et al. 2010).

Restricting the choice of medication can impact nocebo responding. Many health care systems are now limiting patients' choice of funded medications as a way of controlling costs. In a study where participants were randomized to either have a choice of two beta blocker medications (placebos) or have the medicine assigned, the group with no choice attributed more side effects to the medication immediately following ingesting the tablet and at 24-hour follow-up than the group who was given their choice of medication (Bartley et al. 2016). This suggests that switching to a single funded drug or restricting the choice of funded medication may in itself cause an increase in side effect reporting. In these situations, nocebo responding and lower perceived efficacy of the new drug seem to be made worse by lower levels of trust in drug companies and governmental pharmaceutical agencies (K. MacKrill and K.J. Petrie, unpublished manuscript; Webster et al. 2018).

Social transmission. Seeing another person report side effects after receiving a medical treatment can also influence the nocebo response by increasing expectations of a similar response. Vögtle and colleagues (2013) demonstrated that watching a model display more pain after application of an ointment followed by pressure pain resulted in participants reporting more pain after the

ointment was applied, compared to control conditions. There is also some evidence that females may be more sensitive to the effects of modeling than males, but it seems likely that empathy may underlie this difference (Faasse & Petrie 2016). In a study where a model reported either symptoms or no symptoms after inhaling a substance described as being potentially toxic, participants who saw the model report side effects also reported more side effects, and this effect was stronger in females (Lorber et al. 2007). A recent study using both male and female models, in contrast to previous studies using only one gender, found that social modeling increases side effects following administration of modafinil (placebo), with the effect being stronger in participants with higher levels of baseline empathy (Faasse et al. 2018).

The transmission of nocebo effects can occur on a wider scale through media reports. Experimental studies have demonstrated that television reports can increase symptoms and intensify somatic experiences (Witthöft et al. 2018). Bräscher and colleagues (2017) demonstrated that watching a television report on the adverse effects of exposure to weak electromagnetic fields intensified the ratings of nonpainful electrical stimulation to the palm of the hand when participants believed that they were exposed to Wi-Fi signals, compared to the ratings of a group that had previously watched a neutral television report. A similar study showed that media reports can increase symptom reports following sham Wi-Fi exposure, especially in more anxious individuals (Witthöft & Rubin 2013).

A real-world example of this process comes from a health scare in New Zealand following the change in formulation of a drug used to treat hypothyroidism (Faasse et al. 2010). After the color and appearance (but not the active ingredient) of the medication changed, there was a large increase in adverse drug reports. This was covered by television news reports, which highlighted different negative patient reactions to changes in the appearance of the medicine. A detailed examination of the specific symptoms reported by patients in television news reports showed an increase in reports of these symptoms to the Centre for Adverse Reactions Monitoring in the days following the news bulletins (Faasse et al. 2012).

Learning. Conditioning can also generate nocebo effects. Classical conditioning, where two stimuli are paired repeatedly, can result in the previously neutral stimulus becoming able to elicit a physiological response similar to the original conditioned stimulus. Patients who are receiving chemotherapy in oncology clinics can develop nausea when they see or even smell a stimulus associated with their treatment, such as the treatment room, the clinic, or a staff member (Roscoe et al. 2011). Such conditioned reactions can also occur in patients with a history of adverse drug reactions. A study of 600 such patients given an inert pill found that approximately one-quarter reported adverse reactions such as headache and itching (Liccardi et al. 2004). Another study using a sample of healthy controls was also able to show that side effects of antidepressants can be learned (Rheker et al. 2017). After participants received four doses of 50 mg of amitriptyline (one per day), an administration of a placebo pill also provoked amitriptyline-specific side effects. If patients have learned to become side effect responders, they might be at risk of developing side effects in future treatments, even if the drugs have different pharmacokinetics.

In a series of studies, Van den Bergh and colleagues (1999, 2002) examined how physical symptoms can be conditioned when paired with an odor or even a mental image. In these conditioning studies, odors or thought cues were paired with breathing CO_2, which typically causes smothering sensations, chest tightening, increased heart rate, and anxious feelings. Following the acquisition phase, the odor alone induced physical symptoms, and this reaction was stronger in participants with higher rates of negative affectivity, as well as in patients with medically unexplained symptoms. This research group has also shown that symptoms are more strongly conditioned with unpleasant

odors and fearful thoughts, such as being stuck in an elevator (Van den Bergh et al. 2001), suggesting that pre-existing expectations about a stimulus may intensify the effects of conditioning (Stewart-Williams & Podd 2004). Support for this idea was provided by a recent meta-analysis showing that nocebo effects were largest when they were induced by a combination of conditioning and expectations (Petersen et al. 2014).

Symptom misattribution. An important factor underlying the nocebo effect is the frequency of physical symptom reporting in the general population. While symptoms are commonly thought to only occur when individuals are suffering from an illness, studies show it is actually more normative to have symptoms and more unusual not to report any physical symptoms. A recent general population survey showed that the median number of symptoms experienced in the previous week was 5 and that 23% of the sample reported experiencing 10 or more symptoms (Petrie et al. 2014). Only 11% of the sample reported no symptoms in the previous week. The most common symptoms reported in this general population sample were back pain (38%), fatigue (36%), headache (35%), nasal symptoms (34%), joint pain (34%), insomnia (29%), cough (28%), and muscle pain (23%).

The high level of background symptom reporting and the types of symptoms commonly reported in the general population can offer insights into the level of misattribution to medical treatment that can easily occur. A recent study of adverse reactions to commonly used medications found a large overlap between the most common background symptoms and the types of symptoms listed as drug adverse reactions for frequently prescribed medicines (Tan et al. 2014). This study found that 8 of the 20 most commonly experienced symptoms in a general population survey were listed as an adverse effect for over 90% of the drugs. These same symptoms also frequently appear in studies of adverse effects reported by patients taking placebos (Rief et al. 2006).

At the heart of the nocebo response is a misattribution process. However, the misattribution of symptoms is a complex process due to the fact that both new and existing symptoms can be misattributed to the effect of a treatment or other stimulus. For example, some of the symptoms that individuals may attribute to the effects of medication after taking a placebo pill could be symptoms that the individual was previously experiencing, such as a headache, that are now being either wholly or partially attributed to the medication (e.g., "My headache got worse"). New symptoms that the individual has experienced since taking the placebo pill also may or may not be attributed to the medicine. The time since starting the treatment, the number of background symptoms available for attribution, and the type of treatment can all strongly influence the misattribution process (Faasse & Petrie 2013, Webster et al. 2018).

An important influence on the misattribution of symptoms is negative affectivity. In a study of symptoms attributed to a travel vaccination, trait negative affectivity, while not associated with immediate symptoms following the injection, was associated with a much wider range of symptoms being attributed to the vaccination a week later (Petrie et al. 2004). Similar findings have been shown in a common cold study where participants were exposed to a cold virus. Negative affectivity was associated with higher rates of symptom reporting, regardless of whether participants developed objective indicators of a cold (Feldman et al. 1999).

It seems that negative affectivity may have the greatest influence over the longer term, rather than immediately following treatment, where more proximal expectations, such as perceived sensitivity to medicine, have a greater influence. Negative affect seems to be associated with a greater tendency to misattribute common symptoms to the effects of treatment. This may be due to the fact that individuals with higher negative affect tend to report more physical symptoms, so there is more opportunity to attribute these to the effects of a treatment (Watson & Pennebaker 1989). High negative affect is also related to the tendency to make more negative attributions or interpretations about background symptoms (Barsky et al. 2002). In a study of women taking tamoxifen to

reduce the likelihood of breast cancer reoccurrence, high levels of negative affect were associated with a greater number of reported symptoms and the tendency to attribute more symptoms to the drug (Cameron et al. 1998). Similarly, Davis and colleagues (1995) found that higher levels of negative affect were associated with more symptom complaints in those participants randomized to the placebo arm of a drug trial examining the side effects of moclobemide.

Reducing the Nocebo Effect

Given the widespread nature and clinical significance of the nocebo effect, it is surprising that little research has focused on reducing its negative consequences. Various approaches have been proposed, but as yet there is little evidence that favors one particular intervention. Contextualized informed consent has been proposed as a way to reduce the nocebo response by allowing doctors to tailor the information about possible treatment side effects to the patient (Wells & Kaptchuk 2012). Using this method, the physician would provide less information about possible side effects to patients believed to be at risk of developing a nocebo response to the treatment. Others have criticized this approach for being inconsistent with the principle of informed consent (Miller 2012) and for violating patients' autonomy (Bromwich 2012).

Another method has focused more on optimizing treatment expectation by balancing the presentation of adverse effects with expected benefit information. This may involve framing side effect information in a positive way ("95% of patients tolerate this treatment without any problems"), addressing patients' anxiety before starting the therapy, and improving patients' ability to manage or access to support for managing negative side effects should they occur (Bingel 2014, Enck et al. 2013). In a study of individuals receiving an influenza vaccine, participants randomized to receive a positive framing of side effects—describing the local side effect of a sore arm but claiming that 60% do not have a problem with this side effect—were compared to a group who received a negative framing—40% will get a sore arm. The results showed that those participants who received a positive framing of the likelihood of side effects had fewer systemic side effects and lower work absenteeism (O'Connor et al. 1996). A more recent study found that receiving a positive framing of the likelihood of side effects before taking a sham medicine (framing side effects as uncommon, i.e., "90% of people will not be affected") reduced symptoms attributed to the medicine by 34% compared to standard side effect risk information (framing side effects as common, i.e., "1 in 10 will be affected") (Webster et al. 2018). The balance inherent in this approach is to give patients all the relevant information about a new treatment (albeit framed in a more positive way) so that the patient may make an informed decision, while minimizing the harm that may occur through the nocebo effect. The value of this approach is likely to reduce as the number and range of expected side effects increase.

A third method takes a different approach. Instead of reducing or reframing the information about the possible side effects given to patients, it provides information about the nocebo effect itself and how it is relevant to their treatment experience (Crichton & Petrie 2015). This method provides a lay definition of the nocebo effect and how it works, along with examples of the nocebo effect in daily life, and demonstrates how the provision of side effect information about the treatment could in itself cause the patient to experience these same symptoms or other symptoms that may not be caused by the treatment. Explaining the nocebo effect as a method of reducing adverse effects has been employed in a laboratory study of environmental wind turbine noise, and the method successfully reduced the number of symptoms following exposure to the sound (Crichton & Petrie 2015). However, this method, like the other methods covered in this section, has yet to be evaluated in more common medical contexts where patients are about to undergo new medical treatments or procedures.

CONCLUSION AND FUTURE DIRECTIONS

Placebo mechanisms contribute to a significant proportion of the outcome of clinical interventions. The neurobiological and psychological consequences that are associated with expectation effects constitute an evolutionarily developed advantage for the human species, and thus, these consequences should be considered a healthy response and a mostly helpful human characteristic. Up until recently, medicine and clinical research has tried to minimize or eliminate placebo effects in clinical interventions. However, we are now at an important moment in placebo research where the potential of using placebo mechanisms to enhance existing treatments is beginning to be appreciated.

The nocebo effect has a major impact on medical treatment but is relatively understudied and unrecognized compared to the placebo effect. There are clear evolutionary advantages to being vigilant about substances that are likely to cause harm and to monitoring the body for early signs of problems. Survival has depended on paying attention to possible bad outcomes and avoiding them if possible, and this may help explain why the nocebo effect is so pervasive and so quickly established (Baumeister et al. 2001). The nocebo effect has considerable costs in terms of impaired patient quality of life, nonadherence, and impact on medical visits and hospitalizations. Potential interventions that reduce these negative outcomes have, to date, received scant attention.

Considering the substantial power of placebo and nocebo effects, an improved understanding and systematic assessment and application of the underlying mechanisms are urgently required. Research on mechanisms so far has mainly focused on associative learning, observational learning, instructions, and some aspects of clinician–patient interactions. However, this is a relatively narrow selection of potential psychological and contextual mechanisms. Furthermore, most psychobiological pathways of placebo and nocebo effects have been investigated in pain research. An extension into areas of medicine with the greatest patient burden, such as hypertension, depression, cancer, and metabolic disorders, should be part of the focus of future research.

Research on placebo and nocebo effects has mainly focused on isolating and investigating a single mechanism. However, clinician encounters are characterized by the presence of various mechanisms that can contribute to treatment success. It is a highly simplified assumption that these effects are simply additive (e.g., the placebo mechanisms and the drug's pharmacodynamics). More and more studies confirm that these mechanisms can show complex interactions. A study by Berna and colleagues (2017) showing that an analgesic only reveals its positive effect if some active placebo is added provides an example that more research on the interaction among mechanisms is needed and that a simple additive model is insufficient.

The gap between clinical research, which attempts to minimize or even eliminate placebo mechanisms, and clinical practice, which requires understanding of the maximum potential of an intervention, must be further reduced. More clinical trials should include natural course arms, but also arms that try to maximize the benefit for patients by making use of placebo mechanisms and minimizing nocebo effects. While our knowledge about the difference between artificial double-blinded drugs and placebo pill treatments is overwhelming, our knowledge about the maximum potential of treatments remains neglected.

Expectations are the fundamental drivers of placebo and nocebo effects. While research has typically focused on how to establish expectations, the clinical challenge is more frequently to change (dysfunctional) expectations. Further work to improve our understanding of how expectations are maintained and changed and a closer examination of these processes should steer the development of more effective interventions to shift expectations. It is an exciting time for researchers working in this area, as the potential is now clear for making placebo processes part of mainstream medicine.

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