Clinical and Ethical Implications of Placebo Effects: Enhancing Patients' Benefits from Pain Treatment

Regine Klinger and Herta Flor

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R. Klinger (✉)
Outpatient Clinic of Behavior Therapy, Department of Psychology, University of Hamburg, Hamburg, Germany
e-mail: rklinger@uni-hamburg.de

H. Flor
Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany
e-mail: herta.flor@zi-mannheim.de

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Abstract

Expectancy and learning are the core psychological mechanisms of placebo analgesia. They interact with further psychological processes such as emotions and motivations (e.g., anxiety, desire for relief), somatic focus, or cognitions (e.g., attitudes toward the treatment). The development of placebo responsiveness and the actual placebo response in a person is the result of the complex interaction between factors traced back to the individual learning history related to analgesic drugs or treatments and factors of the current context referring to the analgesic or placebo treatment. The aim of this chapter is to depict these complex interactions in a new model of analgesic placebo effects. It joins aspects of the learning history (preexisting experiences and preexisting expectations) of a patient with aspects of the current context (current expectation as a result of external and internal situation in which a pain medication/treatment/placebo is taken, e.g., current information about pain medication, current specific context/cues, desire for pain relief, certainty about upcoming pain relief, current expectation about pain reducing course, current selective attention, increased pain experience, or decreased pain experience). In order to exploit placebo efficacy for an analgesic treatment it is worthwhile to assess in which direction each of these factors exerts its influence in order to maximize placebo effects for a specific patient. By applying placebo mechanisms in this differentiated way, the efficacy of pain treatment can be deliberately boosted.

Keywords

Placebo analgesia • Psychological and neurobiological mechanisms of placebo analgesia • Clinical implications • Model of analgesic placebo effects

1 Introduction

The good evidence for the efficacy of analgesic placebo effects raises the question how to exploit them for clinical pain treatment. Until now, the fact that patients can reduce their pain via placebo effects has rarely been explicitly used in the treatment of acute and chronic pain. In this chapter, we will discuss how the research on placebo effects can be utilized in clinical pain treatment and how the efficacy of pain treatment can be boosted by the exploitation of placebo effects. We believe that specific knowledge about the psychological and neurobiological mechanisms underlying placebo effects aids both patients and the therapists in maximizing their

use. Most studies on placebo effects were conducted in healthy participants raising the question if analgesic placebo effects act in a similar manner in patients. This question needs to be addressed in more detail in clinical research.

2 Theoretical Concepts for the Clinical Application of Placebo Effects

As noted above, a better understanding of the psychobiological mechanisms of placebo analgesia is needed to enhance the transfer of placebo effects into clinical applications. The research conducted in recent years has mainly focused on the neurobiological correlates of the placebo effect and the active mechanisms of shaping expectancy via "instruction," "classical conditioning," and "social learning." At the same time, little attention has been paid to possible specific interactions between existing attitudes toward medication in general (e.g., positive/negative attitudes) or prior experience with analgesic treatments and the efficacy of placebo interventions. In most research, the placebo manipulation itself (inducing specific expectations) is an independent variable, but not the already existing pattern of attitudes and learning experiences. In this section we describe the psychological and psychobiological underpinnings of placebo effects and integrate them into a model of processes of analgesic placebo effects, which can be used as a starting point for clinical interventions.

2.1 Psychological Mechanisms of Placebo Analgesia

2.1.1 Shaping Expectancy and Inducing Learning via "Classical Conditioning"

Based on the model of classical conditioning, the placebo effect is viewed as a learnt response, which is triggered by the placebo stimulus ("classically conditioned stimulus"). According to the traditional stimulus substitution model (Ader 1993; Price et al. 2008) the repeated association of an initially neutral stimulus (appearance, color, flavor of the drug) with the unconditioned stimulus (US; pharmacological effect of the drug) leads to a conditioned response (CR; placebo effect). The placebo stimulus therefore becomes a conditioned stimulus (CS; inert "vehicle" of a drug, e.g., appearance, color, and flavor of a tablet). It leads to a placebo response or CR, which is similar to the original pharmacological effect of the corresponding active drug (UR). After this association has been established, the inert agent alone (the placebo) can trigger the effect. Thus, treatments (e.g., analgesic therapies) can have a positive effect based on their associations with previously experienced successful treatments. The nocebo effect can be viewed similarly using the model of classical conditioning. Here the UR refers to the adverse side effects of a drug. They become associated with the agent, in this case the "active (negative) component (US)," which in turn produces the nocebo effect as a CR. It is important to note that the classical conditioning processes shape

overt expectancies about positive or negative effects of treatments but also form associative experiences that can be out of the patient's awareness but can still have an effect on his or her behavior, for example, by adding a positive or negative emotional response to certain contexts or cues that were associated with drug effects. Although most research has been conducted on pharmacological analgesic interventions, it is important to realize that placebo effects are also active in other pain treatments, for example, physiotherapy or psychological interventions.

2.1.2 Shaping Expectancy via "Instruction"

According to expectancy theory, the placebo effect is produced by instructions and the anticipatory expectations or response expectancies they induce (Kirsch et al. 2004; Price et al. 1999; Kirsch 1997). Similarly, a negative expectancy, e.g., the expectation that a drug will produce adverse side effects, can produce a nocebo effect. From this point of view, placebo/nocebo effects are a subcategory of expectancy effects and their strength and certainty directly modulate the placebo response. A range of mediating mechanisms and concepts has been proposed to explain why expectancies should trigger a placebo effect. On the one hand, higher control beliefs are postulated, which reduce anxiety and stress (Weisenberg et al. 1996). On the other hand, an altered (selective) attention to pain reduction can be assumed, where negative components are disregarded (Turner et al. 1994). Conversely, negative expectancies can reduce control beliefs, thereby increasing anxiety and stress as well as the selective attention paid to negative components.

2.1.3 Shaping Expectancy and Inducing Learning via "Social Learning"

Pain is influenced by social interactions and can be modulated through the observation of others (Craig 1987). The observation of a painful experience of another person can cause a more painful sensation in the observer when he or she experiences the same situation like in the observation. Colloca and Benedetti (2009) showed that the participants, who were observing an analgesic effect in another person when a special light occurred, also displayed analgesia when they were exposed to the same light (analgesic placebo). This social or observational learning thus also plays an important role in placebo effects. It generates a substantial placebo analgesia in the observer, which is positively correlated with the grade of empathy for the observed person (Colloca and Benedetti 2009). Social learning produces placebo effects of the same magnitude as classical conditioning. Recent research has shown that also nocebo hyperalgesia also undergoes social and observational learning (Świder and Bąbel 2013; Vögtle et al. 2013). Observational learning of placebo and nocebo effects may be of special relevance in inpatient clinical settings where patients observe the interaction of other patients with the healthcare personnel and their responses to pain. They are also relevant in outpatient clinical settings, e.g., when patients are sitting in the dentist's waiting room and can hear other patients crying out in pain in the doctor's office.

2.2 Interaction Between Conditioning, Social Learning, and Expectancy in Placebo Analgesia

Conditioning, social learning, and expectancy processes cannot be expected to occur independently. These core psychological mechanisms interact closely with each other in the placebo effect (Klinger et al. 2007). During conditioning, connections between events are learned, the CS provides information about the US, and previous experiences are represented. If placebos are viewed as conditioned stimuli, they can trigger these previous experiences and response patterns. However, it is also important that the relationship between the events is learnt. This suggests that cognitive processes are involved also in the conditioning process and that conditioning processes can increase the expectation for a positive or negative effect. Specifically, a previous positive experience with a drug (US, pain relief) leads to an association between characteristics of the drug (e.g., appearance, flavor, smell) and the response (UR, pain relief): the "surrounding stimuli" of the drug become the CS ("placebo stimulus") and supply the information that a similar effect (pain relief) may be expected the next time the drug is taken. The placebo on its own can then trigger a response (CR, placebo effect). If the information content of the CS ("placebo"), for which a subject has as an expectancy, is further amplified (by the suggestion of a positive drug effect), the CR (placebo effect) can be further increased. In social learning, conditioning and expectancy processes are also thought to interact in their effect on the observer.

2.3 The Neurobiological Basis of Placebo Analgesia

The described placebo and nocebo mechanisms are associated with specific physiological responses in the central nervous system and the periphery. From a neurobiological point of view, placebo analgesia is closely connected with the endogenous opioid system. Levine et al. (1978) showed that placebo analgesia is in fact a highly complex psychobiological process leading to the release of endogenous opioids. Naloxone, an opioid receptor antagonist, reversed the analgesic placebo effect on postoperative pain following a dental extraction (Levine et al. 1978).

Placebos activate brain circuits that are also involved in opioid analgesia. For example, Petrovic et al. (2002) applied heat pain stimuli to healthy subjects and either administered the opioid remifentanil or a placebo (i.v. NaCl labeled as a "potent analgesic"). Under both conditions, areas of the rostral anterior cingulate cortex (rACC) were activated. In addition, there was an increased connectivity between the rACC and the periaqueductal gray. The dorsolateral prefrontal cortex was also found to be activated during placebo analgesia. The strength of its activation, which was especially high during the phase of anticipating pain, was correlated with the subsequent reduction in pain by a placebo (Eippert et al. 2009b; Wager et al. 2004; Watson et al. 2009). Thus, placebos seem to activate the endogenous descending pain-modulating system (Basbaum and Fields 1978),

which inhibits afferent nociceptive information (Millan 2002). This leads to a reduction in perceived pain. If pain stimuli are applied in the placebo condition, the majority of the functional imaging studies indicate a reduced activity in brain areas involved in the processing of pain (Bingel et al. 2006; Petrovic et al. 2002; Wager et al. 2004). Functional imaging studies of the spinal cord show that this effect occurs already at the level of the spinal cord (Eippert et al. 2009b).

Positron emission tomography (PET) studies also confirmed that the endogenous opioid system plays a key role in placebo analgesia. Using [11C] Carfentanil PET, Wager et al. (2007) and Zubieta et al. (2005) showed an amplification of opioid-induced neurotransmission in cingulo-frontal areas and subcortical relay stations during placebo analgesia. As noted above, placebo analgesia can be canceled or considerably reduced by administering the opioid antagonist naloxone (Benedetti et al. 1999; Eippert et al. 2009a, b; Levine et al. 1978; Wall 1999), indicating the important role of the endogenous opioid system; however, Benedetti et al. (1999) showed that both opioid-independent mechanisms are also involved in placebo analgesia. The endocannabinoid system was shown to also play an important role in nonopioid placebo effects (Benedetti et al. 2011). Interesting systems for future studies include, for example, the dopaminergic or the serotonergic effects.

3 A Model of Analgesic Placebo Effects

Beyond expectancy and learning, the described core psychological mechanisms interact with further psychological processes such as emotions and motivations (e.g., anxiety, desire for relief), somatic focus, or cognitions (e.g., attitudes toward the treatment) (Colloca and Benedetti 2007; Geers et al. 2006; Finniss and Benedetti 2005; Price et al. 1999, 2008; Vase et al. 2003; Lyby et al. 2012). The development of placebo responsiveness and the actual placebo response in a person is the result of the complex interaction between factors traced back to the individual learning history related to analgesic drugs or treatments and factors of the current context referring to the analgesic or placebo treatment. Figure 1 depicts these complex interactions, which are discussed in detail below. In order to exploit placebo efficacy for an analgesic treatment it is worthwhile to assess in which direction each of these factors exerts its influence in order to maximize placebo effects for a specific patient.

3.1 Learning History

3.1.1 Preexisting Experiences and Preexisting Expectations

As noted above, in most placebo research, the placebo manipulation itself (inducing specific expectations) is an independent variable, but not the already existing pattern of attitudes. However, it is obvious that a positive attitude compared to an existing negative attitude toward pain medication will result in a stronger placebo effect after the appropriate conditioning and expectancy manipulation. Thus it is

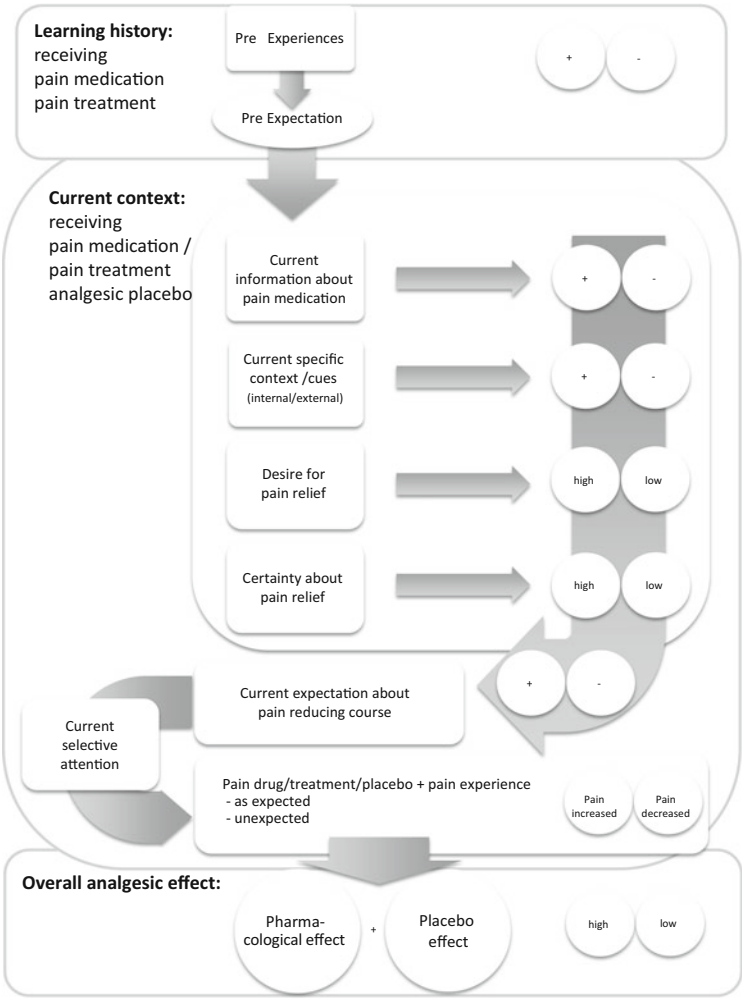

Fig. 1 A model of analgesic placebo effects

important to assess prior learning with analgesic treatment when treating persons with pain.

A history of intake of analgesic medication can be seen as a recurrent association between the pharmacological action and visual or other sensory or emotional aspects of an analgesic. People learn how analgesics act, they learn to presume their effects, and they build up attitudes toward them. Their *preexisting experiences* with analgesics form their *preexisting expectations* about the effects of pain medication. This constitutes the background for receiving current medication or

placebos and needs to be considered as an important influence on the efficacy of the current intervention.

The current intake of pain medication or placebos that goes along with current expectancy about the placebo effect might also be seen as a conditioned stimulus that reactivates earlier stimulus associations stemming from learning history.

Thus, not only prior experience but also associations evoked by the current context act upon the analgesic response.

3.2 Current Context

3.2.1 Current Expectation

The current context comprises both the external and internal situation in which a pain medication/treatment/placebo is taken. Initially, the *current information* about pain treatment plays an important role. Is the information positive (e.g., explanations about the positive action of the drug) or negative (e.g., predominant explanation of side effects of the drug/treatment)? Furthermore, the *current external context* is important. Does the current external context contain cues that are associated with healing or cure and do these cues create confidence in the drug/treatment? The *current internal context* of the patient plays an important role as well. Is the patient in an emotionally positive (e.g., confident, relaxed, balanced, concentrated) or in an emotionally negative (e.g., depressed, anxious, angry, distracted) mood? Is the patient's *desire for pain relief* pronounced (e.g., the patient absolutely needs pain relief) or is it rather weak? Moreover, the patient's *certainty about upcoming pain relief* should be explored. How certain is the patient that the pain drug/treatment will reduce his/her pain?

In summary, these factors shape the *current expectations about the course of the analgesic treatment*. This current expectation about the course of analgesic treatment determines the *current selective attention* of a patient. The patient pays attention to either the positive or the negative effects of the pain medication, treatment, or analgesic placebo—thus the pain medication or treatment or at least the analgesic placebo is associated with either *increased pain experience* or *decreased pain experience*. This current pain experience can be in line with the expected pain (reinforcement) or can be different from this expectation (uncertainty, disappointment). Depending on the direction, the current pain experience is increased in the case of an unexpected pain experience as uncertainty and disappointment of the patient will channel his or her attention on pain-increasing features; the current pain experience is decreased in the case of an expected pain experience because reinforcement and assurance of the patient will channel his or her attention on pain-decreasing features (placebo effect). In the case of the intake of an analgesic this current context variable can either increase or decrease the total amount of the drug efficacy by enhancing or reducing the additional placebo component, which adds to the pharmacological component of the drug.

4 Transfer of the Model to the Clinical Application of Analgesic Placebo Effects

The model opens a wide range of placebo applications in the realm of pain treatment in clinical settings while considering ethical standards. This applies to any analgesic and defines the "placebo" component as an additive to the pharmacological component of the analgesic. However, it applies also to other medical and psychological treatments used in pain management. Knowing the principles and mechanisms behind the placebo effect allows for a wide range of interventions (also cf. Finniss and Benedetti 2005), which must be based on a defined concept.

4.1 Learning History: Analgesics Can Reactivate Previous Experiences and Expectations

The model of classical conditioning indicates that previous experiences with pain and pain reducing interventions are remembered as a learned response. Every new experience occurs on the basis of this learning history and is influenced by it (Colloca et al. 2008a, b). If, for example, a new analgesic drug is prescribed and the patient takes it, then its additional, additive placebo effect will greatly depend on previous experiences with analgesic drugs. Expectations that are produced by instructions can also become conditioned stimuli, which can reactivate previously learned associations.

For the routine clinical situation this can have both positive and negative consequences and meanings. Reactivating positive associations could channel the experiences with a new analgesic in a positive direction. For example, the physician or therapist who is delivering a new medication can ask about earlier experiences with analgesics and can emphasize earlier positive associations. However, asking about prior experiences can also reveal negative associations that need to be counteracted for the new substance in the dialogue with the patient (e.g., "Your previous medication had a different spectrum of activity, so it cannot be compared with the new medication you are taking now").

4.2 Current Context in Which the Analgesic Is Given

4.2.1 Current Information About Pain Medication

The power of instructions is one of the important results that placebo research has revealed. When an analgesic is given, the current information about its effects shapes the current expectation about its efficacy (c.f. Fig. 1). One important point for the prescribing physician is to emphasize positive drug effects and to avoid overemphasizing side effects. Due to limited contact hours in clinical settings, there is a high probability that the focus of an interaction between the patient and the therapist is on informing patients about side effects rather than the provision of information on positive drug effects. It is therefore important to explain the positive

drug effects as well as the mechanisms of drug action. Personal interaction rather than only written material is especially helpful (Kaptchuk et al. 2008) and supports the patient in accepting the medication and profiting from it.

Building Realistic Positive Expectancy About Analgesic Treatment

The expectation of a positive effect enhances and strengthens drug efficacy. A patient's expectation toward an analgesic is produced to a considerable extent by the information provided about the product. The positive effect of a drug or intervention used in pain management should be explained to the patient as fully as possible. This allows the additive placebo effect of analgesics and other therapeutic measures to be fully exploited. What is important here is that the provided information should be guided as closely as possible by the expected range of effects of the analgesic, in order to maintain credibility and avoid disappointment should the envisioned success fail to materialize (cf. Klinger et al. 2007). Although few conclusive facts are known as yet about the interaction between existing attitudes of patients toward the drug and the placebo effect, it seems reasonable to assume that this will have a key influence. If pain therapists are aware of these attitudes, they will be able to use existing positive attitudes as a starting point and build on them. It should be noted in this context that aspects of the therapist's own personality, acting as a provider of this information, must also be taken in to account when interacting with the patient.

Avoiding Negative Expectations About Analgesics

Negative expectancies about the effect of an analgesic can reduce its efficacy (nocebo effect) (Colloca and Benedetti 2007; Price et al. 2008). In this context, the provision of information on the analgesic treatment in question is once again clinically relevant. In order to avoid nocebo effects, one-sided negative and frightening information should be minimized when administering analgesics. For example, the information "We can try this pain killer, but I don't think it will do any good" will have more chances of being effective if you communicate it as "This pain killer does not help all patients with your condition, but those in whom it works profit a great deal." Apart from this channeling of expectancy, it is very important to determine the patient's preexisting attitude to the drug. Potentially negative attitudes can be addressed and corrected. Whether certain anxieties in the communication of information can also have a positive effect on the mode of action of a drug remains to be investigated. However, it is conceivable that the presence of side effects will in fact enhance the attribution of a positive effect, because it increases the credibility of the substance.

4.2.2 Current Specific Context and Cues

Enhancing and Strengthening the Analgesic Efficacy of a Drug

The open administration of an analgesic, where it is in full view and perceived by the patient, produces better results than its hidden administration (cf. Colloca et al. 2004; Benedetti et al. 2003). The easier it is to perceive the administration

of a drug, for example, by seeing, feeling, smelling, and/or tasting it, the better the placebo effect can be exploited. The basis for this is the principle of classical conditioning (association between external stimuli of a medication and its effect). This learning process can also refer to associations between internal (psychological and/or psychophysiological) stimuli and the analgesic effect. For example, a psychologically poor preoperative condition (e.g., anxiety, depression) in patients undergoing surgery leads to a higher postoperative consumption of analgesics (Taenzer et al. 1986), because the negative precondition will reduce placebo and can enhance nocebo effects. Both internal and external context variables can be easily controlled for the exploitation of the analgesic placebo effect in everyday clinical practice.

External Current Specific Context and Cues

In the light of the importance of the immediate context of the use of an analgesic, it is advisable to direct the patient's attention toward the drug, the infusion, or the injection in everyday inpatient practice in order to assign a positive value to the context of pain management and link it to the effect of the drug. The problem in postoperative pain management is that the analgesic medication mostly disappears in the stimulus-saturated patient's room. The pillbox comprises many tablets and in most cases the patient cannot identify the specific analgesics. Often the night nurse allocates the medication and neither the day nurse nor the ward physician knows which analgesics the patient receives. Thus, postoperative pain management approximates in many cases a hidden medication condition and both the nurse and the physician are virtually blinded. To enhance open medication and thus the effects of analgesics, it is important to highlight the current analgesics, for example, by labeling them or enhancing their value by a special design which enables the patient to focus attention on them. Also information about the medication, for example, through written material, could emphasize the analgesic effects. This can also be achieved with patient-controlled analgesia, which is positive, because it enhances the sense of control of the patient. Here the provision of the analgesic can also be emphasized by visual and/or auditory cues. Moreover, the therapist's attire, the appearance of the office or the sick room, as well as the interaction and communication of therapist play an important role in establishing confidence in the medication that is being used (Kaptchuk et al. 2008; Chung et al. 2012).

Internal Current Specific Context and Cues

The internal context of a patient is an important factor that influences the efficacy of drug action. For example, if a patient is in a pain catastrophizing, anxious, or depressed mood, the analgesic effect will be decreased (Pavlin et al. 2005; Khan et al. 2011; De Cosmo et al. 2008; Ip et al. 2009). Moreover, a patient who is exposed to feelings of helplessness and surrenders to the pain experience feels more pain than a patient who experiences control over the pain (Weisenberg et al. 1996). Thus, the pain therapist should support the patient in decreasing catastrophizing and should convince the patient that he or she can control the pain situation with both analgesics and by strengthening control beliefs.

Minimizing Withdrawal Symptoms in Analgesic Detoxification: Hidden Reduction of the Analgesics Makes Withdrawal Easier

The coupling with context variables does not only apply to the analgesic efficacy of drugs, but also to their negative effects (nocebo) and withdrawal symptoms. Just as the hidden administration of an analgesic can switch off its additive placebo component (Colloca et al. 2004), the hidden reduction of medication can ameliorate adverse effects of the medication reduction or withdrawal symptoms. As already noted by Fordyce (1976) who suggested the use of a pain cocktail (the medication dissolved in juice) at fixed time points to reduce negative learning effects associated with medication reduction, withdrawal from medication can be made less negative to the patient if the patients is informed that the reduction will be performed so that it is unnoticed by the patient. This eliminates all stimuli in the context of drug intake that previously predicted its use and led to anticipatory conditioned responses. This can, for instance, be implemented by administering the drug in a beverage (associative cue) and reducing the amount of the drug while a constant amount of the beverage is maintained. The beverage takes on the function of a placebo agent and can maintain the psychological effect of the drug beyond the physical withdrawal. The same mechanisms can also be used to extend the effect of a drug by inserting placebo trials between verum trials. This may be useful when drugs have strong side effects that can be lowered by interspersing placebos.

4.2.3 Desire for Pain Relief

Besides expectation, desire for pain relief plays a central role in the efficacy of the placebo effect (Price et al. 2008; Price and Fields 1997). To examine the contribution of desire for pain relief, the comparison between patients and healthy controls is interesting. Patients with pain disorders have a higher desire to find possibilities that reduce their pain than healthy people. Patients depend on medication for pain relief and their desire for help is therefore high. Thus, they could be more tuned to their bodily sensations and might, as a consequence, expect more immediate relief from medications. Klinger et al. (2007) compared a sample of patients with atopic dermatitis to healthy controls with respect to their analgesic placebo response. For the patients, in contrast to the healthy controls, the verbal instructions alone were not sufficient to maintain placebo analgesia over time. In these patients the induction of expectancies that are not followed by the experience of analgesia produced a loss of the placebo analgesia in a second trial and this effect could be interpreted as disappointment. For clinical use it is important to bear in mind that pain therapists can disappoint their patients when they promise highly effective medication and provide them with ineffective analgesics. Therefore, overstatements or false promises of placebo efficacy and analgesia should be avoided. This topic requires further investigation.

4.2.4 Certainty About Pain Relief

There is evidence that certainty about pain relief following the intake of an analgesic increases the magnitude of its placebo component. Elsenbruch et al. (2012) showed that the probability of attributed certainty to receive a pain

reducing medication was positively correlated with pain relief. For the clinician it is a challenging task to balance the information about the analgesic effects without overestimating them and without giving information that is too uncertain about the outcome.

4.2.5 Current Expectations About the Course of Pain Reduction

The current expectation about the course of pain reduction by an analgesic or a supposed analgesic is the result of these complex interactions between the learning history and the current context of the intake of pain medication. It can be positive or negative. In case of a still negative expectation, the healthcare provider should attempt to discuss the patient's concerns about the medication. The direction of the expectation modulates the subsequent selective attention.

4.2.6 Current Selective Attention

As noted, pain can be modulated by attentional processes (Tracey and Mantyh 2007; Aldrich et al. 2000; Crombez et al. 2005; Van Damme et al. 2010). A positive expectation, i.e., expected pain reduction toward the pain medication, leads to a selective attention for pain reducing effects. In case of a negative expectation, the focus is on negative aspects thus making pain more prominent and the analgesic effect is reduced. In clinical practice it is important to support the patient to focus on the pain reducing aspects after receiving pain medication, for example, through information. This could also entail the use of pain diaries that focus on being pain free rather than on the amount of pain that is experienced (Flor 2012) to turn the patient's attention on indicators of the pleasant state of having less pain and to enhance placebo effects. This is especially interesting with respect to chronic pain because of its association with a shift of attention to indicators of pain and with alterations in the processing of rewards and goals (Scott et al. 2007), where pain relief supersedes other goals and reinforcers.

4.2.7 Current Pain Experience: Expected or Unexpected Pain Event?

Pain is evaluated in terms of prior expectancy and thus based on differences between expected and experienced pain. A confirmation of expectation will lead to decreased pain (placebo effect) or to increased pain in the case of non-confirmation (reduction of the placebo effect) (Nakamura et al. 2012). When a person expects a pain-free intervention and experiences pain then this pain will be rated higher because it was unexpected.

4.2.8 Overall Analgesic Effect: Addition of Pharmacological and Placebo Components

The overall analgesic effect comprises the pharmacological and the additional placebo component (Colloca and Benedetti 2005). The variance of this effect primarily results from the variance in the placebo component. Therefore, the effectiveness of an analgesic can be enhanced by exploiting the placebo component. Conversely, the effect of an analgesic could be decreased when its internal placebo effect is suppressed. For example, when an analgesic is applied in a

confidential atmosphere and the patient has received sufficient and predominantly positive information about its effectiveness, the probability that its placebo component will be enhanced is high and this supports the overall analgesic effect and vice versa.

5 Ethical Aspects of Placebos and Patient Information

From an ethical point of view it is mandatory that patients are informed and that they consent when verum medication is substituted by placebos in a clinical context. But also the maximization of naturally occurring placebo effects can profit from educating the patient about placebo and nocebo effects. In order to use the placebo effect in clinical practice in a way that is ethically acceptable, it is important to explain the mechanism through which the effect operates in a transparent way. Such an educational provision of information ought to explain the placebo effect based on the models of classical conditioning and expectancy, but also its neurobiological foundations. The ability of patients to understand such neurophysiological and neurobiological connections tends to be underestimated; yet such an education has in itself a significant positive effect on the perception of pain (Moseley et al. 2004). It can increase the conviction that the analgesic placebo effect can be usefully applied. Patients can be included within their own competencies. For example, if patients have understood the principles of classical conditioning as applied to the placebo effect, they themselves will be able to shape the context of taking the medication to optimize the administration of the drug (e.g., taking medication consciously rather than on the side, increasing the effect combining it with positive coping skills such as relaxation exercises). Similarly, they can specifically examine their own expectations toward the drug and possibly seek out additional information in order to improve their attitude to the drug. Table 1 gives examples how one can provide the patient with this placebo-relevant information.

Conclusions and Outlook

The evidence basis of placebo analgesia argues clearly for its effectiveness. It is of great clinical interest to use this phenomenon for clinical pain treatment. This presumes that the placebo effect can be reliably applied within ethical borders. This chapter pointed out the basic psychological mechanisms and the psychobiological underpinnings, which represent the core functioning of analgesic placebo effects and which can be reliably replicated according to current evidence.

Furthermore, this chapter focused on the interaction of placebos with other central influencing factors by presenting an integrated model for placebo analgesia. Based on this model, starting points for interventions that use placebo analgesia were shown. The main applications are within the open medication practice. To exploit the additional placebo component of a pain medication is a very important intervention in the clinical area and improves pain treatment.

Table 1 Clinical application of placebo effects: starting points for open medication

	Transparent explanation of placebo mechanisms	Examples
1.	General information with neurobiological implications	Today we know that every pain medication has a pharmacological and a psychological component, which is the placebo effect. The placebo effect is due to learning and instruction. When a placebo effect is created, the intervention that causes it can on its own create almost the same effect as the actual treatment Neurobiological studies have shown that placebos affect the same structures in the brain as the actual pain treatment. In the case of placebo analgesia the opioid system is involved and endorphins, which act as the body's own pain medication, are released. You can learn to produce this effect yourself by maximizing the placebo effect
2.a	Explanation of classical conditioning mechanisms	The placebo effect is produced and maintained via the coupling of the pain-relieving action of a drug or another treatment with the context in which it is provided or with certain cues that signal its presence. Once there is a sufficient association, the context or cue such as the sight of the shape or color of a pill or the box in which the pill is kept can by itself elicit an effect which is comparable to the pain-relieving effect of the treatment
2.b	Explanation of implications (classical conditioning)	Create your personal positive context of healing and take your pain medication consciously in this context For example – Associate the look, smell, taste, or feeling of the drug with its positive effects including positive thoughts, pleasant surroundings, relaxing strategies – Be aware of the positive components of the pain medication – Pain medication reactivates previous experiences. Recall positive memories to counteract negative pain-related reminders
3.a	Explanation of expectancy via instruction	Instructions and expectancy play an important role in placebo (positive) and nocebo (negative) treatment effects. The way you will be instructed about the pain medication will influence its effectiveness. When you will be told that it will decrease your pain, you expect a pain reduction and this expectancy will additionally help to decrease your pain. When you are only told about the side effects, you might concentrate on them and the pain reducing effect will be less

(continued)

Table 1 (continued)

	Transparent explanation of placebo mechanisms	Examples
3.b	Explanation of implications (expectancy via instruction)	As your physician/doctor/therapist I will realistically emphasize the positive aspects of the presrcibed pain treatment and I will explain the realistic effects of it without overestimating its side effects: For example – Your pain treatment is very effective in reducing your back pain; however, a small amount of pain could remain – It is important that you feel informed about the action of your pain medication. Information based on facts will enable you to focus on the positive, pain reducing aspects of the medication; this will bring out the placebo efficacy, probably because of a selective, specific perception of the positive aspects – Take into consideration that the drug will not act at once, due to its releasing factors it will take (tell the specific duration: . . .) time – Concentrate on the treatments' pain reducing components In case of previous positive experiences with this medication: – You have had a positive experience with this kind of medication in the past, so this is a good prognosis for this type of pain medication In case of previous negative experiences: – You have had a negative experience with this kind of medication in the past; you will now receive a pain treatment related to a different class of medication; this will act through different pathways and should therefore be more beneficial

Further studies should show this additional effect in contexts other than pain medication treatments, e.g., physical therapy and psychological pain therapy.

One of the future tasks of the public health system must be to educate medical and psychological staff about the properties and underlying mechanisms of placebos so that they can optimize the placebo component of their active treatments.

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