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Clinical Use of Placebo Effects in Patients With Pain Disorders

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Abstract

The analgesic placebo effect is well documented by numerous studies. Many important influencing factors, however, are yet to be discovered. In the arena of placebo effects and clinical implications, expectancies play a central role. Expectancies are shaped by processes of classical and social learning as well as verbal instructions and are strongly related to emotional factors. Expectancies trigger a cascade of endogenous opioids and nonopioids, which alter the experience of pain. For clinical application it is important to know, that placebo research yields ethical possibilities to use placebo effects without deception and without using placebos. Since placebo effects contribute to responses to active anal-gesics, it is feasible to enhance patients' benefits from pain treatments by increasing the additional placebo effect. There are several possibilities to use the placebo effects via shaping and adapting information about analgesic medication and via associating medication intake with a positive context. A positive patient–clinician communication atmosphere is very important to generate clinically meaningful placebo effects in pain medicine.

1. INTRODUCTION

Placebo hypoalgesia is one of the most investigated placebo phenomenon. Many important influential factors have already been discovered with regard to psychological and neurobiological mechanisms (Benedetti, 2006, 2014; Bingel, Colloca, & Vase, 2011; Colloca & Benedetti, 2009; Finniss & Benedetti, 2005; Finniss, Kaptchuk, Miller, & Benedetti, 2010). In the context of pain, the activation of endogenous opioids plays a crucial role—in the case of placebo responders, the cholecystokinin is activated (Colloca, Klinger, Flor, & Bingel, 2013) while in the nonresponders case, it is the dopaminergic system that is de-activated (Scott et al., 2008). These neuro-biological processes are triggered by expectancies which are the result of psychological mechanisms and interact closely with emotions and motivations (e.g., anxiety, desire for relief), somatic focus, or cognitions (e.g., attitudes toward the treatment) (Colloca & Grillon, 2014; Finniss & Benedetti, 2005; Geers,

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Helfer, Weiland, & Kosbab, 2006; Price, Finniss, & Benedetti, 2008; Price et al., 1999; Vase, Petersen, Riley, & Price, 2009). Thus, current research focuses on the clinical relevance of analgesic placebo effects to facilitate better treatment outcomes. To achieve this objective, it is important to make optimal use of placebo effects. Broad evidence exists for the effects of placebo treatments in clinical, neurobiological, and laboratory applications, especially for the area of pain. For clinical applications, it is important to know that placebo research yielded ethical possibilities to use placebo effects without deception and without the use of placebos (c.f. Colloca & Howick, 2018). In other words, the placebo effect can be achieved without inert substances (i.e., placebos) or deception.

2. HOW IS THE ANALGESIC PLACEBO EFFECTS DEFINED IN RESEARCH AND CLINICAL PRACTICE?

A pain reduction after the intake of analgesics does not automatically provide conclusions about the effectiveness of the analgesics. To examine the real effectiveness of a pain killer, the clinical research considers the comparison of a verum and a placebo control group as the gold standard (Bothwell, Greene, Podolsky, & Jones, 2016). In this context, if the verum does not show significant superior results compared to the placebo group, the medication is considered as ineffective even if the symptoms are reduced after medication intake. Such an observed analgesic effect and the related symptom reduction are not automatically due to analgesics. The reduction could be due to other factors as well, such as, natural course of the disease or spontaneous recovery. On the other hand, a treatment with a placebo could also wrongly be interpreted as effective (Kaptchuk, 1998). Consequently, a pain reduction does not automatically indicate the true effectiveness of a placebo; that is, the outcome could result from the natural course of the disease or spontaneous healing. To show the true effect, it is necessary to include a third group consisting of patients who were not treated at all—the so called Natural History (NH) Group. The significant difference in pain reduction between the placebo group and the NH-Group can be interpreted as the real placebo effect (see Fig. 1). Thus, placebo analgesia occurs when alterations in pain perception appear that exceed the specific effect of the pharmacological, psychological, or physical pain treatment (Klinger, Colloca, Bingel, & Flor, 2014).

3. CLINICAL APPLICATION OF ANALGESIC PLACEBOS: ETHICAL TENABLE, USEFUL, AND NECESSARY?

Laboratory studies showed that patients with chronic Irritable Bowel Syndrome (Kaptchuk et al., 2008; Vase, Robinson, Verne, & Price, 2003, 2005), idiopathic and neuropathic pain (Petersen et al., 2014, 2012; Vase, Petersen, & Lund, 2014), and low back pain (Carvalho et al., 2016; Hashmi et al., 2012; Klinger, Kothe, Schmitz, Kamping, & Flor, 2017), show robust placebo hypoalgesic responses.

Moreover, analgesic placebos can lead to excellent clinical results for patients with chronic pain (Carvalho et al., 2016; Klinger et al., 2017), idiopathic and neuropathic pain (Petersen et al., 2014, 2012; Vase et al., 2014), migraine (Kam-Hansen et al., 2014), and knee osteoarthritis (Gollub et al., 2018; Tetreault et al., 2016). Therefore, why should analgesic

placebos not be used in daily clinical practice? The administration of placebos with the assertion that these are analgesics can lead to difficulties in mid- and/or long term. As soon as patients find out that they were deceived, it is highly likely that they lose trust in their physician. This is because patients usually base their trust mostly on the therapist's credibility. Other contributing factors which create trust are (perceived) competence, compassion, confidentiality, and communication skills (Pearson & Raeke, 2000). At the same time, the concealed application of placebos in the daily clinical practice can greatly tarnish the trust in the relationship between patients and physicians (Miller & Colloca, 2009).

Once the trust relationship between patients and physicians is tarnished, it makes a successful treatment almost impossible.

It seems, however, that there is a very wide range in the application of improper verum medication with the intention of creating placebo effects (Colloca, Jonas, Killen, Miller, & Shurtleff, 2014). Colloca et al. (2014) conducted a cross-cultural, systematic review in which they examined 22 cross-sectional, qualitative, and longitudinal studies. They explored the frequency of placebo use among health care professionals from 12 countries and indicated that the prevalence of placebo use in clinical practice range from 17% to 80% among physicians and from 51% to 100% among nurses. In a sample of 1200 internists and rheumatologists in the United States, the rate of pure placebos used was reported to be 5%. Moreover, 46% of the internists and rheumatologists stated that they recommend a placebo treatment primarily to enhance patient expectancy (Tilburt, Emanuel, Kaptchuk, Curlin, & Miller, 2008). The dissimilar prescription of drugs, which are not medically indicated, is of particular concern, because they can have little actual benefit but potentially serious side effects (Miller & Colloca, 2009). One reason for this medical practice is the pressure of expectancy by the patients to receive medication or a medical prescription. It is possible that physicians receive better ratings when they prescribe medication instead of pointing out the natural healing process (NH). In this context, the prescription of antibiotics for minor illnesses or mild colds, as compared to the prescription of opioids for patients with chronic but not radicular back pain is an important example.

The increased opioid prescription leads to considerable health concerns (Vowles et al., 2015). The United States even declared the opioid crisis a national emergency (Hirschfeld Davis, 2017). Therefore, the legal regulation of placebos, which are not openly labeled as placebos (i.e., hidden placebos), should be reconsidered.

In the United States, drug overdose deaths related to opioids prescribed to treat noncancer chronic pain other than methadone has increased from 2000 to 2014 (Rudd, Aleshire, Zibbell, & Gladden, 2016), with over 47,055 drug overdose deaths. Opioids have identified as "the main drugs associated with overdose deaths" with a recent rate three-times higher than in 2000 (Centers for Disease & Prevention, 2013; Rudd et al., 2016).

4. THE APPLICATION OF ANALGESIC PLACEBO EFFECTS: ETHICAL TENABLE ALTERNATIVES

The placebo research results of the last years demonstrate useful and ethically tenable alternatives to the deceptive use of placebos. The “open-label placebo treatment” use (Carvalho et al., 2016; Kaptchuk et al., 2010), in which patients are openly told that they receive a placebo and are informed about the basic principles of the effectiveness of the placebo effect represents an example of potential use of placebos.

In a randomized controlled trial, Carvalho et al. (2016) investigated whether placebo effects in chronic low back pain could be achieved through open-label placebo (OLP) treatment. They compared the OLP treatment to a group which received a treatment as usual (TAU). They were able to show that OLP elicited greater pain reduction and reduced disability compared to TAU.

Importantly, OLP treatment involves the use of “open medication” (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti, Amanzio, & Maggi, 1995; Colloca, Lopiano, Lanotte, & Benedetti, 2004) and the *additive* placebo effect. The principle of the additive placebo effect is based on the basic concept that the effectiveness all analgesics consist of both, a pharmacological and a psychological (placebo effect) component. The additive placebo effect stands for the psychological component which complements the pharmacological component.

Overtly administered analgesics—whereby patients are fully aware of taking the drug—have a better effect than analgesics given in a covert fashion (e.g., through a computer-controlled infusion pump or as part of a drug cocktail) (Benedetti, 2006; Colloca et al., 2004). The more the administration of a drug is perceived (e.g., sight, smell, taste, touch, and information), the better the placebo effect can be exploited. Consequently, the placebo effect can occur without the use of deception and without the deceptive use of medication with inert substances (placebo), which are misleadingly declared as pharmacological effective. The application of placebo mechanisms can influence patients’ expectancies, which results in alterations of pain perception that exceed the specific effect of pharmacological, psychological, or physical pain treatment. An open question becomes: Is the benefit of the OLP equally strong when the patient knows he/she is taking a placebo, as compared to when the patient does not know one of his/her medications is in reality a placebo? In a post-operative setting, acute pain patients were told that they could receive a pain treatment or a placebo (language used from a double-blind clinical trial); told that the pain treatment was an active drug (deceptive administration); or told nothing about the drug (NH-Group) (Pollo et al., 2001). A continuous-drip saline infusion was added to the buprenorphine treatment and the total number of requested doses of buprenorphine over the 3-day treatment was used as outcome (i.e., reduction of buprenorphine request). The requests of buprenorphine decreased in both the deceptive and double-blind groups as compared to the NH-Group with a reduction by 33.8% in the deceptive group and 20.8% in the double-blind group as compared to the NH-Group in which the reduction equaled 16.4% (Pollo et al., 2001). Importantly, a more transparent disclosure promoted a pain improvement and buprenorphine overall intake.

5. UNDERLYING PSYCHOLOGICAL MECHANISMS OF ANALGESIC PLACEBO EFFECTS

The underlying psychological mechanisms of the placebo effect have been intensively researched in the past decades (Enck, Bingel, Schedlowski, & Rief, 2013). At the center of attention of the placebo effect is the patient's expectancy, which plays a crucial role for the possible formation of the placebo effect. The expectancy is mediated and modulated through a variety of psychological mechanisms (see Fig. 2) including learning by instructions, learning by experience, and social observational learning (Colloca, 2014; Colloca & Miller, 2011a, 2011b; Kirsch, 2018).

The placebo effect is achieved through a positive prior experience, the observation of others or/and an instruction that initiates a positive expectancy toward a medication or treatment and that this expectancy initiates the placebo effect (Colloca, 2014; Kirsch, 2018; Kirsch, Lynn, Vigorito, & Miller, 2004). Expectation can be reinforced via a conditioning paradigm, in which the repeated association of a neutral stimulus (e.g., sight, taste of a pill) with the pharmacological effect of the agent leads to a conditioned reaction that is similar to the original response to the pharmacological agent and is then triggered by the placebo (Ader, 1993; Colloca, Enck, & DeGrazia, 2016; Price et al., 2008). Furthermore, according to the social learning model placebo effects can be learned by observation of other patients' treatment effects (Colloca & Benedetti, 2009; Schenk, Krimmel, & Colloca, 2017).

From a neurobiological perspective, the placebo analgesic effect has been linked to the endogenous opioid system. Psychological mechanisms such as verbally induced expectancies, cued and contextual conditioning, and social learning trigger the cascade of endogenous opioids and non-opioids (Colloca et al., 2013). Many functional Magnetic Resonance Imaging and Positron Emission Tomography studies showed, that the analgesic placebo effect takes place in the same brain regions as the "real" analgesic effect (Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Eippert et al., 2009; Elsenbruch et al., 2012; Kosslyn, 2005; Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004). Placebo analgesia leads to reduced brain activity in brain areas such as dorsolateral prefrontal cortex, thalamus, insula, periaqueductal area, and anterior cingulate cortex. The placebo analgesia involves the descending pain modulating system. Expectancy plays a central role for the placebo effect. Through the modulation of the expectancy, it is possible to either develop or suppress placebo effects (Colloca et al., 2013). In other words, the patient's expectancy can be systematically modulated by applying these central mechanisms—expectancy is a neural process, it mediates and increases self-efficacy in case of a positive treatment expectancy. Expectancy, for example, can be increased through attention control toward positive aspects of the treatment and their treatment effects. Negative aspects, such as fear of treatment, can be decreased concurrently through the use of positive expectancies (Klinger et al., 2014). However, negative treatment expectancies trigger fear of treatment and reduce the treatment effects (Bingel, Wanigasekera, et al., 2011; Sonthalia et al., 2015). Moreover, there is evidence that the expectancy is influenced by previous experiences (Muller et al., 2016). Though, little research has examined the mechanisms of the expectancy effect yet. In particular, it is unclear which previous experiences are perceived as positive or negative.

Furthermore, the rules for the interaction between previous experiences and current manipulation of the experiences to attain a positive treatment expectancy are not known yet. These insights would be highly clinically relevant, because they would enable a decisive influence achieving better treatment result.

6. REQUIREMENTS FOR A CLINICAL APPLICATION OF PLACEBO EFFECTS

The clinical application of placebo effects in a mechanistic-driven medicine has to be differentiated from approaches, which are not evidence based, such as anthroposophical medicine or alternative medicine. “Evidence-based Medicine” (Cochrane, 1972) states that intuitions, unsystematic clinical experiences, and pathophysiologic rationales are not sufficient grounds for clinical decision making and stresses the importance of examining the evidence from clinical research (Guyatt, 1992). Therefore, the clinical application of placebo effects has to fulfill certain requirements:

1. Placebo research results must be transferable to patients.

Most studies are conducted with healthy controls and it is important to show, that the placebo response in healthy people is the same as in patients.

2. Placebo effects must be applied deliberately.

It is important to understand the underlying mechanisms of placebo effects and to translate them into clinical application.

6.1 Translation of Placebo Research Results to Patients With Pain

Only a few studies which investigate analgesic placebo effects deal with patients. The majority of studies, however, are conducted with healthy controls instead. The following studies which were conducted with pain patients outline the evidence for analgesic placebo effects:

First, Vase et al. (2005) examined patients suffering from irritable bowel syndrome. They were able to show that the effect of Lidocaine during a painful rectal examination could also be yielded through a placebo. Hence, Lidocaine and placebo significantly reduced pain levels compared to a NH-Group.

Second, Kaptschuk et al. (2008) investigated practitioners' influences on the placebo effect on patients with irritable bowel syndrome. They compared the effects of two placebo acupuncture treatments, which were realized by using so called Streitberger needles, who disappear in the handle (tube) when located on the skin. One was a placebo acupuncture with personal interactions, and the other was a placebo acupuncture limited to neutral, standard hospital interactions. Both groups were compared to a waiting list group. One very interesting result was, that both placebo acupuncture treatments led to symptom improvements that were beyond the NH-Group (waiting list). The positive therapeutic relationship increased further the effects of placebo acupuncture in comparison to a treatment, in which the practitioners minimized the interaction with patients. Hence, this

study shows that placebo effects not only help healthy participants but also patients with chronic pain.

Third, Kam-Hansen et al. (2014) examined placebo effects in patients suffering from migraine headaches. In a sample of 66 patients, they showed that altered placebos and drug labeling changes the outcome of migraine attacks. They compared three different instructions for the analgesic (10 mg rizatriptan) and a corresponding placebo. The participants were either assigned to the “rizatriptan” group, “placebo” group, or “rizatriptan or placebo” group. Interestingly, the placebo treatment mislabeled as 10 mg rizatriptan reduced headache severity as effectively as rizatriptan mislabeled as placebo, and the OLP treatment was superior to no treatment. This study shows that patients’ expectancy is highly influenced by instructions and plays a significant role in efficacy of pain medication and pain reducing placebos.

Fourth, Klinger et al. (2017) were able to reduce experimental and clinical pain and to improve the patients’ physical capacity in a sample of 48 patients suffering from chronic back pain. These results were generated by using a placebo tincture combined with the instruction that the tincture is a “highly effective opioid” and provided additional conditioning. The pain reduction was of high clinical relevance, as the highly chronic patients had a reduction on average from 5.0 on a numerical rating scale (0=no pain, 10=worst imaginable pain) to about 2.5.

Despite the fact that there is evidence for analgesic placebo effects in patients, it is arguable that placebo effects are the same in patients as in healthy controls. There are many differences due to patient’s characteristics (e.g., treatment history and illness beliefs). However, very important distinguishing features are the different expectancies resulting from the different previous experiences with treatment, medication, and the healing context (Muller et al., 2016). Studies which compare the placebo effect in healthy people and patients are required to determine whether the placebo response is the same in both samples. Only one study compared the patients’ placebo response with the responses of healthy participants so far, concluding that patients and healthy people differ in the maintenance of the placebo effect. Patients only maintained the placebo effect when they experienced a conditioning procedure (Klinger, Soost, Flor, & Worm, 2007).

6.1.1 Do Patients Have Different Expectancies Than Healthy Individuals?—

Peerdeman et al. (2016) showed in their meta-analysis that pain in patients could be reduced by modulation of expectancy with medium to large effects for experimental and acute procedural pain and small effects for chronic pain. Expectancies are believed to be a core mechanism of placebo effects (Enck, Benedetti, & Schedlowski, 2008; Price et al., 2008). Patients, for example with acute or chronic pain, have in contrast to healthy individuals’ different expectancies toward a treatment (Constantino, Arnkoff, Glass, Ametrano, & Smith, 2011). Patients with chronic pain have a long history of treatments and therefore entirely different previous experiences with medical treatment. Their expectancies toward the effectiveness of an anal-gesics may be different than the expectancy of generally healthy people who want to take medication because of minor acute pain.

Treatment expectancies depend on prediction of treatment results (Klinger et al., 2014). This prediction plays an important role for the patient. Patients want to know from the clinicians which treatment, with corresponding effect, will be carried out to relieve their pain. For example, prior to a surgery, most patients want to know how intense the post-operative pain will be. For this purpose, they formulate a prediction from the treatment team on which they can base their specific expectancies on. Moreover, patients observe the course of their diseases and treatments in relation to their expectancies and observe if the clinician's prognosis comes true. Perceived discrepancies seem to alter the perception of pain (Wiech, 2016). If patients expect that they will be pain free after the surgery, low pain levels will be perceived stronger and evaluated as too much. If the physician explains to the patients prior to the surgery, that a low level of pain is normal after the surgery, their pain tolerance will be greater and their pain experience lower. The interaction between the prognosis and "true" pain reduction seems to be of great importance for the placebo effect and influences positively the course of treatment. Gonzalez Sáenz de Trejada et al. (2010) showed this in a study which included 881 patients with a knee- and coxarthrosis who received a total joint replacement surgery. The patients, whose own previous high expectancies were fulfilled, had better results in their health-related quality of life three to 12 months after the surgery (Health related Quality of Life/HRQoL (Ethgen, Bruyere, Richy, Dardennes, & Reginster, 2004); Short-Form-36-Questionnaire/SF-12, (Bullinger, 1995); Western Ontario and McMaster Universities Osteoarthritis Index/WOMAC, (Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988)) than patients with unmet expectancies. Consequently, health-care providers should assist their patients in developing realistic expectancies.

Another study investigated the placebo effect on patients with atopic dermatitis in comparison with healthy individuals (Klinger et al., 2007). This study showed that the patients reacted much stronger if their own prognosis, or more specifically their invalidated prediction, became reality. Furthermore, this study found higher initial placebo responses in patients than for healthy controls. However, patients could only maintain placebo responses when they had received a positive reinforcement (learning experiences) subsequently. When the patients did not receive a learning experience, the placebo effect decreased significantly. However, this response did not occur in healthy controls. A possible interpretation of this phenomenon is that the patients are more attentive to their body sensations and expect more from the medication. The lack of expected pain relief (invalidation of their prognoses and wish) led to a sense of disappointment which seemed to cancel out their placebo effect. Therefore, it is clinically relevant to keep in mind that patients are very sensitive to what clinicians say about their pain reducing medication. The pain reducing medication has to be explained realistically in order to avoid a disappointment response. The difference between patients and healthy controls is essential for the clinical practice, because it means that patients react differently—they are more sensitive to the described treatment manipulations than healthy controls and consider positive predictions made by clinicians more critically. Consequently, results from the placebo research on non-patients can not necessarily be transferred to patients. That means for the patient–physician relationship that physicians should carefully choose their words and statements in regards to treatment prognosis. Physicians should tailor the predicted treatment results individually to the patient and to the experiential realistic course and should avoid empty promises.

6.1.2 Patients' Expectancies and Their Impact on Treatment—Patients'

expectancies are important predictors of the outcome of analgesic treatments, as demonstrated predominantly in research on placebo effects. In their systematic review, Peerdeman et al. (2016) demonstrated that patients' pain can be relieved and functioning can be improved by increasing expectancy. In their study on joint arthroplasty Gandhi, Davey, and Mahomed (2009) found a relationship between prior expectancies (expectancies patients have preoperative) and surgical outcome related to their functioning. Patients with high prior expectancies had significant better results in pain reduction and functioning than patients with low prior expectancies.

Furthermore, Davidge et al. (2009) investigated the relationship between prior expectancies and function-related surgical outcome (e.g., disability, functioning, and participation) and the health related quality of life in patients with extremity soft tissue sarcoma. The prior expectancies refer to the following three areas: (1) length of recovery, (2) complications, and (3) difficulties with performing daily activities.

Prior expectancies regarding performance of daily activities proved to be a significant predictor for disability ($P=0.0016$) and the ability to reintegrate into their life's roles ($P=0.044$) 1 year later. However, prior expectancies did not predict health related quality of life.

Nevertheless, Engel, Hamilton, Potter, and Zautra (2004) could show that prior expectancies and self-efficacy had a positive influence on the length of recovery period after a total knee replacement surgery. In this study, the surveyed prior expectancies focused on the probability of recovery and the expected change in quality of life (i.e., mental and physical health, pain, and functioning). Consequently, prior expectancies, as well as self-efficacy, predicted physical and mental health outcomes.

Lutz et al. (1999) found a relationship between prior expectancies (i.e., expected recovery time and expected state of health after the surgery, preferring the surgery over waiting whether sciatica improved over time on its own) and the surgical outcome (i.e., satisfaction with the surgery, change in symptoms and overall functioning) in patients with sciatica after surgery. Patients who expected a shorter recovery period were more satisfied with the treatment outcome after 12 months (odds ratio: 2.2; 5% margin of error) than patients who expected a longer recovery period. The comparison between these two groups did not elicit a significant difference in overall functioning and changes in symptoms.

Patients' treatment expectancies result from treatment history and modulate the magnitude of the placebo effect. Therefore, clinical research of analgesic placebo effect should focus on clinical pain and requires investigation models for chronic pain rather than experimental pain. Most studies conducted on patients use experimental or acute pain (Peerdeman et al., 2016; Vase et al., 2009).

6.2 Deliberate Application of Placebo Effects: Making Use of Placebo Effects in Clinical Practice

Clinical work must be a comprehensible process—random positive results are a pleasant benefit but are not usable and therefore not helpful for clinical practice. Accordingly, patient care relies on reliable and predictable results.

Research on placebo effects offers a variety of possibilities to use placebo effects in ethical acceptable ways. One key finding of previous research is that the pharmacological effect of pain medication can be enhanced by the additive effect of analgesic placebo effect (Amanzio et al., 2001; Benedetti et al., 1995; Colloca et al., 2004).

The application of placebo effects in clinical settings does not mean that pain medication should be substituted with placebos. It rather stands for increasing the effectiveness of pain medication by amplifying their inherent placebo component. Every effective pain medication has a pharmacological active component and a psychological (placebo) component. In clinical practice, it is possible to boost an analgesic therapy by supporting it with the placebo component. The principles are to modulate expectancies by a targeted use of verbal instructions, cues, associations, and social learning models in the healing context of pain treatment. According to Amanzio et al. (2001), Benedetti et al. (1995), and Colloca et al. (2004) the open application of medication is an ethical way of using placebo effects in a clinical context. In this approach, physicians and other providers of pain treatment draw patients' attention to the positive aspects of analgesics or other treatments. They give supporting information about the medication, take care of the patients, and try to establish a positive patient–clinician atmosphere.

6.2.1 Modulation of Expectancy via Verbal Instruction—A basic requirement for a successful treatment is to give verbal supporting information about the advantages (positive action) of pain treatments.

The conversation in which the advantages of pain treatments are discussed should follow the following guidelines:

1. Emphasize the positive side of pain medication:
 - Do not overestimate the side effects, if there is a need to inform the patient about the side effects, balance the proportion of negative and positive information and let the patient focus on the positive facts.
 - Explain the mechanisms of the drug action as easy as possible to ensure that the patient understands what is said.
2. Explain the course of the drug action:
 - Explain when effects of pain medication will start being felt by the patient, and prevent any distraction in this critical phase.
3. Avoid unrealistic promises:
 - Explain the realistic effects of the drug which the patient can then validate.

4. Reactivate positive associations, relativate negative associations:

- Let the patients speak about previous or current negative and positive aspects related to their use of pain medication. Let them associate positive and relativate negative memories.

Modulation of expectancies by different information can completely alter the effectiveness of pain treatment. Bingel, Wanigasekera, et al. (2011) assessed the effects of remifentanyl on constant heat pain under three experimental conditions in a within-subject design: (1) no expectation of anal-gesia (hidden analgesic infusion), (2) expectation of a positive analgesic effect (instruction that the infusion will reduce pain), and (3) negative expectation (infusion is still running but instruction that the infusion is turned off). Positive treatment expectancy enhanced the analgesic benefit of remifentanyl, whereas negative treatment expectancy abolished remifentanyl analgesia. These results underline that negative communication during treatment can significantly reduce pharmacological effectiveness.

6.2.2 Modulation of Expectancy via Cues and Context Associations—There are several possibilities to strengthen the positive attention to pain medication in order to allow the patient to experience the effect of pain medication in a positive context:

- Advise patients to pay attention when taking pain medication: sight, smell, taste, and feeling. Encourage them to take time and concentrate on the intake of pain medication to create positive moments to strengthen the association between the conditions and positive analgesic effects from the treatment.
- Advise patients to take pain treatments in a positive internal and external situation/context (association with positive conditions), (e.g., in association with relaxation or positive, pain coping oriented thoughts, or a pleasant situation like a warm perfumed bath).
- Encourage the patient to associate pain medication with other pain reducing techniques (e.g., relaxation or other psychological pain interventions).
- Reactivate previous experiences with pain medication: support the patients to recall positive memories or—in case of negative experiences—to relativize their negative memories.

Respectively, in some clinical situations, it is beneficial to suppress context factors such as association with negative physiological or psychological states (Ader, 2003). For example, patients who undergo a physical withdrawal from medication (e.g., back pain patients with iatrogenic opioid misuse) will experience negative symptoms. These withdrawal symptoms will probably be associated with being withdrawn and are very closely connected with their negative expectancies associated with reduction of the quantity of medication. To cancel out these associations, it is possible to hide the amount of medication, (e.g., in a colored liquid), so that the patients are unaware of how much medication they receive. This way the cognitive and emotional mediated withdrawal phenomenon symptoms can be suppressed. There is also evidence, that this approach is a very successful way to inhibit the development of nocebo nausea (Colagiuri & Zachariae, 2010; Quinn & Colagiuri, 2015).

6.2.3 Open Label Placebos—There is encouraging evidence that OLPs in the treatment of patients with different pain disorders is effective (Carvalho et al., 2016; Kam-Hansen et al., 2014; Kaptchuk et al., 2010). Patients are informed about the fact that they will receive placebos instead of a pharmacological product and are given information about how the placebo effect induces analgesia. This is an ethical way of using placebos in clinical practice (Blease, Colloca, & Kaptchuk, 2016; Colloca & Howick, 2018).

Another useful clinical application is using OLPs to substitute pain treatments (e.g., when a patient undergoes a medication withdrawal). Such procedures can minimize symptoms of an withdraw phenomenon.

Future research should concentrate on strengthening the experience of self-efficacy associated with the intake of a placebo, so that patients can learn to rely on themselves to reduce pain rather than being dependent on a placebo. An OLP could be helpful for the transition from professional pain treatment into self-management of pain by using pain coping strategies learned in multidisciplinary pain centers which also include psychological pain treatments.

6.2.4 Modulation of Expectancy via Social Learning—The social context plays a crucial role in shaping negative or positive expectancies in patients. There are several situations which provide potential risks for negative or positive modulations of expectancies via observation of other patients:

- The waiting area
- Shared rooms on a ward
- Group therapy context
- Patients' observation of other patients' course of disease and treatment on TV, the internet, in lay press and newspapers etc.

Clinicians should be aware of these unsolicited sources of observation and social learning. They should ask what the patient has heard about pain treatments from others and seek positive or negative statements. If negative hearsay is reported, the differences between patients' histories could be discussed. Whereas, if positive experiences with pain treatments were exchanged, the effects of pain medication could be used as a vicarious model.

6.2.5 Positive Patient–Clinician Communication During Treatment—A positive patient–clinician relationship—characterized by trust, warmth, and empathy—is essential to make optimal use of placebo effects for the therapeutic efficacy of a treatment. Every pain physician, psychologist or physiotherapist is responsible to arrange a confiding and confident interpersonal patient–clinician relationship. One very important element for a positive atmosphere is the therapeutic alliance, which involves the bond between the therapist and the patient as well as agreement about the therapeutic goals and tasks (Hatcher & Barends, 2006; Horvath & Bedi, 2002). Del Re, Fluckiger, Horvath, Symonds, and Wampold (2012) showed that the therapists' development of stronger alliances with their patients results in a better outcome at the end of the therapy. Indicators of a strong therapeutic alliance include the patient's perception of feeling respected and cared for

(Epstein & Street, 2007). Patient's perception of such a relationships can promote emotional well-being (Salkeld, Solomon, Short, & Butow, 2004; Thorne, Hislop, Kuo, & Armstrong, 2006). The clinician–patient alliance will become stronger when clinicians are optimally informative and show empathy with the patient's circumstances, when patients have an opportunity to express their concerns, and when the patient receives consistent messages and coordinated care from the clinical team. Clinician–patient communication which ensures that the patients feel accepted, validated, hopeful, worthy, reassured, and comforted can enhance the therapeutic outcome (Hack, Degner, Parker, & Team, 2005).

Moreover, a trusting and successful clinician–patient communication is also influenced by a shared understanding. Patients should have an understanding about illness, risks, and benefits of various treatment options in order to make informed decisions about medical treatment (e.g., to adopt analgesic medication). Clinicians need to understand patient's values, preferences, and beliefs about health (Street, Makoul, Arora, & Epstein, 2009). Both, clinicians and patients, need skills to present their perspective. A successful clinician–patient communication enables an effective management of information and can increase the patient's commitment to treatment (DiMatteo et al., 1993).

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FURTHER READING

Colloca L, & Benedetti F (2005). Placebos and painkillers: Is mind as real as matter? *Nature Reviews Neuroscience*, 6(7), 545. [PubMed: 15995725]

Fig. 1.

If a pain reduction is yielded via both, a verum as well as a placebo, this is not a synonym for the existence of a placebo effect: A pain reduction via a placebo does not automatically indicate the true effectiveness of a placebo. The outcome could result from the natural course of the disease or spontaneous healing. A real placebo effect is the significant predominant difference between the level of pain reduction via a placebo and the pain level reported by a Natural History Group (NH).

Fig. 2.

Placebo analgesia occurs when alterations in pain perception appear that exceed the specific effect of the pain treatment, be it pharmacological, psychological, or physical. Placebo effects are mediated through expectation, which are modulated by a variety of psychological mechanisms including learning by instructions; learning by experience and social observational learning. These mechanisms trigger the endogenous release of opioids and non-opioids.