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Placebo analgesia: Clinical applications

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Introduction

Over the past 15 years research into analgesic placebo effects has been intense and several psychological and neurobiological mechanisms have been discovered [10]. Placebo analgesia occurs when alterations in pain perception appear that exceed the specific effect of the pain treatment, be it pharmacological, psychological or physical. Neurobiological studies have revealed great similarity between the molecular basis of drug action and the related placebo response suggesting that a placebo can partially replace the verum and enhance its effects as detailed in our previous review on neurobiological mechanisms [10]. Core psychological mechanisms include expectancy [[33],[39]] and learning such as classical conditioning and social learning [[6], [11], [32]], and these processes closely interact [[7], [27]] with emotions and motivations (e.g. anxiety, desire for relief), somatic focus or cognitions (e.g. attitudes towards the treatment) [[8],[17],[15],[32],[33],[35],[37],[39]]. In line with these findings, Benedetti [4] suggested that the effect of analgesic medication is composed of two components: a pharmacological and a psychological component. In this sense, the analgesic placebo effect can be considered to be “additive”, supplementing pain management and enhancing analgesic medication beyond its purely pharmacological effect within ethical borders. However, placebo effects not only occur in pharmacological

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interventions but are part of any analgesic treatment and thus also of psychological interventions, physical therapy or alternative medicine applications.

A number of meta-analyses have demonstrated the efficacy of placebo analgesia [[37],[38]], however, high variance is apparent in different study designs [[20],[21],[37],[38]]. Furthermore, long-lasting efficacy of placebos has been demonstrated for psychological treatments [e.g. [16]] or acupuncture [[19]]. The modifiability of the analgesic placebo response led to proposals to make better use of it in clinical practice [[15],[26],[32]] to optimize treatment outcome and to provide patients with an additional placebo-based benefit. Here we propose several approaches how to exploit placebo mechanisms to improve pharmacological and non-pharmacological pain interventions in a more systematic manner than what naturally occurs in clinical settings.

Enhancing expectancy

The placebo effect can be produced by instructions and the anticipatory expectancy of pain relief [25] in the context of the interaction and communication between health practioners and patients [[29], [23]].The strength and certainty of positive expectancies will influence the magnitude of the placebo effect by increasing self-control beliefs and attention to positive effects, which can in turn reduce anxiety and stress [36].

Placebo effects in pain treatment can be enhanced by informing the patients about placebo mechanisms and by explaining their effects to them. Such an educational informative approach ought to explain the placebo effect based on the models of classical conditioning and expectancy, but also its neurobiological bases without overstraining the patient [31] (e.g. the therapist can inform about pharmacological and psychological effects of analgesics, emphasize learning and the fact that placebos alter neurobiological processes such as opioid release). The analgesic placebo effect can be usefully applied to enhance the patient's knowledge and self-management competence. For example, if patients understand the basic principles of the placebo effect, they can attempt to shape the context of taking medication to optimize its administration (e.g. taking medication attentively with focus on taste, smell, look of the drug rather than inattentively). They can examine their own expectancies towards the drug and seek out additional information in order to improve their attitude to the drug. In addition, health care providers can shape the context in which therapeutic interventions are given and can thus influences the outcome via maximizing expectancy. Kaptchuk et al. [23] showed that placebo acupuncture combined with a positive therapeutic relationship was more effective than a placebo treatment with minimal, business-like therapist contact, underlining the importance of the therapeutic interaction in the efficacy of placebo effects. Negative expectancy about the effect of an analgesic can reduce its efficacy and increase side effects and induce a nocebo effect. Here, the information provided along with the treatment is again clinically relevant. When analgesics are admininistered. nocebo effects can be induced when the information about the medication is focused on adverse events. Balancing information on positive and negative effects and emphasizing potential benefits despite of negative effects can enhance positive expectancies. It is also important to determine the patient's pre-existing attitude to the treatment. Potentially negative attitudes can be addressed and corrected but side effects should not be downplayed. 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.

The cost or the perceived invasiveness of a treatment also influences the analgesic effect since more costly or more invasive interventions are associated with higher expectancies [[29; 40],[22]]. This suggests that enhancing the value of treatment by highlighting its special assets and efficacy through better information and perceptible (e.g. optical, tactile, gustatory or olfactory) appreciation.

It is also important that the therapists themselves believe in the efficacy of a certain treatment. It was previously shown that therapists who were told that a drug would be less effective also achieved lower placebo effects [[18]] compared to those who believed in a high efficacy of the drug. Table 1 lists some possible placebo interventions based on expectancy.

Enhancing learning

From a learning point of view, an originally neutral stimulus such as the sight, taste or smell of a medication when associated with the pharmacological effect of a drug, elicit the analgesic effect on its own. Analgesic interventions can have an additional positive effect based on their association with previously experienced successful treatments. This experience does not have to be direct but can also be acquired by social learning [[9]].

Moreover, 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 cocktail of drugs) [[2],[11]]. The better the administration of a drug is perceived (e.g. sight, smell, taste, touch and information), the more the placebo effect can be exploited. In outpatient and especially in in-patient practice, unintentionally hidden administration of treatment is frequent. Most of the patients cannot identify their pain medication in the complex hospital context and in their unlabeled pillbox. This most likely dramatically reduces the efficacy of the medications. It would be important to direct the patient’s attention towards the drug, the infusion or the injection in order to enhance the contextual value of the treatments to optimize pain management. This point especially applies to medication in nursing homes. Here open medication should involve not only the use of labels but also of colors, descriptions of the effects of the drugs that are given and positive social interaction around the drug. This might be particularly relevant for patients with dementia or Alzheimer’s disease. In these patients a loss of the efficacy of placebo responses was observed that correlated with reduced connectivity of the frontal lobes and the rest of the brain [3]. This altered connectivity was related to short attention span, poor working short term memory and therefore a reduced capacity to acquire and maintain explicit expectancies in the form of declarative or explicit memory. By contrast, non-declarative or implicit memory was intact in these patients so that conditioning related to placebo effects might be more effective than verbal instructions [5].

Learning studies suggest that previous experience of analgesia and hyperalgesia is remembered, thus creating a memory of successful and unsuccessful treatment effectiveness. Every new experience occurs on the basis of this learning history and is influenced by it

[24]. Extending pioneering clinical work of Laska and Sunshine [30] to an experimental setting, Colloca and Benedetti [6] found that the prior experience of a beneficial effect of a drug led to a higher placebo response than the experience that a drug had been ineffective, and these effects last several days.

Klinger et al. [27] showed that such learning experiences are more relevant in patients than healthy controls. Here, experimental pain stimuli were reduced during the administration of a placebo (conditioning) thus giving the participants the experience of actual pain relief. In the patients, the placebo effect was only present in this conditioning condition, expectancy alone only worked in the controls. Patients depend on medication for pain relief and their desire for help is high. Therefore they could be more tuned to their bodily sensations and might thus expect more immediate relief from medications. For some patients verbal instructions alone might not be sufficient to augment placebo analgesia in a clinical setting. In these patients the induction of expectancies that are not followed by the experience of analgesia might even produce disappointment. Therefore, overstatements or false promises of placebo efficacy and analgesia should be avoided in clinical practices. This topic requires further investigation.

Placebo analgesia has also been associated with reward. For example, Scott et al. [35] and Schweinhardt et al. [34] showed that there are person-related differences in activation in the dopaminergic mesolimbic reward pathway that predict not only the response to reward but also a large proportion of the variance in the placebo response. Thus reward processing and placebo analgesia may share common pathways. Maximizing the chance to activate the reward system may thus also improve placebo analgesia, for example, by enhancing motivation in the patients by rewarding interactions.

In addition to the use of conditioning principles verbal instructions can be employed to have patients recall and reactivate previously learned associations that are otherwise implicit and not accessible by verbal report [25]. The reactivation of prior experiences can have both positive and negative consequences. Reactivating positive associations could channel the experiences with a new analgesic in a positive direction. Questions about earlier experiences with analgesics could bring out such acquired positive associations. However, this procedure could also reveal negative associations such as previously experienced insufficient analgesia or side effects which could then be distinguished from the new drug during the dialogue with the patient (e.g. by emphasizing that although prior negative experiences with a certain medication are present, the new medication will have different effects and be more beneficial).

Prior positive effects as “pre-conditioning” of pain management lead to positive expectancy towards subsequent pain management and can maximize the placebo aspects of this treatment [[12],[13]]. Similarly, effective pain management can confirm and maintain existing (placebo) expectancy [27]. In both cases, the previous experience of pain relief modulates the size of the placebo effect, i.e. a highly effective analgesic can potentially also generate a higher degree of additional placebo effectiveness. This effect could be used with drugs, which are likely to be discontinued due to strong side effects. Along these lines the alternating administration of an active drug and a placebo and the corresponding lowering of

the (pharmacological) dose may reduce the side effects while maintaining the analgesic (placebo) effect [[14],[1]]. This principle can also be viewed as an “intermittent amplification” of the placebo effect. A study on psoriasis showed that the intermittent partial-dose of the verum (here a corticosteroid) and placebo was as effective as continuous medication in reducing the frequency of relapse [1]. Table 1 lists potential learning-based uses of the placebo effect in clinical settings.

Outlook

Our knowledge about the underlying mechanisms of placebo analgesic responses has grown substantially over the past decades. Knowing these principles and mechanisms behind placebo analgesia allows to increase the placebo component inherent in any active treatment. However, more research in clinical settings is needed to determine the practical value of the use of placebos. For example, a comparison of the efficacy of health care personnel trained in the explicit use of placebo principles as compared to those who provide care as usual might be fruitful. Nevertheless, some recommendation for incorporating placebo effects in clinical practice can already be made. Although many clinicians may employ the placebo effect in an intuitive manner, we propose to systematically exploit these effects as part of any analgesic treatment to optimize treatment outcomes. This implies a wide range of applications [also cf. [15]], that can and should be incorporated in everyday clinical practice as, for example, suggested by the German guidelines for the treatment of acute perioperative and posttraumatic pain [[26],[28]]. Following these principles could facilitate pain management and clinician - patient interaction.

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Table 1

Clinical applications of the placebo effect

Techniques of negotiations for explaining or applying an acute pain medication, e.g. during consult for acute (postoperative) pain management in the hospital or when prescribing new medication for chronic pain management.
Enhancement of expectations
• Emphasis on positive drug effects, avoidance of overemphasis on side effects
• Explanation of the effects of the drugs and the mechanism of drug action
• Personal interaction rather than only written materials
• Explanation of the course of drug action, avoidance of unrealistic promises
Enhancement of learning components:
• Applications of analgesics in an open manner including many sensory aspects
• Association of analgesic medication with positive internal states and in positive external conditions
• Combination of the intake of analgesics with other pain-relieving techniques
• Time- rather than pain contingent analgesic medication on an intermittent schedule
• Exploration of analgesic-associated experiences and attitudes and reinforcement of positive and devaluation of negative experiences