Published in final edited form as:

Z Psychol. 2014 ; 222(3): 121–123. doi:10.1027/2151-2604/a000175.

Placebo effects: Basic mechanisms and clinical applications

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There is probably no other human phenomenon that better reflects the inseparable interaction between psychological and somatic factors than the "placebo effect". This phenomenon is a complex psychobiological process consisting of learning and expectancy components acting on neurophysiological systems, and its efficacy has been confirmed empirically in a range of fields such as pain and the immune system. Inert substances such as sugar pills can trigger placebo effects, and these effects can also enhance the response to active treatments.

During the past decades the most impressive demonstrations of these effects have been presented in the field of pain and placebo analgesia. The effectiveness of analgesic placebo responses remains unchallenged and our knowledge about the underlying mechanisms that produce the placebo effect is expanding rapidly. Together with expectancy theories, classical conditioning has been discussed as being a major explanatory model. However, other learning principles, such as social learning (via vicarious reinforcement), are thought to play an important role in the development and maintenance of placebo analgesia. From a neurobiological viewpoint, research findings have revealed the involvement of cortical, subcortical and recently spinal structures in the placebo-induced modulation of pain that cognitively triggers the release of endogenous opioid and non-opioid substances (c.f. Colloca, Klinger, Flor & Bingel, 2013).

Insights into the underlying mechanisms and the neurobiological foundation (Colloca, Klinger, Flor & Bingel, 2013) of the analgetic placebo effect have now made it possible to develop principles for clinical application (Klinger, Colloca, Bingel, Flor, 2013). These principles must, of course, be justifiable within ethical boundaries. In their article addressing this issue, Colloca et al. (c.f. this topical issues) point out that in the current state of medicine there are numerous examples of inappropriate uses of placebos, often justified by the patient's urgency for help on the one hand, and the lack of appropriate medication on the other. The authors emphasize the need to focus on elements of the clinical encounter and the patient-physician relationship to increase the placebo effect. Clearly caution is necessary in harnessing placebo effects in medicine to treat patients while avoiding deception. Accordingly, the study of the placebo effect should be incorporated in the core clinical practice curriculum of all health practitioners.

Benedetti, Amanzio, Maggi (1995) and Colloca, Lopiano, Lanotte, Benedetti (2004) showed that pain treatments (e.g. opioids) consist of a verum component (active pharmacological

component) and a placebo component. Regarding the latter, there are many associated contextual factors associated with the treatment, such as expectancy, fear, previous experiences with clinical staff and co-interventions, but also illness-related factors and personality variables. It is necessary to boost these specific aspects systematically to ultimately enhance the analgesic effect. This innovative thought has already been implemented in the S3 guidelines of the AWMF (DIVS 2009, <http://www.awmf.org>) for the “treatment of acute and perioperative pain“. It is recommended therein to use the potential of the placebo effect in the clinical context and to avoid nocebo effects (Klinger, Thomm, Bryant, Becker, 2009). The placebo effect has thereby become more acceptable amongst health practitioners. It is important to note that the aim is expressively not about replacing effective pain medication with placebos but to recognize the placebo effect as an additive component that can optimize every pain medication beyond its pure pharmacological-based effectiveness. This paradigm shift toward the explicit usage of the placebo effect offers a completely new opportunity for the prevention and the treatment of chronic pain. Therefore, the clinical value of the placebo effect needs to be discussed with patients. This approach should involve using psychological strategies in assisting the patient to establish positive, yet realistic expectations regarding the medical pain treatment.

Placebo effects are highly specific. Finniss, Kaptchuk, Miller & Benedetti (2010) described 12 different mechanisms of placebo effects. Keeping this in mind, one can think of the placebo effect as being a form of mimicry of bodily procedures caused by the medication. For example, analgesic placebos activate the endorphin system, and placebos used as Parkinson Disease medication activate dopamine in the striatum and changes the activity of neurons in basal ganglia and thalamus. However, a specific mechanism is not always detectable. The underlining placebo mechanisms of antidepressant drugs seem to be somewhat dubious. In his provocative contribution of antidepressants and the placebo effect published in this issue, Kirsch shows that regardless of contradictory mechanisms of antidepressant medication, antidepressant placebos are almost as effective as antidepressants, yet eliciting far fewer side effects.

This theme issue presents the complexity of the phenomenon called „placebo effect“. The articles included here describe different research approaches to this topic and adhere to different models and facets of the placebo phenomenon. For example, Carlino et al. focus on placebo effects on physical performance and show how it can be manipulated via verbal suggestions. Geers et al. focus on involvement in treatment decision-making and show that depending on the prior experience with treatments, the involvement can enhance and hinder the placebo effects respectively. Hofmann et al. demonstrate that carry-over-effects after treatment failure can be minimized by changing the route of application, e.g. a pill replaced by a cream. Vase et al. review placebo and nocebo effects in chronic pain patients and reveal the influence of expectations and emotional feelings on the experience of pain. Kamping et al. also focus on chronic pain patients, considering the influence of attitude, experience and expectation on the placebo effect and present an instrument to assess both specific attitudes towards pain medication and experiences with pain medication. The similarity between pain and itching sensations suggests a transfer of the placebo analgesic effect to anti-itching medication. In their review, Sölle et al. show how classical conditioning and expectancy

produce placebo effects with itching. Finally, Vits and Schedlowski review the current literature about learned placebo effects in the immune system.

The current state of placebo research holds sufficient evidence for careful considerations of clinical implications of placebo effects. Employing the placebo effect according to its mechanisms and strictly following the underlying mechanisms in the development and the maintenance of the placebo effect is required.

Acknowledgments

This research was supported by the Intramural Program of the National Center for Complementary and Alternative Medicine, National Institute of Mental Health, Bethesda, USA

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