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Sham opioids relieve multidimensional aspects of chronic back pain

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Recent studies on placebo effects have expanded the dearth of knowledge on neurobiological mechanisms of endogenous nociceptive inhibition [4], showing that patients suffering from pain disorders may benefit from the activation of descending pain systems and cognitive modulation of treatment expectancy. Patients with chronic Irritable Bowel Syndrome [16; 17; 8], idiopathic and neuropathic pain [12; 11; 15], low back pain [6; 1], migraine [7] and knee osteoarthritis [14] have been targeted as populations for studies with either a translational (e.g. reduction of pain and improvement of quality of life over trial period) or mechanistic (e.g. reduction of pain and associated objective outcomes in an functional magnetic resonance imaging setting) goals.

Klinger and colleagues investigated how verbally-induced expectations (e.g. via instructions) and reinforced expectations (e.g. via exposure to a pain reduction using a behavioral conditioning manipulation) would affect not only the perception of experimental acute pain intensity but also pre-existing clinical pain, as well as back pain-related behaviors and functional capacity in patients with history of chronic back pain [9]. An inactive solution (NaCl) was presented as an effective treatment (sham “opioid” solution) to chronic back pain patients. Based on the group assignment, patients were either told that the “solution reduces pain and improves physical capacity” or that the “solution is neutral, a placebo”. Half of study participants were also conditioned (surreptitious reduction of experimental pain), and patients' acute and clinical back pain ratings (both examined by numerical rating scale 0-10), as well as self-rated functional capacity (0-100%; time required for the exercise) were measured. Expected pain relief before and after solution intake was assessed.

Patients experienced a reduction of clinical and experimental pain with an improvement of pain-related behaviors and dysfunctions. Patients' expectations were highly correlated with the magnitude of placebo-induced reduction of pain, confirming an essential role of expectations in shaping placebo effects [9]. Furthermore, this indicates that systematically

exploring the extent to which patients expect pain to improve from a pharmacological or nonpharmacological intervention can have a significant value within the clinical encounter.

Based on the impact of expectations and placebo effects on clinical and experimental pain, some might also raise the question about whether placebos should enter the pharmacopeia as a legitimate treatment for doctors to prescribe. Klinger's study used deceptive information, making it difficult to translate the results in real-world settings. Patients consented to participate in a study in which they were misled about the nature of the study: "We now would like to inform you about the high-efficacy painkiller: In this study, we are comparing the efficacy of an analgesic solution with a placebo solution without an active ingredient. The active ingredient in the solution belongs to the group of high-efficacy painkillers (opioids). The dose, which has been previously determined for your individual case, is introduced into your body by means of a cotton swab on the oral mucosa. This drug acts on central mechanisms (the brain) and, therefore, the reaction occurs evenly throughout the body after onset. The active ingredient is characterized by its particularly fast release and efficacy in the organism".

Using deception with patients is always controversial and debatable [10]. Alternative strategies, including an authorized deception approach followed by debriefing study participants at the end of the study should be encouraged in experimental and clinical placebo research. Moreover, new studies cast doubt on whether deception is necessary at all [3]. For example, a recently published randomized controlled trial by Carvalho and colleagues investigated placebo effects in chronic low back pain adding open-label placebo treatment to treatment as usual for 3 weeks. Pain severity was assessed on three 0- to 10-point Numeric Rating Scales, and other outcomes such as back-related dysfunction were assessed as well. Compared to treatment as usual, open-label placebos elicited greater pain reduction with moderate to large effect sizes. Open-label placebos reduced disability, suggesting that placebo pills presented in a positive context may be helpful in chronic low back pain [1].

Theoretically, Klinger's and Carvalho's approaches can be combined to create a therapeutic strategy whereby placebos in the context of reinforcement can act as dose-extenders of active medication action [5]. Patients can be presented with a rationale for entering a trial in which they know that they are going to receive placebos (or lower dose of active treatments) intercalated with active treatments in blister packs. Based on learning principles, conditioned effects can be obtained that can reduce the total medication intake with a clinically-relevant benefit (for a full description of the scientific rationale and ethical/clinical requirements, see [5]). Such an approach may bypass deception while placebo effects are intentionally harnessed based on reinforced expectancies and exposure to effective active treatments. Conditioned responses have been largely shown to be larger than other kinds of placebo effects. In Klinger and colleagues' article, sham opioids given along with a conditioning procedure resulted in larger improvements than in the verbally-instructed group for clinical pain (Cohen's *d*: 1.83 vs. .83), acute experimental pain (Cohen's *d*: 1.79 vs 1.11), and pain behaviors (Cohen's *d*: 0.58 vs 0.36).

Perhaps one of the most interesting aspects of Klinger's study is the fact that a sham opioid produces a significant reduction of clinical pain and associated pain dysfunctions in both opioid and non-opioid users. This can be relevant when facing the currently challenging epidemic of deaths related to opioid prescriptions. Drug overdose deaths related to pain relievers other than methadone increased significantly from 2000 to 2014 [13], with a total of 47,055 drug overdose deaths in the United States. Opioids were identified as 'the main drugs associated with overdose deaths', composing an astonishing 61% of all drug overdose-related deaths, a rate three-times higher than in 2000 [2; 13].

While placebo research studies have just started translating mechanistic findings from the laboratory setting to the clinical context, leaving a set of unanswered questions about the efficacy, feasibility and safety of using placebos in pain patients under opioid therapy, it is worth considering the array of strategies that can harness placebo effects to mollify pain and improve pain coping strategies.

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