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Hypoalgesic placebo effects can occur with transparent disclosures

Luana Colloca^{1,2,3}

¹Department of Pain and Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, USA

²Departments of Anesthesiology and Psychiatry, School of Medicine, University of Maryland, Baltimore, University of Maryland, Baltimore, USA

³Center to Advance Chronic Pain Research, University of Maryland, Baltimore, USA

Placebo research often involves elements of deception to create expectations of benefit. Typically, it consists in deliberate misleading communication about the goal of the research, and the nature of the experimental manipulation and treatment. Specifically, in the context of placebo pain-related research, misleading information is used to make participants believe that certain procedures (e.g. placebo creams, saline solution injections, sham electrodes and so on) can induce a reduction in pain they experience. Study participants can be informed about the use of deception (i.e. authorized deception) during the informed consent process and then at the end of their participation in the study during the debriefing phase (for example, see [2]), told about the true nature of research and the features of the protocol making the research ethically sound.

However, it remained to be determined whether effective placebo manipulations can be performed in experimental settings in the presence of honest and transparent disclosures about the procedure and intervention.

Locher and colleagues (2017) tested the effectiveness of open-label placebo given with a rationale in a standardized experimental heat pain modulation paradigm [4]. One hundred sixty participants were randomly assigned to open-label placebo without rationale, open-label placebo with rationale, deceptive placebo and no-intervention. All groups except the no-intervention group received an application of a placebo cream. Primary outcomes were baseline and post-treatment measurements of pain tolerance, pain intensity and pain unpleasantness ratings. The group in which the open-label placebo was given with a rationale and the group in which the placebo was given deceptively showed lower pain intensity and unpleasantness ratings than the group receiving the open-labeled placebo treatment without a rationale. The pain report changes were independent from the level of

Correspondence to: Luana Colloca, MD, PhD, 655 W. Lombard Street Suite 729, 21201 Baltimore, MD; Phone: +1 410-706-8244; Fax: +1 410-706-5427; colloca@umaryland.edu.

Conflicts of interest

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pain tolerance. These findings suggest that providing study participants with open-label placebos with rationale is as efficacious as giving deceptive placebos [4].

These results expand upon other recent studies demonstrating that the inclusion of authorized deception did not influence the size of placebo-induced analgesia, nor did it affect recruitment, and retention of study participants who were randomly assigned to an authorized deception group or a deceptive group [5]. These results are also in line with prior research that showed that placebo conditioned hypoalgesic effects persist after revealing that the cream used to reduce the experimental heat pain was merely Vaseline [10]. Therefore, it appears that informing study participants about the precise nature of the placebo manipulation and its mechanisms yields no negative reactions or negative consequences and actually may favor outcome improvements throughout increasing participant engagement.

The critical question is whether placebo treatments require deception to work in patients [6]. Park and Covi (1965) were the first to attempt to test the apparent paradoxical effect of open-labeled placebos in patients suffering from a range of anxiety symptoms [8]. The patients were told that they would have received sugar pills but that they would have perceived benefits in terms of symptom relief. Despite the small number of enrolled patients (fourteen), significant symptom improvement was reported after taking open-labeled placebos for a week. In pain medicine, other more recent studies have shed light on the potential efficacy of open-labeled placebos without deception in patients suffering from irritable bowel syndrome [3] and low back pain [1].

Yet placebo hypoalgesic effects appeared to be larger when a full-deceptive placebo was given as compared to a placebo given with the information that either a potent painkiller or a placebo was going to be administered. The comparison of patients in a post-operative setting told that they could receive a basal infusion of either a potent painkiller or a placebo (similarly to a double-blind clinical trial); told that the basal infusion was a potent painkiller (deceptive administration); or told nothing about the analgesic effect (natural history) induced different placebo hypoalgesic effects [9]. Operationally, the placebo effect was defined as the amount of requested doses of buprenorphine over the three-day treatment when, in reality, a continuous-drip saline infusion was added to the buprenorphine treatment. The buprenorphine requests decreased significantly in both the deceptive and double-blind groups as compared to the natural history group, leading to a significant reduction of the buprenorphine opioid intake (i.e. reduction by 33.8% in the deceptive group, 20.8% in the double-blind group, and 16.4 % in the natural history, respectively) [9]. Although the uncertainty resulted in a reduction of the genuine placebo analgesia, it appears that more transparent disclosures may still promote pain improvements.

A recent qualitative analysis of perceptions of placebo use collected in a one-time telephone surveys conducted in a diverse patient population identified lack of harm and potential benefit as the most common themes to justify the acceptability of placebo use [7]. All of the 853 participants had been seen in an outpatient clinic for a chronic health problem at least once in the prior six months. Those participants with higher education mentioned potential benefit as a reason to justify placebo use. Older age was associated with an increased likelihood of identifying overall physician-related themes (e.g. honesty, obligation, trust), as

opposed to treatment-related themes (e.g. lack of harm, potential benefits, power of the mind). Most importantly, patients emphasized honesty and the patient's right to know as critical factors for acceptable use of placebos.

While health providers face a variety of challenges and questions about the transparent use of placebos and the need for providing placebos within an educational frame which includes a rationale, the absence of harm, the evaluation of potential benefits, and the physician's obligations to treatment and care remain of paramount importance.

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References

1. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*. 2016; 157(12):2766–2772. [PubMed: 27755279]
2. Colloca L, Pine DS, Ernst M, Miller FG, Grillon C. Vasopressin Boosts Placebo Analgesic Effects in Women: A Randomized Trial. *Biol Psychiatry*. 2016; 79(10):794–802. [PubMed: 26321018]
3. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*. 2010; 5(12):e15591. [PubMed: 21203519]
4. Locher C, Nascimento AF, Kirsch I, Kossowsky J, Meyer A, Gaab J. Is the Rationale More Important than Deception? A Randomized Controlled Trial of Open-Label Placebo Analgesia. *PAIN*. 2017 (in press).
5. Martin AL, Katz J. Inclusion of authorized deception in the informed consent process does not affect the magnitude of the placebo effect for experimentally induced pain. *Pain*. 2010; 149(2):208–215. [PubMed: 20172652]
6. Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. *Am J Bioeth*. 2009; 9(12):39–47.
7. Ortiz R, Chandros Hull S, Colloca L. Patient attitudes about the clinical use of placebo: qualitative perspectives from a telephone survey. *BMJ open*. 2016; 6(4):e011012.
8. Park LC, Covi L. Nonblind Placebo Trial: An Exploration of Neurotic Patients' Responses to Placebo When Its Inert Content Is Disclosed. *Arch Gen Psychiatry*. 1965; 12:36–45. [PubMed: 14258363]
9. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain*. 2001; 93(1):77–84. [PubMed: 11406341]
10. Schafer SM, Colloca L, Wager TD. Conditioned placebo analgesia persists when subjects know they are receiving a placebo. *J Pain*. 2015; 16(5):412–420. [PubMed: 25617812]