Published in final edited form as:

Pain. 2011 June ; 152(6): 1215–1216. doi:10.1016/j.pain.2011.02.043.

Learned placebo analgesia in sequential trials: What are the Pros and Cons?

Luana Colloca

National Center for Complementary and Alternative Medicine, Department of Bioethics, National Institutes of Health, 10 Center Drive, 10/1C118, Bethesda, MD 20892-1156, USA

Significant progress has been made in the investigation of the placebo effect [5] and most of our knowledge about the neurobiology and clinical relevance of the phenomenon comes from the field of pain and analgesia [8]. Placebo analgesic responses can be created through verbally-induced expectations, observation of other patients' outcomes and conditioning [3,4].

In the present issue of *Pain*, André-Obadia et al. [2] provide evidence that the size of placebo analgesic responses in patients suffering from chronic neuropathic pain depends on prior exposure to successful or unsuccessful interventions. They evaluated the placebo effect of repetitive transcranial magnetic stimulation (rTMS) in a cross-over study design in which neuropathic pain patients resistant to pharmacological therapy were randomized to one of two possible arms – sham rTMS applied before or after the conventional one. All the patients were informed that they would receive two sessions of rTMS, which differed only for imperceptible changes in the stimulation parameters. To rule out post-stimulation rTMS effects, the two rTMS sessions were performed two weeks apart – carry-over effects of a single session of rTMS do not exceed a week [6]. In the second group, in which the sham rTMS was applied after the active one, the authors specifically contrasted the differential effect of the sham intervention with respect to the success, or lack of success, of the previous exposure to the conventional rTMS. The authors report that the study participants experienced a positive placebo response when they received the sham intervention after a session of real rTMS that induced an analgesic effect; conversely, they experienced greater pain when they received the sham session after the ineffective rTMS intervention. These findings confirm the evidence that in sequential trials, the exposure to biologically significant treatments induces the formation of analgesic placebo responses that are stronger as compared to responses following placebos given first [3]. The long-lasting positive and negative effects of previous therapeutic experiences can explain, at least to some extent, the large variability of the placebo responses in experimental and clinical pain studies.

Interestingly, this concept has important and probably contrary, implications for clinical trials and practice. On one hand, the fact that there was no significant difference between the

Tel.: +1 301 435 8715; fax: +1 301 496 0760. luana.colloca@nih.gov.

Conflict of interest

The author declares no conflict of interest. The opinions expressed are the views of the author and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the US Department of Health and Human Services.

effects of the conventional and sham rTMS when the latter was applied after a successful rTMS session, suggests that learning effects may confound the results of sequential trials, such as cross-over designs. On the other hand, it is interesting to note how a difficult population such as patients suffering from neuropathic pain refractory to pharmacological interventions, can still be susceptible to learned placebo analgesic responses.

Strikingly, André-Obadia et al. [2] reasoned that if previous treatment efficacy shapes the size of subsequent placebo responses, it may become difficult to interpret outcomes of crossover design in medical research. Generally, the importance of counterbalancing the order of treatment and placebo interventions in cross-over designs is widely recognized. Comparatively, less attention has been devoted to counterbalancing the effects on placebo interventions of prior beneficial and non-beneficial responses to treatment interventions in order to control sequential learning effects. André-Obadia et al. [2] emphasized the need for the inclusion of an intermediate evaluation by a third party that, without breaking the double-blind, judges whether the proportion of patients responsive and non-responsive to the active treatment and thereby potentially responding differentially to the sham intervention in the second part of the study is adequately balanced. Further work will be needed to confirm this interpretation, to clarify the reasons to use a cross-over design when learning effects can be anticipated, and to improve the methodological quality of longitudinal and observational studies where patients are exposed to a sequence of either placebo (arm A) or drug (arm B) and later switched from A to B and vice versa.

Learning-induced placebo effects may have clinical significance in the management of pain and other symptoms [1]. For example, placebos given after an effective treatment may work to extend the effects of pharmacological and non-pharmacological treatments (e.g. rTMS), with the possibility to maintain therapeutic outcomes over time and to reduce the occurrence of potential adverse effects. A similar improvement as observed by André-Obadia et al. [2] in active and placebo arm (e.g. sham rTMS after the successful intervention), may be per se clinically significant. If patients with chronic pain can benefit from learned placebo analgesic effects, then it may be desirable to take advantage of the placebo response strategically in therapeutic plans [7].

Hopefully, future research will help to identify ways to appropriately minimize placebo responses in clinical trials, but fruitfully maximize them in clinical practice.

References

- [1]. Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, Kimball AB, Fiorentino D. Conditioned pharmacotherapeutic effects: a preliminary study. *Psychosom Med* 2010;72:192–7. [PubMed: 20028830]
- [2]. André-Obadia N, Magnin M, Garcia-Larrea L. On the importance of placebo timing in rTMS studies for pain relief. *Pain* 2011;152:1233–7. [PubMed: 21342747]
- [3]. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain* 2006;124:126–33. [PubMed: 16701952]
- [4]. Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. *Pain* 2009;144:28–34. [PubMed: 19278785]
- [5]. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686–95. [PubMed: 20171404]

- [6]. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol* 2007;6:188–91. [PubMed: 17239806]
- [7]. Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. *Am J Bioeth* 2009;9:39–47.
- [8]. Tracey I Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med* 2010;16:1277–83. [PubMed: 20948533]