Preface

The placebo effect is a widespread phenomenon in virtually all fields of medicine and has represented a nuisance and a troublesome artifact in clinical research for decades. Physicians, clinical scientists, and drug companies have always focused their attention on active treatment and have dismissed the placebo group as the less-interesting and less-exciting part of a clinical trial. Only at the end of the 1970s did the placebo response acquire a respectable status in the biological and biomedical sciences, as it was recognized as a real biological phenomenon worthy of scientific inquiry and mediated by endogenous mechanisms of opioid activation.

Recently, advances in the neurobiological understanding of the placebo response have been dramatic, and this issue of Seminars in Pain Medicine represents the best proof of these achievements. In particular, it should be emphasized that the field of pain and analgesia has been the most productive in placebo research and that most of the psychophysiological mechanisms we know today are the result of both basic and clinical research in the field of placebo analgesia. However, I believe that the integration of knowledge coming from different pathological conditions is essential to better understand this complex phenomenon. Therefore, in this issue, pain mechanisms will be associated and integrated with other mechanisms in Parkinson’s disease, the immune system, depression, and others.

Why is the neurobiological understanding of the placebo response important, and how can it help improve clinical practice? In 1995, we ran a classical clinical trial in postoperative pain. One arm of the trial was represented by a group treated with a cholecystokinin antagonist, proglumide, whereas the other arm was represented by the group that received the placebo. The outcome showed that proglumide was better than placebo in relieving postoperative pain, thus indicating, according to classical clinical trial methodology, that the cholecystokinin antagonist was a good painkiller. However, we showed that this conclusion was erroneous because a hidden injection of proglumide was totally ineffective, thus indicating that it had no analgesic properties. Today we know that proglumide is not a painkiller, but rather it acts on placebo-activated opioid mechanisms. I believe that this example is enough to explain why we have the urgent need to understand the neurobiological mechanisms of the placebo response.

This issue is mostly devoted to the neurobiological mechanisms of placebo, although the first two articles provide a general, clinical, and ethical background about the relevance of placebo research in modern science and clinical practice. The different issues, problems, and findings described by our distinguished contributors turn out to be an exciting adventure, as placebo effects encompass a number of phenomena and applications, from brain functioning to mind–body interaction, and from clinical trial design to medical practice.

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