Harnessing the Placebo Effect in Pediatric Migraine Clinic

Vanda Faria, PhD[1,2], Clas Linnman, PhD[1], Alyssa Lebel, MD, PhD[1,3], and David Borsook, MD, PhD[1,3]

"The cure for the headache was a kind of a leaf, which required to be accompanied by a charm, and if a person would repeat the charm at the same time that he used the cure, he would be made whole; but that without the charm the leaf would be of no avail."

Socrates, according to Plato[1]

Placebo response rates are known to be high in pediatric migraine trials.[2,3] Although this constitutes a major burden for clinical trials that struggle to find effective drugs for the treatment of pediatric migraine, the placebo effect has an important but overlooked potential in clinical care. As captured in our opening quote, a healer's capacity to stimulate positive expectations was fundamental in ancient medicine. Unfortunately, this lesson seems to be undervalued, and its potential underutilized in modern clinical practice. From a clinical perspective, placebo responses are likely one of the best allies of good clinical care if they can be effectively, efficiently, and ethically harnessed. Migraine, because of its susceptibility to stress and allostatic load,[4] is an excellent paradigm to examine the potential analgesic and clinical benefits resulting from positive and motivational therapeutic interventions taking advantage of the placebo effect.

Expectations of clinical benefits seem to be at the heart of the placebo effect.[5] Understanding how expectancies of improvement (triggered by verbal suggestions, or learning procedures) interact with distinct biological systems to shape therapeutic outcomes has been the focus of past pharmacologic and neuroimaging studies in the field of placebo.[6] These studies have highlighted the importance and clinical relevance of these responses. However, little has been done to translate the accumulated knowledge into improved clinical care. This might be due partially to the lack of a defined model guiding the implementation of these complementary processes in clinical practice but also due to the need for more clinical studies showing their benefit. In pediatrics, the opportunities for using methods that decrease the use of medication that might have long-term side effects on the child's brain makes this approach even more salient.

Here we focus on how physicians may take advantage of high pediatric placebo responsivity in the migraine clinic to optimize treatment outcomes and to provide patients with an additional therapeutic placebo benefit. We begin by reviewing current pediatric migraine treatments, summarize candidate mechanisms underlying clinical relevant placebo effects, and conclude by suggesting ways to maximize the clinical value of this psychobiological response in pediatric migraine practice.

IBS	Irritable bowel syndrome

Pediatric Migraine

Frequently starting in childhood and extending into adulthood, migraine is a central nervous system disorder affecting nearly 15% of the population worldwide.[7] According to the World Health Organization, migraine is among the most prevalent health conditions, and it is in the top 20 causes of global disability.[8] Despite the high prevalence and the negative personal and societal impact, migraine is considered to be both underdiagnosed and undertreated, especially in children.[9] The estimated cumulative prevalence of pediatric migraine is about 8%, increasing with age.[10] However, the prevalence of pediatric headaches is estimated at approximately 60%,[10] and migraine is thought to be a common underdiagnosed cause behind some of these recurrent headaches in children.[11] The spectrum of migraine symptoms varies as a function of age.[12] When compared with the clinical manifestation of migraine in adults, pediatric migraine attacks tend to be shorter and bilateral. Besides, children may often display a wider variety of gastrointestinal, autonomic, and non-nociceptive symptoms, characterized as migraine variants.[2]

Treating Pediatric Migraine

Like many disorders of the central nervous system, there are no therapies that are fully effective across patients with migraine. The therapeutic approach in pediatric migraine usually involves a multimodal approach combining pharmacotherapy, which can be abortive or prophylactic, with biobehavioral, and psychoeducational interventions that address the long-term management of the disorder.[13] Therefore, depending on the degree of disability and impaired quality of life resulting from migraine, successful management of this disorder entails identifying triggering factors, providing pain relief, and considering prophylaxis.

With regard to pharmacotherapy, abortive and prophylactic options for pediatric populations have been largely based on evidence originating from adult studies. In the past decade, however, there has been a growing awareness that children are not merely small adults. Studies have shown that when

From the [1]Center for Pain and the Brain, Boston Children's Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Department of Psychology, Uppsala University, Uppsala, Sweden; and [3]Chronic Headache Program, Boston Children's Hospital, Harvard Medical School, Boston, MA

Supported by National Institute of Neurological Disorders and Stroke (K24NS064050 and R01NS0750182 to D.B.) and National Center for Complementary and Alternative Medicine (R21 AT007530-01 to D.B.). V.F. supported by the Ryochi Sasakawa Young Leaders Fellowship Fund. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.06.040

comparing pediatric and adult populations, one-fifth of the studied drugs have important differences with regard to effectiveness, dosing, or safety.[14] Such data suggest that the efficacy and safety established for adults cannot be inferred to children without further research. Placebo-controlled clinical trials have been performed to assess the effectiveness of candidate migraine pharmacological treatments for children.[2] However, the majority of these trials have failed to demonstrate effectiveness of active drugs over placebo. Only 2 triptans (almotriptan and rizatriptan) have been approved by the Food and Drug Administration to be safe and effective for the abortive treatment of pediatric migraine.[15] With regards to prophylactic treatments, only 1 antiepileptic drug (topiramate) and 1 antidepressant (trazodone) have been shown to be more effective than placebo.[2] However, the evidence supporting these drugs is limited, which constitutes a challenge for physicians when trying to prescribe effective drugs. Importantly, the most frequent reason for the lack of positive results in trials of both acute and prophylactic pediatric migraine pharmacotherapy is the high placebo analgesia response rates.

The high number of patients reporting stress as a precipitating factor for migraines, together with the high comorbidity of migraine with stress related psychiatric disorders,[4] and the success rates of stress management therapies emphasizes the importance of the nonpharmacologic interventions as successful alternatives to pharmacologic treatment in managing pediatric migraine. Adding a nonpharmacologic treatment approach like cognitive behavioral therapy (including pain coping training and biofeedback), seems to successfully boost the therapeutic benefits of pharmacotherapy (ie, amitriptyline).[16] Moreover, comparing a psychological intervention, such as stress management training, with a pharmacological intervention (ie, the ß-blocker metoprolol), greater clinical improvement has been reported with the psychological intervention.[17]

Widely used for migraine prophylaxis, studies have reported that acupuncture may be as effective, or possibly more effective than, prophylactic pharmacological migraine treatments, and with fewer adverse effects.[18] Furthermore, homeopathic therapies, commonly used in the treatment of migraine have been also suggested to result in a significant decrease in frequency, severity, and duration of pediatric migraine attacks.[19] Notably, however, both acupuncture and homeopathic interventions do not seem to perform better than placebos in controlled clinical trials.[20,21] The observable beneficial responses resulting from these interventions most likely are a reflection of the placebo effect, perhaps enhanced by a more elaborate administration ritual bordering on spiritual beliefs in the efficacy of the remedy, a close patient-practitioner interaction, and the practitioner's belief in the treatment.

Placebo Responses in Clinical Trials of Pediatric Migraine

Placebo analgesia is traditionally viewed as the reduction in pain following the administration of an inert/sham treatment. Because of the increased interest in medical research and clinical practice, current definitions of placebo effects have become more comprehensive.[22] It is known that placebo effects or responses do not depend on placebo administration. Placebo responses, translated into genuine psychobiological events, are attributable to the overall therapeutic context of any intervention, which is why placebos (ie, inert/sham treatments) are used as controls in clinical trials.

As reported above, placebo effects seem to underlie a substantial portion of the therapeutic effects observed after nonpharmacologic and pharmacologic pediatric migraine interventions. From a methodological perspective, high placebo responsivity represents a major burden in clinical trials as significant differential outcomes between active interventions and placebos become more difficult to detect.[2,3] Whereas pharmacologic placebo effects have been estimated around 35% in adult migraine trials, pediatric trials suggest placebo response rates of 50% or higher,[23] indicating an even greater challenge for pediatric trials. Moreover, an inverse relationship between age and placebo response rates has been reported in migraine.[24] This inverse relationship has been suggested to continue into adulthood. Younger adults appear to be more likely to respond to placebo as compared with older adults who are more likely to respond to pharmacotherapy.[25]

Such findings have sparked debates on ways to address and minimize placebo responses in pediatric migraine trials.[26] However, from a clinical perspective, one cannot ignore the fact that migraine symptoms significantly improve after placebo administration in more than one-half of the children.[23] Placebo pills decrease the average occurrence of headaches to fewer than 3 a month from a starting point of nearly 6 a month.[2] Moreover, as stated above, the nonpharmacologic and alternative interventions considered to be driven by placebo mechanisms, seem to be particularly effective in pediatric populations.[19] Therefore, instead of focusing on eliminating placebo responses in clinical migraine trials, the focus should be redirected towards understanding the underlying mechanism responsible for high placebo response rates in children with migraine (after excluding confounding factors such as spontaneous remission) in order to maximize and use them therapeutically.

The Clinical Relevance of Placebo Responses and Its Underlying Mechanisms

With evidence-based medicine, the development of effective pharmacotherapies, increased emphasis on informed consent, and the use of placebos (ie, inert treatments) unbeknown to the patients is considered deceptive and ethically controversial. This ethical dilemma has hindered the implementation of placebos in the practice of medicine. However, whereas in the past it was believed that deception was essential to obtain successful placebo responses, recent research on open-label placebo (ie, patients are aware that a placebo is being administered) suggests that deception is no longer needed to achieve the desired therapeutic outcomes. In a study for