EXPERT REVIEWS

Migraine treatment and placebo effect

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Placebos are typically defined as physiologically inactive substances that elicit a therapeutic response. The antipode of the placebo effect is the nocebo effect, or the negative effects of placebo, where unpleasant symptoms (e.g., adverse events) emerge after the administration of placebo. Placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception. Herein we focus on the importance of placebo in headache research. We first review the mechanisms of the placebo effect. We then focus on the importance of placebo in the acute treatment of migraine. We follow by discussing the importance of placebo on the preventive treatment of migraine and our perspectives for the 5 years to come regarding the study of the placebos.

KEYWORDS: acute treatment • migraine • placebo • placebo effect • preventive treatment

The term 'placebo' derives from the Latin 'I shall please' [1]. Placebos are typically defined as physiologically inactive substances that elicit a therapeutic response. In other words, placebos induce changes in symptoms or conditions, modifying the outcome (relative to what would be expected by natural history only) [2]. The antipode of the placebo effect (PE) is the nocebo effect, or the negative effects of placebo, where unpleasant symptoms (e.g., adverse events) emerge after the administration of placebo [3].

As well positioned by Diener and colleagues, "the perception of pain is a highly subjective experience that is influenced by cognitive factors, such as expectation, attention, anxiety and previous experiences; placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception" [4]. Accordingly, at least a basic comprehension of placebos is essential for those treating or studying pain and a point worth emphasizing in this regard. Doctors and scientists have, to a large extent, very different 'needs' regarding the PE. While doctors benefit from the PE (gaining additional efficacy or further increasing tolerability) [5,6], scientists often see the PE as a nuisance in basic research and particularly in clinical research, focusing on strategies to neutralize it, in order to properly demonstrate the benefits of active medications [7]. Nonetheless, understanding the topic is of importance for all; compliance to placebo affects outcomes and nocebo responses can explain some adverse clinical outcomes. Additionally, a doctor may be an unwitting contributor to placebo and nocebo responses.

Accordingly, herein we focus on the importance of placebo in migraine research. We first briefly review the mechanisms of the PE and then focus on the importance of placebo in the acute treatment of migraine. We follow by discussing the importance of placebo on the preventive treatment of migraine and conclude by presenting our perspectives for the 5 years to come regarding the study of the placebos.

Mechanisms of placebo response

Placebo as one component of response to therapies

Revising the mechanisms of placebo response in detail is outside the scope of this review and for a deeper discussion, readers are referred to [3,8]. Nonetheless, both the PE and the nocebo effect arise from highly active processes in the brain [3].

It is established that the efficacy of treatments overall, and of headache treatment specifically, is a function of basically three factors [9]. First, headache is likely to improve because of natural history only, as well as by regression to the mean. Headache is also likely to improve because of the Hawthorne effect, the tendency of people to change their behavior or condition simply as a consequence of being observed or studied, which can lead to reduced pain among patients simply because they are in a clinical

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trial or because they want to 'please' their therapist [10]. A second component of clinical improvement is due to the PE itself. Finally, there is the benefit of clinical treatment. Accordingly, clinical improvement is a summation of natural history and other factors not related to treatment, placebo response and treatment-related factors.

Psychological factors associated with placebo response

Placebo-induced analgesia has long been considered to be a purely psychological phenomenon, and this is no longer accepted as true [11]. Nonetheless, psychological mechanisms are certainly of importance and two of them deserve special attention, the conditioning and expectancy mechanisms.

The conditioning mechanism, or the Pavlovian learning mechanism, refers to the conditioned response, which is the property of repetitive innocuous stimuli or treatments to elicit a response after contrasts with active stimulus/treatment [12]. In other words, past experience influences future outcomes and past response to pain therapy influences future analgesia.

Expectancy, as suggested, regards the expectation of therapeutic and adverse responses to the treatment being administered [13]. It is well established that people that believe they have received an effective medication are more likely to respond to placebo than people that do not. Also, efficacy after receiving the true drug is reduced in individuals that believe they have been treated with placebo [3].

As splendidly reviewed by Fillingim and Price [10], in addition to conditioning and expectancy, other experienced factors contributing to the PE are the desire for relief and the phenomena of memory distortion, where distorted memory of recent pain also contributes to the PE (subjects tend to remember prior pain intensities as being much greater than they actually were) [14].

Neurological mechanisms & placebo response

Substantial evidence supports the role of the endogenous opioid system in eliciting the PE, which can indeed be largely blocked by preadministration of the opioid-antagonist naloxone [11]. Nonetheless, nonopioid mechanisms are certainly involved in the PE as well. Indeed, in a study where a conditioning procedure was used to induce placebo analgesia, conditioning using morphine could be reversed by naloxone, while conditioning induced by ketorolac could not [15].

Neuroimaging studies substantiate the importance of the endogenous opioid system by demonstrating activations of the rostral anterior cingulate cortex (rACC) and the brainstem (periaqueductal gray) after both opioid and systemic placebo analgesia [16]. Indeed, neuroimaging studies suggest a common underlying mechanism of expectation-induced placebo analgesia that is dependent both on the enhanced functional connectivity of the rACC with subcortical brain structures that are crucial for descending inhibition of nociceptive information [4]. The activations in the rACC and periaqueductal gray are accompanied by deactivations in the thalamus, insula and somatosensory regions, suggesting that analgesia induced by placebo results from active inhibition of nociceptive input [17].

The prefrontal cortex seems to also be involved in the PE, probably by generating, maintaining and integrating internal representations and expectations. Finally, placebo administration has been found to activate both dopamine and endogenous opioid peptides in the nucleus accumbens, thus suggesting an involvement of reward mechanisms in some types of PEs [8].

Placebo & the acute treatment of migraine

Measuring the PE in the acute treatment of migraine is not an easy task. The PE is influenced by several factors, including the methods of the study (single attack vs multiple attacks), age and gender of participants, prior participation in clinical trials and past exposure to the drug being tested.

Other factors influencing the PE that are not often reported include: proportion of participants using preventive medications; number of doses allowed and time to rescue; methods of assessing the adverse events (prompted or unprompted); frequency of headache attacks per month; time from onset of headache to treatment; proportion of individuals naive to other migraine medications; number of sites included in the study; and characteristics of the medication (e.g., size, color and encapsulation) [18–20]. Finally, lack of appropriate controls sometimes limits the study of placebo.

Nonetheless, acute clinical trials on migraine have several similarities, including [21]:

- Use of standard diagnostic criteria
- Exclusion of patients with chronic daily headaches
- Similar designs (mostly double-blind, parallel, 1:1 randomization rate)
- Similar demographic characterization (age and proportion of women)
- Similar ratio of migraine with/without aura
- Use of standard primary and secondary end points and methods of assessment of pain (four-point scale) (**Box 1**).

Even when all the parameters are fixed and similar, the PE varies as a function of the headache attack being treated. In a study that included individuals with migraine seeking medical treatment for their acute headaches (not necessarily migraine headaches), the PE varied as a function of the phenotype of the attack being treated; it was lowest if the attack was of migraine with aura, intermediate if it was migraine without aura and highest if it was of tension-type headache (after adjusting for severity) [22].

Box 1. Definitions typically used in acute migraine studies.

Pain relief
Percentage of patients with a decrease in headache from severe or moderate to none or mild at a specific time (usually 2 h), without using rescue medication.

Pain free
Percentage of patients pain free at a specific time (usually 2 h) before any rescue medication.

Given that it is well established that route of administration influences the PE [23], we subsequently review this topic as a function of treatment type. We first review the PE in studies of oral triptans, followed by nonoral triptan studies and nontriptan studies.

PE in oral triptan clinical trials

In an excellent review on the topic, Loder *et al.* discusses the PE after oral treatment with triptan medications, focusing mainly on three end points: 2-h headache relief, 2-h pain free and tolerability [21]. Studies published from 1991 and 2002 were included.

A total of 31 studies provided good quality information and the main findings are presented in Table 1. In brief, after placebo, 2-h pain-relief rates ranged from 17 to 50% (mean = 28.5 ± 8.7%). For pain free, rates ranged from 5 to 17% (6.1 ± 4.4). Adverse events after placebo varied enormously (probably reflecting methodological discrepancies), from 4.9 to 74% (23.4 ± 14.0%).

Few papers reported concomitant use of preventive medications or if participants were naive to the active medications or to clinical trials. Nonetheless, the use of preventive medication did not seem to alter the PE, which was significantly lower in European studies as compared with US studies. An interesting finding was that the nocebo effect was of lower magnitude when dissolving tablets were used. The PE itself was not influenced by this variable.

Finally, rates were higher in children and adolescents relative to adults (pain relief = 48.5%; pain free = 25.5%) [21], a well-established finding [24]. This last statement deserves further discussion. The high placebo response in some pediatric migraine trials makes it difficult to prove efficacy of a verum drug. To better understand this topic, Evers and colleagues analyzed all available placebo-controlled trials on acute and on prophylactic migraine treatment in children and adolescents with respect to different placebo rates (pain free and pain relief at 2 h; rate of responders with ≥50% attack frequency decrease). They found that placebo response rates were considerably lower in crossover trials than in parallel group trials (19.2 vs 27.1% for pain free after 2 h and 39.4 vs 56.9% for pain relief after 2 h). Other factors associated with a lower placebo rate in childhood and adolescence trials on the acute treatment of migraine were single-center (vs multicenter) trials and small sample size. They suggested that parallel group trials on the acute treatment of migraine in children and adolescents show a very low therapeutic gain, due to a high placebo rate. The verum response rates, however, were very similar to those seen in adulthood trials [25].

A second systematic review on placebo responses seen in clinical trials of triptans was conducted by Tfelt-Hansen and colleagues (Table 2) [26]. For efficacy, findings are very similar to what was reported by Loder *et al.* [21], while the nocebo rate is slightly higher in Tfelt-Hansen's review.

Other important findings from the triptan studies are that the PE is increased when placebo is given while pain is mild (although proportionally less increased than the increased efficacy of the active medication) versus when pain was moderate or severe. In these studies, the nocebo effect was also of smaller magnitude when dissolving tablets were tested [4].

PE in nonoral triptan clinical trials

Route of administration influences the PE [4]. Although this is true overall, it seems to be of particular importance in pain studies. The following properties seem to exist: intervention towards the site of pain elicits higher placebo responses than 'distance' interventions (e.g., injection on the head and neck seem to be associated with higher placebo rates than systemic injections) [27]; and magnitude of the PE for pain seems to be oral, nasal and then injection [28].

Therefore, it comes as no surprise that the PE of nasal triptans seems to be higher than of oral triptans. Placebo given as nasal sprays is associated with mean pain relief of 28.9–32.3% [21,26]. Interestingly, the nocebo effect seems to be lower after nasal versus oral administration.

A single study assessed the PE of suppositories given for headache treatment. Pain relief happened in 39% and adverse events in 14% [29].

Although the PE is higher after parenteral administration, for headache treatment a single paper was associated with 2-h pain relief of 50%, while the other studies found rates aligned with what is seen after oral administration. For pain free, however, rates were considerably higher after injection (mean = 24%) [29].

PE in nontriptan clinical trials

No systematic review exists regarding the PE associated with nontriptan medications. For oral medications, pain relief at 2 h is approximately 34%, higher than the results for triptans, although pain-free rates are similar and the nocebo effect seems to be lower. This information comes with an important caveat. Some of these trials assessed over-the-counter medications and excluded individuals with migraine disability, or treated pain while mild [30,31]. Therefore, mean values cannot be simply compared with what is seen in the triptan trials.

Table 1. Placebo effect in clinical trials of triptan medications.

Parameter	Oral administration			Dissolving tablets; mean (%)	Conventional tablets; mean (%)
	Response (%)	*Standard deviation*	*Range (%)*		
Adult studies					
2-h pain relief	28.9	8.5	17–50	24.7	28.8
2-h pain free	6.1	4.8	5–17	8.5	5.4
Adverse events	23.4	14.1	4.8–74	8.5	23.7
Adolescent studies					
2-h pain relief	48.5				
2-h pain free	25.4				
Adverse events	32.3				

Adapted from data in [21].

Table 2. Placebo effect in clinical trials of triptan medications.

Treatment	Treatment of moderate or severe attacks (%)			Treatment of mild attacks (%)	
	Pain relief	*Pain free*	*AE*	*Pain relief*	*Pain free*
Oral tablets	28.3	11	29.3	37.3	23
Dissolving tablets	26	NR		NR	8
Nasal	32.3	NR	16.2	NR	NR
Rectal	39	NR	14	NR	NR
Subcutaneous†	50/20.2	18	NR	NR	NR

†After 1 h.
AE: Adverse event; NR: Not reported.
Adapted from data in [25].

Several nontriptan medications are available in an effervescent form and the PE seems to be very similar to what is seen for oral tablets, with a smaller nocebo effect [32]. For parenteral medications, rates are aligned with what is seen for subcutaneous sumatriptan.

Placebo in acute migraine treatment: summary

With all the caveats already exposed, the PE in acute migraine treatment may be summarized as follows:

- The PE is higher for nontriptans than for triptans and this is probably explained by methodological differences (such as treating mild pain in many studies of nontriptans vs treating while pain was moderate or severe in most triptan studies) [21,29,30];
- The PE is higher when placebo is used when attacks are mild versus moderate or severe [4];
- The PE for migraine pain is higher in the pediatric versus adult population [4,25];
- The PE for migraine pain is higher in nasal versus oral administration [4];
- The PE after parenteral migraine medications seems to be surprisingly equivalent to the PE seen with oral placebo for headache relief, but it is higher for headache-free [4];
- The nocebo effect is lowest for dissolving tablets and highest after parenteral administration [4].

Placebo & the preventive treatment of migraine

The placebo response in migraine preventive clinical trials ranges from 14 to 50%, depending on the duration of the study and the study design [33–38]. The nocebo effect is also relevant in preventive studies (side effects seen after administration of placebo).

Preventive options for migraine treatment consist of two major categories: nonpharmacological and pharmacological treatments. The use of medications for migraine preventive treatment is widespread and more commonly used than non-pharmacological strategies. Accordingly, the literature on PE is more abundant for pharmacological therapies. In this section we separately discuss the placebo and nocebo effect in four different types of migraine prevention treatments: daily oral preventive drugs, botulinum toxin, acupuncture and other nonpharmacological treatments.

Daily oral preventive drugs

Oral preventive therapies consist of daily use of medications with the goal of reducing migraine frequency and severity. Clinical trials typically test the efficacy and safety of these medications versus placebo over 3 months. The primary end point is usually reduction in number of monthly days of headache at month 3 versus baseline.

In this setting, placebo response (at month 3) ranges from 14 to 31%. As previously discussed, several aspects may influence the PE. Among the most relevant factors for preventive clinical trials, age figures prominently. As in acute trials, pediatric clinical trials also yield higher preventive placebo rates, compared with trials in adults. Children are definitely more prone to suggestion. Other factors of importance include the place where patients are enrolled. In regions with poor quality healthcare, the controlled and rigorous environment of a clinical trial would translate into improved medical care during the trial (better attention from the staff than in a typical consult, visiting a better structure for their headache treatment). All these factors influence the placebo response. Gender may also affect clinical and placebo responses.

Several migraine prevention trials are available. Better studied classes are: anticonvulsants, antidepressants, β-blockers, calcium channel blockers and others (e.g., vitamins, herbs and minerals). The placebo and nocebo responses vary according to the type of drug studied and the number of treatment arms in the trial (higher chance of receiving placebo is associated with reduced PE; lower chance is associated with higher PE, as expectations of receiving the true drug are different). Placebo response rates range from 14 to 21% for valproic acid [33,34], and are approximately 16% for magnesium [35], 22% for bisoprolol [36] and 31% for propranolol [37]. A recent meta-analysis of 32 studies has found an overall placebo response rate of 21%. The placebo response rates were significantly higher in parallel group studies compared with crossover trials [38]. Altogether, studies of prophylactic treatment of migraine have demonstrated a higher variability in the rate of the placebo response than studies of the treatment of acute migraine attacks. This is probably due in part to the different primary end points used in studies of migraine prophylaxis, and to the inherent variability in response measured over a period of months compared with one measured over a period of hours.

In a recent systematic review of the nocebo effect in antimigraine clinical trials [32], 69 studies were analyzed. Of them, nine dealt with the preventive treatment of migraine (anticonvulsants). A high rate of adverse events in the placebo arms was seen. Anorexia and memory difficulties, typical adverse events of anticonvulsants, were present in the placebo arm of these trials, suggesting that adverse events in the placebo arms of

clinical trials depend on the active medication profile (as patients get knowledge on the most common adverse events by reading the consent form).

Botulinum toxin

While several trials failed to demonstrate the efficacy of botulinum toxin type A (BtA) in the treatment of migraine and tension-type headaches, a recent trial found it superior to placebo in the preventive treatment of chronic migraine. One suggested reason for the failure of BtA in the treatment of migraine was the elevated PE found in those trials [39,40].

Clinical trial methodology in BtA trials for headache prevention is complex. First, the treatment appeal of injecting a product on the head, its innovative concept associated with few adverse effects commonly found in migraine medications, and the cosmetic effects, all may increase the willingness to participate in a trial. Not surprisingly, placebo responses are impressive in BtA trials. In addition, the trials used electronic diaries where patients had to access the diary and respond to questions daily. If patients responded negatively, the duration of the interview was much shorter than if they responded positively. This 'punishment' may have biased some patients to provide inaccurate responses (pain free). Finally, there was an issue of adequately blinding the study (since patients receiving placebo would not experience muscle paralysis). The PE is the major player in the complex analysis of BtA effect in headache disorders.

Duration of PE was surprisingly longer in BtA trials than expected in other migraine prevention randomized controlled trials. Placebo response was not only sustained for 9 months, but increased after each of the three successive placebo injections. Spontaneous remission of migraine was not a plausible explanation, as one would not expect remission rates higher than 40% over an 11-month period of time when these same patients suffered from migraine for an average of 15 years [39,40].

Acupuncture

Several studies suggest the effectiveness of acupuncture over no treatment or oral placebo [41–43], but in most of them, verum and sham (placebo acupuncture, same quantity of needles are placed in nonacupuncture points) were not different. Sham acupuncture has been shown to be effective in many other disorders. Studies discuss how difficult it is to blind sham acupuncture, and how sham acupuncture in some trials may actually be real acupuncture. The ideal sham methodology has not been established yet, making the studies' results difficult to interpret. For example, of 1295 patients screened in a trial [42] only 443 patients were analyzed, raising the potential for strong biases. Furthermore, acupuncture trials are likely to raise participation biases, where individuals 'sympathetic' to the procedure are more likely to participate in these trials; accordingly, even if the sham procedure was ideal, placebo responses would still be high. Another interesting fact extracted from Diener's study is the trend toward a lower clinical response in patients who thought they were not receiving placebo, suggesting the influence of expectation on results [42].

Other nonpharmacological treatments

Controlled trials for other nonpharmacological treatments for migraine prevention are as difficult to conduct as for acupuncture. Psychotherapy, physical therapy, biofeedback, relaxation training and massage all impose real challenges for blinding. As in BtA and acupuncture trials, high placebo response rate may be one of the main reasons of failure of nonpharmacological trials.

A waiting list control group (where patients are randomized to intervention vs placebo intervention vs waiting list with no intervention) could be included in these trials in order to obtain more information on the natural history of the disorder and also on the PE of the intervention. Additionally, more than 50% headache response (≥50% headache frequency reduction from baseline to last treatment month) is the typical primary end point; however, stratified headache response (headache reduction ≥25%, ≥50%, ≥75% and complete response) would be a better way to analyze headache response in these trials. This stratified analysis could give a different idea of placebo versus treatment arms responses as a function of disease severity.

Expert commentary

The rudiments of the science beyond the PE need to be disseminated. Placebos are relevant in several levels of medical practice, including:

- Interpretation of clinical research. In the context of a clinical trial, no conclusive arguments can be made in the absence of placebo. The alternative, using active comparators, requires previous validation against placebo (of the comparator) and substantially increased sample size. Nonetheless, several professionals still oppose resistance to the use of placebo in human investigation. Accordingly, strong positioning statements from authoritative bodies, medical societies and regulators continue to be necessary;
- Given that the placebo response varies as a function of the route of administration and level of intervention, comparisons between different formulations or interventions require specific clinical trials. Conclusions cannot be inferred based on systematic reviews or meta-analyses;
- The therapeutic effect of any intervention is the result of the PE and of the efficacy of the intervention. Similarly, the tolerability of medications results from adverse events and of nocebo. Accordingly, doctors should try to maximize the PE while minimizing the nocebo effect. This is of particular importance in pediatrics, since children are especially susceptible to placebos;
- The dogmatic concept that placebos are inert substances, without biological action, should be promptly dismissed as not supported by scientific knowledge.

Placebos should indeed be part of academic curricula at graduate and postgraduate levels.

Five-year view

Understanding the PE (and determinants of placebo and nocebo) is of importance not only for migraine trials, but also for several other areas (e.g., in depression studies, typically five large trials

are conducted in order to generate two positive trials necessary for regulatory approval). Although meaningful advance in the understanding of placebo will require more than 5 years, we envision advances in the following areas:

- Since the PE is so relevant and powerful, uncontrolled studies will be increasingly disregarded as being scientifically relevant;
- Clinical studies will focus on identifying predictors of placebo and nocebo response. When advances are conducted in this area, efforts will be made to enroll placebo nonrespondents in the clinical trials;
- Designs of randomized clinical trials will increasingly focus on the PE (e.g., run-in period, first exposure to placebo in order to exclude placebo respondents);
- Neuroimaging studies will better map areas involved with the PE and will study potentially easy strategies to reduce the PE;
- Better comprehension on the nonopioid mechanisms of placebo response will be defined;
- While scientists try to minimize the PE, providers will take advantage of it, and use the lessons generated by research on the mechanisms of placebo to indeed maximize the PE, yielding higher therapeutic benefit for their patients.

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Key issues

- Placebos are defined as physiologically inactive substances that elicit a therapeutic response. Nocebos, or the negative effects of placebo, are unpleasant symptoms (e.g., adverse events) emerging after the administration of placebo.
- Doctors and scientists have, to a large extent, very different 'needs' regarding the placebo effect. While doctors benefit from the placebo effect (gaining additional efficacy or further increasing tolerability), scientists often see the placebo effect as a nuisance.
- The efficacy of treatments is basically a function of three factors. First, pain is likely to improve because of natural history only, as well as by regression to the mean. A second component of clinical improvement is due to the placebo effect itself. Finally, there is the benefit of clinical treatment.
- In the acute treatment of migraine (triptans), 2-h pain-relief rates after placebo range from 17 to 50% (mean = 28.5%). Adverse events after placebo vary enormously.
- Placebo rates are higher in children and adolescents, relative to adults, both in acute and in preventive clinical trials.
- Several factors influence the placebo effect in preventive trials. Among them, patient-related factors (e.g., age and gender), site-related factors, study design-related factors and route of administration are of particular importance.
- Based on what has been discussed, it must be stated that the use of placebo is absolutely ethical and necessary. Indeed, the International Headache Society Clinical Trials Subcommittee states that drugs used for migraine can be reliably evaluated only in randomized, double-blind, clinical trials, and that placebo control should also be included in order to test the reactivity of the patient sample.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Ernst E. A historical perspective on placebo. *Clin. Med.* 8(1), 9–10 (2008).

2 Thompson WG. Placebos: a review of the placebo response. *Am. J. Gastroenterol.* 95(7), 1637–1643 (2000).

3 Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron* 59(2), 195–206 (2008).

•• **Relevant and updated article reviewing the mechanisms of placebo and nocebo.**

4 Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. *Cephalalgia* 28(10), 1003–1011 (2008).

•• **Recent review on placebo in the field of headache.**

5 Bostick NA, Sade R, Levine MA, Stewart DM Jr. Placebo use in clinical practice: report of the American Medical Association Council on Ethical and Judicial Affairs. *J. Clin. Ethics* 19(1), 58–61 (2008).

6 Cahana A, Romagnioli S. Not all placebos are the same: a debate on the ethics of placebo use in clinical trials versus clinical practice. *J. Anesth.* 21(1), 102–105 (2007).

7 Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication – a review. *Cephalalgia* 24(5), 321–332 (2004).

8 Haour F. Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation* 12(4), 195–200 (2005).

9 Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *JAMA* 271(20), 1609–1614 (1994).

10 Fillingim RB, Price DD. What is controlled for in placebo-controlled trials? *Mayo Clin. Proc.* 80(9), 1119–1121 (2005).

•• **Extraordinary editorial where the putative mechanisms of placebo and the relevance for clinical trials is discussed.**

11 Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. *J. Neurosci.* 25(45), 10390–10402 (2005).

• **Splendid review on the neurological mechanisms of placebo.**

12 Voudouris NJ, Peck CL, Coleman G. Conditioned placebo responses. *J. Pers. Soc. Psychol.* 48(1), 47–53 (1985).

13 Colagiuri B, Morley K, Boakes R, Haber P. Expectancy in double-blind placebo-controlled trials: an example from alcohol dependence. *Psychother. Psychosom.* 78(3), 167–171 (2009).

14 Pollo A, Benedetti F. The placebo response: neurobiological and clinical issues of neurological relevance. *Prog. Brain Res.* 175, 283–294 (2009).

15 Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* 19, 484–494 (1999).

16 Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-imaging a shared neuronal network. *Science* 295, 1737–1740 (2002).

•• **Study highlighting the importance of opioid mechanisms on placebo analgesia.**

17 Faria V, Fredrikson M, Furmark T. Imaging the placebo response: a neurofunctional review. *Eur. Neuropsychopharmacol.* 18(7), 473–485 (2008).

18 Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-blind clinical trials: a review of interactions with medications. *Lancet* 344(8933), 1347–1349 (1994).

19 Finniss DG, Benedetti F. Mechanisms of the placebo response and their impact on clinical trials and clinical practice. *Pain* 114(1–2), 3–6 (2005).

20 Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: a review of the recent literature. *Pain Pract.* 7(1), 4–20 (2007).

21 Loder E, Goldstein R, Biondi D. Placebo effects in oral triptan trials: the scientific and ethical rationale for continued use of placebo controls. *Cephalalgia* 25(2), 124–131 (2005).

•• **Review of placebo response in acute triptan trials.**

22 Bigal ME, Bordini CA, Sheftell FD, Speciali JG, Bigal JO. Migraine with aura versus migraine without aura: pain intensity and associated symptom intensities after placebo. *Headache* 42(9), 872–877 (2002).

23 Vecsei L, Gallacchi G, Sagi I *et al.* Diclofenac epolamine is effective in the treatment of acute migraine attacks. A randomized, crossover, double blind, placebo-controlled, clinical study. *Cephalalgia* 27(1), 29–34 (2007).

24 Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Med.* 5(8), e166 (2008).

25 Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs* 60(6), 1259–1287 (2000).

26 Tepper SJ, Bigal ME, Sheftell FD, Rapoport AM. Botulinum neurotoxin type A in the preventive treatment of refractory headache: a review of 100 consecutive cases. *Headache* 44(8), 794–800 (2004).

27 Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.* 59, 565–590 (2008).

28 Saxena PR, Tfelt-Hansen P. Triptans, 5-HT 1B/1D receptor agonists in the acute treatment of migraines. In: *The Headaches.* Olesen J, Goadsby PJ, Tfelt-Hansen P, Welch KM (Eds). Lippincott, Williams & Wilkins, PA, USA 469–475 (2006).

29 Goldstein J, Silberstein SD, Saper JR, Ryan RE Jr, Lipton RB. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* 46(3), 444–453 (2006).

30 Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch. Intern. Med.* 160(22), 3486–3492 (2000).

31 Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T *et al.* Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 24(11), 947–954 (2004).

32 Amanzio M, Corazzini LL, Vase L, Benedetti F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* 146(3), 261–269 (2009).

33 Mathew NT, Saper JR, Silberstein SD *et al.* Migraine prophylaxis with divalproex. *Arch. Neurol.* 52, 281–286 (1995).

34 Klapper J; on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 17, 103–108 (1997).

35 Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 16, 257–263 (1996).

36 van de Ven LLM, Franke CL, Koehler PJ; on Behalf of the Investigators. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia* 17, 596–599 (1997).

37 Diener H, Krupp P, Schmitt T *et al.* Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. *Cephalalgia* 21, 66–70 (2001).

38 Macedo A, Banos JE, Farre M. Placebo response in the prophylaxis of migraine: a meta-analysis. *Eur. J. Pain* 12, 68–75 (2008).

•• **Important meta-analysis of the placebo response in migraine preventive trials.**

39 Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache* 45, 293–307 (2005).

40 Silberstein SD, Gobel H, Jensen R *et al.* Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia* 26, 790–800 (2006).

41 Linde K, Streng A, Jurgens S *et al.* Acupuncture for patients with migraine: a randomized controlled trial. *JAMA* 293, 2118–2125 (2005).

42 Diener HC, Kronfeld K, Boewing G *et al.* Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol.* 5, 310–316 (2006).

43 Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Eval. Health Prof.* 28, 9–26 (2005).

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