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Placebo and nocebo in the treatment of migraine: How much does real world effectiveness depend on contextual effects?

Hauke Basedau[1], Raffaele Ornello[2], Eleonora De Matteis[2], Bolortsetseg Davaasuren[3], Begimai Kadyrova[4], Doga Vuralli[5], Myroslav Bozhenko[6], Ilaha Azizova[7], Natia Bitsadze[8], Elnura Eralieva[9], Messoud Ashina[10], Dimos Mitsikostas[11] and Francesca Puledda[12]

Abstract

Purpose: Treatments in medicine impact individuals beyond their intended effects, due to phenomena such as the placebo and nocebo effects. The placebo effect arises from the positive expectation of a treatment being beneficial, while the nocebo effect stems from the negative expectation of a treatment causing harm. Both in real-world practice and clinical trials, treatments can lead to outcomes unrelated to their intended mechanism of action, which we categorize as placebo and nocebo responses. These responses, combined with the inherent fluctuation in a condition's natural progression, regression to the mean, and random comorbidities, make up a significant part of the therapeutic experience. Particularly in pain management, placebo and nocebo effects play a substantial role. By addressing modifiable contextual factors such as patient expectations, lifestyle choices, and the therapeutic relationship, healthcare providers can enhance the effectiveness of migraine treatments, paving the way for a more comprehensive, individualized approach to patient care. We must also consider non-modifiable factors like personal experiences, beliefs, and information from social media and the internet.

Conclusion: This review offers a summary of our current understanding of the placebo and nocebo effects in migraine management.

Keywords

Migraine, contextual effects, placebo, nocebo, headache

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[1]Department of Systems Neuroscience, University Medical Center Hamburg- Eppendorf, Hamburg, Germany
[2]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[3]Department of Neurology, State Special Servant Hospital of Mongolia, Ulaanbaatar, Mongolia
[4]Department of Special Clinical Disciplines, International School of Medicine of International University of Kyrgyzstan, Bishkek, Kyrgyzstan
[5]Department of Neurology and Algology, Neuropsychiatry Center, Neuroscience and Neurotechnology Center of Excellence (NÖROM), Gazi University, Ankara, Turkey
[6]Department of Neurology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[7]Neurological Clinic "New Medical Technologies", Baku, Azerbaijan
[8]Caucasus Medical Centre, Tbilisi, Georgia
[9]Osh City Clinical Hospital, Osh, Kyrgyzstan
[10]Danish Headache Center, Department of Neurology, Rigshospitalet-Glostrup, University of Copenhagen, Copenhagen, Denmark
[11]Department of Neurology A, Aegintion Hospital, National and Kapidistrian University of Athens, Athens, Greece
[12]Headache Group, Wolfson SPaRC, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Corresponding author:
Francesca Puledda, Headache Group, Wolfson SPaRC, Institute of Psychiatry, Psychology and Neuroscience, Wellcome Foundation Building, Denmark Hill Campus West, King's College London, London, SE5 9PJ, UK.
Email: francesca.puledda@kcl.ac.uk

Introduction

Contextual effects, which include placebo and nocebo, play an important role in treatment outcomes of headache medicine (1,2). Etymologically, while the first uses of the term 'placebo' ('I shall please') appear in the bible, the term was first described in medical terms in the 18th century, and in non-medical dictionaries in the 19th century (3). The term nocebo, on the other hand, signifying 'I shall harm', was introduced by Kennedy in 1961 (4).

The placebo response includes all health changes that result from the administration of an inactive treatment, whereas the placebo effect refers to changes specifically attributable to the placebo mechanisms, such as: patient expectations, genetics, disease severity, patient–physician relationship, environmental circumstances, and external factors such as the route of administration (5–7). Conversely, a nocebo response refers to any unfavorable consequence of a therapeutic act, whereas the nocebo effect is represented by unfavorable health changes that are observed after a nocebo administration or application, and are attributed to the nocebo mechanisms exclusively (8). Therefore, placebo and nocebo effects represent the favorable or unfavorable outcomes from before to after treatment that are powered by the patients' mind entirely. Just as with placebo, nocebo effects can result from factors such as expectation, conditioning, observational learning, and generally from the patient's concern that treatment might be harmful (9). They include both non-specific adverse events (AEs), which the pharmacological action of the treatment cannot explain, and symptoms that resemble treatment-related AEs (10,11).

Importantly, placebo and nocebo are not simple psychological effects, as they involve specific brain circuits and activity such as the dopaminergic circuits of reward (9,12,13), and, in case of pain, in the descending opioid system (13). Recent research has shown that nocebo responses in particular might be due to altered activation of the anterior cingulate cortex (ACC), thus representing an evolutionary adaptation for the avoidance of dangerous events by reinforcing mechanisms of negative anticipation within the limbic system (14).

The high incidence of placebo response is a distinctive feature of most randomized clinical trials (RCTs) of migraine medication (15). However, RCTs do not provide estimates of nocebo effects which affect compliance and response to treatment (16). In the real-world, many individual and external factors, such as disease and treatment characteristics, can enhance these contextual effects and thus require proper evaluation in the effort to maximize treatment effectiveness (Figure 1).

This narrative review summarizes the main pathophysiological and clinical aspects of placebo and nocebo responses in migraine, with the aim of

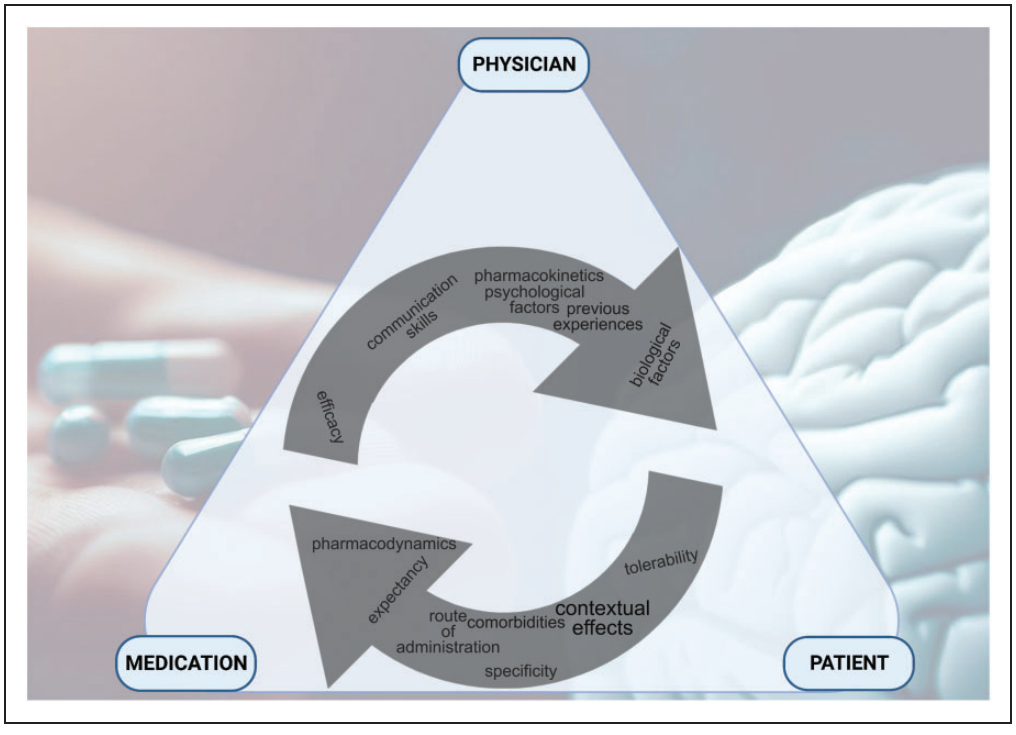

Figure 1. Individual and external factors can enhance contextual effects that require proper evaluation in the effort to maximize treatment effectiveness.

improving the assessment of contextual responses and patient care in clinical practice.

The neurophysiologic bases of placebo and nocebo effects in migraine

The knowledge of mechanisms underlying placebo and nocebo responses allows us to understand their importance in migraine treatment. From a neuropsychological point of view, placebo and nocebo effects involve the mechanisms of conscious anticipation and unconscious conditioning (17). The first mechanism is linked to expectation and anticipation of clinical benefit, while the second is linked to contextual cues. Specifically, these include taste and smell of a drink or color and shape of a pill that may act as a conditioned stimulus, capable alone of inducing a clinical improvement after repeated associations with the active pharmacological agent (18). One study even demonstrated that the magnitude of a clinical effect can be significantly influenced by the simple labelling of a placebo as an active treatment and vice versa, highlighting the importance of expectancy in therapeutic success rates of medication (19).

Functional neuroimaging studies performed through fMRI or PET in non-headache pain have shown that placebo analgesia involves the activation of the descending opioid system. This occurs in several areas, including the periaqueductal gray, nucleus accumbens, and dorsolateral prefrontal cortex, similarly to opioid-induced analgesia (20). However, a wide individual participant data meta-analysis showed that the pattern of brain areas activated by placebo analgesia are different from those involved in pain processing (21). The dopaminergic system is also involved in placebo-related analgesia, as it is known that brain circuits involved in motivation and reward can be activated by placebo (22–25). The activation of reward systems associated with placebo correlates well with the psychological mechanisms of anticipation of benefit, which in itself motivates patients in 'believing' the efficacy of placebo. Further, brain circuits involved in placebo responses include the endocannabinoid system as an enhancer (26) and the cholecystokinin system as an antagonist (24), as suggested by pharmacological studies.

Ultimately, the placebo response represents an excellent tool to understand the brain and its learning and developmental mechanisms (27). One concept that has emerged thanks to the study of the placebo effect is in fact that words and rituals are capable of modulating the same biochemical pathways that are targeted by certain drugs. Experimental evidence also shows that there are genetic variants in placebo responsiveness (28–30).

Neuroimaging has also been essential for the study of nocebo effects, showing that the anticipation of pain and its intensity can activate several brain regions involved in nociceptive processing, including: the thalamus, prefrontal cortex, secondary somatosensory cortex, anterior cingulate cortex and insula (31,32). The hypothalamus–pituitary–adrenal axis and cholecystokinin systems are also directly involved in anticipatory anxiety and nocebo-induced hyperalgesia (33,34).

An overview of these mechanisms can be found in Table 1.

Context of therapy regimes in migraine clinical trials

The treatment of migraine includes acute and preventive therapies, which can be classified as migraine-non-specific or migraine-specific, and pharmacological or non-pharmacological treatments. Regarding acute treatments, migraine non-specific drugs include non-steroidal anti-inflammatory drugs, paracetamol/acetaminophen, caffeine, and antiemetics. Migraine-specific drugs are triptans, ditans, and gepants (35–37). Pharmacological non-specific migraine preventatives include oral drugs – beta-blockers, anti-epileptics, tricyclic antidepressants, anti-hypertensive agents (angiotensin converting enzyme inhibitors and angiotensin 2 receptor blockers), calcium channel blockers – and onabotulinumtoxinA (for chronic migraine). Pharmacological migraine-specific treatments consist of the novel CGRP monoclonal antibodies and gepants (38). Non-pharmacological preventives include neuromodulation, psychotherapy, biofeedback, relaxation

Table 1. Key points of the pathophysiology of placebo and nocebo effects.

Neuropsychological mechanisms	• Conscious anticipation • Unconscious conditioning
Brain areas involved	• Descending opioid system (analgesia) • Dopaminergic reward circuit (anticipation of benefit) • Endocannabinoid system (placebo enhancer) • Cholecystokinin system (placebo antagonist) • Thalamus, prefrontal cortex, secondary somatosensory cortex, anterior cingulate cortex, insula (nociceptive processing)
Body systems involved	• Hypothalamus-pituitary-adrenal axis (anticipatory anxiety) • Cholecystokinin system (anticipatory anxiety)

techniques, physical therapy, and acupuncture (37,39,40). Pharmacological treatments are more widely used compared with non-pharmacological treatments; thus, greater evidence is available on their contextual effects.

Trials of pharmacological prevention are usually compared against a placebo to ensure that the assessment of efficacy of the medication is disentangled from contextual effects. The assessment of placebo responses for non-pharmacological treatments is more complex: these are usually compared to sham interventions and complete blinding is difficult to achieve. Interestingly, the nocebo effect can characterize both pharmacological and non-pharmacological treatments, as patients treated with non-pharmacological interventions can develop adverse events even in sham treatment groups (41).

Factors involved in placebo and nocebo responses in clinical trials can include age, gender, methods of the study, prior use of the drug being tested, frequency of the attacks, and if the study tests acute or preventive treatments. As discussed further below, these can be distinguished into modifiable and non-modifiable (8).

In the case of acute attack management, for example, the factors most known to alter the placebo effect include: concomitant use of preventive treatment, number of rescue doses allowed, and the interval between headache onset and treatment.

Response to preventive treatment can also include different aspects that are disjointed from the efficacy of treatment itself. In general, studies of migraine preventives have shown a higher variability in placebo response rate compared with studies of acute treatments (2), while increased nocebo effect and trial dropouts are more common in these studies (1). One meta-analysis in particular has shown that AEs and dropout ratios in migraine patients allocated to placebo are higher in preventive trials compared with acute treatment trials (1). This finding could be due to several reasons. First of all, migraine preventive trials often include patients with chronic or high-frequency episodic migraine, who can present psychiatric comorbidities capable of enhancing negative expectations for AEs (42).

The route of administration is also crucial in determining placebo and nocebo responses. Placebo rates seem to be higher for injectable treatments, such as onabotulinumtoxinA, compared to oral placebos (43,44), and even higher when injections are delivered closer to the site of the pain, such as in the head and neck (7,45). This also applies to intranasal administration (2,46) and to orally dissolving formulations, with respect to regular tablets (47). A meta-analysis has shown that sham acupuncture results in a more pronounced decrease in headache frequency compared to oral pharmacological placebos (48).

The intrinsic nature of the drug being used can also have an effect on placebo and nocebo responses. Although direct comparisons are lacking, the proportion of placebo responses seems comparable between triptans and other acute drugs (49). Conversely, RCTs on preventives showed a high placebo response in patients treated with anti-CGRP monoclonal antibodies (mAbs) (50). This effect can be attributed not only to the parenteral administration of those drugs, but also to their specific mechanism of action (51–58), which enhances the patients' expectations of benefit. In the meta-analysis conducted by Forbes et al., (59) up to 67% of the decrease in monthly migraine days (MMD) following treatment with monoclonal antibodies acting on the CGRP pathway was shown to be due to contextual effects, including placebo. In fact, the overall reduction in MMD following use of CGRP monoclonal antibodies is small compared to placebo, on average 1.5 days/month in episodic migraine (EM) patients and 2.2 days/month in chronic migraine (CM) patients. The estimated proportions of contextual effects (placebo) over the overall efficacy of the drugs were 66% in EM and 68% in CM. This data shows that, in two-thirds of treated patients, benefit is due to contextual effects rather than the direct biological effect of CGRP mAbs (59). Authors estimated the proportion of contextual effects for commonly used oral preventives and reported similar contextual effect proportions for sodium valproate, propranolol and topiramate (57%, 58% and 73% respectively). OnabotulinumtoxinA, on the other hand, showed a proportion of contextual effect of 75%, which is even higher than that of CGRP mAbs (59).

Finally, disease history, and particularly chronicity, can directly affect treatment response, often enhancing the nocebo effect. Patients with a long history of migraine usually have a long history of preventive treatment failures. This can certainly impair their expectations on the efficacy of future treatments, and further enhance nocebo responses. For instance, a subgroup analysis of the STRIVE trial evaluating the efficacy of erenumab showed a greater placebo response in patients with $\geq$50% and $\geq$75% response rate with no prior preventative failures compared with those with $\geq$1 or $\geq$2 prior failures (60). Chronicity affects treatment response as well as, in the context of primary headaches, concomitant medication overuse headache (MOH). CM and MOH are conditions that often coexist, posing challenges in their treatment. The treatment of choice of withdrawal of acute medications in MOH is a good example of the strong influence of nocebo in this context. Many otherwise proven effective escape medications (61) or effective prophylactics (62) and

behavioral interventions (63) have often failed to add value to the treatment of withdrawal, and placebo rates have decreased notably compared to other prophylaxis studies in MOH cohorts (64,65). Thus, in the presence of MOH, the nocebo effect often appeared to superimpose placebo analgesia and lowering differences between treatment groups.

A summary is shown in Table 2.

Randomized-controlled trials compared with the real-world

External factors in migraine therapy

Aside from the type of drug, route of administration and the other contextual factors explored in the previous paragraph, one must consider the differences in placebo and nocebo effects between RCTs and the real-world. On average, the placebo incidence is up to 32.4% for acute treatments (45) and up to 30.4% for migraine preventives (66). At the same time, it has been shown that the placebo rate for preventive therapy has gradually increased over the last decades (67). There are many factors that can influence response to medications outside of the context of an RCT, and these include natural disease evolution, price and availability of the drug, packing and labelling, branding, public perception, and media exposure.

The genuine placebo response designates what is observed in the placebo arm of a clinical trial (68) that comes as a direct consequence of the expectation of receiving 'verum' treatment (69). When one enriches this pure biological phenomenon with other factors known to contribute to symptom amelioration, it is possible to observe the actual 'placebo effect', which is perhaps most relevant for clinical practice. These factors include intrinsic biases, natural disease history, and regression to the mean (where repeated measurements of a phenomenon yield values that are nearer to the average and are thus more representative of reality). All these factors can become even more relevant when measuring the placebo effect outside of clinical trials. In a life-long condition such as migraine, natural fluctuations and worsening within the same individual can in fact make RCTs not fully representative of the disease, as they typically tend to include patients in more symptomatic phases of disease evolution. The extent of these types of effects, however, is difficult to measure, as it would require studies to include a 'no treatment' group to compare with the placebo group, and this can prove particularly challenging, not least due to ethical reasons.

Table 2. Factors that can influence placebo and nocebo response.

Patient-related	• Age • Gender • Frequency of migraine • (Psychiatric) comorbidities • Patient-physician relationship (communication)
Acute medication-related	• Prior exposure to the tested drug • Concomitant preventive medication • Severity of attacks • Route of administration • Rescue medication • Interval between headache onset and treatment
Preventive medication-related	• Prior exposure/prior preventive failures • Route of administration

Nocebo is even more difficult to estimate, both in RCTs and real-world studies. A meta-analysis of trials for treatment of primary headaches concluded that the nocebo incidence for acute migraine therapy was up to 18.4% and for preventative therapy about 47% (70). Another meta-analysis including all RCTs on human models of migraine carried out in Denmark provided quite similar data on the incidence of migraine attacks or headache after infusion of placebo. The work showed that a higher proportion of patients with migraine developed attacks and delayed headaches after placebo when compared with healthy controls (8% and 26% of patients vs 0.5% and 11% of healthy controls, respectively) (71). Interestingly, the proportion of migraine attacks in patients remained lower compared with delayed headaches, thus, nocebo effect lacks migraine-specific features. This meta-analysis shed light on the presence of nocebo effects in patients with migraine, which requires greater identification and minimization both in research and clinical settings through questionnaires (72) and proper communication (73). Overall, nocebo is difficult to study experimentally, but with the introduction of anti-CGRP mAbs and the requirement to evaluate the success of the therapy after a certain period of time using a cessation-test, another effect of nocebo could be demonstrated: It could be shown that after the cessation and the re-initiation of the anti-CGRP mAb preventative treatment, the initial response rates were no longer observed and decreased. It could thus be shown that the discontinuation trial even had a downside effect on the general efficacy of migraine preventative treatment (74). In addition, nocebo effect is enhanced in migraine compared with other diseases; evidence suggests that AEs reported with topiramate in the migraine field are more relevant than those reported by patients with epilepsy (75). The adverse events reported by

migraine patients correspond to those attributed to the drugs, even in the placebo arms of RCTs, suggesting that communication with patients on AEs is a key trigger for potential nocebo effects (10).

It is relatively easy to imagine how branding and advertising strategies by manufacturers can cause a profound impact on treatment response, when drugs are sold and made available to the public. While branded medications have been shown to produce a greater placebo effect, generics are linked to higher nocebo (76,77). A study testing branded and un-branded forms of aspirin for the acute treatment of headache showed that branding can account for up to one-third of pain relief response (78). Further, this effect seems more noticeable in patients that are previous users of the brand, possibly due to the strong links between placebo effects and expectation (79). This aspect is particularly important in a condition where self-medication is very common, making patients a potential target of exploitation for marketing purposes.

Another extrinsic factor that can influence the response to a medication is the cultural milieu, where complex interactions between people and society can impact the placebo effect on the individual (80). This type of effect is much more pronounced in clinical reality with respect to research settings and even stems back to social modelling, in which behavior is learnt by observing the actions of others. For example, witnessing a colleague or a friend experiencing side effects to a medication can modulate placebo and nocebo responses in significant ways (76).

A summary is given in Table 3.

Modifiable and non-modifiable factors involved in placebo/nocebo effects

Previous therapies and experience can play a role in the placebo and nocebo response to migraine treatment. Patients who have had positive experiences with migraine treatments may more likely experience a placebo effect when receiving a new treatment due to the expectation that the treatment will be effective (81). A study has shown that patients with prior response to preventatives showed a higher reduction in headache days than patients without prior treatment experience (82). Similarly, patients with negative experiences from previous treatments may be more prone to experience a nocebo effect due to the expectation that the treatment will be ineffective or even harmful (82). In addition, a patient's personality, age, cultural aspects, education levels, genetics and gender all represent non-modifiable factors that may influence the generation of placebo and nocebo effects (83). With regard to age, for example, there are two groups that require special attention: children or adolescents (<18 years) and patients over 65 years of age. Both categories are typically excluded from large studies. Thus, acute and prophylactic treatments for these patient groups often fall outside the approval of the medication. This leads to additional sources of bias in clinical efficacy as well as in the study of efficacy, such as the increase in side effects due to nocebo effects and a larger variance in placebo response (16,84–86).

Studies using functional MRI have shown that altered resting functional network connectivity within the triple-network model – which includes the default mode, executive control and salience network - predicts the efficacy of non-steroidal anti-inflammatory drugs in migraineurs without aura (87). As anxiety and depression are crucial in the interaction of these three networks in the formation of a person's psycho-emotional state (88,89), and given that affective and cognitive traits represent modifiable factor in the placebo/nocebo response (8), this aspect should be taken into account when choosing drugs and evaluating their effectiveness.

There is no clear reason for why contextual effects are more evident in headache disorders than in other diseases. A possible role lies in the high prevalence of psychiatric traits in patients with migraine, such as anxiety and depression (90–92), that are further enhanced by recurrent headache episodes. A further factor enhancing the nocebo effect of currently available migraine treatments is that many of these drugs are

Table 3. Contextual factors in randomized controlled trials and in clinical practice of migraine treatment.

Randomized controlled trials	Clinical practice
"Placebo response": response purely related to placebo administration	"Placebo effect": complex interaction of factors contributing to symptom amelioration
Patients tend to be in a highly symptomatic phase of the disorder	Fluctuations in the disorder are frequent and might be interpreted as due to the drug
Communication of therapeutic and adverse effects is conducted in a standard manner	Communication of therapeutic and adverse effects can be personalized
No branding or advertising	Branding, advertising
Lower influence of socio-cultural factors	High influence of socio-cultural factors

not specifically designed for migraine. This might negatively affect expectations on drug efficacy and decrease tolerance for adverse events. The use of non-specific drugs can also lead to poor efficacy and consequently to low differences between non-specific drugs and placebo (93). Conversely, the specificity of peripherally acting agents such as onabotulinumtoxinA and monoclonal antibodies acting on the CGRP pathway might generate positive expectations that enhance placebo.

The high placebo effect of migraine treatments also seems to affect the results of RCTs performed in paediatric patients. For example, the CHAMP study of topiramate and amitriptyline in paediatric migraine failed not only because of low efficacy – which was comparable to adult trials – but because of the low difference between active and placebo groups (94). The study showed that topiramate, amitriptyline and placebo did not differ in their effectiveness over 24 weeks of treatment (94), and clinical outcomes were similar even three years after treatment discontinuation (95).

The patient-physician relationship

Individual characteristics of the patient and the doctor-patient relationship can have a significant impact on treatment outcomes and represent a directly modifiable factor in the generation of placebo and nocebo. Physician empathy positively affects migraine treatment outcomes and compliance with management plans (96). A significant percentage of pain relief may be attributed to patients being informed about how their new drug treatment will likely impact on their headache, thus channeling an effective placebo response (97). In a recent publication, Schmidt et al. showed that positive treatment expectation was associated with better treatment outcomes (82). Another study by Zheng et al. demonstrated that in their research on post-treatment expectations of acupuncture in patients with migraines, high expectations after the first four weeks of treatment played an important role in predicting improvement in outcomes. The follow-up outcomes correlated with the level of expectation measured after treatment, but not with the level of expectation before treatment (98). This shows that expectancy is difficult to study and is also highly dependent on the research question and methodological design. Nevertheless, a clear and realistic outcome agreement with patients is advisable, without creating exaggerated expectations that may promote a higher rate of placebo or even nocebo rate, depending on the individual patient (99).

Headache education is another crucial element of migraine treatment that has been shown to improve patient outcomes (100). Catastrophizing tendencies, severe feelings of helplessness, and more substantial ruminative thinking are associated with migraine chronification and worse treatment outcomes (101). Positive treatment expectations depend not only on the doctor's ability to share information about the possibilities of therapy correctly, but also on the patient's involvement in the decision-making process regarding the therapeutic method and drug choice (102). Among common decision-making practices, making recommendations is still the most commonly used approach in neurology (103). Nevertheless, there is a need for further research comparing the effectiveness of option listing versus recommending in migraine treatment prescriptions. The importance of communication between a migraine patient and a doctor is also demonstrated by the fact that the most common reason for non-compliance in chronic migraine patients is appointment availability in a specialized headache clinic (104). All of these aspects need to be taken into account by the headache physician whenever a new treatment for migraine is planned or attempted.

Implications for clinical practice

From the above presented data and considerations, it emerges that contextual effects have a great importance in clinical practice. While clinical trials are important to unravel the true pharmacological effect of compounds used for migraine treatment, subjects involved in headache care should be made aware that patients' expectations play a fundamental role when treatments are marketed. Migraine is a disease in which no reliable biomarker has been identified to date and for which effective care is based upon careful recording and management of patients' reported experiences. Therefore, communication between physicians and patients is key in order to enhance placebo and avoid nocebo. Positive expectations are an important factor of adherence to and persistence with treatments, mostly when titration is needed or when efficacy increases with time, such as with onabotulinumtoxinA (105). Patients should also be reassured that failure of previous treatments does not imply failure of novel treatments, as medications' mechanisms of action vary widely. This assumption is especially true for the most recent, migraine-specific treatments, which demonstrated efficacy even in patients with multiple prior preventive treatment failures (106,107). Similarly, to prevent nocebo, patients should be reassured that the adverse event profile of different treatments are very different from one another, and poor tolerance to one treatment does not imply that the patient is intolerant to all the available medication. Reassurance on the high tolerability of some options, such as CGRP mAbs, might reduce nocebo effects. Profiling patients' psychological

characteristics is also a very important task for professionals involved in migraine care. Psychiatric traits or comorbidities that can increase negative expectations should be carefully screened and managed if necessary. The option of referring to multidisciplinary care should be considered in order to enhance the efficacy of migraine treatments when psychiatric comorbidities emerge. Non-pharmacological preventative strategies such as cognitive-behavioral therapies (CBT) are a suitable strategy in both adults and children, either on their own or in addition to pharmacological treatments (108,109). Patients with comorbidities enhancing the nocebo effect could be managed with more frequent visits in order to enhance the patient-physician relationship. Adverse events should be carefully monitored and discussed with patients; all tolerability, compliance, and persistence issues should be identified. Future clinical strategies to improve headache care should take into due account the enhancement of communication skills of both patients and professionals (110). Alongside drug prescription, narrative medicine approaches might provide a significant contribution to improving placebo and decreasing nocebo (111).

Conclusions

In conclusion, incorporating the understanding of contextual effects like placebo and nocebo into clinical practice has important implications. By recognizing the interplay between biological, psychological, and social factors, healthcare providers can optimize the effectiveness of migraine treatments by limiting nocebo and enhancing placebo effects and provide comprehensive care to individuals suffering from migraine. This can lead to improved patient outcomes, enhanced treatment compliance, and increased patient satisfaction.

Key findings

- Factors such as prior treatment experience, patient personality, cultural aspects, and the patient-physician relationship can influence placebo and nocebo effects in migraine therapy, highlighting the importance of modifiable factors in treatment outcomes.
- The route of administration and the intrinsic nature of the drug being used can impact placebo and nocebo responses in migraine treatment, with injectable treatments and drugs with specific mechanisms of action often eliciting higher placebo responses.

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ORCID iDs

Hauke Basedau https://orcid.org/0000-0002-4605-0172
Raffaele Ornello https://orcid.org/0000-0001-9501-4031
Elnura Eralieva https://orcid.org/0000-0002-5533-5292
Dimos Mitsikostas https://orcid.org/0000-0002-4691-3388
Francesca Puledda https://orcid.org/0000-0002-1933-4049

References

1. Mitsikostas DD, Mantonakis LI, Chalarakis NG. Nocebo is the enemy, not placebo. A meta-analysis of reported side effects after placebo treatment in headaches. *Cephalalgia* 2011; 31: 550–561.
2. Speciali JG, Peres M, Bigal ME. Migraine treatment and placebo effect. *Exp Rev Neurotherapeutics* 2010; 10: 413–419.
3. Shapiro AK. Semantics of the placebo. *Psychiatric Quart* 1968; 42: 653–695.
4. Kennedy WP. The nocebo reaction. *Med World* 1961; 95: 203–205.
5. Liu T. Route of placebo administration: Robust placebo effects in laboratory and clinical settings. *Neurosci Biobehavioral Rev* 2017; 83: 451–457.
6. Evers AWM, Colloca L, Blease C, et al. Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychother Psychosomat* 2018; 87: 204–210.
7. Swerts DB, Benedetti F, Peres MFP. Different routes of administration in chronic migraine prevention lead to different placebo responses: a meta-analysis. *Pain* 2022; 163: 415–424.
8. Mitsikostas DD, Blease C, Carlino E, et al. European Headache Federation recommendations for placebo and nocebo terminology. *J Headache Pain* 2020; 21: 117.
9. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron* 2008; 59: 195–206.

10. Amanzio M, Corazzini LL, Vase L, et al. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* 2009; 146: 261–269.
11. Mitsikostas DD. Nocebo in headaches: implications for clinical practice and trial design. *Curr Neurol Neurosci Rep* 2012; 12: 132–7.
12. de la Fuente-Fernández R, Schulzer M, Stoessl AJ. Placebo mechanisms and reward circuitry: clues from Parkinson's disease. *Bio Psychiatry* 2004; 56: 67–71.
13. Scott DJ, Stohler CS, Egnatuk CM, et al. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008; 65: 220.
14. Kravvariti E, Kitas GD, Mitsikostas DD, et al. Nocebos in rheumatology: emerging concepts and their implications for clinical practice. *Nat Rev Rheumatol* 2018; 14: 727–740.
15. Diener H-C, Schorn CF, Bingel U, et al. The importance of placebo in headache research. *Cephalalgia* 2008; 28: 1003–1011.
16. Mitsikostas DD. Nocebo in headache. *Curr Op Neurol* 2016; 29: 331–336.
17. Benedetti F. *Placebo Effects*. Oxford: Oxford University Press, 2020.
18. Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and nocebo effects. *Swiss Med Wkly* 2020; 150: w20340.
19. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med* 2014; 6: 218ra5.
20. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 2009; 63: 533–543.
21. Zunhammer M, Bingel U, Wager TD, et al. Placebo effects on the neurologic pain signature: *A meta-analysis of individual participant functional magnetic resonance imaging data*. *JAMA Neurol* 2018; 75: 1321–1330.
22. Wager TD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004; 303: 1162–1167.
23. Scott DJ, Stohler CS, Egnatuk CM, et al. Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* 2007; 55: 325–336.
24. Benedetti F. Placebo effects: From the neurobiological paradigm to translational implications. *Neuron* 2014; 84: 623–637.
25. Jarcho JM, Feier NA, Labus JS, et al. Placebo analgesia: Self-report measures and preliminary evidence of cortical dopamine release associated with placebo response. *NeuroImage: Clin* 2015; 10: 107–114.
26. Benedetti F, Amanzio M, Rosato R, et al. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. *Nat Med* 2011; 17: 1228–1230.
27. Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and nocebo effects. *Swiss Med Wkly* 2020; 150: w20340.
28. Benedetti F, Piedimonte A. The neurobiological underpinnings of placebo and nocebo effects. *Semin Arthritis Rheum* 2019; 49: S18–s21.
29. Benedetti F, Frisaldi E, Shaibani A. Thirty years of neuroscientific investigation of placebo and nocebo: The interesting, the good, and the bad. *Annu Rev Pharmacol Toxicol* 2022; 62: 323–340.
30. Meijers MC, Stouthard J, Evers AWM, et al. Possible alleviation of symptoms and side effects through clinicians' nocebo information and empathy in an experimental video vignette study. *Sci Rep* 2022; 12: 16112.
31. Manaï M, van Middendorp H, Veldhuijzen DS, et al. How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *Pain Rep* 2019; 4: e699.
32. Thomaidou MA, Blythe JS, Veldhuijzen DS, et al. A randomized pharmacological fMRI trial investigating D-cycloserine and brain plasticity mechanisms in learned pain responses. *Sci Rep* 2022; 12: 19080.
33. Benedetti F, Amanzio M, Giovannelli F, et al. Hypothalamic-pituitary-adrenal activity in adverse events reporting after placebo administration. *Clin Pharmacol Ther* 2021; 110: 1349–1357.
34. Benedetti F, Frisaldi E, Barbiani D, et al. Nocebo and the contribution of psychosocial factors to the generation of pain. *J Neural Transm (Vienna)* 2020; 127: 687–696.
35. Diener H-C, Holle-Lee D, Nägel S, et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. *Clin Translat Neurosci* 2019; 3: 2514183X18823377.
36. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol* 2021; 17: 501–514.
37. Ashina M, Buse DC, Ashina H, et al. Migraine: Integrated approaches to clinical management and emerging treatments. *Lancet* 2021; 397: 1505–1518.
38. Ashina M, Buse DC, Ashina H, et al. Migraine: integrated approaches to clinical management and emerging treatments. *Lancet* 2021; 397: 1505–18.
39. Coppola G, Di Lorenzo C, Serrao M, et al. Pathophysiological targets for non-pharmacological treatment of migraine. *Cephalalgia* 2016; 36: 1103–1111.
40. Puledda F, Shields K. Non-pharmacological approaches for migraine. *Neurotherapeutics* 2018; 15: 336–345.
41. Najib U, Smith T, Hindiyeh N, et al. Non-invasive vagus nerve stimulation for prevention of migraine: The multicenter, randomized, double-blind, sham-controlled PREMIUM II trial. *Cephalalgia* 2022; 42: 560–569.
42. Lipton RB, Seng EK, Chu MK, et al. The effect of psychiatric comorbidities on headache-related disability in migraine: Results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache* 2020; 60: 1683–1696.
43. Mathew NT, Kailasam J, Meadors L. Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. *Headache* 2002; 42: 796–803.

44. Silberstein SD, Göbel 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* 2006; 26: 790–800.
45. de Craen AJM, Tijssen JGP, de Gans J, et al. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol* 2000; 247: 183–188.
46. Wang SJ, Fuh JL, Wu ZA. Intranasal sumatriptan study with high placebo response in Taiwanese patients with migraine. *J Chin Med Assoc* 2007; 70: 39–46.
47. Loder E, Goldstein R, Biondi D. Placebo effects in oral triptan trials: the scientific and ethical rationale for continued use of placebo controls. *Cephalalgia* 2005; 25: 124–131.
48. Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Int Med* 2013; 173: 1941–1951.
49. Lipton R, Bigal M, Goadsby P. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication—a review. *Cephalalgia* 2004; 24: 321–332.
50. Kokoti L, Drellia K, Papadopoulos D, et al. Placebo and nocebo phenomena in anti- CGRP monoclonal antibody trials for migraine prevention: a meta-analysis. *J Neurol* 2020; 267: 1158–1170.
51. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *New Eng J Med* 2017; 377: 2123–2132.
52. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017; 16: 425–434.
53. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018; 38: 1026–1037.
54. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 Randomized Clinical Trial. *JAMA Neurol* 2018; 75: 1080–1088.
55. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; 38: 1442–1454.
56. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018; 91: e2211–e2221.
57. Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet* 2019; 394: 1030–1040.
58. Ashina M, Lanteri-Minet M, Pozo-Rosich P, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol* 2022; 21: 597–607.
59. Forbes RB, McCarron M, Cardwell CR. Efficacy and contextual (placebo) effects of CGRP antibodies for migraine: systematic review and meta-analysis. *Headache* 2020; 60: 1542–1557.
60. Goadsby PJ, Paemeleire K, Broessner G, et al. Efficacy and safety of erenumab (AMG334) in episodic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2019; 39: 817–826.
61. Cevoli S, Giannini G, Favoni V, et al. Treatment of withdrawal headache in patients with medication overuse headache: a pilot study. *J Headache Pain* 2017; 18: 56.
62. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 treatment strategies for medication overuse headache: A randomized clinical trial. *JAMA Neurol* 2020; 77: 1069–1078.
63. Pijpers JA, Kies DA, van Zwet EW, et al. Behavioural intervention in medication overuse headache: A concealed double-blind randomized controlled trial. *Eur J Neurol* 2022; 29: 1496–504.
64. Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain* 2020; 21: 114.
65. Haghdoost F, Puledda F, Garcia-Azorin D, et al. Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: A systematic review and network meta-analysis of phase 3 randomised controlled trials. *Cephalalgia* 2023; 43. DOI: 10.1177/03331024231159366.
66. Evans K, Romero H, Spierings EL, et al. The relation between the placebo response, observed treatment effect, and failure to meet primary endpoint: A systematic review of clinical trials of preventative pharmacological migraine treatments. *Cephalalgia* 2021; 41: 247–255.
67. Tepper SJ, Cirillo J, Kim E, et al. The temporal trend of placebo response in migraine prevention from 1990 to 2021: a systematic literature review and meta-analysis with regression. *J Headache Pain* 2023; 24: 54.
68. Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. *Patient Ed Counsel* 2011; 84: 413–419.
69. Autret A, Valade D, Debiais S. Placebo and other psychological interactions in headache treatment. *J Headache Pain* 2012; 13: 191–198.
70. Zhang Y, Xu Y, Liu S, et al. The nocebo response in pharmacologic treatments of primary headache: A systematic review and meta-analysis. *J Clin Pharmacol* 2022; 62: 1257–1272.
71. Ghanizada H, Iljazi A, Ashina H, et al. Nocebo response in human models of migraine: A systematic review and meta-analysis of randomized, double-blind, placebo-controlled, two-way crossover trials in migraine

without aura and healthy volunteers. *Cephalalgia* 2021; 41: 99–111.
72. Mitsikostas DD, Deligianni CI. Q-No: a questionnaire to predict nocebo in outpatients seeking neurological consultation. *Neurological Sci* 2015; 36: 379–381.
73. Bingel U, Team PC. Avoiding nocebo effects to optimize treatment outcome. *JAMA* 2014; 312: 693–694.
74. Raffaelli B, Terhart M, Overeem LH, et al. Migraine evolution after the cessation of CGRP(-receptor) antibody prophylaxis: a prospective, longitudinal cohort study. *Cephalalgia* 2022; 42: 326–334.
75. Romoli M, Costa C, Siliquini S, et al. Antiepileptic drugs in migraine and epilepsy: Who is at increased risk of adverse events? *Cephalalgia* 2018; 38: 274–282.
76. Faasse K, Martin LR, Grey A, et al. Impact of brand or generic labeling on medication effectiveness and side effects. *Health Psychol* 2016; 35: 187–190.
77. MacKrill K, Kleinstäuber M, Petrie KJ. The effect of rebranding generic medicines on drug efficacy and side effects. *Psychol Health* 2019; 34: 1470–1485.
78. Branthwaite A, Cooper P. Analgesic effects of branding in treatment of headaches. *Br Med J (Clin Res Ed)* 1981; 282: 1576–1578.
79. Benson H, Epstein MD, Zeiger D, et al. *The Placebo Effect: A Neglected Asset in the Care of Patients. Health For The Whole Person*. New York: Routledge, 1980.
80. Anderson S, Stebbins GT. Determinants of placebo effects. *Int Rev Neurobiol* 2020; 153: 27–47.
81. Tfelt-Hansen PC, Hougaard A. Differential effects of placebos in migraine clinical trials. *Nat Rev Neurol* 2014; 10: 10–11.
82. Schmidt K, Berding T, Kleine-Borgmann J, et al. The beneficial effect of positive treatment expectations on pharmacological migraine prophylaxis. *Pain* 2022; 163: e319–e327.
83. Loder EW, McGeeney B. Disentangling placebo effects in the treatment of migraine. *Nat Rev Neurol* 2020; 16: 657–658.
84. Fernandes R, Ferreira JJ, Sampaio C. The Placebo Response in Studies of Acute Migraine. *J Pediatrics* 2008; 152: 527–33.e1.
85. Le K, Yu D, Wang J, et al. Is topiramate effective for migraine prevention in patients less than 18 years of age? A meta-analysis of randomized controlled trials. *J Headache Pain* 2017; 18: 69.
86. Bingel U, Colloca L, Vase L. Mechanisms and clinical implications of the placebo effect: Is there a potential for the elderly? a mini-review. *Gerontology* 2010; 57: 354–63.
87. Wei H-L, Yang W-J, Zhou G-P, et al. Altered static functional network connectivity predicts the efficacy of non-steroidal anti-inflammatory drugs in migraineurs without aura. *Front Molecular Neurosci* 2022; 15.
88. Duran M, Miller C. Functional connectivity of the triple network model in major depressive disorder: A meta-analysis. *Biological Psychiatry* 2020; 87: S290.
89. Baggio T, Grecucci A, Meconi F, et al. Anxious brains: A combined data fusion machine learning approach to predict trait anxiety from morphometric features. *Sensors* 2023; 23: 610.
90. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, et al. Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry* 2016; 87: 741–749.
91. Peres MFP, Mercante JPP, Tobo PR, et al. Anxiety and depression symptoms and migraine: a symptom-based approach research. *J Headache Pain* 2017; 18: 37.
92. Caponnetto V, Deodato M, Robotti M, et al. Comorbidities of primary headache disorders: a literature review with meta-analysis. *J Headache Pain* 2021; 22: 71.
93. Jackson JL, Cogbill E, Santana-Davila R, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. *PloS One* 2015; 10: e0130733.
94. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *New Eng J Med* 2017; 376: 115–124.
95. Powers SW, Coffey CS, Chamberlin LA, et al. Prevalence of headache days and disability 3 years after participation in the childhood and adolescent migraine prevention medication trial. *JAMA Network Open* 2021; 4: e2114712.
96. Attar HS, Chandramani S. Impact of physician empathy on migraine disability and migraineur compliance. *Ann Ind Acad Neurol* 2012; 15: S89–94.
97. Annoni M, Miller FG. Placebo effects and the ethics of therapeutic communication: A pragmatic perspective. *Kennedy Inst Ethics J* 2016; 26: 79–103.
98. Zheng H, Huang W, Li J, et al. Association of pre- and post-treatment expectations with improvements after acupuncture in patients with migraine. *Acupuncture Med* 2015; 33: 121–128.
99. Kelman L. The broad treatment expectations of migraine patients. *J Headache Pain* 2006; 7: 403–406.
100. Wells RE, O'Connell N, Pierce CR, et al. Effectiveness of mindfulness meditation vs headache education for adults with migraine: A randomized clinical trial. *JAMA Int Med* 2021; 181: 317–328.
101. Pistoia F, Salfi F, Saporito G, et al. Behavioral and psychological factors in individuals with migraine without psychiatric comorbidities. *J Headache Pain* 2022; 23: 110.
102. Toerien M, Shaw R, Reuber M. Initiating decision-making in neurology consultations: 'recommending' versus 'option-listing' and the implications for medical authority. *Sociol Health Illness* 2013; 35: 873–890.
103. Reuber M, Chappell P, Jackson C, et al. *Evaluating Nuanced Practices for Initiating Decision-Making In Neurology Clinics: A Mixed-Methods Study*. Southampton: NIHR Journals Library, 2018.
104. Yuan D, Zhang Y, Li Q, et al. Factors affecting preventive treatment outcomes for patients with newly diagnosed chronic migraine and their compliance with treatment recommendations in Chongqing province, China: An open-label prospective study with retrospective baseline. *Front Neurol* 2020; 11: 227.
105. Silberstein SD, Dodick DW, Aurora SK, et al. Per cent of patients with chronic migraine who responded per

onabotulinumtoxinA treatment cycle: PREEMPT. *J Neurol Neurosurg Psychiatry* 2015; 86: 996–1001.
106. Scheffler A, Messel O, Wurthmann S, et al. Erenumab in highly therapy-refractory migraine patients: First German real-world evidence. *J Headache Pain* 2020; 21.
107. Lambru G, Hill B, Murphy M, et al. A prospective real-world analysis of erenumab in refractory chronic migraine. *J Headache Pain* 2020; 21: 61.
108. Kroon Van Diest AM, Powers SW. Cognitive behavioral therapy for pediatric headache and migraine: Why to prescribe and what new research is critical for advancing integrated biobehavioral care. *Headache* 2019; 59: 289–297.
109. Sharpe L, Dudeney J, Williams ACdC, et al. Psychological therapies for the prevention of migraine in adults. *Cochrane Database Systematic Rev* 2019; 7: CD012295.
110. Buse DC, Lipton RB. Facilitating communication with patients for improved migraine outcomes. *Curr Pain Headache Rep* 2008; 12: 230–6.
111. Lampl C, Sacco S, Martelletti P. Narrative-based medicine in headache disorders. *J Headache Pain* 2022; 23: 66.