



## Satellite Symposium Proceedings

### Expert Perspectives — Migraine Prevention for Highly Impacted Patients

Highlights of an Alder BioPharmaceuticals-  
sponsored symposium held at the 18th  
Congress of the International Headache Society,  
Vancouver, Canada

Richard B Lipton, Merle L Diamond,  
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# US Neurology

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# Expert Perspectives—Migraine Prevention for Highly Impacted Patients

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Migraine affects more than 10% of the global population, and in 2016 was the second leading cause of disability worldwide. Current guidelines recommend preventive treatments for people who experience frequent and disabling migraine headaches. However, only one-third of people eligible for preventive treatments receive them, and of these over three-quarters discontinue the treatment over the course of 1 year. Leading causes for discontinuation include a lack of efficacy and side effects. Current treatments can also take weeks or even months to develop clinical benefits. New, rapidly effective and well-tolerated treatment options are required for the prevention of migraine. Calcitonin gene-related peptide (CGRP) is a neuropeptide implicated in migraine in many ways. CGRP receptors are located at multiple sites involved in migraine pathophysiology. Plasma levels of CGRP are elevated during migraine episodes, and an infusion of CGRP has been shown to evoke a migraine in patients with the condition. These findings make CGRP a promising therapeutic target for the prevention of migraine. Currently there are two approaches to CGRP preventive therapy under investigation: small-molecule CGRP receptor antagonists (collectively known as ‘gepants’) and anti-CGRP or anti-CGRP receptor monoclonal antibodies. Small-molecule CGRP receptor antagonists, such as telcagepant, have shown clinical efficacy as an acute treatment for migraine. However, telcagepant was also associated with liver toxicity when used as a migraine preventive. By contrast, four new anti-CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, galcanezumab) have met clinical trial efficacy endpoints for episodic and chronic migraine while demonstrating tolerable adverse event profiles. They also show efficacy benefits that are apparent in less than 1 week. As such, anti-CGRP monoclonal antibody therapies may potentially change the treatment paradigm for migraine, though cost and access to therapy will be important factors in the paradigm shift.

### Keywords

Calcitonin gene-related peptide (CGRP), monoclonal antibody, migraine, preventive, prophylaxis

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## Introduction

Presented by: Richard B Lipton

Albert Einstein College of Medicine, Bronx, NY, US

Current guidelines recommend preventive treatments for people who experience frequent and disabling migraine headaches, specifically those suffering headaches on 4 or more days/month.<sup>1</sup> However, only one-third of people eligible for preventive treatments actually receive them, and of these, over three-quarters discontinue the treatment over the course of 1 year due to efficacy and safety limitations.<sup>1-3</sup> Here we discuss the burden of migraine, barriers to the use of preventive treatments, and current and emerging approaches to treating migraine in highly impacted patients.

### Scope and burden of the migraine problem

Migraine is a global problem that affects more than 10% of the population worldwide — an estimated 1.04 billion people.<sup>4</sup> Of these, many experience at least 4 days/month of migraine and should therefore be considered potential candidates for preventive treatment.<sup>5</sup>

Several studies have assessed the impact of migraine. The American Migraine Prevalence and Prevention (AMPP) study used a validated, self-

administered questionnaire to assess disease burden in over 18,000 individuals with migraine.<sup>1</sup> Migraine episodes resulted in severe impairment or necessitated bed rest in 53.7% of cases and caused some impairment in 39.1% of cases, with normal function reported in only 7.2% of cases.<sup>1</sup> As a result of this impairment, migraine headaches caused substantially reduced participation in everyday activities as assessed by the Migraine Disability Assessment (MIDAS) questionnaire: in 3 months, more than a quarter of patients missed at least a day of work/school, nearly half were unable to do housework or chores for a day or more and nearly one third missed at least a day of family or social activity.<sup>1</sup>

The Global Burden of Disease study assessed the burden of over 300 diseases and injuries between 1990 and 2016 based on the number of years of healthy life lost as a result of a disability (years lived with disability [YLD]).<sup>4</sup> In 2016, migraine was found to be the second leading cause of YLD worldwide with 45.1 million YLD, ahead of conditions such as major depression, diabetes, and anxiety disorders.<sup>4</sup> □

## Which patients are highly impacted by migraine?

Presented by: Richard B Lipton

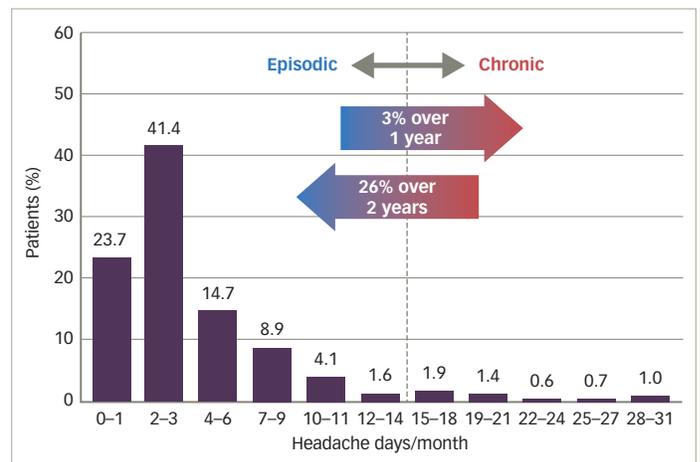
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### Who needs preventive treatment?

Several factors should be taken into account when considering preventive treatment for a patient with migraine. These include the frequency of headaches, interference with routine activities, migraine subtype, issues with acute medications, elevated risk for headache progression or other adverse neurological outcomes, and patient preference. That said, traditional criteria for preventive treatment focus, in part, on the frequency of headaches.<sup>5,6</sup> The frequency of headaches in patients with migraine varies over time and exists on a dynamic spectrum. Emerging evidence shows that patients transition from episodic migraine (less than 15 headache days/month) to chronic migraine (15 or more headache days/month; a process termed “chronification”<sup>7,8</sup>) and *vice versa* (Figure 1).<sup>9-11</sup> Highly impacted patients can include those with high-frequency episodic migraine, chronic migraine, or medication-overuse headache. Highly impacted patients typically have 4 or more migraine days/month associated with significant interference in routine activities despite the use of acute treatment.<sup>5</sup> In these patients, acute medications may be ineffective, overused, poorly optimized, or associated with troublesome adverse events (AEs), and in some patients triptans or non-steroidal anti-inflammatory agents may be contraindicated. Highly impacted patients may also present with uncommon subtypes of migraine, for example, hemiplegic migraine, migraine with brainstem aura, migraine with prolonged or persistent aura, or migrainous infarction.

Numerous predictors of headache progression from episodic to chronic migraine have been identified. These include headache features,

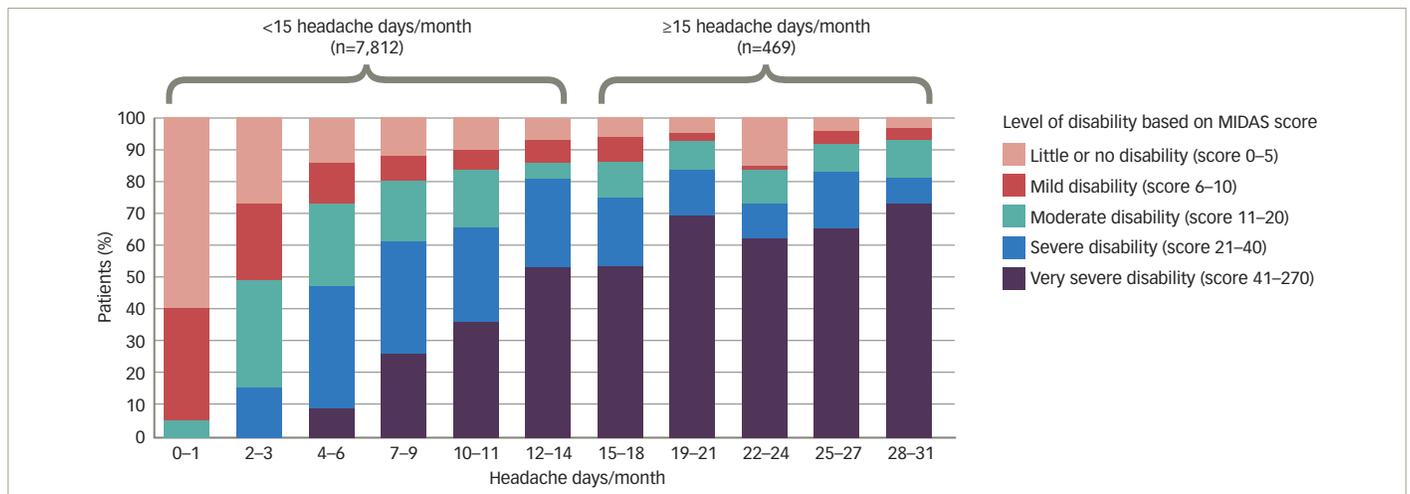
Figure 1. The frequency of headache days in patients with migraine (n=8,281)<sup>8</sup>



Data source: Bigal M, Krymchantowski AV, Lipton RB, 2008;<sup>16</sup> Blumenfeld AM et al., 2011;<sup>9</sup> Manack A et al., 2011.<sup>11</sup>

comorbidities, and treatment-related factors. Persons with higher headache frequencies and allodynia are at increased risk for progression.<sup>12-14</sup> Comorbidities associated with worsening headache include obesity, sleep disorders, depression, anxiety, asthma, and other respiratory disorders.<sup>11,13,14</sup> Poor response to acute treatment and medication overuse are associated with

Figure 2. Increased migraine disability assessment (MIDAS) questionnaire score with increasing headache frequency



MIDAS = migraine disability assessment questionnaire. Reproduced with permission from Blumenfeld AM et al. 2011.<sup>8</sup>

chronic migraine onset in persons with episodic migraine.<sup>12,14</sup> Progression from episodic to chronic migraine is also associated with increasing disability, and disability increases with an increased frequency of headache days (Figure 2).<sup>8</sup> Reducing the frequency of headache days is therefore a key treatment goal that effective preventive treatments should address.

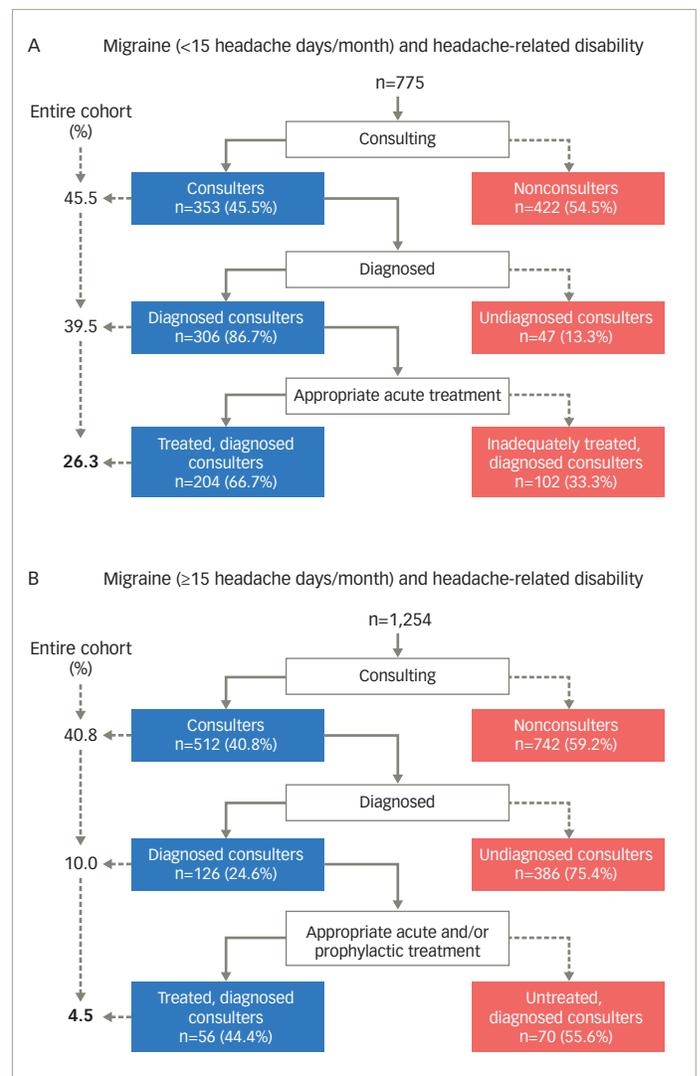
Factors associated with reversion from chronic to episodic migraine have also been identified. A multivariate analysis of data from the AMPP study showed that baseline headache frequency is a predictor of remission from chronic to episodic migraine, i.e. a lower frequency of headache days is associated with a higher transformation from chronic to episodic migraine (15–19 versus 25–31 headache days/month; odds ratio: 0.29 [95% confidence interval: 0.11–0.75]).<sup>10</sup>

### What are the barriers to preventive treatment?

Preventive treatments for migraine are currently underused. Indeed, results of the AMPP study showed that approximately two-thirds of individuals with migraine who would qualify for preventive treatment do not receive it.<sup>1,15</sup> Potential barriers to achieving optimal, or even satisfactory, migraine control occur at three levels: consultation, diagnosis, and treatment. Some people with migraine may never seek medical care or lapse from care, and many diagnosed patients may not get adequate treatment, either acute or preventive, at the time of diagnosis or with follow-up.<sup>16</sup> Follow-up is important as the initial treatment may be suboptimal or a patient’s condition may change over time, therefore treatments may need to be adjusted to account for changes in efficacy, tolerability, adherence and/or persistence.

To quantify the impact of these barriers to effective migraine management, a retrospective analysis of data from the AMPP study and the Chronic Migraine Epidemiology and Outcomes (CaMEO) study was performed.<sup>17,18</sup> For episodic migraine, only 26.3% of people with migraine traversed all three barriers and received minimally appropriate treatment. For chronic migraine, only 4.5% of people traversed these barriers (Figure 3).<sup>17,18</sup> Diagnosis and treatment rates are lower for chronic migraine because the diagnostic rates are lower in consulters and because preventive treatment is part of the start-of-care for chronic migraine (and underused). Overall, these findings highlight the substantial unmet medical need in patients with migraine.

Figure 3. Assessing barriers to migraine care



Reproduced with permission from Lipton RB et al., 2013<sup>17</sup> and Dodick DW et al., 2016.<sup>18</sup>

### Who discontinues preventive treatment and why?

Current preventive treatments (both on- and off-label) include antiepileptics (e.g. topiramate, divalproex), antidepressants (e.g. amitriptyline, venlafaxine), beta-blockers (e.g. timolol, propranolol, metoprolol), angiotensin-converting enzyme inhibitors (e.g. lisinopril), and angiotensin receptor blockers (e.g. candesartan).<sup>5,19</sup> However, adherence to these treatments is poor; a retrospective claims database analysis of 8,688 patients experiencing 15 or more headache days/month found that only 17–20% of patients remained adherent (defined as prescription claims covering at least 80% of days) to preventive medication after 1 year.<sup>2</sup>

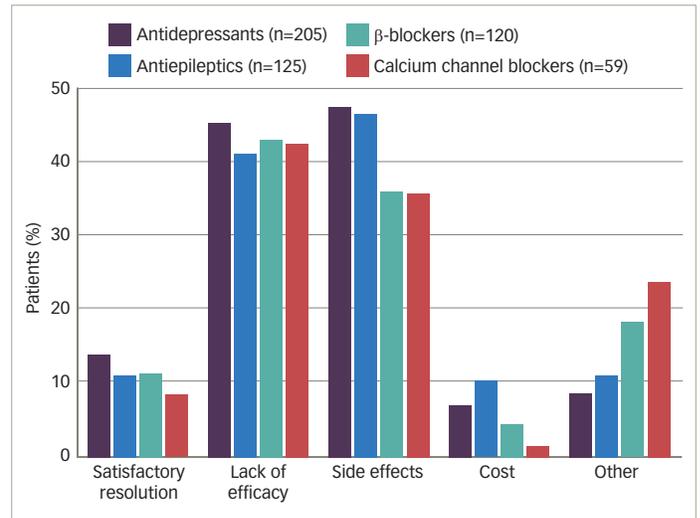
Reasons for this poor adherence were assessed in the second International Burden of Migraine study, IBMS-II, an international, web-based, cross-sectional survey study in 1,165 adults with migraine during 2010.<sup>3</sup> Discontinuation of preventive therapy was reported by 24% of respondents with episodic migraine (n=672) and 41% of patients with chronic migraine (n=493).<sup>3</sup> The two most common reasons for discontinuation were a lack of efficacy and side effects (Figure 4).<sup>3</sup> This highlights the unmet medical need for effective and tolerable preventive treatments for migraine.

### How do we decide if preventive treatment works?

The main goals of migraine prevention are: (i) decreasing migraine frequency, intensity, duration and disability; (ii) improving acute treatment response, functional ability and quality of life; and (iii) preventing disease progression.<sup>6</sup> For preventive medications, the standard definition of treatment success is a 50% reduction in the number of migraine days over 3 months.<sup>5</sup> However, this definition is only a realistic goal based on the effectiveness of current preventive treatments.<sup>5</sup> In general, patients would prefer greater reductions in the number of migraine days and to achieve this more quickly; the high discontinuation rates with current preventive treatments may reflect inadequately managed patient expectations. To address this, the patient should be involved in their care and the rationale, use, side effects, and goals of treatment should be discussed.<sup>5</sup>

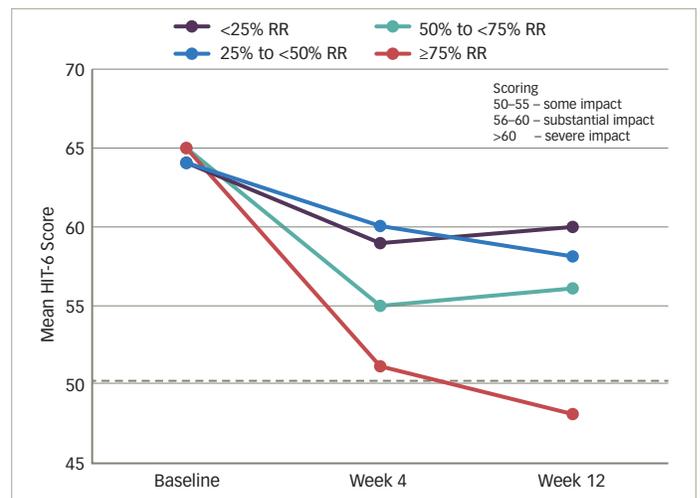
A recent analysis of 588 patients receiving a single intravenous infusion of the anti-calcitonin gene-related peptide antibody eptinezumab showed that achieving a migraine response of at least 75% has a clinically meaningful impact on a patient's daily life (indicated by a five-point or greater difference on the six-item Headache Impact Test [HIT-6] score)<sup>20</sup> and that higher migraine responses were associated with greater improvements in HIT-6 score (Figure 5).<sup>21</sup> A greater reduction in migraine days/month also delivers a greater clinical benefit. To achieve this goal, highly effective, well-tolerated preventive therapies are required. □

Figure 4. Patient-reported reasons for discontinuation of preventive treatments for migraine (IBMS-II study; n=1,165)<sup>3</sup>



IBMS-II = the second International Burden of Migraine study.  
Data source: Blumenfeld AM et al., 2013.<sup>3</sup>

Figure 5. Improved response rates are associated with clinically meaningful reductions in the impact of migraine on a patient's daily life



HIT-6 = six-item Headache Impact Test; RR = response rate.  
Difference is indicated by a five-point or greater difference on HIT-6 score.  
Source: Lipton RB et al., 2017.<sup>21</sup>

## Unmet needs of the patient with debilitating migraine—a case-based presentation

Presented by: Merle L Diamond

*Diamond Headache Clinic, Chicago IL, US*

### Addressing the unmet need in preventive treatment for migraine

As detailed previously, approximately 80% of patients discontinue preventive therapy after 1 year of treatment.<sup>2</sup> In addition, the AMPP study reported that 40.7% of patients receiving treatment for episodic migraine still experienced at least one migraine-related issue (including headache-related disability, treatment dissatisfaction and/or excessive opioid use),<sup>22</sup> and a retrospective claims study showed that up to 13.2% of patients receiving treatment (acute and/or preventive) for migraine still have at least one emergency department visit/year.<sup>23</sup> Here we present case studies to further highlight this unmet medical need from the perspective of the patient and/or healthcare provider.

### Case studies

Case studies of three patients with long histories (at least 30 years) of frequent migraine headaches were presented: one was a 42-year-old mother of three whose headaches began at age 12 and who still experiences near daily headaches and five migraine episodes/month; one was a 50-year-old retired woman whose headaches started during puberty, but who was only diagnosed with migraine at age 40 and still experiences daily headaches and up to 12 migraine headaches/month; and one was a 40-year-old male oncologist who has experienced 20 migraine headaches per month since childhood.

In all three cases, the patients had tried multiple preventive therapies, discontinuing them due to a lack of efficacy, a progressive decrease in efficacy, or side effects. The headache impact on their daily lives has been substantial, not only because of the migraine headaches themselves (and the associated clinic visits and hospital interventions), but also because of the side effects of the preventive therapies. As a result, both the patients and healthcare providers were frustrated with multiple failed medications, felt that they were on a constant search for new treatments, and thought the effectiveness of treatment was insufficient to improve quality of life.

It is clear that there are specific clinical challenges in providing support and managing treatment for patients highly impacted by migraine, such as (i) managing patient expectations on the slow onset of preventive benefit, (ii) the setting of realistic expectations on AEs and treatment goals, (iii) the management of co-morbidities, (iv) the balance that has to be struck between AEs and efficacy, and (v) the integration of acute treatment and preventive strategies.<sup>5</sup> If positive results are seen with preventive therapies, then the potential long-term risks also need to be managed (e.g. concerns around pregnancy, or the risk of osteoporosis with topiramate).<sup>5,24</sup> There is a need for new and more effective therapies that will go some way to eliminating these challenges, as current preventive treatments for migraine are associated with safety, efficacy and tolerability limitations,<sup>3</sup> as well as a slow onset of effect, and clearly fail to meet the needs of most patients. □

## The future of prevention for patients highly impacted by migraine

Presented by: Stewart J Tepper

*Geisel School of Medicine at Dartmouth, Hanover, NH, US*

### Limitations of current preventive treatments for migraine

Current preventive treatments are associated with four key limitations. Firstly, a lack of specificity for migraine: co-existing conditions must be considered when selecting from the currently available preventive treatments, as some may aggravate an existing condition (e.g. beta-blockers in patients with asthma, Raynaud's, or depression<sup>25</sup>). Secondly, AEs: many of the preventive treatments currently used are associated with side effects that can severely impact a patient's daily life. Thirdly, poor adherence: a lack of persistence with treatment is due primarily to a lack of efficacy and the side effects of treatment.<sup>3</sup> Fourthly, the long time to achieving clinical benefit, sometimes up to 12 weeks or more.

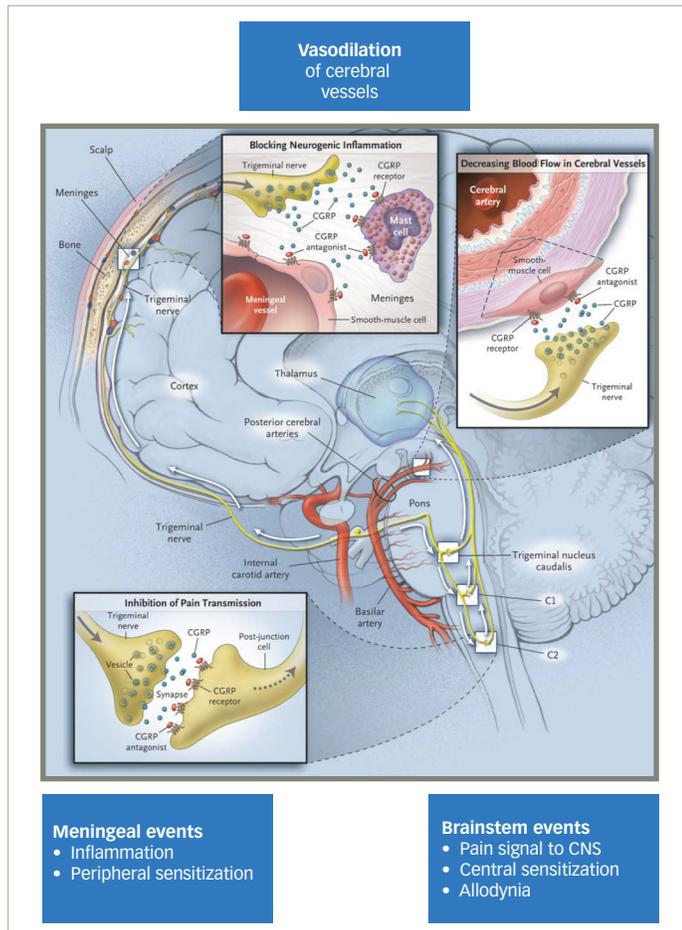
As such, there is a pressing need for novel treatments that address these limitations. In order to design and develop these, it is first necessary to review the pathophysiology of migraine in order to identify potential therapeutic targets.

### Migraine pathophysiology and calcitonin gene-related peptide

In migraine, the pain mechanisms are peripheral, driven by meningeal neurogenic inflammation and vasodilation. These pain mechanisms activate both peripheral trigeminal nociceptive afferents and transmission of pain signals to the central nervous system and central processing, steps associated with peripheral and central neuronal sensitization respectively (*Figure 6*).<sup>26</sup>

Calcitonin gene-related peptide (CGRP) is a neuropeptide belonging to the calcitonin family.<sup>27</sup> It acts as a potent vasodilator, is primarily released from sensory nerves, and is thought to be involved in both vascular homeostasis and nociception.<sup>28</sup> CGRP receptors are located at all sites involved in migraine pathophysiology,<sup>29</sup> and the release of CGRP has a variety of actions that may play a role in the pathophysiology of migraine, including neurogenic inflammation via the activation of the arachidonic acid cascade,<sup>30</sup> vasodilation,<sup>31</sup> A $\delta$ -fiber and c-fiber activation, facilitation of pain transmission,<sup>31</sup> and development and maintenance of both peripheral and central nervous system sensitization, believed to be important factors in migraine genesis.<sup>32</sup>

Figure 6. Migraine pathogenesis—activation of the trigeminovascular system



CGRP = calcitonin gene-related peptide; CNS = central nervous system. Adapted with permission from Durham PL et al., 2004.<sup>26</sup>

CGRP has been associated with migraine in clinical studies, with levels of CGRP in blood being substantially elevated during migraine episodes.<sup>33</sup> Infusion of CGRP also evokes a migraine in patients with pre-existing migraine.<sup>34</sup> CGRP is therefore a promising therapeutic target.

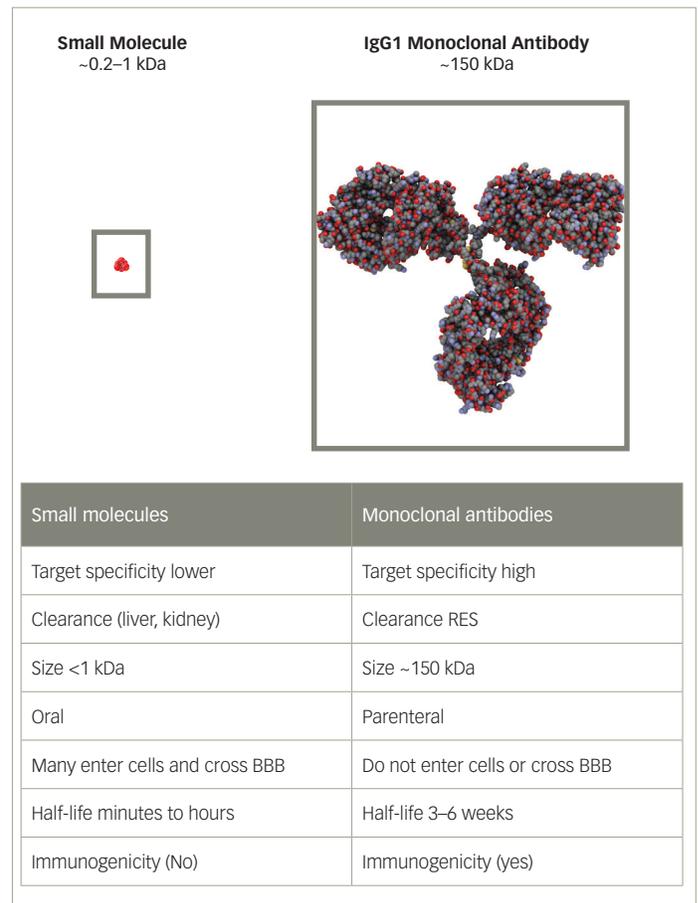
### Small-molecule calcitonin gene-related peptide antagonists and anti-calcitonin gene-related peptide monoclonal antibodies

Currently there are two approaches to CGRP preventive therapy under investigation: small-molecule CGRP receptor antagonists (collectively known as ‘gepants’) and anti-CGRP or anti-CGRP-receptor monoclonal antibodies.

Small-molecule CGRP receptor antagonists, such as telcagepant, have shown clinical efficacy as acute treatments for migraine headaches.<sup>35–39</sup> Telcagepant was also associated with liver toxicity when used daily as a migraine preventive.<sup>40,41</sup> Monoclonal antibodies are large molecules that do not cross the blood-brain barrier and are eliminated by the reticuloendothelial system, thereby eliminating the risk of metabolic liver toxicity (Figure 7).<sup>42,43</sup>

Because of their potential, specific treatment goals for novel anti-CGRP monoclonal antibodies have been proposed to address the current unmet

Figure 7. Differences between small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists and CGRP/CGRP receptor monoclonal antibodies<sup>44</sup>

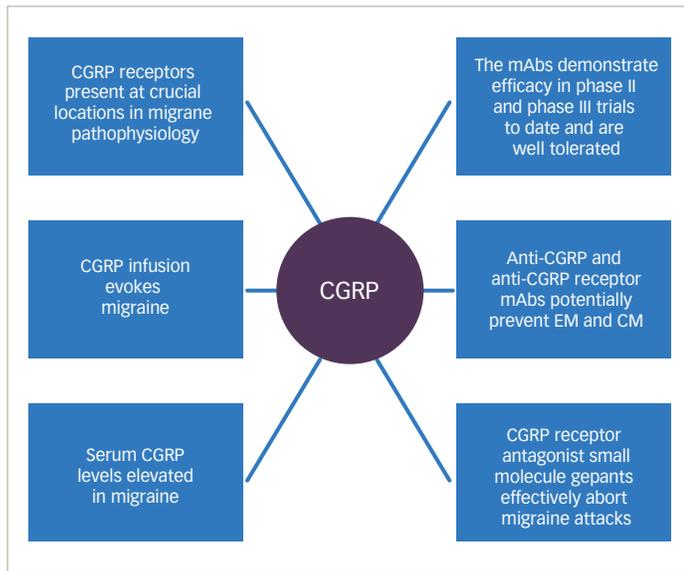


BBB = blood-brain barrier; CGRP = calcitonin gene-related peptide; IgG = immunoglobulin G; RES = reticuloendothelial system. Images from stock.adobe.com © lolya1988, molekool.be.

needs of preventive therapies: (i) the treatment should be mechanistically specific for the prevention of migraine, thereby reducing the potential effects on comorbid conditions; (ii) the treatment should achieve a migraine response of at least 75%, rather than the 50% migraine response currently defined as treatment success; (iii) there should be rapid onset of efficacy; (iv) the efficacy should be consistent and maintained over time; (v) the treatment should be both well tolerated with a favorable safety profile; and (vi) the patient adherence should be better than current preventive therapies.

To date, clinical data suggest that four anti-CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, galcanezumab) meet these key treatment goals, address the unmet needs in migraine prevention, and could change the therapeutic landscape.<sup>45–52</sup> Not only have they been designed to specifically target either the CGRP receptor or ligand, but all four have shown clinical efficacy in phase III studies for the prevention of episodic migraine and demonstrated effectiveness in registration or pivotal trials for the prevention of chronic migraine and medication over-use headache.<sup>46–52</sup> The primary endpoint in the pivotal studies was the reduction in mean monthly migraine days. There have also been positive results on secondary endpoints, including reduced acute medication days, reduced impact, reduced disability and/or improved quality of life,

**Figure 8. The current status of calcitonin gene-related peptide-directed treatments for migraine**



*CGRP = calcitonin gene-related peptide; CM = chronic migraine; EM = episodic migraine; gepants = small molecule CGRP receptor antagonists; mAb = monoclonal antibody.*

and responder rates.<sup>46–52</sup> Importantly, benefits have also been seen in the most impacted patients.<sup>45,51</sup> All four have shown early onset of clinical benefit in both patients with episodic and chronic migraine, irrespective of medication over-use. Most monoclonal antibodies require quarterly or monthly dosing via intravenous or subcutaneous administration.<sup>45</sup> Discontinuation rates in phase II and registration studies were also substantially lower than those reported for the currently available oral preventive treatments (in studies or in clinical practice), with 0.0–3.7% of patients discontinuing active treatments compared with 8.0–27.0% discontinuing placebo. These findings could reflect both the

improved efficacy and tolerability of monoclonal antibody therapies. The monoclonal antibody treatments were all generally well tolerated, with most AE rates similar to placebo.<sup>45–52</sup>

Overall, the current landscape of CGRP-directed treatment for migraine is summarized in *Figure 8*. All four of the anti-CGRP monoclonal antibodies have now shown positive results in phase III or regulatory/pivotal clinical studies; three are projected to receive US Food and Drug Administration approval in 2018, with the fourth anticipated in 2019.

## Conclusions

Current preventive medication options are associated with efficacy, safety and tolerability limitations,<sup>3,25</sup> and take a long time to achieve efficacy. The new anti-CGRP monoclonal antibodies are the first migraine-specific preventives that have met clinical trial efficacy endpoints for episodic and chronic migraine while demonstrating tolerable adverse event profiles.<sup>45–52</sup> They may show an onset of action of less than 1 week, with the potential for onset within 1 day if administered via infusion, and sustained clinically significant benefits observed within 1 month.<sup>45</sup> The clear clinical benefits, which include reduced migraine days, reduced use of acute migraine medications, reduced impact and disability, and improved quality of life and responder rates,<sup>46–52</sup> combined with the rapid speed of onset and a reduced dosing frequency may improve adherence to treatment and patient satisfaction, particularly in highly impacted patients, despite a subcutaneous or intravenous route of administration.

As such, anti-CGRP monoclonal antibody therapies may potentially reduce the burden of migraine and change the treatment paradigm, although safety, cost, and access to therapy will be important factors in the paradigm shift. Patient preference will also play a major role, particularly with regard to the mode and frequency of administration, and it is anticipated that there will be a palette of anti-CGRP-directed therapies available in the future to enable individualized preventive treatment for various types of migraine. □

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