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Emerging drugs for migraine treatment: an update

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ABSTRACT

Introduction: Migraine is a very frequent and disabling neurological disorder. The current treatment options are old, generally poorly tolerated and not migraine-specific, reflecting the low priority of migraine research and highlighting the vast unmet need in its management.

Areas covered: Advancement in the understanding of migraine pathophysiological mechanisms and identification of novel potentially meaningful targets have resulted in a multitude of emerging acute and preventive treatments. Here we review the known putative migraine pathophysiological mechanisms in order to understand the rationale of the most promising novel treatments targeting the Calcitonin-Gene-Related Peptide receptor and lidagand and the 5 hydroxytryptamine (5-HT)\textsubscript{1F} receptor. Key findings on the phase II and phase III clinical trials on these treatments will be summarized. Furthermore, a critical analysis on failed trials of potentially meaningful targets such the nitric oxide and the orexinergic pathways will be conducted. Future perspective will be outlined.

Expert opinion: The recent approval of Erenumab and Fremanezumab is a major milestone in the therapy of migraine since the approval of triptans. Several more studies are needed to fully understand the clinical potential, long-term safety and cost-effectiveness of these therapies. This paramount achievement should stimulate the development of further research in the migraine field.

1. Background

Migraine is a brain disorder affecting globally about 12% of the general population [1,2]. The lifetime prevalence of migraine is 33% in women and 13% in men [3]. Migraine is associated with a significant detrimental effect on health-related quality of life (HRQoL) and important socioeconomic impact [4]. The World Health Organization (WHO) ranks migraine as the most disabling condition amongst the diseases worldwide under the age of 50 [5]. Migraine is considered a disturbance of sensory processing with wide implications within the central nervous system [6]. It is characterized by a multiphasic process that includes a premonitory phase, when systemic, psychological and neurological symptoms, the commonest of which are fatigue, impaired concentration, irritability, yawning, nausea and craving for food can occur; an aura phase, which occurs in about 20–30% of subjects with migraine and is characterized by reversible transient visual, sensory, speech, motor, and/or brainstem disturbances occurring before, during, after the pain phase or in absence of it. These symptoms usually last between 5 and 60 min before the headache begins; the migraine pain phase, often characterized by moderate to very severe throbbing uni-bilateral head pain episodes lasting 4–72 hours and potentially accompanied by various neurological symptoms, namely photophobia, phonophobia ophthalmobia, nausea, vomiting and/or diarrhoea, dizziness, and vertigo. Over 70% of patients have cutaneous allodynia, which is the perception of pain when non-painful stimuli are applied to the painful skin area. Finally, the postdromal phase, is described as a period where the severe head pain has settled but other symptoms, namely, asthenia, fatigue, somnolence, impaired concentration, photophobia, and irritability continue for hours to few days [7]. These multiphasic process of a broad constellation of signs and symptoms highlight the complexity and the diffuse involvement of multiple neural networks and anatomical brain regions.

According to the International Classification of Headache Disorders 3 (ICHD-3), subjects with at least 15 headache days of which at least eight fulfill the criteria for migraine with or without aura per month for at least three consecutive months have chronic migraine (CM) [8]. CM affects around 2–4% of the general population, with an annual incidence among people with episodic migraine is 2 · 5–3 · 0% [9]. This type of migraine is related to a higher degree of headache-related disability than episodic migraine and is commonly linked with medication overuse headache (MOH) [10].

Refractory migraine is still a debated definition. It refers to those subjects predominantly with CM who fail to tolerate and/or respond to adequate trials of established acute and preventive treatments. Up to 5% of the migraine population fulfills the criteria for refractory CM. This group of patients suffers from tremendous disruption of their quality of life because of the migraine [11].
2. Existing pharmacological treatments

The current management of migraine includes treatments aiming to abort a migraine episode when it occurs and treatments to prevent future migraine occurrence, along with reducing the severity of symptoms and/or duration of the episode. The selection between abortive, preventive, or both strategies for a given patient, depends upon several factors including the severity of the migraine pain and associated symptoms and the frequency of occurrence of the migraines and disability associated. Broadly speaking, abortive strategies should be the main treatment for people with an episodic migraine with infrequent attacks, whereas preventive treatments should be offered in people with episodic ‘high frequency’ migraine and CM. These later group of patients should also be educated upon the potential risk of MOH, a very common chronicization factor in migraine sufferers, which often interferes with the full potential effect of concomitant prophylactic treatments [12].

Non-steroidal antiinflammatory drugs (NSAIDs), triptans and prokinetics remain the mainstay of acute migraine treatment. Stepped-up and stepped-down approaches are adopted in most Countries. In stepped-up care the patient is started on the simplest treatment and increasingly efficacious medications are prescribed until a satisfactory response is obtained. A caveat of this approach can be the delays until an effective treatment is found. A stepped-down care involves starting with the most effective treatment or combination of treatments and subsequently reducing the dose or number of abortive treatments taken to allow effective treatment with the minimum amount and number of treatments. A stepped-down approach is recommended by National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom (U.K.), in view of its cost-effectiveness. NICE suggests a combination of a triptan, NSAID or paracetamol, and an antiemetic taken as soon as possible after the start of the headache [13].

Over-the-counter medications, such as NSAIDs and acetaminophen, are often chosen first drug-class for mild-to-moderate migraine attacks. NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and, thereby, the synthesis of prostaglandins and thromboxanes, exerting an unspecific antiinflammatory effect. Potential gastrointestinal and renal side effects along with lack of efficacy in a significant proportion of patients, limit their use in the migraine population. Triptans are widely considered to be first-line drugs for patients with migraine attacks associated with moderate or severe pain intensity [14]. This class of drug was specifically designed to abort migraine by agonizing the subtypes 1B/D 5-hydroxytryptamine (5-HT) receptors, although some triptans also act at the 5-HT1F receptor site [15]. This receptors binding leads to vasoconstriction, mediated through activation of the postsynaptic 5-HT1B receptors at the level of the vascular smooth muscle, and inhibition of neuronal transmission along the trigeminal system by acting on pre-junctional 5-HT1B/D receptors, which can also result in inhibition of calcitonin gene-related peptide (CGRP) release from perivascular sensory nerve terminals. Their pharmacological profile, as well as more recent positron emission tomography (PET) studies suggest that the site of action of triptans is outside the blood-brain barrier [16]. Interestingly, despite the perception that triptans mechanisms of action tackle paramount migraine-specific pathways, a proportion of migraine patients find them ineffective. Alongside with those who do not tolerate their side effects, about 30–40% of migraine subjects are considered triptan-non responders [14]. Furthermore, in view of their vasocostrictive effect, their use is contraindicated in uncontrolled hypertension, coronary artery disease, peripheral vascular disease, or stroke. Nausea and vomiting during migraine attacks are common symptoms that affect at least 60% of patients suffering from migraines. These symptoms are often more disabling than the headache itself, causing a great burden on the patient’s life. Antiemetics, such as metoclopramide or domperidone, are often prescribed as a combined treatment to NSAIDS and triptans aiming to increase abortive treatment’s gastric absorption and tackle the nausea and vomiting during their migraines [14].

Preventive pharmacological treatments are considered if headaches occur on four or more days per month; if abortive treatment is contraindicated and/or ineffective and if abortive treatments need to be used ten of more days per month every month. The preventive treatment of migraine include different classes of drugs, namely, β-blockers, tricyclic antidepressants, antiepileptics, calcium channel blockers or angiotensin-converting enzyme inhibitors. The choice of preventative treatment depends upon the individual drug’s efficacy and side-effect profile, the presence of any comorbid conditions and patient’s preferences. However very often migraine subjects fail to adhere to these oral medications long enough to obtain a migraine preventive effect [17].

The only two approved medications for CM are topiramate and more recently Onabotulinum toxin type A (BoNTA). The introduction of BoNTA has significantly advanced the management of CM in view of its favorable tolerability profile and high responder rate found in clinical trials [18,19] and replicated in real-world studies [20]. Caveats in the use of BoNTA in clinical practice include the three-monthly administration in a hospital setting and the multiple injection sides, which can put strain on headache services. Besides, about one-third of patients do not respond to BoNTA [20].

For pharmacological and injectable treatments non-responders, the label of refractory CM is used [21]. For this severely disabled group of patients, no pharmacological treatment has hitherto been showed to be effective. Occipital nerve stimulation has gathered positive open-label evidence, which were not confirmed in randomized controlled trials [22–26]. However these trials were criticized for methodological issues. The use of noninvasive neuromodulation techniques, including vagus nerve stimulation, single-pulse transcranial magnetic stimulation and transcutaneous electrical nerve stimulation have recently emerged as alternatives to pharmacological treatments as well as to invasive neuromodulation approaches. Their different mechanisms of action [27,28] along with different patients selection may account for the mixed efficacy outcomes observed in clinical practise [29–31].
3. Medical need

Despite the broad arsenal of treatments, there is still a vast unmet need for novel migraine treatments. This includes:

1. Better tolerated abortive treatments, which could also be used in specific subgroup of migraine patients, namely, the pediatric population, pregnant women, subjects with comorbid cardiovascular and/or cerebrovascular diseases and the elderly migraineous population.
2. More effective abortive treatments that may be beneficial in the triptan non-responder population.
3. Preventive treatments with better tolerability profiles, long-term safety, and patient-friendly administration routes.
4. Specifically-designed migraine preventive treatments, which tackle pivotal pathways involved in migraine pathophysiology.
5. Preventive treatments for CM refractory to established medical treatments. At present no pharmacological treatments hold compelling evidence of efficacy in this challenging-to-treat group of people. Furthermore, invasive neurostimulation approaches, such as occipital nerve stimulation, have failed to demonstrate a meaningful therapeutic effect in clinical trials.

4. Scientific rationale

Current research directions aim to produce therapies that are able to tackle known migraine underlying putative pathophysiological mechanisms. Based on current theories, migraine is considered a brain disorder where subcortical and potentially cortical modulatory structures fail to modulate normal sensory afferent trigemino-cervical inputs from the trigeminovascular system [6]. The consequence of activation of this system is thought to be responsible for the perception of head pain in migraine.

During the premonitory phase of migraine, a number of brain imaging studies have demonstrated altered blood flow changes in the hypothalamic region [32,33], and in some studies also in the visual cortex [34,35]. How functional changes in the hypothalamus can eventually drive activation of the trigeminovascular system is not understood, but likely it involves alterations in descending pain pathways to the trigemino-cervical complex (TCC) [36]. The trigeminovascular system consists of trigeminal nociceptive nonmyelinated and thinly myelinated fibers innervating the meninges and dural vasculature. These trigeminal afferents arrive predominantly from the ophthalmic (V1) division of the trigeminal nerve, but also to a lesser extent, from the maxillary (V2) and mandibular divisions (V3). Centrally, they project to the TCC, which extends from the trigeminal nucleus caudalis to the upper cervical spinal cord, mainly C2-C3 [37].

Activation of the trigeminovascular system results in the release of a number of vasoactive neuropeptides, including CGRP and substance P [38]. The dural vascular tone is also regulated by sympathetic and parasympathetic fibers innervation. Sympathetic fibers contain vasoconstrictive peptides, including Neuropeptide Y and norepinephrine, while the parasympathetic vasodilatory innervation is characterized mainly by Vasoactive Intestinal Peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) [39]. The ascending trigeminothalamic pathway is modulated by a complex descending network of midbrain and brainstem nuclei, which communicate to one another via a plethora of neurotransmitters, including serotonin, glutamate, GABA, dopamine, and endocannabinoids [40].

At a cortical level, cortical spreading depression (CSD) is thought to be the physiological substrate of migraine aura [41]. It results from depolarization, followed by a sustained hyperpolarization of cerebral cortical neurons and glial activation, and it also induces an initial hyperemia, followed by oligoemia, resulting in profound disturbance of the cortical vascular tone [42]. CSD is driven by the release of glutamate which is modulated by calcium, potassium and sodium currents [43,44]. It is not yet clear whether CSD can activate the trigeminovascular system and, hence exacerbate pain in migraine. Electrophysiological studies in animal models suggest that both peripheral and central mechanisms are possible [45,46]. Nevertheless, disease mechanisms involved in migraine aura are of interest also for the migraine without aura prevention, since some of the treatments that can block CSD, namely sodium valproate, topiramate, and sTMS, can also prevent migraine without aura episodes [47,48].

5. Current research goals

Targeting the peptides, or their receptors, found to be released during a migraine attack, or blocking activation of the trigeminovascular system along with the neurotransmitters’ receptors involved in the migraine process, have been considered of pivotal relevance for the development of novel acute and preventive pharmacological migraine-specific treatments. In view of the pitfalls in the use of triptans, research development programmes have had the objective to develop novel acute treatments as, or more effective and better tolerated than triptans, with an exquisite neural, migraine-specific mechanism of action that when possible avoid modulation of the vascular tone. To this purpose two main pathways have been studied: the CGRP and the serotonin pathways, which produced two new family of drugs: the Gepants and the Ditans. Targeting the CGRP pathway has also led to the development of therapies potentially effective as preventive treatments, the anti-CGRP monoclonal antibodies. These classes of drugs are in an advanced stage of development and some of these therapies will be on the market shortly.

6. Competitive environment

6.1. Calcitonin gene-related peptide

CGRP is one of the most potent vasodilators known. It exists in 2 forms in humans: α-CGRP (37-amino acid peptide), mainly expressed in primary sensory neurons of the dorsal root ganglia, trigeminal ganglia and vagal ganglia, and β-CGRP primarily found in intrinsic enteric neurons. CGRP is an ubiquitous peptide distributed within the cerebral and cerebellar cortex,
thalamus, hypothalamus inhibitory nociceptive nuclei of the brainstem, the trigemino-cervical complex and the trigemino-vascular system [49]. Within the trigeminal ganglia CGRP is expressed in cells that give rise to thinly myelinated A delta-fibers and in unmyelinated C-fibers [50]. CGRP receptors have been identified within the above-mentioned cortical and subcortical structures, while on trigeminal fibers CGRP receptors function as autoreceptors, regulating CGRP release [51].

CGRP levels have been found to be elevated during a migraine attack, although some studies also suggest otherwise [52,53]. Intravenous infusion of CGRP in migraine patients has been also shown to induce a migraine attack in about 60% of the patients [54]. Of interest, patients with familial hemiplegic migraine, a rare form of migraine with aura, are not sensitive to CGRP [55], potentially due to changes of CGRP levels in their trigeminal system [56]. Experimental activation of trigeminal ganglion cells is known to result in the release of CGRP, which is dose-dependently inhibited by 5-HT1B/D agonists, highlighting the trigeminal system as a key site that may be targeted by CGRP receptor antagonists and triptans [57,58]. In addition to its vascular effects, CGRP has emerged as a key modulator of neuronal function, which has important effects on neurotransmitter systems such as the glutamatergic system [59].

Based on these findings, drugs directed at modulating CGRP activity in migraine have emerged as particularly promising future treatments. CGRP receptor antagonists, which compete with endogenous CGRP at the receptor binding sites, have been developed as novel anti-migraine drugs and found to be effective in the treatment of acute migraine attacks. Other ways to modulate CGRP activity have been introduced recently through the development of monoclonal antibodies (mAb) against CGRP and the CGRP receptor.

6.1.1. CGRP receptor antagonists (the Gepants)

CGRP receptor antagonist are small compounds that compete with endogenous CGRP at the receptor binding sites. To date, it is not clear if the CGRP receptor antagonists cross the blood-brain barrier. The progress of the new emerging CGRP antagonists has followed a previous successful development of antagonists, named olcegepant (BIBN4096BS), telcagepant (MK-0974) and MK-3207, which had good efficacy as acute treatments for migraine, however, their safety profile was rather unfavorable.

In a proof of concept study in acute migraine treatment, intravenously administered Olcegepant 2.5 mg was significantly superior to placebo at 2 h response rate (66% versus 27% of placebo-treated patients, \( p = 0.001 \)), suggesting a potential role in acute migraine treatment [60]. Subsequently, telcagepant, developed as an oral CGRP receptor antagonist, was tested in a phase II proof-of-concept study demonstrating the efficacy of 300–600 mg dose [61]. A dose of 150 mg, 300 mg were then tested in a randomized placebo-controlled, parallel-treatment trial compared with zolmitriptan 5 mg in acute migraine. Telcagepant 300 mg was found to be superior to placebo and similarly effective to zolmitriptan 5 mg in pain-freedom, pain relief, and other secondary outcomes. Side effects did not differ much from placebo [62]. However, when Telcagepant was tried on a daily basis as a preventive migraine treatment, it caused liver enzymes derangement and the trials were discontinued [63].

MK-3207 was the third oral CGRP receptor antagonist developed and tested in migraine. A phase II multicenter, double-blind, randomized, placebo-controlled, parallel-group study showed superiority to placebo above the dose of 10 mg in 2-h pain freedom, whether secondary outcomes of 2 h freedom from photophobia/phonophobia/nausea and 2 to 24 h sustained pain freedom were significant at a much higher dose (200 mg) only [64]. Similarly to other gepants however, MK-3207 development was discontinued because of liver toxicity issues.

BI 44370 TA was another CGRP receptor antagonist used in a phase II study which assessed its safety, tolerability, and efficacy in the treatment of an acute migraine attack in episo-dic migraine sufferers. The doses of 50 mg, 200 mg, and 400 mg were tested against placebo and eletriptan 40 mg. The dose of 50 mg and 200 mg did not meet the primary endpoint pain-free at two hours. The 400 mg dose of BI 44370 TA and eletriptan 40 mg were more effective than placebo. BI 44370 TA 400 mg and eletriptan 40 mg were also superior to placebo on the absence of photophobia, phonophobia and nausea as well as a reduction in functional disability at 2 h [65]. Although outcomes from this study did not support a concern for unfavorable side effects, studies on this agent are now discontinued.

6.1.1.1. Ubrogepant (MK-1602). Ubrogepant (MK-1602) is a novel oral CGRP receptor antagonist chemically distinct from telcagepant and MK-3207 (Figure 1). The safety and efficacy of Ubrogepant at different doses (1 mg, 10 mg, 25 mg, 50 mg, 100 mg) was explored in a Phase IIb, multicenter, randomized, double-blind, placebo-controlled trial [66]. Study primary efficacy endpoints were pain freedom at two hours post-dose (reduction in headache severity from grade 2 or 3 at baseline to grade 0) and headache response at two hours post-dose (reduction in headache severity from grade 2 or 3 at baseline to grade 1 or 0). Several other secondary endpoints including safety endpoints were also analyzed. A total of 834 participants were randomized to 1 mg, 10 mg, 25 mg, 50 mg, 100 mg of ubrogepant and placebo. The study showed a positive response trend across ubrogepant doses regarding the 2-h pain freedom endpoint. Ubrogepant 100 mg was statistically superior to placebo for 2-h pain freedom (25.5% vs 8.9%, \( P = 0.003 \)), followed by ubrogepant 50 mg (21.0% vs 8.9%, \( P = 0.020 \)) and ubrogepant 25 mg (21.4% vs 8.9%, \( P = 0.013 \)). However the two-hour headache response did not significantly differ between different ubrogepant doses and placebo. Ubrogepant 100 mg showed significant improvements vs placebo on all secondary endpoints except the absence of nausea at 2 h. With regards to adverse events (AEs), their overall incidence were similar for ubrogepant groups and placebo. The most common ubrogepant side effects were dry mouth, nausea, fatigue, dizziness, and somnolence. The incidence of triptan-associated AEs in the ubrogepant groups was comparable to that of placebo. There were no serious AEs within 14 days post-dose. Importantly, there were no observed post-treatment elevations of ALT >3 ULN.
and no other abnormal laboratory values of clinical relevance, as found with the earlier CGRP antagonists. This promising results supported further progression into phase 3 clinical trials. Initial positive efficacy and safety results of two phase III multicenter randomised, double-blind, placebo-controlled clinical trials comparing ubrogepant 50 mg and 100 mg versus placebo (Achieve 1) and ubrogepant 25 mg and 50 mg versus placebo (Achieve 2) were recently presented at the American Headache Society (AHS) conference in San Francisco, California (28 June to 1 July 2018).

Overall the available data support the role of this new treatment in the acute management of migraine, although data on consistency of effect as well as safety data on subjects in whom triptans are contraindicated are needed to confirm its role as an alternative treatment to triptans.

6.1.1.2. Rimegepant (BMS-927711). Rimegepant is also a novel CGRP-receptor antagonist chemically distinct from telcagepant (Figure 1). Rimegepant’s efficacy and safety in the acute treatment of migraine were tested in a phase II, double-blind, randomized, placebo-controlled, dose-ranging trial in 885 participants [67]. Patients were randomized to receive one of six doses of BMS-927711 (10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg), sumatriptan (100 mg), or placebo for the treatment of a moderate or severe migraine attack. The primary endpoint was pain freedom at two hours post-dose. Secondary endpoints included a composite end-point consisting of freedom from headache pain coupled with no symptoms of photophobia, phonophobia, and nausea, at 2 h post-dose. Other secondary efficacy and safety endpoints were studied. The percentage of participants who met the primary endpoint of pain-freedom at two hours was higher in the group taking Rimegepant 150 mg (32.9%) compared to the other Rimegepant doses (p < 0.001): 31.4% in the 75 mg, 29.7% in the 300 mg dose, 15.3% in the placebo group. Sumatriptan 100 mg was superior to all dose of Rimegepant (35%). The dose of Rimegepant 75 mg was the most effective in meeting the secondary efficacy endpoint of total migraine freedom (28.2%) and it was statistically superior than placebo. Sumatriptan 100 mg was superior to each dose of Rimegepant at this secondary endpoint. The percentage of patients with headache freedom up to 24 h post-dose was superior to placebo for several doses of Rimegepant and for sumatriptan. Most of the AEs were mild to moderate in intensity. No patients discontinued because of AEs. Two patients had increased hepatic enzymes reported as an adverse event, one in the Rimegepant group and one in the placebo group.

The findings of this study suggest that Rimegepant has similar efficacy to sumatriptan 100 mg in the treatment of a migraine attack, with potentially less triptan-related side effects, namely paresthesia, and chest discomfort. A phase III study comparing the efficacy of Rimegepant 75 mg versus placebo has been recently completed. Furthermore a prospective multicentre open-label long-term safety study is underway and recruitment is anticipated to be completed by late 2019. The finding of these two studies will shed more lights on the consistency and safety of this molecule in migraine therapy.

6.1.1.3. Atogepant (AGN-241689). Atogepant, a small molecule with distinct, but similar structure to that of ubrogepant (Figure 1) is currently the only CGRP receptor antagonist used in a study for the prevention of migraine. It has a higher potency and longer half-life than ubrogepant, making it suitable for preventive treatment. A phase II/III, multicentre randomized, double-blind, placebo controlled, parallel-group study evaluated the efficacy, safety, and tolerability of multiple dosing regimens of oral atogepant in episodic migraine prevention (NCT02848326). Adult patients were randomized to placebo, 10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID, respectively, and treated under double-blind conditions 12 weeks for the prevention of episodic migraine. The primary efficacy endpoint was the change from baseline in mean monthly migraine/probable migraine headache days across the 12-week treatment period. All active treatment groups demonstrated a statistically significant reduction from baseline in the primary efficacy parameter (10 mg QD vs placebo, Δ −1.15, p = 0.0236; 30 mg QD vs placebo, Δ −0.91, p = 0.0390; 60 mg QD vs placebo, Δ −0.70, p = 0.0390; 30 mg BID vs placebo; Δ −1.39, p = 0.0034, 60 mg BID vs placebo, Δ −1.29, p = 0.0031). Atogepant appeared to be well tolerated with the most common adverse events being nausea, fatigue, constipation, nasopharyngitis, and urinary tract infection. The liver safety profile for atogepant was similar when compared to placebo, with no indications of hepatotoxicity with the daily administration over 12 weeks. The development program of this treatment is going to be moving to the next stage.

Figure 1. Chemical structures of (a) ubrogepant, (b) rimegepant, (c) atogepant.
6.1.2. Anti-CGRP and anti-CGRP receptor monoclonal antibodies

The CGRP pathway has been targeted also via antibodies against CGRP and the CGRP receptor. This is the first time engineered antibodies are used in the field of migraine and initially their development was faced with some skepticism. Three monoclonal antibodies (mAbs) target the ligand preventing the binding of CGRP to its receptor. These are: galcanezumab (LY2951742), a fully humanized mAb anti CGRP, fremanezumab (TEV-48125), a fully humanized mAb anti-CGRP and eptinezumab, a genetically engineered humanized anti-CGRP antibody. Erenumab (AMG 334), is a fully humanized mAb targeting the CGRP receptor.

The favorable pharmacological profile of these compounds includes their long half-life, the lack of a vasoconstrictive effect or other relevant hemodynamic changes [68]. Given their high molecular weight, these compounds do not cross the blood-brain barrier, indicating a reduced likelihood of central nervous system-related side effects, which are commonly observed with pharmacological prophylaxis treatments currently used in migraine. Furthermore, their administration route, which is either subcutaneously (sc) or intravenously (IV) at different rates ranging between once every three months to twice a month depending on the compound, may improve long-term patients’ treatment compliance compared to oral treatments.

Methodologically similar randomized, double-blind, placebo-controlled Phase II and III clinical trials explored the efficacy and safety of these novel treatments in the prevention of episodic and CM.

6.1.2.1. Erenumab (AMG334). In a phase II trials in participants with episodic migraine, erenumab 70 mg given monthly for three months was found to significantly reduce the number of migraine days per month by 3.4 days compared to placebo (−2.3 days) at 12 weeks [69].

Subsequently, the STRIVE study, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III trial, assessed the efficacy and safety or subcutaneous (sc) injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo in episodic migraine prevention monthly for 6 months. The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary endpoints included the proportion of participants with ≥50% reduction in mean migraine days per month. Amongst other secondary endpoints the study evaluated changes in scores on the physical-impairment and every day-activities domains of the Migraine Physical Function Impact Diary (scale transformed to 0 to 100, with higher scores representing greater migraine burden on functioning) [70]. The overall mean number of migraine days/month was 8.3 at baseline. Table 1 showed the main efficacy outcomes of the study, highlighting the superiority of both doses of erenumab compared to placebo in reduction of migraine days and responder rate. The study showed also a significant improvement of the disability questionnaires for both doses of Erenumab compared to placebo (p < 0.001).

The ARISE trial consisted in a randomized, double-blind, placebo-controlled, phase III study assessing the efficacy and safety of erenumab 70 mg only vs placebo in episodic migraine participants [71]. The primary endpoint was changed in monthly migraine days. Secondary endpoints included ≥50% reduction in monthly migraine days and changes in migraine disability scores. The efficacy outcomes of the study were superior to placebo and interestingly similar to the STRIVE study ones as summarised in Table 1. However this study, unlike the STRIVE study, did not show significant improvement in the migraine disability scores. Both the STRIVE and ARISE trials indicate a favorable safety and tolerability profile of erenumab. Most frequent adverse events were upper respiratory tract infection, injection site pain, and nasopharyngitis.

The interim analysis of the planned 5-year long open-label extension of the phase II clinical trial [69] with Erenumab 70 mg included 383 episodic migraine participants who had

| Table 1. Efficacy outcomes in phase II and phase III clinical trials using mAbs anti-CGRP for the prevention of episodic migraine. |
| Change in migraine days |
| active | placebo | Δ (p-value) | 50% response rate |
| Erenumab | STRIVE (70,140 mg) | −3.2 | −1.8 | −1.4 | Active: 43.3%-50%* |
| | (70 mg) | −3.7 | −1.9 | (<0.001) | Placebo: 26.6% |
| Galcanezumab | ARISE (70 mg) | −2.9 | −1.8 | −1.0 | Active: 39.7%* |
| EVOLVE-1 (120, 240 mg) | −4.7 | −2.8 | −1.9 | (<0.0001) | Placebo: 29.5% |
| | EVOLVE-2 (120, 240 mg) | −4.6 | −2.3 | −1.8 | (<0.001) |
| | Fremanezumab | −4.3 | −2.3 | −1.9 | (<0.001) | Placebo: 36.0% |
| Phase IIb (225, 675 mg) | −6.2 | −3.4 | −2.8 | (<0.0001) | Placebo: 28.0% |
| Phase III (225, 675 mg**) | −4.0 | −2.6 | −1.5 | (<0.001) | Active: 47.7%-44.4%* |
| Eptinezumab IV (1000 mg) | −5.6 | −4.6 | −1.0 | (p = 0.030) | Placebo: 54.0% |

*Statistically significant difference compared to placebo
**One single injection quarterly
failed up to two previous preventive treatments [72]. This study looked at 1-year changes in migraine days, percentage of participants achieving ≥50%, ≥75% and 100% reduction in monthly migraine days, change in disability score using HIT-6, MIDAS and MSQ and safety profile. From an average baseline of 8.8 migraine days/month of those who took part in the open-label trial, at week 64, 28% of participants discontinued the treatments for various reasons. Of the remaining participants, a mean reduction of 5 migraine days was found. Looking at participants who were treated with erenumab 70 mg since month 1 of the randomized controlled phase, from month 3 to month 64 the mean number of migraine days diminished from −3.4 to −5 days/month, with an estimate gain of −1.6 migraine days less after 52 months. At week 64, 65%, 42%, and 26% achieved, respectively, 50%, 75%, and 100% reduction in migraine days. Disability and quality of life scores displayed a meaningful improved at week 64. No safety concerns emerged during the open-label extension.

The safety and efficacy of Erenumab in the prevention of CM were evaluated in a randomized, double-blind, placebo-controlled phase II clinical trial [73]. Patients were randomly assigned (3:2:2) to subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg, given every 4 weeks for 12 weeks. The primary endpoint was the change in monthly migraine days from baseline to the last 4 weeks of double-blind treatment (weeks 9–12). Secondary endpoints included the percentage of participants achieving 50% reduction in monthly migraine days, change in the use of monthly acute migraine treatments and change in cumulative headache hours from baseline. Safety endpoints were also analyzed. At baseline the mean monthly migraine days ranges between 17.8 and 18.2 days. Table 2 outlines the reduction in migraine days compared to placebo with erenumab 70 mg and 140 mg and the 50% response rate. There was a significant reduction in monthly acute medicines intake in both erenumab groups, but no significant reduction in cumulative monthly headache hours. No safety issues emerged during the trial.

Erenumab (Aimovig) obtained FDA approval in May 2018 for the prevention of migraine in adults.

### 6.1.2.2. Galcanezumab (LY2951742).

Galcanezumab is a humanized monoclonal antibody that blocks CGRP activity by blocking the ligand and not the receptor. Phase II proof-of-concept trials conducted in episodic migraine participants. LY2951742 (150 mg) or placebo were given as a sc once every 2 weeks for 12 weeks. The primary endpoint was the mean change in number of migraine headache days [74]. Safety outcomes were also assessed. The primary endpoint was met with a mean reduction of 4.2 monthly migraine days compared to a reduction of 3.0 days in the placebo arm (p = 0.003). Erythema, upper respiratory tract infections, and abdominal pain were the most frequently adverse events reported in the trial. No serious adverse events were reported in the active arm.

A recently published phase IIb clinical trial of Galcanezumab and placebo in episodic migraine sufferers aimed to assess the superiority of galcanezumab administered sc monthly at different doses (5, 50, 120, 300 mg) for three months compared to placebo. The primary efficacy outcome was mean change from baseline in migraine days from week 9 to 12 post-randomization. Galcanezumab 120 mg significantly reduced migraine headache days compared with placebo (−4.8 days vs −3.7 days) [75].

These initial findings led to the development of two phase III randomized, multicenter, double-blind, placebo-controlled trials in episodic migraine patients (EVOLVE-1 and EVOLVE-2) [76,77]. In the both trials, the efficacy and safety of monthly sc injections of galcanezumab 120 and 240 mg versus placebo for 6 months were assessed. Participants were subsequently followed-up for 5 months after the last injection. Primary endpoint was overall mean change from baseline in monthly migraine headache days. Secondary outcomes included ≥50%, ≥75%, and 100% reduction in monthly migraine headache days. Disability, quality of life, and safety measures were also analyzed. Both studies met the primary and secondary efficacy endpoints for both doses at 6 months as shown in Table 1. There was no significant difference in migraine improvement between 120 mg and 240 mg. Migraine disability outcomes were significantly improved compared to placebo. Injection site pain was the most common AE.

### Table 2. Efficacy outcomes in phase II and phase III clinical trials using mAbs anti-CGRP for the prevention of chronic migraine.

<table>
<thead>
<tr>
<th></th>
<th>Change in migraine days</th>
<th>% of participants achieving 50% migraine days reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>active</td>
<td>placebo</td>
</tr>
<tr>
<td>Erenumab (Phase II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(70, 140 mg)</td>
<td>−6.6</td>
<td>−4.2</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Galcanezumab (Phase III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(120, 240 mg)</td>
<td>−4.8</td>
<td>−2.7</td>
</tr>
<tr>
<td></td>
<td>−4.6</td>
<td>−1.9</td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>−6.04</td>
<td>−4.2</td>
</tr>
<tr>
<td>Phase IIb (675/225, 900 mg)</td>
<td>−6.16</td>
<td>−4.2</td>
</tr>
<tr>
<td>Phase III (225, 675 mg)**</td>
<td>−4.6</td>
<td>−2.5</td>
</tr>
<tr>
<td>(100, 300 mg)</td>
<td>−7.7</td>
<td>−5.6</td>
</tr>
<tr>
<td>Eptinezumab (Phase III)</td>
<td>−8.2</td>
<td>−5.6</td>
</tr>
</tbody>
</table>

*Statistically significant difference compared to placebo
**One single injection quarterly
The REGAIN study (NCT02614261) is a double-blind, randomized, placebo-controlled, 3-month study with a 9-month open-label extension for the prevention of a migraine in participants in CM. The study preliminary results were presented as a poster at the AHS 2018. Participants were randomized 2:1:1 to sc placebo, galcanezumab 120 mg or 240 mg given monthly for three months. The primary endpoint was the overall mean change from baseline in the number of monthly migraine days during the 3-month double-blind treatment phase. Secondary efficacy outcomes included the percentage of patients with 50%, 75%, and 100% reduction in monthly migraine days, along with migraine-related disability and quality of life scores. The study met the primary endpoint at 3 months as it is shown in Table 2. Compared to placebo there was a higher incidence of injection site reaction, erythema, and sinusitis in the galcanezumab arms.

6.1.2.3. Fremanezumab (TEV48125). Fremanezumab is a fully humanized monoclonal antibody targeting CGRP. Similarly to the other monoclonal CGRP antibodies, favorable Phase I studies encouraged the development of phase II studies in the prevention of migraine. The efficacy and safety of sc TEV-48125 (225 mg and 675 mg) versus placebo was studied in a multicentre, randomized, double-blind, placebo-controlled, phase 2b study in episodic migraine. Participants were randomized to receive either TEV-48125 225 mg or 675 mg or placebo every 28 days for 3 months. The primary efficacy endpoint was the mean decrease from baseline in the number of days migraine days during the third treatment cycle (weeks 9–12). Primary safety parameters were also analyzed. In post-hoc analyses, the proportion of participants obtaining at least 50% and 75% decrease in the number of migraine-days compared to baseline was evaluated. The study met the primary efficacy outcome with both doses of TEV-48125 (Table 1). No safety or tolerability issues were identified. The most common treatment-related adverse events were mild injection-site pain or erythema [78].

Subsequently, the preventive effect of TEV-48125 (fremanezumab) in episodic migraine was studied in a randomized, double-blind, placebo-controlled, parallel-group phase III trial [79]. The design of the trial implied the injection of monthly sc fremanezumab 225 mg, or 675 mg following a quarterly dose regimen, or placebo. The primary study endpoint was mean change in number of monthly migraine days/month at the 12-week period. Secondary efficacy end points included the proportion of patients obtaining at least a 50% reduction in the mean number of monthly migraine days from baseline to week 12 as well as changes in migraine-related disability scores. The mean number of monthly migraine days at baseline ranged between 8.9 and 9.3 days in the three study arms. The study met the primary efficacy endpoint for both monthly and quarterly regimens, showing superiority to placebo in reduction of mean migraine days. No significant difference was noticed between the two different fremanezumab regimens. The most common AEs were injection site reactions. Similar low proportion of participants in the different arms discontinue because of AEs (2%). The main strength of this study includes for the first time the outcomes of a single dose therapy given quarterly. Given the similar results compared to monthly injections, this strategy may open interesting avenues on potentially effective multiple injection regimens in migraine prevention.

The safety, tolerability, and efficacy of TEV-48125 (fremanezumab) were also tested in CM in a multicentre, randomized, double-blind, placebo-controlled, phase IIb study [80]. The dose of the active treatment differ from the episodic migraine trials. TEV-48125 was administered at the dose of 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles, or at the dose of 900 mg monthly for three months versus placebo. The efficacy endpoints also differed from the episodic migraine studies. For this trial, change from baseline in the number of headache-hours during the third treatment cycle (weeks 9–12) was set as primary outcome. The change in the number of moderate or severe headache-days was considered a secondary endpoint. At baseline, participants had a mean of 162 headache-hours/month, 21.1 headache-days of any duration and 16.8 migraine days/month. The majority of participants had not tried any preventive treatment at baseline. During weeks 9–12, a significant reduction in a number of headache-hours was demonstrated for both doses compared to placebo (675/225: − 59.84; 900 mg: − 67.51 h; placebo: − 37.10 h, p = 0.0386 and p = 0.0057). Similarly, a significantly greater reduction in mean number of headache days was found for both doses compared to placebo (Table 2). The higher fremanezumab doses were fairly well tolerated and no serious concerns emerged in terms of AEs from this trial.

On the basis of the promising results of the phase II study, a randomized, double-blind, placebo-controlled, parallel-group trial was subsequently conducted to confirm the efficacy of fremanezumab for the prevention of CM [81]. Participants with CM were randomized in a 1:1:1 ratio to receive fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8) or placebo. The primary end point was the mean change from baseline in the average number of headache days, defined according to the International Headache Society (IHS) criteria. Interestingly the mean number of monthly migraine days at baseline was higher than the number of headache days but lower than the number of days of any severity and duration. Furthermore, the majority of participants did not use topiramate or BoNTA at baseline. The study met the primary endpoint for both doses and showed a significantly greater percentage of participants obtaining at least 50% reduction in headache days with fremanezumab compared to placebo (Table 2). Discontinuation of the trial due to adverse events was infrequent. Similarly to other trials, fremanezumab was associated with a higher incidence of injection-site reactions than placebo, though the severity of such reactions did not differ significantly among the trial arms.

Fremanezumab (Ajovy) was granted FDA approval on the 14th of September 2018, making it the second anti-CGRP monoclonal antibodies approved for the preventive treatment of migraine in adults and the first one with quarterly and monthly dosing options.
6.1.2.4. Eptinezumab (ALD403). ALD403 (Eptinezumab) is a genetically engineered, humanized antibody targeting both forms of human CGRP. Its efficacy, safety, and tolerability have been evaluated in a phase II proof-of-concept study in participants with an episodic migraine [82]. The primary aim of the study was to assess the safety of a single dose of 1000 mg of ALD403 administered intravenously compared with placebo. Secondary outcomes included efficacy and migraine-related disability measures at 12 weeks post infusion. In particular change from baseline to weeks 5–8 in migraine days was evaluated. The frequency of migraine days at baseline was 8.8 in the placebo and 8.4 in the active group. Adverse events were experienced by 52% participants in the placebo group and 57% in the ALD403 group. The most frequent AEs were upper respiratory tract infection, urinary tract infection, fatigue, back pain, nausea and vomiting, and arthralgia. Most of them were mild or moderate in severity. None of the infrequent serious adverse events were considered related to the active drug. In terms of the efficacy endpoints, there was a significant reduction in the mean number of migraine days between baseline and weeks 5–8 for ALD403 compared to placebo (Table 1). Interestingly a very high proportion of participants obtained 50% reduction of migraine days at weeks 5–8. It was also noted that the placebo response rates in this trial were remarkably high compared to the previous trials using anti-CGRP monoclonal antibodies, possibly because of the intravenous administration of the drug.

These preliminary findings led to the development of a phase III randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of different doses of eptinezumab in episodic migraine (PROMISE 1) (NCT02559895). The primary endpoint was the mean change in migraine days over weeks 1–12 compared to a 28-day baseline. Baseline migraine days averaged 8.5 days/month across groups. Participants were randomized to receive eptinezumab 300 mg, 100 mg, 30 mg, or placebo by intravenous infusion every 12 weeks. The study met the primary efficacy endpoint. A significantly greater reduction of migraine days was achieved at all eptinezumab doses compared to placebo (−4.3, −3.9, −4.0 vs −3.2). Furthermore, a significantly greater proportion of participants given eptinezumab had a 50% reduction in migraine days (49.8%–56.3% vs placebo: 37.4%). No AEs issues emerged in this trial. In most of the anti-CGRP monoclonal antibodies trials have emerged the remarkable fast response compared to placebo normally within the first month for active drug administration. Eptinezumab was shown to be able to reduce migraine from day 1 and to maintained similar improvement at four and 12 weeks post-infusion. The preliminary findings of this study were presented at the American Academy of Neurology 2018 (AAN) Conference, Los Angeles, California.

The efficacy, safety, and tolerability of eptinezumab in CM were assessed in a phase II and a phase III trial. A randomized, double-blind, placebo-controlled phase II study tested various doses of ALD403 versus placebo. Participants were randomized to receive a single intravenous dose of ALD403 300 mg, 100 mg, 30 mg, 10 mg, or placebo. Unlike other anti-CGRP monoclonal antibodies trials, the primary endpoint here was the percentage of patients achieving a 75% reduction in migraine days per month from baseline to week 12. The percentage of participants achieving 75% reduction in migraine days with ALD403 300 mg and 100 mg was significantly greater than the one receiving placebo (33% and 31% vs 21%). These results were presented at the AAN 2018 conference Los Angeles, California.

The PROMISE 2 (PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy 2) is a Phase III, randomized, double-blind, placebo-controlled trial evaluating the safety, and efficacy of eptinezumab for the prevention of CM. Patients were randomized to receive eptinezumab (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks (NCT02974153). The primary endpoint was the mean change from baseline to monthly migraine days over the 12 week, double-blind treatment period. Secondary efficacy, migraine-related disability, and safety outcomes were also analyzed, including the percentage of participants showing reduction in migraine prevalence at day 1 post-infusion. The baseline mean frequency of migraine days was 16.1 across the groups. Both eptinezumab doses met the primary endpoint with mean migraine reduction of 7.7 days (dose 100 mg), −8.2 days (dose 300 mg) versus placebo (−5.6 days) (p < 0.0001) (Table 2). Interestingly, 51% who received 100 mg and 52% who received 300 mg of the active drug compared to 27% of those who received placebo, showed a reduction in migraine risk beginning at day one post-infusion, which was then sustained through day 28. The safety profile of eptinezumab in this study was comparable to the one of previous studies. These preliminary results were presented at the AAN 2018 Conference, Los Angeles, California.

6.2. 5-HT$^{1}$F receptor and 5-HT$^{1}$F receptor agonists (the DITANS)

The 5-hydroxytryptamine (serotonin) receptor 1F, also known as 5-HT$^{1}$F receptor, is a member of the 5-HT1 subfamily of the 5-HT serotonin receptors that bind to the endogenous neurotransmitter serotonin. Like other 5-HT1 receptors, 5-HT$^{1}$F is a protein coupled to G$i/o$ and mediates inhibitory neurotransmission. Interestingly, this receptor is found at the presynaptic site of the trigeminal fibers but is lacking from the vascular smooth muscles. Centrally is found in the TCC, cerebellum, and cortex [83].

Triptans, mediate part of their effect through modulation of 5-HT$^{1}$F receptors on trigeminal sensory neurons; hence, 5-HT$^{1}$F agonist compounds were postulated to have an abortive antimigraine effect without the vasoconstrictive effect [84]. This led to the development of the first 5HT$^{1}$F agonist LY334370 which was investigated in a small randomized, double-blind, placebo-controlled, parallel-design clinical trial, and proved to be effective for the acute treatment of migraine attacks at 60 mg and 200 mg. Unfortunately, frequent adverse events such as asthenia, dizziness, and somnolence, as well as, compound-specific safety concerns stopped further clinical developments [85].

Following this, lasmitidan (COL-144, LY573144), a more specific 5-HT$^{1}$F receptor agonist with a novel pyridinyl-piperidine structure, was developed. Lasmitidan showed promising
results in a proof-of-concept study where doses above 20 mg infused intravenously, produced pain relief at 2 h in a significantly higher percentage of cases than placebo during an acute migraine attack. The efficacy became evident at 20–40 min after administration, in the absence of serious adverse events [86]. Subsequently, a phase II study with oral lasmiditan tested at the doses of 50, 100, 200 and 400 mg for the acute migraine attack, showed superiority with respect to placebo at 2 h. Also, migraine-associated symptoms improved with all doses. Fifty percent of treated subjects reported a return of headache within 24 h after treatment. The most severe adverse events included dizziness [87].

Two Phase III randomized, double-blind, placebo-controlled studies have been tested lasmiditan in an episodic migraine acute treatment. In the SAMURAI trial (NCT02439320), participants were randomized to lasmiditan 200 mg, 100 mg or placebo. In the SPARTAN study (NCT02605174) participants were randomized to lasmiditan 200, 100, 50 mg or placebo. Key studies endpoints were the proportion of participants who become headache-free at 2 h post-dose and the proportion of participants who free from the most bothersome symptom at 2 h post-dose. Secondary outcomes including headache recurrence, changes in pain-killers utilization and freedom from migraine-associated symptoms. A statistically significant proportion of participants using Lasmitidan 50 mg, 100 mg, and 200 mg were headache-free and most bothersome symptom-free compared to placebo at 2 h post-dose. In particular 32.2% in the SAMURAI study and 38.8% of the participant in the SPARTAN study receiving lasmiditan 200 mg compared to 15.3% and 21.3%, respectively, in the placebo group, became headache-free and 40.7% in the SAMURAI and 48.7% in the SPARTAN study were free from the most bothersome symptom compared to 29.5% and 33.5%, respectively, in the placebo group. Lasmiditan 50, 100 and 200 mg was also superior to placebo in proportion of participants with headache relief, percentage of participants needing to use rescue medication, percentage of participants reporting photophobia and phonophobia-freedom at two hours, but not in nausea-freedom. The most common side effects with lasmiditan were dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy. These data were presented at the AAN 2018 Conference, Los Angeles, California.

An open-label Phase III study, called GLADIATOR aiming to evaluate the long-term safety of lasmiditan for the acute treatment of migraine is underway. Furthermore, a global, multicenter, double-blind, modified parallel, placebo-controlled study has been planned to assess the safety, efficacy, and consistency of lasmiditan in the acute treatment of multiple migraine attacks with or without aura. The results of these studies will confirm the long-term efficacy and consistency of response of this novel medication for the acute treatment of migraine.

6.3. Pituitary adenylate cyclase-activating polypeptide (PACAP) and pituitary adenylate cyclase-activating polypeptide type 1 receptor (PAC1)

Pituitary adenylate cyclase-activating polypeptide (PACAP) is another neuropeptide that has been implicated in migraine pathophysiology [88]. PACAP is closely related to VIP and is found in two isoforms, PACAP-38 and PACAP-27 with PACAP-38 to be more abundant. In neuronal tissues, the isoform PACAP-38 predominates [89]. It is known to play hypophysiotropic, neuromodulatory, and neurotransmitter roles, and has been associated with differentiation- and proliferation-inducing effects in the developing nervous system, as well as with cytoprotective, anti-apoptotic, and anti-inflammatory features within various target organs [90]. Within the trigeminal ganglia, PACAP is localized in small neurons which in addition store CGRP [91]. Other structures relevant to the pathogenesis of migraine, such as in trigeminal afferents in the dura mater, the cerebral vessels, the TCC, brainstem nuclei, as well as the sphenopalatine and otic ganglia also express PACAP [92–94]. In a recent preclinical study, it was found that both VIP and PACAP similarly cause transient vasodilation of meningeal arteries, yet only PACAP was able to trigger a delayed sensitization of second order trigeminocephalovascular neurons [95,96]. In migraine patients, elevated levels of plasma PACAP-38 were revealed in the ictal migraine period but not during interictal phase in migraineurs [97,98]. Stimulation of the trigeminal ganglion was shown to increase PACAP expression in the trigeminal neural nucleus, a phenomenon blocked by kynurenic acid analogues and NMDA receptor antagonists [99]. Additionally, intravenous infusion of PACAP-38, but not VIP, was shown to trigger migraine-like headaches in migraine patients [100,101].

The pituitary adenylate cyclase-activating polypeptide type 1 receptor (PAC1) has been identified as a receptor which binds the PACAP molecule with high affinity [90]. A novel molecule, AMG 301, is a PAC1 receptor selective monoclonal antibody which has been developed for the prevention of migraine, potentially by inhibition of trigeminal autonomic signaling. A phase IIa randomized double-blind placebo-controlled study that aims to evaluate the efficacy and safety of AMG 301 in migraine prevention is currently underway (NCT03238781).

6.4. Unresolved questions from previous clinical trials

6.4.1. Nitric oxide synthase

Nitric oxide synthases (NOS) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. Nitric oxide is a gaseous molecule which involved in a variety of functions including endothelial-dependent vasodilation, neural signaling, and development. Nitric oxide is produced in mammals by the endothelial (eNOS) and neuronal (nNOS), while the inducible isoform, iNOS produces NO as an immune response. NO donors are known to induce a delayed migraine attack in a portion of migraine patients and are used for the experimental induction of migraines [102]. NO donors are widely used in animal models of migraine and have been shown to induce fos activation in many migraine-related areas, including the TCC, brainstem, and hypothalamus [103]. Hence, the development of selective NOS inhibitors has been suggested as an emerging therapy for migraine [104].

Research has focused on other specific NOS inhibitors, with the initial study of a specific iNOS inhibitor GW274150 failing to reach its clinical end point in both an acute and preventive...
study [105]. A mixed triptan and nNOS inhibitor NXN-188 was also found to be ineffective in both migraine without aura and specifically in the aura phase [106]. The question about a possible effect of a specific nNOS inhibitor remains unresolved.

On the other hands the role of peripherally produced NO as a therapeutic agent is currently investigated in a clinical trial using B244- ammonia-oxidizing bacteria (AOB). AOB is a naturally occurring type of nitrifying bacteria that metabolize the ammonia found in sweat, creating nitrite and nitric oxide [107]. In an ongoing randomized, vehicle-controlled, double-blind, phase II study the safety, tolerability, and efficacy of B244 delivered as an intranasal spray is tested for preventive treatment in subjects with an episodic migraine (NCT03488563). The hypothesis that is being tested is that by increasing local and systemic NO levels, this bacteria exert an anti-inflammatory effect that may have a potential therapeutic effect in migraine.

6.4.2. Orexin receptors
Orexin A and B are neuropeptides that are synthesized in the hypothalamus and thought to play a role in nociception. They exhibit their action by activating their receptors orexin 1 (OX1) and orexin 2 (OX2). In an animal models of trigeminovascular activation, activation of the OX1 and OX2 receptor in the posterior hypothalamus has been shown to differentially modulate nociceptive dural input to the TNC [108]. Activation of the OX1 receptor was found to elicit an anti-nociceptive effect whereas OX2 receptor activation elicits a pro-nociceptive effect. Filorexant, is a dual OX1 and OX2 receptor antagonist which was originally developed to treat insomnia [109] and was found to have some effect in animal models of migraine [110]. In a phase IIa trial for the prophylaxis of migraine, Filorexant was found to be ineffective [111]. It remains to be evaluated though if a more specific OX2 receptor antagonist or a specific OX1 agonist will have different outcomes in migraine prevention.

6.4.3. Glutamate receptor antagonists
Glutamate is the main excitatory neurotransmitter of the nervous system and the neurotransmitter that manifest transmission from primary trigeminal neurons to second-order neurons in the TCC, along the ascending trigeminothalamic pathway and from third order thalamic neurons to the cortex. Glutamate is implicated in many aspects of migraine pathophysiology, including trigeminovascular activation, central sensitization, and CSD [112]. Glutamate exhibits it actions on ionotropic glutamate receptors, namely: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainite, and metabotropic glutamate receptors (mGluR), namely: mGluR1-8. Antagonizing glutamate transmission along the ascending trigeminovascular-trigeminotralamic pathways would have been an ideal treatment for migraine. However, blockade of central glutamatergic transmission can have tremendous results for the brain.

Small clinical trials using specific glutamate receptor antagonists, that do not antagonize the main ionotropic receptors NMDA and AMPA, aimed to investigate their efficacy in an acute migraine. Such treatments could offer a non-narcotic, non-vascular approach to the management of headache pain and represent a potentially promising alternative to current migraine treatments. Tezampanel (LY293558) was a small molecule initially developed against the GluK5 subunit of the kainite receptor, although further studies demonstrated an additional competitive action for the AMPA receptor [113]. Preclinical studies have demonstrated a role for kainite receptor in migraine pathophysiology and selective antagonists in the trigeminovascular model were shown to suppress trigeminal stimulation [114]. In a placebo and active-controlled phase II trial in patients with acute migraine, the compound, administered intravenously, achieved statistical significance in all primary and secondary endpoints which included pain relief at two hours and relief of nausea, photophobia, and phonophobia. Tezampanel demonstrated an attractive safety and pharmacokinetic profile [113]. Unfortunately, no further developments were carried on with this molecule or other kainite receptor-specific antagonists, although this is an avenue worth exploring further.

ADX10059 was an mGluR5 negative allosteric modulator used in a small clinical trial for the acute treatment of a migraine. The primary efficacy endpoint for the clinical trial, 2 h pain-free, demonstrated a significant effect of ADX10059 375 mg, 17%, versus placebo, 5%, with transient dizziness being the most common treatment-emergent event in about half the patients [115]. ADX10059 was also used in a phase II randomized, double-blind, placebo-controlled study for the prevention of a migraine. However, the study was terminated early following the emergence of a higher than expected rate of liver enzyme abnormalities [116]. Targeting mGluRs was thought to be a more safe approach to blocking glutamate in the CNS. Although mGluR5 did not meet this expectation, positive allosteric modulators against other mGluRs may have a therapeutic value for migraine that remains to be investigated [117].

6.5. Future targets for emerging treatments

6.5.1. The tryptophan-kynurenic pathway
An increasing number of preclinical studies highlight the importance of the kynurenine pathway in the pathophysiology of migraine [118]. The tryptophan-kynurenic pathway is the second most prevalent metabolic pathway of tryptophan and accounts for approximately 90% of tryptophan catabolism, with the synthesis of the synthesis of 5HT to account for the metabolism of ~3% or less of non-protein tryptophan [119]. Major components of the pathway – quinolinic acid and kynurenic acid – were shown to act on NMDA receptors, with quinolinic acid having an excitatory action and kynurenic acid being an antagonist of ionotropic glutamate receptors [120].

A number of preclinical studies implicated the kynurenine pathway in the nociceptive activation of the trigeminal system. Administration of nitroglycerine, which induces migraine to patients, sensitizes the trigeminal system of animal and was shown to downregulate a number of enzymes of the kynurenine pathway, with a potential influence on the glutamatergic system [121]. Pre-treatment with kynurenic acid was shown to prevent the nitroglycerine-induced neuronal activation and
sensitization in the TCC in rodents [122]. In the same model, the kynurenine acid analog 1 was shown to suppress nitroglycerine-induced hyperalgesia and to suppress the increased levels of CGRP, nNOS, and cytokines in the trigeminal system [123,124]. Kynurenic acid and its derivatives have been also shown to suppress nociceptive activation of the trigeminal pathway [125–128], and to reduce the release of glutamate, the excitatory neurotransmitter that drives activation of the ascending trigeminotalamic pathway [125].

Recent studies in CM patients found altered serum levels of all kynurenine metabolites [129]. Of interest, altered serum levels of kynurenine metabolites were also found in cluster headache patients [130]. Further studies for the potential utilization of the kynurenine pathway in the treatment of migraine may open new therapeutic perspectives.

6.5.2. Cannabinoids
Cannabinoids may have therapeutic use in pain and may also have a role in the treatment of migraine. There are two cloned cannabinoid receptors the cannabinoid receptor 1 (CB1) is present on neurons in the peripheral and central nervous system, while the CB2 receptor is found predominantly in immune cells [131,132]. CB1-immunoreactive neurons are found in the trigeminal ganglia and TCC [133]. In animal models of migraine endogenous cannabinoids and cannabinoid agonists have an inhibitory effect on trigeminovascular activation through the cannabinoid receptor 1 (CB1) [134].

Very few studies exist on the potential role for the cannabinoid system in migraine. CB1 binding was shown to be increased interictically in female migraine patients [135], while variations in the CB1 CNR1 gene were suggested to predispose to migraine [136]. Despite the lack of solid evidence for the potential role of CB1 in migraine pathophysiology, many individuals are currently using cannabis for the treatment of migraine with positive results [137]. Currently, there is not enough evidence from well-designed clinical trials to support the use of cannabis for headache, but there are sufficient anecdotal and preliminary results, as well as plausible neurobiological mechanisms, to warrant properly designed clinical trials. Such trials are needed to determine short- and long-term efficacy for specific headache types, compatibility with existing treatments, optimal administration practices, as well as potential risks.

6.5.3. Advanced botulinum toxin molecules
BoNTA is an approved treatment with established efficacy in migraine prevention [138–140]. Its limitations include its toxicity and the unwanted muscle paralysis that limit a potentially higher dose-effect. Finding a potentially better injections-paradigm has been suggested as a new way forward in advancing its clinical outcomes and currently a clinical trial is underway to investigate the effect of 90U of BoNTA injected along the skull sutures (NCT03543254), where trigeminal fibers may be exiting the skull [141].

However, the field of BoNT engineering has progressed significantly in recent years. A number of approaches have been used in the engineering of novel BoNT molecules. Such approaches include among others, recombinating of the BoNTA protein domains, creating of BoNTA/E chimeras, chimera proteins that incorporate the endopeptidase and translocation domains of BoNTA combined with targeting binding ligand [142,143].

Senrebotase (AGN-214868) was a retargeted endopeptidase with a synthetic nociceptin receptor-binding BoNT molecule which was used in clinical trials for painful overactive bladder and post-herpetic neuropathy. The trials ended earlier due to the lack of statistically significant differences in the long-term observations. Although no attempts have been made in studying advanced BoNT molecules in clinical trials of migraine, an increasing number of data now suggests an emerging role for such molecules in migraine treatment.

BiTox is the first synthetic recombinant BoNTA chimera that appears to lack paralytic effects, while it suppresses trigeminal activation in animal models of migraine [144,145]. BiTox has been also shown to attenuate inflammatory mediators in animal models of inflammatory pain [146]. In the pain field other advanced BoNT molecules have been tested with significant outputs. Using the BoNTA binding domain as a delivery vehicle to selected cell populations has very recently shown to be an exciting new avenue in the field of pain. A dermorphin-botulinum and a SP-botulinum constructs have been shown to target pain-processing neurons in the dorsal horn upon intrathecal application and to suppress chronic pain in animal models [147]. Dolly et all, produced a recombinant BoNTA/E chimera by attaching the BoNTE protease moiety to an enzymatically inactive mutant of BoNTA. The resultant molecule is a long-acting superior inhibitor of motor neuron and C-fibre-mediated transmission. In vivo, local injection of this recombinant BoNTA/E molecule resulted in extended amelioration of inflammatory pain [142].

7. Conclusion
There is a vast unmet need in the current migraine treatment options that can be summarised into efficacy, tolerability issues and lack of migraine-specific treatments besides the triptans. This review summarises the current understanding of the pathophysiological mechanisms known to be relevant targets for the development of novel migraine treatments. A multitude of abortive and preventive migraine-specific treatments are currently in advanced stages of their development. The positive phase III trials results for CGRP receptor antagonist Ubrogepant and 5-HT1F receptor agonist lasmiditan, suggest that these treatments may be available in the near future in triptans nonresponders or in those category of patients in whom triptans are contraindicated. Some of the anti-CGRP monoclonal antibodies have already been approved by the FDA and the EMA and currently used in some Countries as migraine preventive treatments (Tables 3 and 4). These treatments could dramatically improve the way migraine has been managed so far, besides promoting new research in the development of further antibodies against other relevant targets such as PACAP.
Table 3. Competitive environment: abortive migraine treatments.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olcegepant</td>
<td>Boehringer Ingelheim</td>
<td><img src="image1" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase II (discontinued)</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>Telcagepant</td>
<td>Merck &amp; Co.</td>
<td><img src="image2" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase II (discontinued)</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>MK-3207</td>
<td>Merck &amp; Co.</td>
<td><img src="image3" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase II (discontinued)</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>BI 44370 TA</td>
<td>Boehringer Ingelheim</td>
<td><img src="image4" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase II (discontinued)</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>Ubrogepant</td>
<td>Allergan</td>
<td><img src="image5" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase III</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>Rimegepant</td>
<td>Biohaven Pharma</td>
<td><img src="image6" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase III</td>
<td>CGRP receptor antagonist</td>
</tr>
<tr>
<td>Lasmitidan</td>
<td>Eli Lilly</td>
<td><img src="image7" alt="structure" /></td>
<td>Abortive migraine treatment</td>
<td>Phase III</td>
<td>5-HT₁F receptor agonist</td>
</tr>
</tbody>
</table>

8. Expert opinion

The migraine field has recently been experiencing an explosion of novel, specifically-designed acute and preventive treatments, reflecting advances in the understanding of this disorder and better acknowledgement of its global detrimental impact on sufferers’ quality of lives.

The chemically modified CGRP receptor antagonist Ubrogepant seems to overcome the disappointing safety issues that stopped this class of medication from further development. Along with selective 5-HT₁F agonist Lasmitidan, both these novel compound could play a role in the future of acute migraine treatments as an alternative to triptans in triptans non-responders or in those in whom triptans are contraindicated or not tolerated. Future studies in patients with cardiovascular comorbidities are necessary to determine the benefit of the lack of arterial tone modulation, mechanism, that distinguishes these novel medications from the triptans.

The most promising data come from the anti-CGRP monoclonal antibodies. All phase II and III trials performed have shown consistent superiority to placebo. Beside remarkable efficacy outcomes, this class of medication seems to offer a fast onset of migraine frequency reduction, along with potentially cumulative benefit overtime, at least according to some initial evidence. Further meaningful findings that emerged from published trials highlight the high adherence to treatment, along with the efficacy of different injections regimens. No particular issues in terms of safety and tolerability have emerged as confirmed by the very low dropout rates shown across the clinical trials. Their excellent
Tolerability profiles seem to be one of the major advantages compared to the established oral preventive treatments currently used in migraine. One of the problems with the use of mAbs may be the long-term risk effect in women of childbearing age, given their longer half-life. The use of an oral CGRP receptor antagonist like atogepant may overcome this issue.

Future studies should concentrate on long-term preventive efficacy and safety of these treatments. Indeed the risk of long-term blockade of CGRP signaling is unknown [148]. Furthermore studies in challenging-to-treat migraine patients are needed to establish whether the promising results showed in clinical trial environment, will be replicated in real-life patients.

Although, the anti-CGRP treatments are not the cure for migraine, they have undoubtedly stimulated further research into different migraine targets that could be inhibited by specifically designed antibodies. This will hopefully facilitate the development of treatments for those patients who currently do not respond to treatments targeting the CGRP pathway.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


71. One of the pivotal studies demonstrating efficacy of Erenumab in episodic migraine.


75. Important study demonstrating efficacy of LY2951742 in episodic migraine.


80. Study demonstrating efficacy of Fremanezumab in episodic migraine.


84. Study demonstrating efficacy of Fremanezumab in chronic migraine.


86. Study demonstrating the safety and efficacy of the only anti-CGRP monoclonal Ab administered intravenously.


Important paper summarising the potential therapeutic role of treatment targeting PACAP in primary headaches.


