Received: 15 January 2021 | Revised: 28 July 2021 | Accepted: 2 August 2021

DOI: 10.1111/bph.15657

REVIEW ARTICLE

Pharmacological treatment of migraine: Drug classes, mechanisms of action, clinical trials and new treatments

Farzin Zobdeh[1,2] | Aziza ben Kraiem[1,2] | Misty M. Attwood[2] | Vladimir N. Chubarev[1] | Vadim V. Tarasov[1,3] | Helgi B. Schiöth[2,3] | Jessica Mwinyi[2]

[1]Department of Pharmacology, Institute of Pharmacy, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

[2]Functional Pharmacology, Department of Neuroscience, Uppsala University, Uppsala, Sweden

[3]Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Correspondence
Jessica Mwinyi, Functional Pharmacology, Department of Neuroscience, Uppsala University, Uppsala, Sweden.
Email: jessica.mwinyi@neuro.uu.se

Funding information
Svenska Läkaresällskapet, Grant/Award Number: SLS-935235; Novo Nordisk Fonden, Grant/Award Number: 0063805; Hjärnfonden, Grant/Award Number: 2019-01066; Vetenskapsrådet, Grant/Award Number: 2013-02892

Migraine is the sixth most prevalent disease globally, a major cause of disability, and it imposes an enormous personal and socio-economic burden. Migraine treatment is often limited by insufficient therapy response, leading to the need for individually adjusted treatment. In this review, we analyse historical and current pharmaceutical development approaches in acute and chronic migraine based on a comprehensive and systematic analysis of Food and Drug Administration (FDA)-approved drugs and those under investigation. The development of migraine therapeutics has significantly intensified during the last 3 years, as shown by our analysis of the trends of drug development between 1970 and 2020. The spectrum of drug targets has expanded considerably, which has been accompanied by an increase in the number of specialised clinical trials. This review highlights the mechanistic implications of FDA-approved and currently investigated drugs and discusses current and future therapeutic options based on identified drug classes of interest.

KEYWORDS
CGRP, clinical trials, migraine, migraine acute treatment, migraine chronic treatment, 5-HT

1 | INTRODUCTION

Migraine is currently the sixth most prevalent disease globally, and it is a major cause of disability, which imposes an enormous personal and socio-economic burden (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). The economic burden of migraine is the second highest of all brain diseases, with an estimated annual cost of €111 billion in the European Union alone (Linde et al., 2012).

Migraine triggers can be divided into two groups: internal (hormonal fluctuations, stress, fasting or hunger, and sleep disturbance) and external (weather, odours, alcohols and heat) (Kelman, 2007; Turner et al., 1995). Some of these triggers overlap with the premonitory symptoms of migraine (Schulte et al., 2015), Schulte et al. reported a clear association between the presence of certain symptoms during the premonitory phase of migraine and certain trigger factors corresponding to these symptoms, such as photophobia, as a premonitory symptom, and flickering or bright light as a corresponding trigger factor. Consequently, this misinterpretation leads to an over-reporting of certain trigger factors that are most likely to have been misevaluated as premonitory symptoms in patients (Schulte et al., 2015).

Abbreviations: CSD, cortical spreading depression; GON, greater occipital nerve; HVA, high-voltage-dependent; MOH, medication-overuse headache; PAG, periaqueductal grey; PPE, plasma protein extravasation; TNC, trigeminal nucleus caudalis; VPA, valproic acid.

The current work provides a comprehensive overview of the historical and current trends of the development of drugs for migraines. This work highlights and discusses the drug classes and their molecular targets that have been in focus within the last 50 years, and this reflects the gained knowledge of migraine pathophysiology over time.

Migraine is classified into two major clinical types: migraine without aura (MO) and migraine with aura (MA). Each type is partly different in the composition of clinical features and molecular biological susceptibility factors (Pisanu et al., 2017, 2020). Visual, sensory or other CNS symptoms generally precede the headache followed by associated migraine symptoms (Headache Classification Committee of the International Headache Society, 2018). In addition to these two major types of migraine, other subtypes or forms are known, including vestibular, ocular and/or abdominal migraine (Headache Classification Committee of the International Headache Society, 2018). Dependent on the frequency of attacks, migraine is furthermore divided as chronic or episodic.

Sumatriptan was approved in 1992 by the US Food and Drug Administration (FDA). Since then, triptans have been the leading option for treating acute migraines. As for preventive treatment, various classes of medicines, such as beta-blockers (**propranolol** and **metoprolol**), calcium channel blockers (flunarizine), tricyclic antidepressants (**amitriptyline**) and also anti-epileptics (such as **valproic acid** [VPA] and **topiramate**), have been used (Parikh & Silberstein, 2019). Such a heterogeneous group of drugs with varying mechanisms of action (MOAs) reflect the partial understanding of the pathomechanisms underlying migraine. Subsequently, these drugs have various efficacy and tolerability. The recent approval of anti-**CGRP** therapies is a milestone in the development of migraine therapy, as this new group of therapeutic agents allows an unprecedented targeted therapeutic approach to migraine prophylaxis based on the modulation of the signalling pathways that are known to play a crucial role in migraine (Edvinsson, 2017). Recent preclinical and clinical investigations have provided evidence for the critical role of the trigeminovascular system, particularly as a site of action of CGRP, in migraine initiation (Lassen et al., 2002; Storer et al., 2004).

Of note, several recent publications have focused on providing an overview of a single treatment option and discussing the CGRP system. We aim to systematically analyse the trends of the development of novel treatment compounds and targets in the field of migraine by assessing the agents approved between 1970 and 2020, as well as the investigational agents in clinical trials during the last 3 years. This review highlights drug development for acute migraine and migraine prophylaxis and provides an update on the latest developments, including the CGRP system, as well as other therapeutic pathways and targets.

2 | MIGRAINE PATHOGENESIS

A migraine attack can be divided into several pathogenic mechanisms relevant to the different phases of migraine, that is, premonitory phase, the aura phase, the headache phase and the postdrome phase (Charles, 2013), which are briefly described in the following sections.

2.1 | Premonitory phase

The premonitory phase of migraine can start as early as 3 days before a migraine attack. This allows approximately 75% of patients to correctly predict a migraine incidence for up to 12 h before its onset (Giffin et al., 2003). The most common premonitory symptoms include fatigue, impaired concentration, neck stiffness, photophobia, yawning and food craving (Karsan et al., 2016). PET studies of triggered (Maniyar et al., 2014) and spontaneous attacks (Denuelle et al., 2007) provided evidence for a hypothalamic activation in the premonitory phase. Activation of this region and its central connections to the limbic system may explain symptoms during the premonitory phase, such as yawning, polyuria, food craving and mood changes (Maniyar et al., 2014), and the fact that migraine is commonly triggered by alterations in homoeostasis (e.g., changes in sleep–wake cycles and missed meals). Moreover, structural and functional imaging studies have demonstrated differences in thalamic and thalamo-cortical activities in patients with migraine and controls during migraine attacks (Coppola et al., 2016). Studies have shown that the thalamus is a key mediator of cutaneous allodynia (Wang et al., 2015) and exacerbation of headache by light (Noseda et al., 2016).

2.2 | Aura phase

One of the components of migraine headaches in less than 25–30% of patients is the occurrence of aura (Russel et al., 1996). Migraine aura is defined as a focal neurological disturbance that manifests as visual, sensory or motor symptoms (Headache Classification Committee of the International Headache Society, 2018). The exact pathological mechanism underlying aura is not fully understood. To date, cortical spreading depression (CSD) is considered to be the physiological cause of the aura phase of migraine attacks (Pietrobon & Moskowitz, 2013). CSD is an abnormal phenomenon characterised by a slowly propagating wave of depolarisation of cortical neuronal and glial cells followed by a depression of electrical activity (Leo & Morison, 1945). CSD is associated with toxic alterations in transmembrane ion gradients, which result in a massive influx of Na, Ca and water, and the efflux of K, proton, **glutamate** and **ATP** (Harriott et al., 2019). Several metabolic factors are associated with CSD. For instance, hyperglycaemia causes resistance against CSD initiation and hastens CSD recovery, in contrast with hypoglycaemia, which prolongs CSD (Hoffmann et al., 2013).

2.3 | Headache phase

The headache phase of migraine is due to the activation of the trigeminovascular system (Burstein et al., 2015; Stankewitz et al., 2011). One possible mechanism underlying this process is the opening of **pannexin 1** channels in neurons, which are associated with the **P2X7** ligand-gated ion channel (Bolay et al., 2002), which lead to the activation of astrocytes that may induce the formation of cytokines and prostanoids that sensitise meningeal nociceptors (Karatas et al., 2013). Sensory transmission of nociceptive signals involves the release of several neurotransmitters, including CGRP, pituitary adenylate cyclase-activating polypeptide-38 (**PACAP-38**), glutamate and **NO** (Goadsby, Holland, et al., 2017). The release of CGRP and PACAP-38 also results in cranial vessel dilation and mast cell degranulation, both of which could further

activate vascular and meningeal nociceptors and contribute to migraine headache. Several studies have shown that the **TRP channels**, a large family of non-selective cation channels that are important in pain signalling pathways are particularly involved. TRP channels are considered to play an important role in migraine pain and associated symptoms, including hyperalgesia and allodynia (Benemei et al., 2013). However, Summ et al. (2011) reported that a blockade of the **TRPV1** receptor did not have significant effect on trigeminal nociception in rats. CGRP is known to play a role in spontaneous and triggered migraine headaches. A recent randomised control trial reported that 67% of migraineurs developed migraine attacks after they received CGRP as intravenous infusion (Younis et al., 2019). Additionally, CGRP concentrations have been reported to be increased in migraineurs, in contrast with the concentrations of **vasoactive intestinal peptide**, **substance P** and **neuropeptide Y**, which appeared to be stable during migraine attacks. This underscores the central and specific role of CGRP in the evolution of migraine headache (Goadsby et al., 1990).

3 | DATA COLLECTION

The current review collects and systematically analyses FDA-approved drugs and drugs undergoing clinical trials for migraine treatment to provide insights into the historical and novel trends in pharmacological treatment approaches in this field. The data for FDA-approved drugs were collected manually from the Drugs@FDA database; this dataset was compiled by searching for all drugs with the indications including 'migraine', 'migraine acute' and 'migraine prophylaxis', which had been approved by FDA in the interval between 1970 and 2020. Drugs@FDA includes information about drugs, including biological products, approved for humans. The agents undergoing clinical trials were obtained from ClinicalTrials.gov using the following search terms: 'migraine', 'migraine acute', 'migraine, preventive', 'migraine with aura', 'migraine without aura' and 'migraine disorders'. The search results falling within the time frame from January 2018 to April 2020 were considered. ClinicalTrials.gov was launched to the public in 2000 due to the requirements of the FDA Modernisation Act of 1997, and it is the registry of US clinical trial information. Drug targets and MOAs were obtained from Attwood et al. (2018), Rask-Andersen et al. (2011), Rask-Andersen et al. (2014), the Cochrane database, DrugBank database, IUPHAR/BPS (Armstrong, Faccenda, et al., 2019), PubMed and IBM Micromedex Drug references.

4 | DRUGS APPROVED AND TESTED FOR TREATMENT OF ACUTE MIGRAINE—COMPARISON OF EARLIER AND CURRENT DEVELOPMENT STRATEGIES

4.1 | The evolution of drug approvals for the treatment of acute migraine treatment over time—A quantitative and drug class analysis

Seventeen drugs were approved for acute migraine by the FDA between 1970 and 2020 (Table 1). Drugs that have been approved for migraine within the last 50 years belong primarily to two classes: drugs specifically developed for the treatment of acute migraine, including **5-HT** (serotonin) receptor agonists, and anti-CGRP acting drugs. The second class includes the more general analgesics such as the **COX** inhibitors, which are ubiquitously used for the treatment of different pain-related syndromes (Figure 2). Of note, the four drugs approved between 2018 and 2020 targeted the CGRP and **5-HT$_{1F}$ receptors**, indicating a shift in the drug development strategy for novel drug targets. This shift is based on the new knowledge gained about the role of CGRP and 5-HT$_{1F}$ receptors in migraine pathogenesis. The novel CGRP receptor antagonists (gepants) and 5-HT$_{1F}$ receptor agonists (ditans) are considered promising alternatives, given their better efficacy combined with their milder side effect profile than those of older drugs used for acute migraine, although the entire spectrum of pharmacological effects induced by these agents is not yet fully understood. The overall spectrum of drug targets has considerably widened since 2018 when compared with that of the drugs approved between 1970 and 2018, targeting the 5-HT system and its **5-HT$_{1D/1B}$** receptors (Figure S1).

4.2 | Agents in clinical trials in the interval between 2018 and 2020 for acute migraine—Spectrum of molecular targets

Altogether, 12 drugs that had undergone clinical trials for acute migraine in the interval between 2018 and 2020 were identified (Table 1). Six of these drugs have already been approved by the FDA for treatment of other indications (i.e., not migraine) and are considered repurposed drugs. They primarily act as anaesthetics or analgesics and are currently being tested for their efficacy in treating migraine. Although studies of five of these agents are conducted through medical centres (**dexamethasone**, **lidocaine** and **bupivacaine**) or are university-driven (**ketorolac** and **indomethacin**), **ketamine** is tested through an industry driven study. Interestingly, several of these repurposed drugs function via new MOAs for migraine treatment, including targeting the **NDMA receptor** and the greater occipital nerve (GON), whereas others function via established targets including COX enzymes, the 5-HT receptors and the **CGRP receptor** (Figure 3). Additionally, six of the already FDA-approved drugs for the treatment of acute migraine are currently in additional company-initiated clinical trials for testing of new formulations, novel drug combinations, and long-term safety or expanded indications within the field of migraine. Drugs in this category act via the 5-HT or CGRP systems (Figure S2).

4.3 | Characterisation of drug classes approved and in clinical trials for the treatment of acute migraine

4.3.1 | Drugs targeting the 5-HT system (ergot alkaloids, triptans and ditans)

Ergot alkaloids such as **ergotamine** (approved in 1976) have been used since the 1970s for the symptomatic treatment of acute

TABLE 1 FDA-approved drugs and investigative agents for the treatment of acute migraine

Agent	Therapeutic class	Pharmacological class	MOA	Important contraindications	FDA approval date
FDA-approved new molecular entities					
Ergotamine	Antimigraine	Migraine abortive	Selective agonist of 5-HT_{1D} receptors	Coronary artery disease	1976
Sumatriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease	1992
Dihydroergotamine	Antimigraine	Migraine abortive	Selective agonist of 5-HT_{1D} receptors	Coronary artery disease	1997
Zolmitriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease	1997
Naratriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease	1998
Rizatriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease	1998
Almotriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease, hepatic impairment and hypersensitivity to sulfonyl group	2001
Frovatriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors	Coronary artery disease	2001
Eletriptan	Antimigraine	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D/1F}$ receptors	Coronary artery disease	2002
Sumatriptan/naproxen	Antimigraine/anti-inflammatory	Migraine abortive	Non-selective agonist of 5-$HT_{1B/1D}$ receptors and COX1/2 inhibitor	Coronary artery disease and GI disorders	2008
Lasmiditan	Antimigraine	Migraine abortive	Selective agonist of 5-HT_{1F} receptors	None	2019
Rimegepant	Antimigraine	Migraine abortive	CGRP receptor antagonist	Hypersensitivity to the compound	2020
Ubrogepant	Antimigraine	Migraine abortive	CGRP receptor antagonist	Hypersensitivity to the compound	2019
Vazegepant	Antimigraine	Migraine abortive	CGRP receptor antagonist	Hypersensitivity to the compound	2020
Secondary approval for already established drugs for treatment of acute migraine					
Ibuprofen	Anti-inflammatory	Non-steroidal	COX1/2 inhibitor	GI disorders	2000
Aspirin	Anti-inflammatory	Non-steroidal	COX1/2 inhibitor	GI disorders	2001
Celecoxib	Anti-inflammatory	Non-steroidal	COX-2 inhibitor	Coronary artery disease	1998

	Therapeutic class	Pharmacological class	MOA	Purpose of study	Phase of study
Repurposed FDA-approved drugs in clinical trials for acute migraine					
Dexamethasone	Corticosteroid	Glucocorticoids	Glucocorticoid receptor	Comparison of two different doses of dexamethasone	1 and 4[a]
Lidocaine	Anaesthetic	Local anaesthetic	Greater occipital nerve block	Acute migraine treatment and paediatric migraine	3[a] and 4[a]
Bupivacaine	Anaesthetic	Local anaesthetic	Greater occipital nerve block	Chronic migraine and episodic migraine	4[a]
Ketamine	Sedative/hypnotic	General anaesthetic	Selective antagonist of NMDAR	Chronic migraine	Not applicable[a]
Ketorolac	Anti-inflammatory	Non-steroidal	COX1/2 inhibitor	Paediatric migraine	3 and 4[a]

(Continues)

TABLE 1 (Continued)

Repurposed FDA-approved drugs in clinical trials for acute migraine					
	Therapeutic class	**Pharmacological class**	**MOA**	**Purpose of study**	**Phase of study**
Indomethacin	Anti-inflammatory	Non-steroidal	COX1/2 inhibitor	Migraine	Not applicable[b]
FDA-approved drugs in continued clinical trials					
	Class	**Pharmacological class**	**MOA**	**Purpose of study**	**Phase of study**
Zolmitriptan	Antimigraine	Migraine abortive	Non-selective agonists of 5-$HT_{1B/1D}$ receptors	Novel formulation: nasal spray	1 and 3[a]
Lasmiditan	Antimigraine	Migraine abortive	Selective agonists 5-HT_{1F} receptors	Expanded indication: paediatric	2 and 3[c]
Rizatriptan	Antimigraine	Migraine abortive	Non-selective agonists of 5-$HT_{1B/1D}$ receptors	Efficacy of safety of rizatriptan/meloxicam combination	3[c]
Dihydroergotamine	Antimigraine	Migraine abortive	Selective agonists of of 5-HT_{1D} receptors	Novel formulation: nasal spray Expanded indication: paediatric	2 and 3[c]
Rimegepant	Antimigraine	Migraine abortive	CGRP receptor type 1	Expanded indication: migraine prevention	2 and 3[c]
Vazegepant	Antimigraine	Migraine abortive	CGRP receptor type 1	Long-term safety study	2 and 3[c]

Abbreviations: FDA, Food and Drug Administration; GI, gastrointestinal; MOA, mechanism of action; NMDAR, NMDA receptor.
[a]Pharmaceutical industry driven.
[b]Medical centre driven.
[c]University driven.

migraine. Symptomatic treatment advanced significantly with the development of the triptans, with sumatriptan being the first approved drug in this drug group in 1992. Recently developed novel agents targeting the 5-HT system (ditans) show an efficient pharmacological effect with the absence of unfavourable side effects observed with triptans and ergot alkaloids.

Ergot alkaloids

Dihydroergotamine (DHE) is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. DHE binds with a high affinity to **5-$HT_{1D\alpha}$** and 5-$HT_{1D\beta}$ receptors. Two theories have been proposed to explain the efficacy of the 5-HT_{1D} receptor agonists in migraine: (i) activation of 5-HT_{1D} receptors located on intracranial blood vessels and subsequent vasoconstriction, although this is of minor importance for therapeutic action, and (ii) activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system, which results in the inhibition of the release of pro-inflammatory neuropeptides, such as CGRP, and is the pathway of major therapeutic importance (Silberstein & Kori, 2013). A nasal powder formulation of DHE (STS 101) is currently in a Phase 3 clinical trial for the evaluation of safety and efficacy for the treatment of acute migraine (NCT04406649). Another current clinical trial is a Phase 2 study that compares the clinical efficacy and tolerability of VPA therapy and DHE as an abortive therapy for paediatric migraine (NCT03885154).

Triptans

For approximately 25 years, triptans have been the most effective drugs for treating migraine and thus an important part of migraine therapy. Triptans amplify the 5-HT signal by stimulating 5-HT receptors located in cranial blood vessels and nerve endings and relieve pain by inhibiting the release of peptides such as CGRP and substance P, as well as by acting in other ways that are not yet known. Based on a better understanding of migraine pathophysiology, the vasoconstriction potential of triptans is no longer considered the main path of the pharmacological action of triptans (Edvinsson et al., 2018). At the cellular level, triptans alleviate migraine symptoms by binding to 5-$HT_{1B/1D}$ receptors along with pain signalling circuits and are effective due to high receptor and disease specificity (Ma et al., 2001). **Zolmitriptan** is a 5-HT_1 agonist that mainly targets the 5-$HT_{1B/1D}$ receptors and was first approved by the FDA in 1997. It has two putative mechanisms for therapeutic action: first, inhibiting of the release of vasoactive neuropeptides from the perivascular trigeminal sensory neurons, and second, reduction of pain signal transmission in the trigeminal dorsal horn (Rizzoli, 2014). Zolmitriptan is currently in a Phase 3 clinical trial as a novel formulation as a nasal spray (Zomig) for use in children aged 6–11 years (NCT03275922). **Rizatriptan** is another triptan that was already approved by the FDA in 1998 and is currently in several clinical studies, including a Phase 2 clinical trial for the treatment of episodic dizziness in vestibular migraine, and in a Phase 3 trial in combination with **naproxen** or **meloxicam** for the acute treatment of migraine (NCT04384367). As triptans also have vasoconstrictive

effects on peripheral vessels, including cardiac vessels (Ferrari et al., 2002), these drugs are contraindicated in patients with cardiovascular disease, cerebrovascular disease, uncontrolled hypertension or hemiplegic migraine. Emerging evidence suggests that cerebral vasodilation is not the nociceptive stimulus in migraine; and attention has turned to developing new acute migraine treatments, such as the ditans, that target the trigeminal pathways while avoiding the vasoactive 5-HT_{1B} and 5-HT_{1D} receptors (Oswald & Schuster, 2018).

Ditans

Ditans belong to a novel drug class that targets the 5-HT_{1F} receptor for the treatment of acute migraine. One of this class, **lasmiditan**, a highly selective 5-HT_{1F} agonist, was approved in 2019. Ditans are structurally different from triptans in that triptans possess an indole structure that closely resembles the 5-HT receptor, whereas ditans replace this indole group with a pyridine-piperidine scaffold. Triptans bind non-selectively to 5-HT_{1B} and 5-HT_{1D} receptors and with varying affinity to 5-HT_{1F} receptors, causing direct vascular vasoconstriction. In contrast, ditans are selective for the 5-HT_{1F} receptor, and their MOA is neuronal, without evidence of vasoactive effects (Goadsby & Classey, 2003). Preclinical studies have shown that lasmiditan inhibits CGRP release via binding to 5-HT_{1F} receptors (Labastida-Ramírez et al., 2020). The release of pain-provoking stimuli (CGRP and substance P) from the presynaptic membrane of the trigeminal system can be indirectly measured by quantifying protein extravasation from the dura mater following painful stimulation (Markowitz et al., 1987). Johnson et al. showed that extravasation of dura plasma proteins in guinea pigs significantly decreased with increasing 5-HT_{1F} receptor affinity. Lasmiditan has been shown to block plasma protein extravasation (PPE) (Johnson et al., 1997). However, PPE as a therapeutic target for migraine is still under investigation. Additionally, Shepheard et al. (1999) observed a dose-dependent 5-HT_{1F} response decrease in action potential generation due to electrical dural stimulation, suggesting that 5-HT_{1F} agonists inhibit second-order neurons in the trigeminal nucleus caudalis. Lasmiditan is a promising acute antimigraine therapy, in particular for patients with cardiovascular risk factors, contraindications or unwanted side effects to triptans. However, lasmiditan is associated with CNS-related side effects including dizziness, somnolence and paraesthesia (Goadsby et al., 2019). A Phase 3 study reported that the incidence of dizziness with lasmiditan increased with dose (Tepper et al., 2019). Lasmiditan is currently in a Phase 3 trial testing safety and efficacy in acute migraine treatment in children (NCT04396574).

4.3.2 | Drugs targeting the CGRP system—Gepants

Since the late 1980s, studies have shown that CGRP is significantly involved in the pathophysiology of migraine (Goadsby et al., 1990; Shepheard et al., 1999). CGRP can trigger migraine in patients (Younis et al., 2019), and blockade of the canonical CGRP receptor (Lassen et al., 2002) is effective in the treatment of acute migraine (Goadsby et al., 1990). Low MW CGRP receptor antagonists (gepants) have been investigated regarding their effect in both acute migraine treatment and migraine prevention. Several previously studied low MW CGRP receptor antagonists were effective in Phase 2 and 3 trials; however, their development was halted owing to hepatotoxicity, the inability to develop an oral formulation or other unknown reasons (Ho et al., 2014; Marcus et al., 2014). Blocking of CGRP receptors by gepants inhibits both vascular nociceptive transmission and thalamic trigeminal nociceptive activation (Olesen, Diener, et al., 2004). Olesen, Diener, et al. (2004) reported a 66% response rate by blocking CGRP receptors in migraineurs. Two gepants, **ubrogepant** and **rimegepant**, have been approved by the FDA for acute migraine. Ubrogepant (Ubrelvy™), a potent, orally administered compound, is a highly selective, competitive CGRP receptor antagonist developed by Allergan, under a licence from Merck & Co., for the acute treatment of migraine. In December 2019, the US FDA approved ubrogepant for the acute treatment of migraine (with/without aura) in adults. It is recommended as the first drug for this indication in the class of oral CGRP antagonists (Scott, 2020). Ubrogepant is well tolerated with the most common adverse events reported as nausea, somnolence and dry mouth with a frequency rate below 5% (Ailani et al., 2020). The second drug of this class, rimegepant, was approved by the FDA in February 2020. Rimegepant is given orally and reaches peak plasma concentrations after 2 h (Croop et al., 2018). The side effect profile of rimegepant is mild, with nausea and urinary tract infections being the most commonly occurring events, and it has an overall similar side effect profile comparable with placebo (Croop et al., 2018). However, the therapeutic gain for gepants (rimegepant: 5–7.6%; ubrogepant: 6.4–9.4%) appears to be lower than for sumatriptan (16–21%) or lasmiditan (7.3–17.5%) (Derry et al., 2014). Because gepants do not constrict cranial arteries, they can be used as a first-line anti-migraine treatment in patients at increased risk for cardiovascular events risk or in those with documented cardiovascular disease (Conway et al., 2019). Furthermore, they can be used as a second-line treatment where treatment with triptans has failed (Do et al., 2019).

4.3.3 | Anaesthetics

Ketamine

The hypothesis that ketamine may be used as a drug against migraine is not new and has been studied for more than 20 years (Lauritzen & Hansen, 1992). The interest in ketamine in migraine treatment has increased again recently. Ketamine has been previously investigated as an opioid-sparing agent in the treatment of pain (Motov et al., 2015) and as a treatment option for mood disorders (Lapidus et al., 2014). Compelling evidence exists for each of these indications. In contrast to this, reliable data for the significant effect of ketamine in migraine are still missing. NMDA receptors targeted by ketamine are widely distributed in the CNS. Under resting conditions, the channel pores are blocked by magnesium (Mg^{2+}), which prevents the flow of ions through the receptor channel. During neuronal depolarisation, Mg^{2+} leaves pores allowing the influx of Ca^{2+} (Parsons

et al., 1999). Several preclinical studies suggest the effect of Mg^{2+} on NMDA receptors as a migraine mechanism. Studies have shown that glutamate receptors are located on the superficial laminae of the trigeminal nucleus caudalis (TNC) (Tallaksen-Greene et al., 1992). Local stimulation of these receptors with microiontophoretically administered glutamate induces the postsynaptic facilitation of neuronal activity within the TNC (Hill & Salt, 1982). Ketamine is a selective antagonist of the NMDA receptor, which is believed to be its primary MOA. However, numerous other complex pharmacological actions have been proposed, including effects on extracellular glutamate, **dopamine** and **opioid receptors** (Iacobucci et al., 2017) and an inhibition of CSD (Sánchez-Porras et al., 2014). Two case series have reported transient improvement in headache severity with an infusion of ketamine; however, neither reported statistically significant sustained improvement (Lauritsen et al., 2016; Pomeroy et al., 2017). Ketamine is currently in a clinical trial for evaluating its efficacy in acute migraine treatment (NCT02697071).

Lidocaine and bupivacaine (GON blockers)

The blocking of the GON has a considerable effect on the trigeminovascular system, which plays a key role in migraine pathophysiology. A rat study reported that the excitability of meningeal afferent input increased via stimulation of the GON and cutaneous C-fibre afferents in response to mustard oil. The study reported that there is a functional coupling between nociceptive meningeal afferent and cervical afferents in the GON (Bartsch & Goadsby, 2002). Two medical centre-driven studies have been investigating the use of lidocaine and bupivacaine as treatment alternatives for acute migraine, testing the effect of injectable and intranasal formulations of the agents. The strength of intranasal lidocaine is its route of administration, rapid effectiveness and rare adverse reactions (Avcu et al., 2017; Maizels & Geiger, 1999). Lidocaine has been studied for over 20 years (Maizels & Geiger, 1999) regarding its usability in acute and chronic migraine treatment (Kashipazha et al., 2014; Puledda et al., 2018). Although the number of controlled studies conducted is limited, the blockade of GON using a local anaesthetic alone (Cuadrado et al., 2017) or with a steroid–local anaesthetic combination (Puledda et al., 2018) as well as blockade of the sphenopalatine ganglion (Maizels & Geiger, 1999; Avcu et al., 2017) have been suggested as promising targets for effective treatment of acute migraine (Maizels & Geiger, 1999; Cuadrado et al., 2017). Lidocaine and bupivacaine have been used to block the GON that originates in the dorsal ramus of the C2 as well as the C3 segments of the spinal cord and comprises sensory fibres alone. Its sensory distribution pathway includes the posterior part of the head and extends anteriorly towards the vertex, becoming superficial at the inferolateral part of the occipital protuberance. It has been hypothesised that sensory inputs from the GON and the ophthalmic branch of the trigeminal nerve converge into the TNC, which may explain why occipital neuralgia is sometimes associated with migraine headache symptomatology (Reed et al., 2010). A GON block decreases this afferent input to the TNC, thus resulting in central pain modulation and the reduction of neuronal hyperexcitability at the level of second-order neurons. Furthermore, blocking the sphenopalatine ganglion decreases signals to the intracranial nociceptors that innervate migraine pain (Avcu et al., 2017; Maizels & Geiger, 1999). However, the effect of this mechanism on migraine remains controversial (Avcu et al., 2017; Maizels & Geiger, 1999).

4.3.4 | Glucocorticosteroids and non-steroidal anti-inflammatory drugs

Dexamethasone

Migraine is also characterised by inflammation. Thus, the use of anti-inflammatory agents to inhibit the inflammatory cascade may help to relieve migraine headaches and prevent their recurrence, and anti-inflammatory agents may provide benefits through the mitigation of inflammation (Khazaei et al., 2019). Glucocorticosteroids and non-steroidal drugs are the most appealing, economic and familiar agents for the treatment of migraines. The use of glucocorticosteroids in the emergency department may vary, and published reports suggest that corticosteroids are infrequently used for acute severe migraine (Vinson, 2002). A medical centre-driven study currently investigates optimal dosing of dexamethasone in acute migraine (Phase 4) (NCT04112823) and its efficacy to prevent relapse in acute migraine in children (Phase 1) (NCT02903680).

NSAIDs (ketorolac and indomethacin)

NSAIDs are one of the most common classes of pharmacological interventions to treat acute migraine attacks. They are considered non-specific abortive treatments with a long history and demonstrated efficacy for acute migraine treatment in adults (Lipton et al., 2005; Misra et al., 2004). Two repurposed NSAIDs, indomethacin and ketorolac, are in university-driven clinical trials for treatment of migraine. Indomethacin has been used to treat different forms of indomethacin-responsive headaches such as trigeminal autonomic cephalgias (for instance, paroxysmal hemicranias), Valsalva-induced headaches and primary stabbing headaches (ice pick headache or jabs and jolts syndrome) (Dodick, 2004). Based on the treatment recommendations published by the European Federation of Neurological Societies (EFNS), indomethacin is not directly recommended as a first-line therapy for either migraine or tension-type headaches (Evers, Afra, et al., 2009). However, the efficacy of indomethacin in acute migraine disorder is under investigation. Ketorolac is a non-selective COX inhibitor that was previously approved by the FDA for moderate to severe pain in oral, intravenous and, more recently, nasal spray formulations. These formulations offer several advantages to patients with migraines, including a faster absorption than oral agents and use in those patients with nausea (Rao et al., 2016). Ketorolac is currently in trials comparing the efficacy of intranasal and intravenous application in paediatric migraine. Three NSAIDs that were previously approved for other indications have subsequently been approved for acute migraine treatment. Ibuprofen was approved by the FDA in 2000 and aspirin in 2001, whereas celecoxib was approved in 1998.

TABLE 2 FDA-approved drugs and investigative agents for migraine prophylaxis

FDA-approved new molecular entities					
Agent	**Therapeutic class**	**Pharmacological class**	**MOA**	**Important contraindications**	**FDA approval date**
Erenumab	Antimigraine (monoclonal antibody)	Migraine prophylactic	Blocks CGRP receptor	None	2018
Galcanezumab	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP	Hypersensitivity to compound or excipients	2018
Fremanezumab	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP	Hypersensitivity to compound or excipients	2018
Eptinezumab	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP I	Hypersensitivity to compound or excipients	2020
Secondary migraine prophylaxis approval for already established drugs					
Onabotulinum toxin A (Botox)	Neuromodulator	ACh release inhibitor	Inhibits release of CGRP, substance P via cleavage of SNAP-25 and inhibition of ACh release	Hypersensitivity	2010
Topiramate	Anticonvulsant	Sodium channel inhibitor	Blocks Na channels, inhibits the excitatory glutamate pathway, enhances GABA activity and inhibits Ca activity	Metabolic acidosis, hyperammonaemia, oligohidrosis and hyperthermia	1996
Valproic sodium/valproic acid (combination)	Anticonvulsant	GABA-augmenting agent	Inhibits GABA transaminase	Hepatic dysfunction, hyperammonaemia and hyperthermia	1996
Valproic acid	Anticonvulsant	GABA-augmenting agent	Inhibits GABA transaminase and blockade of Na and Ca channels	Hepatic dysfunction, hyperammonaemia and hyperthermia	1996
Propranolol	Cardiovascular	β-adrenoceptor antagonist	Blocks β-adrenoceptors non-selectively	Bronchospastic lung disease and hypoglycaemia	1973
Timolol	Cardiovascular	β-adrenoceptor antagonist	Blocks β-adrenoceptors non-selectively	Bronchospastic lung disease and hypoglycaemia	1978

Novel agents in clinical trials					
	Therapeutic class	**Pharmacological class**	**MOA**	**Study purpose**	**Phase of study**
IONIS-PKKRx	Antimigraine	Oligonucleotide (antisense)	Inhibition of pre-kallikrein mRNA and reduction of kallikrein and bradykinin	Efficacy and safety for chronic migraine	Not applicable[b]
Atogepant	Antimigraine	Migraine prophylactic	Inhibition of CGRP receptor	Efficacy and safety for chronic migraine	3[a]
Flunarizine	Cardiovascular	Calcium channel blocker	Smooth muscle inhibition and antagonises Ca channels and 5-HT receptors	Efficacy and safety for chronic migraine	4[a]

Repurposed FDA-approved drugs in clinical trials for migraine prophylaxis					
Candesartan	Cardiovascular	AT_1 receptor antagonist	Blocks AT_1 receptors	Migraine prevention	Not applicable[a]
Amiloride	Diuretic	Potassium sparing	Blocks ASICs	Migraine prevention	2[a]

FDA-approved drugs in continued clinical trials					
Topiramate	Anticonvulsant	Sodium channel inhibitor	Blocks Na channels, inhibits the excitatory glutamate pathway, enhances GABA activity and inhibits Ca activity	Expanded indication: episodic migraine	1[a]

(Continues)

TABLE 2 (Continued)

FDA-approved drugs in continued clinical trials					
Erenumab and 4[b]	Antimigraine (monoclonal antibody)	Migraine prophylactic	Blocks CGRP receptor	Expanded indication: episodic migraine, chronic migraine and paediatric migraine	3
Galcanezumab	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP ligand	Expanded indication: vestibular migraine, paediatric migraine and episodic migraine	2
Fremanezumab and 3[b]	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP ligand	Expanded indication: paediatric migraine and patients with MDD	3
Eptinezumab and 4[b]	Antimigraine (monoclonal antibody)	Migraine prophylactic	Binds to CGRP ligand	Expanded indication: acute migraine and treatment-resistant patients	3[b]

Abbreviations: ASICs, acid-sensing ion channels; FDA, Food and Drug Administration; MDD, major depressive disorder; MOA, mechanism of action; SNAP-25, synaptosomal-associated protein 25.
[a]University driven.
[b]Pharmaceutical company driven.

5 | DRUGS APPROVED AND TESTED FOR CHRONIC MIGRAINE—COMPARISON OF DEVELOPMENT STRATEGIES

5.1 | The evolution of drug approvals for the treatment of chronic migraine treatment over time—A quantitative and drug class analysis

In total, 10 drugs have been approved by the FDA for the treatment of chronic migraine in the time interval from 1970 to 2020 (Table 2). As shown in Figure 1, only five drugs were approved from 1970 to 2009, indicating that no strong progress was made regarding novel therapeutic approaches in chronic migraine during this time frame. In contrast, five drugs were approved by the FDA in the period from 2010 to 2020, reflecting a higher activity of development of novel therapeutic options for chronic migraine. Between 2018 and 2020, four drugs were approved for the treatment of chronic migraine, which belongs to the class of anti-CGRP drugs targeting the ligand or receptor as a novel therapeutic strategy. Six repurposed drugs obtained secondary FDA approval for the treatment of chronic migraine. These drugs were initially approved for other indications and were later shown to have a beneficial effect on migraine. These include topiramate (anticonvulsant), propranolol (β-adrenoceptor antagonist), VPA and divalproex sodium (anticonvulsants), **timolol** (beta-adrenoceptor antagonist) and onabotulinum A (Botox). Molecular entities targeted by FDA-approved drugs for chronic migraine show a relatively wide spectrum of their MOA, including **sodium channels**, **GABA transaminase**, β-adrenoceptors, synaptosomal-associated protein 25 (SNAP-25), the CGRP receptor and the CGRP ligand (Figure 2). Anti-CGRP agents target a biological pathway that has been shown to play an important role in migraine pathogenesis, offering novel perspectives for therapeutic options in episodic and chronic migraine.

5.2 | Agents in clinical trials in the interval between 2018 and 2020 for chronic migraine—Spectrum of molecular targets

Ten drugs were identified in clinical trials for the indication of migraine prophylaxis between 2018 and 2020 (Table 2). Three of these drugs are novel agents that target the CGRP receptor, **calcium channels** and prekallikrein mRNA. Two of the agents in clinical trials are repurposed drugs that have already been approved for a different indication and are now being investigated in chronic migraines. These agents target the **angiotensin II receptor**s and acid-sensing ion channels (**ASICs**) (Figure 3). Five drugs already approved for migraine prophylaxis are currently in trials for expanded indications. Examples include two antibodies, one against the CGRP receptor, **erenumab** (chronic migraine in children and episodic migraine) and the other against CGRP itself, **eptinezumab** (treatment-resistant patients with migraine and acute migraine).

The current dataset collected from ClinicalTrials.gov shows various therapeutic agents in the clinical testing phase for migraine

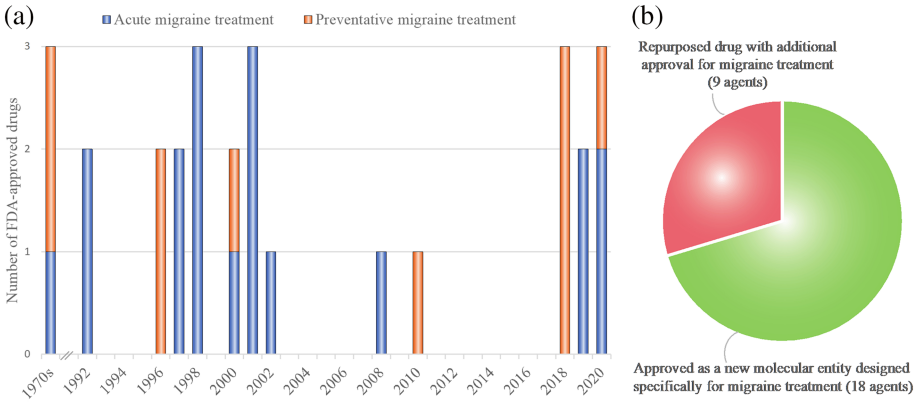


FIGURE 1 (a) Agents approved by the FDA for the acute and prophylactic treatment of migraine from 1970 to 2020. Since the 1970s, 27 agents have been approved by the FDA for migraine treatments. (b) Agents that have been approved as a new molecular entity specifically for migraine treatment and repurposed agents that have additional approval for migraine treatment. In total, 18 agents have been approved as a new molecular entity specifically designed for migraine management, and seven repurposed agents have been approved for either acute or prophylactic migraine treatment

FIGURE 2 FDA-approved agents and their therapeutic targets for acute and prophylactic treatment of migraine. Fourteen agents that were new molecular entities (NMEs) designed specifically to treat acute migraine have been FDA approved, and the therapeutic targets they target are shown in blue. Three repurposed agents, that is, drugs that have been previously FDA approved for a different indication, have had additional approvals for acute migraine treatment and are shown in dark blue. Four FDA-approved NMEs that were specifically designed for prophylactic migraine treatment and their targets in the CGRP pathway are shown in light orange, and six repurposed drugs have also been approved and with their targets are shown in brown

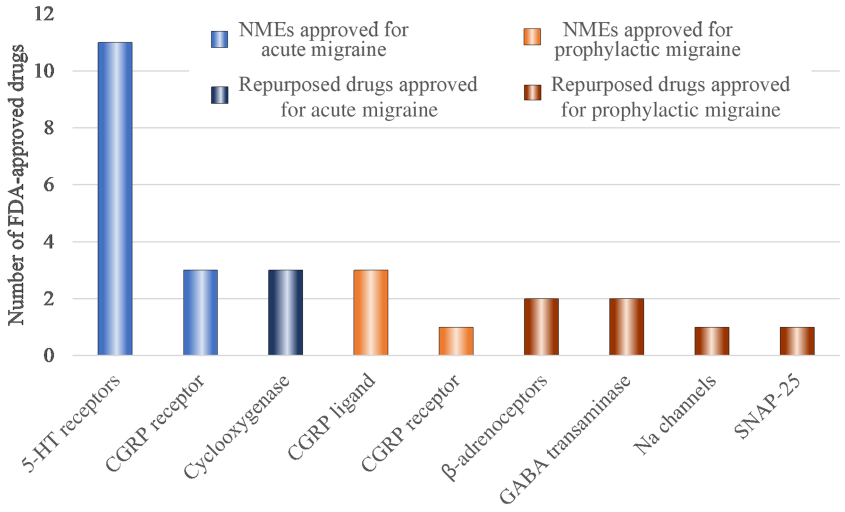
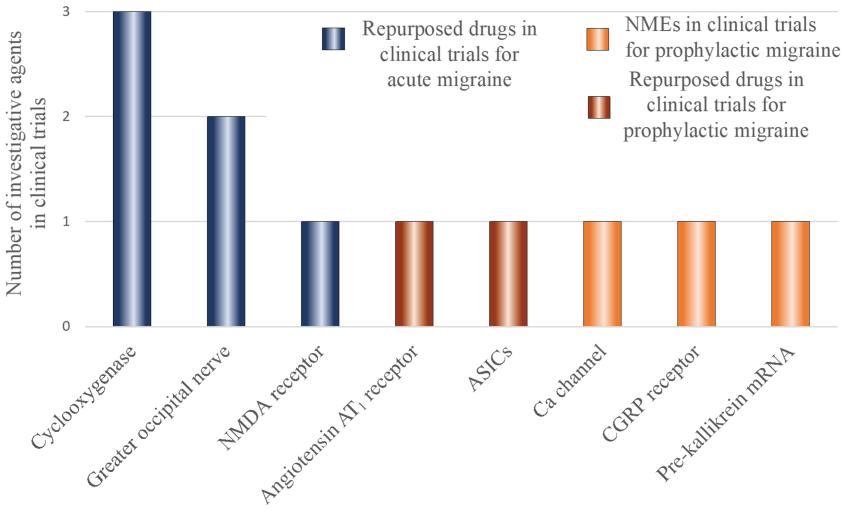


FIGURE 3 Investigative agents and their therapeutic targets for prophylactic migraine treatment. In total, 11 agents are in clinical trials for treatment of preventive or acute migraine. All of the agents in trials for acute migraine treatment are repurposed drugs that target COX enzymes, the greater occipital nerve or the NMDA receptor (all shown in dark blue). Agents in trials for prophylactic migraine treatment are more diverse, with three new molecular entities (NMEs) (shown in light orange) that target two novel targets—pre-kallikrein mRNA and calcium channels as well as the validated CGRP receptor. Additionally, two repurposed drugs (shown in brown) are also in trials that target the angiotensin AT_1 receptor and acid-sensing ion channels (ASICs)



prophylaxis. Drugs act via different molecular targets, including the CGRP receptor, the angiotensin II receptor, ASICs, SNAP-25, calcium channels, prekallikrein mRNA, sodium channels, β-adrenoceptors, GABA transaminase and CGRP ligand (Figure S2).

5.3 | Characterisation of drug classes approved and those undergoing clinical trials for the treatment of chronic migraine

5.3.1 | Anticonvulsants

Since 1970, three anti-epileptics have been recommended as drugs of the first choice (topiramate and valproate) or third choice (**gabapentin**) to prevent migraine attacks (Linde et al., 2013a). The use of anti-epileptics for the prophylactic treatment of migraine is theoretically warranted by several known modes of action, which relate either to the general modulation of pain systems or more specifically to systems involved in the pathophysiology of migraine (Silberstein et al., 2008). However, it is not, currently, possible to state the particular mode or modes of action of anti-epileptics, relevant to migraine prophylaxis (Linde et al., 2013a).

Topiramate

Topiramate is a sulfamate-substituted monosaccharide (2,3:4,5-bis-*O*-[1-methylethylidene]-β-D-fructopyranose sulfamate) derived from the naturally occurring sugar D-fructose (Martella et al., 2008). The efficacy of topiramate in migraine appears to be mediated by the interaction with multiple sites of action. It decreases the frequency of action potentials elicited by the depolarising electric current, which leads to a blockade of voltage-dependent Na^+ channels (McLean et al., 2000). Topiramate modulates cortical excitability in migraineurs; however, it does not appear that this alone explains its efficacy in migraine prophylaxis (Artemenko et al., 2008). Topiramate inhibits the excitatory activity of glutamate at the receptor subtype for kainate/AMPA. It has been shown to inhibit neurons of the trigeminocervical complex via a GABA-mediated mechanism. Furthermore, topiramate inhibits the release of CGRP from prejunctional trigeminal neurons (Akerman & Goadsby, 2005). An inhibitory effect on high-voltage-dependent (HVA) Ca^{2+} channels, particularly in the periaqueductal grey (PAG), is a possible mechanism to explain the therapeutic effect in migraine (Martella et al., 2008). Differential sensitivity to topiramate has been observed for HVA Ca^{2+} channels located on cortical neurons and those in the PAG region. Topiramate inhibits N-, P- and L-type channels in PAG neurons, whereas in cortical neurons, it modulates only P- and L-type channels. Chronic, but not acute, treatment suppresses CSD in rats (Edvinsson & Linde, 2010, 2013b). Collectively, these point towards a reduction in excitatory transmission and increase in inhibitory neurotransmission (Linde et al., 2013a; Linde et al., 2013b). The most common adverse effects of topiramate are paresthesia, fatigue, somnolence, hypoesthesia, nausea and weight loss (Dodick, Freitag, et al., 2009). Topiramate is the only anticonvulsant that has been tested in clinical trials in the last 2 years for migraine treatment and is currently in a Phase 1 clinical trial for the treatment of episodic migraine.

VPA (VPA or sodium valproate or a combination of the two [divalproex sodium])

VPA (2-propylpentanoic acid) was first synthesised in 1882 as an analogue of valeric acid, found naturally in valerian. VPA, sodium valproate or a mixture of the two (divalproex sodium according to the United States Adopted Names and valproate semisodium according to the WHO International Non-proprietary Name nomenclature) has been approved by the FDA in 1996 for the use in migraine prophylaxis (Cutrer et al., 1997). The MOAs of valproate include enhanced neurotransmission by GABA (by inhibiting GABA transaminase) and blockage of voltage-gated sodium channels and T-type calcium channels. Although more than 20 years ago, Cutrer et al. (1997) identified nine stages of the migraine attacks at which valproate might potentially have a beneficial effect, it is still not possible to state with certainty which particular mode or modes of action of valproate are relevant to the prophylaxis of migraine.

5.3.2 | Botulinum toxin type A

Onabotulinumtoxin A (Botox)

Botulinum toxin is a natural product synthesised by the anaerobic bacterium, *Clostridium botulinum*. The clinical use of botulinum toxin for conditions involving excessive muscle contractions began in the early 1980s. It has become the first-line therapy for many conditions, including dystonia, spasticity, hyperhidrosis and some forms of bladder disturbance. Since then, botulinum toxin has shown pain-relieving properties above what might be expected due to the relief of muscle contractions and its use for the treatment of migraine has developed (Herd et al., 2018). For treating migraine, botulinum toxin is administered intramuscularly to multiple sites around the head and back of the neck, with regular retreatment. One preparation of botulinum toxin, onabotulinum toxin A (Botox), has recently been licensed in the United States and the United Kingdom as an agent for the prevention of chronic migraine (a minimum of 15 migraine days·month^{-1}) based on two large randomised, placebo-controlled trials (Aurora, Dodick, et al., 2010; Diener, Dodick, et al., 2010). Botulinum toxin has been reported to alleviate pain in a variety of conditions; however, the MOA is not well understood. It has been postulated that botulinum toxin acts to reduce pain by inhibiting the release of neuropeptides such as CGRP and substance P, which are involved in the initiation of migraine (Aurora, Dodick, et al., 2010; Diener, Dodick, et al., 2010; Herd et al., 2018). Soluble *N*-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) complexes are involved in the mechano-transduction of noxious stimuli. It is thought that botulinum toxin may act to prevent migraine by cleaving SNAP-25, one of the SNARE complex proteins, impairing synaptic vesicle fusion, and the release of neurotransmitters involved in pain sensitivity (Burstein et al., 2014).

5.3.3 | Drugs targeting CGRP signalling

Gepants and anti-CGRP monoclonal antibodies

CGRP is now a validated target for the treatment of migraine, as it has a crucial role in migraine pathophysiology. Therapeutic agents developed to inhibit the CGRP pathway include gepants and monoclonal antibodies (Edvinsson et al., 2018). The mechanism by which monoclonal antibodies are proposed to prevent migraines is by blocking CGRP transmission in the trigeminovascular system (Manoukian et al., 2019). Monoclonal antibodies that target the neuropeptide CGRP (**galcanezumab**, eptinezumab and **fremanezumab**) are proposed to bind and thus deactivate CGRP released by trigeminal sensory nerve fibres (Melo-Carrillo et al., 2017), whereas antibodies that target the CGRP receptor (erenumab) presumably act by preventing access of CGRP to its canonical receptor (Manoukian et al., 2019). There are two known isoforms of CGRP. **CGRPα** is the predominant form in the CNS and peripheral nervous system implicated in migraine pathology, and it is targeted by monoclonal antagonising antibodies. **CGRPβ** is mainly found in the enteric nervous system and has not been well studied (Lassen et al., 2002). There are several components to receptors that CGRP bind with: the calcitonin receptor-like receptor (**CLR**), the calcitonin receptor (**CTR**) and three receptor activity-modifying proteins (RAMPs). The canonical CGRP receptor consists of the CLR/RAMP1 complex and has high affinity to CGRP (Hay et al., 2018). In addition, the CTR/RAMP1 complex, called **AMY_1**, also has high affinity for CGRP and should certainly be considered as a possible player in CGRP action in migraine besides the canonical CLR/RAMP1 CGRP receptor (Hay, 2019). The binding of CGRP to the extracellular binding pocket formed by the heterodimer causes activation of G proteins containing the Gαs subunit bound to CLR, which in turn activates **AC** and **cAMP**-dependent signalling pathways that mediate vasorelaxation in blood vessels (Lassen et al., 2002).

Atogepant is a novel, orally effective, low MW, CGRP receptor antagonist under investigation for migraine prevention. The efficacy and safety of atogepant in migraine prevention were demonstrated in a Phase 2/3 clinical trial in which treatment with atogepant significantly decreased the monthly number of days of migraine days over 12 weeks when compared with placebo (Goadsby et al., 2020). Despite the promising data from the clinical trials of anti-CGRP and anti-CGRP receptor antibodies, the risks of the long-term blockade of CGRP signalling are not known (MaassenVanDenBrink et al., 2016). Much remains to be learned about the physiological and pathophysiological roles of CGRP as this peptide has effects throughout the body (Lassen et al., 2002) and circulating antibodies could affect all peripherally accessible sites where CGRP acts. One concern relates to the role of CGRP as a potent vasodilator throughout the vascular system (Lassen et al., 2002). Consequently, chronic reduction of CGRP has the potential to cause cardiovascular pathophysiologies, such as hypertension, cardiac dysfunction, and episodes of coronary or cerebral ischaemia (MaassenVanDenBrink et al., 2016). To date, no cardiovascular adverse effects or development of hypertension due to use of anti-CGRP and anti-CGRP receptor antibodies have been reported in up to 6 months of Phase 3 clinical testing (Goadsby, Reuter, et al., 2017; Silberstein et al., 2017). In a study published in 2018, erenumab had no effect on patients with angina pectoris (men aged ~65 years) who were monitored using electrocardiography, while exercising on a treadmill until they reported chest pain (Depre et al., 2018). Studies have shown how a reduction in CGRP signalling is likely to interfere with a mild rather than a complete block of CGRP-dependent signalling pathway. Hence, this risk for cardiovascular side effects maybe rather low. It should be noted that CGRP actions in both the peripheral nervous system and CNS are well positioned to contribute to migraine symptoms. Although the critical sites of action remain controversial, it appears likely that both central and peripheral sites may be important in the initiation and treatment of migraine (Russo, 2015).

5.3.4 | Cardiovascular agents and diuretics

Antagonists of β-adrenoceptors

Propranolol is one of the most regularly used drugs for migraine prophylaxis with many clinical trials consistently proving its efficacy in reducing the frequency of migraine attacks since the 1970s (Diener et al., 2002). The MOAs of propranolol in migraine prophylaxis are not fully understood. It has been proposed that propranolol reduces central hyperexcitability through **β_1**- adrenoceptor-mediated inhibition of **noradrenaline** release, thus reducing central catecholaminergic hyperactivity. Furthermore, propranolol inhibits NO production by blocking **inducible NOS** and also inhibits kainate-induced currents and is synergistic with NMDA blockers, which reduces neuronal activity and has membrane-stabilising properties (Dakhale et al., 2019). One recent study has shown a significant reduction in frequency, severity and duration of migraine headaches (Dakhale et al., 2019).

Timolol is a non-selective β-adrenoceptor antagonist that is available for both topical and systemic administration. Topical timolol is primarily used to reduce intraocular pressure in patients with open-angle glaucoma and ocular hypertension (Lazreg et al., 2018); however, systemic administration of timolol can be part of a regimen managing hypertension and, importantly, migraine prophylaxis (Durley et al., 1981; Stellar et al., 1984). Timolol has been an effective method for migraine prophylaxis (Tfelt-Hansen et al., 1984) and was approved in 1978, although the exact mechanism of timolol as migraine prophylaxis is unknown. It is likely to exert its effects through a variety of processes. One proposed mechanism is that blockade of β-adrenoceptors decreases the synthesis and release of noradrenaline, an important intermediate in the pathophysiology of migraine. Another pathway that could contribute to its migraine prophylactic properties is that β-adrenoceptor antagonists can regulate the neuronal firing of PAG matter using GABA. Timolol also appears to play a role in regulating the 5-HT system by inhibiting 5-HT, another important mediator in the pathophysiology of migraine. This modulation of the effects of 5-HT also appears to contribute to the ability of β-adrenoceptor antagonists to reduce the sensitivity of the auditory system and thus reduce the frequency of migraine attacks. There is also a hypothesis that β-adrenoceptor antagonists play a significant role in reducing the

excitability of the visual system in patients with migraines. However, it should be noted that the vast majority of preventive medications for migraine have the potential to diminish multisensory sensitivities to a certain extent. β-Adrenoceptor antagonists, such as timolol, are also thought to reduce the spread of signals through the brain, including the cortical spreading as well as the excitability of the ventroposteromedial thalamic nucleus (Shields & Goadsby, 2005).

Flunarizine

Flunarizine is a well-recognised migraine preventive agent that has been extensively used in some parts of the world in paediatric and adult populations for over three decades. Flunarizine is a non-selective calcium ion channel and **dopamine receptor** antagonist, which has 5-HT receptor antagonist and anti histamine (**H_1** receptor antagonist) actvityies (Karsan, Palethorpe, et al., 2018). It should be noted that flunarizine is not approved by the FDA owing to concerns over its potential to induce Parkinsonism. Currently, flunarizine is being tested in a Phase 4 study to assess **α-lipoic acid** as an add-on therapy for the treatment of adolescent migraine (NCT04064814). Louis (1981), for the first time, reported a significant reduction in the frequency of migraine attacks following flunarizine therapy, compared with placebo. Based on this study, more double-blind placebo-controlled trials were performed (Diener et al., 2002; Sørensen et al., 1986). Calcium antagonists are known to display anti-vasoconstrictive action and to protect tissues from the sequelae of hypoxia and/or ischaemia (Van Reempts et al., 1983). However, the substances have different effects on different calcium channels, different antihypoxic effects on cerebral tissues and several other pharmacological properties. For example, no effect on any type of migraine could be established for the calcium antagonist **nimodipine** (Ansell et al., 1988). Based on the hypothesis that cerebral hypoxia plays a decisive role in the pathogenesis of migraine (Amery, 1987), the anti-hypoxic activity of flunarizine has been discussed as a MOA in the prevention of migraine. Although hypoxia has been well documented in attacks of classical migraine attacks (Olesen et al., 1982), for cases other than simple migraine, this hypothesis cannot be established. This is particularly true as clinical studies do not show a discrepancy in the effectiveness of flunarizine in simple or classical migraine. Adequate insights into the MOA of flunarizine in migraine prophylaxis will probably not be achieved before sufficient explanations concerning the exact pathophysiological process in migraine disease are available.

Candesartan

Hypertension is recognised as a serious risk factor for the development of migraines (Owada, 2004). Candesartan has been reported to provide migraine prophylaxis since 2003 (Tronvik et al., 2003). Candesartan is an angiotensin II **AT_1** receptor blocker that was initially developed as an antihypertensive agent to block the action of angiotensin II (Mizuno et al., 1992). The renin–angiotensin system has the potential to cause organ damage, independent of hypertension (Morgan, 2003), and administration of candesartan is reported to inhibit oxidative stress (Dohi et al., 2003). Based on the migraine mechanisms described earlier, the characteristics specific to candesartan, and the efficacy of treatment in these cases, it can be hypothesised that the mechanism of candesartan migraine prophylaxis involves either or both of the following: (i) inhibition of excessive vasoconstriction due to 5-HT release and (ii) inhibition of neurogenic inflammation. Candesartan inhibits vasoconstriction by blocking of AT_1 receptor stimulation in vascular smooth muscles. This action may break the vicious circle of migraines by inhibiting excessive cerebrovascular constriction (Groth et al., 2003). In addition, recent reports indicate that pretreatment using candesartan acts to regulate the progression of vascular permeability (Groth et al., 2003) and to deactivate the inflammatory nuclear transcription factor NF-κB induced by angiotensin II (Yoshiyama et al., 2001). These findings suggest that candesartan may suppress neurogenic inflammation in the cerebral vasculature, which is conducive to migraine (Mizuno et al., 1992). Candesartan is currently in clinical trials for its efficacy and tolerability in episodic and chronic migraine in adults (NCT04138316 and NCT04574713).

Amiloride (diuretics)

Amiloride selectively antagonises ASICs, a family of ion channels related to degenerin and epithelial sodium channels, first cloned in 1997 (Karsan, Gonzales, & Dussor, 2018). It consists of four members, **ASIC1**–ASIC4, with several splice variants (Akopian et al., 2000). In addition to activation by decreased pH, ASICs are modulated by **nerve growth factor (NGF)** and 5-HT (Hesselager et al., 2004; Munkholm & Arendt-Nielsen, 2017), and latter has recently been found to potentiate **ASIC3** through a non-proton ligand-binding site (Mamet et al., 2002). 5-HT levels have long been linked to migraine (Wang et al., 2013), and NGF levels are increased in the CSF of patients with chronic headache and a history of migraine (Dussor, 2014). NO donors, one of the most reliable migraine triggers in humans, also potentiate ASIC currents (Cadiou et al., 2007). Holton et al. (2020) reported that the blockade of ASIC-3 inhibits durovascular-evoked and NO-induced sensitisation of trigeminal nociceptive responses in rats. Moreover, decreased pH and ASIC activation may also play a role in the initiation or propagation of CSD (Dussor, 2015), and it is known that there is a decrease in pH within the cortex during CSD as well as in related types of spreading depolarisations (Pietrobon & Moskowitz, 2014), which may occur as CSD can increase metabolic demand without a corresponding increase in blood flow leading to hypoxia of cortical tissue (Takano et al., 2007). Increased ASIC1a expression has been found in the spinal dorsal horn neurons following peripheral inflammation, and antagonising this channel reduced pain-related behaviour in rodents (Piilgaard & Lauritzen, 2009). However, there is no clear evidence that shows amiloride is an effective choice for migraine treatment. Amiloride is currently recruiting a Phase 2 clinical trial to evaluate its efficacy in the prophylaxis of migraine with aura in adults (NCT04063540).

5.3.5 | Kallikrein blockers

IONIS-PKKRx

The notion of creating 'antisense' oligonucleotide-based drugs, first enunciated in 1978 (Wu et al., 2004), is seductive as the forces that

determine whether an oligonucleotide binds to its cognate RNA sequence, Watson–Crick hybridisation, are well understood and as such drugs should, in principle, be much more specific than conventional low MW drugs. **Bradykinin** has been shown to produce both excitation and mechanical sensitisation of somatic (Stephenson & Zamecnik, 1978) and meningeal nociceptors (Steen et al., 1992). Migraine, or vascular, headache has been hypothesised by some investigators to be caused by cerebral arterial dilation and stimulation of pain receptors associated with the vasculature (Strassman et al., 1996). Based on these investigations, it has been hypothesised that bradykinin may be involved in the development of vascular headache, through the conversion of endogenous brain kininogens to bradykinin and subsequent bradykinin-dependent cerebral arterial dilation and bradykinin-dependent stimulation of pain fibres (Caviness & O'Brien, 1980). Ionis-PKKRx is an antisense oligonucleotide that targets **KLKB1** (plasma kallikrein), which leads to a decrease in bradykinin biosynthesis. Ionis-PKKRx recently completed a Phase 2 clinical trial evaluating the safety, tolerability, and changes in the number of migraine and headache days in adult patients (NCT03108469).

5.4 | Medication-overuse headache

Medication-overuse headache (MOH) is defined as a headache occurring for 15 or more days·per month, in a patient with a pre-existing primary headache and develops as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days·per month, depending on the medication) for more than 3 months (Headache Classification Committee of the International Headache Society, 2018). A recent epidemiological population-based study in Denmark reported a prevalence of 2% in 55,000 respondents (Westergaard et al., 2020). MOH is classified as ergotamine-overuse headache, triptan-overuse headache, analgesic-overuse headache, opioid-overuse headache, combination-medication-overuse headache and probable MOH (Headache Classification Committee of the International Headache Society, 2018).

6 | CONCLUSION

In this article we have systematically analysed the trends of migraine drug development both qualitatively and quantitatively and described each of the drug classes, MOAs, clinical trials and new treatments. We identified two major classes of FDA-approved drugs for the treatment of acute migraine, which include antimigraine and anti-inflammatory acting drugs. Four primary classes for chronic migraine were identified: anti-migraine, anti-convulsant, cardiovascular and neuromodulatory drugs. In comparison, therapeutic classes in clinical studies for acute migraine treatment also include steroidal acting drugs, whereas chronic migraine also includes diuretic and anticonvulsant acting drugs.

Although the first migraine drugs came into the market in the 1970s, the development of migraine therapeutics has significantly intensified significantly during the last 3 years as shown by our analysis of trends in drug development between 1970 and 2020. Overall, the drugs for migraine treatment approved in the last 50 years are a heterogeneous group of therapeutic agents characterised by widely different MOAs. This is also reflected in an increase in our understanding of the many different mechanisms, proposed to be important for migraine.

In this analysis, we can see that there are two time periods characterised by more intense drug development activities for acute migraine. The first time frame at the end of the last century between 1996 and 2002 comprises the introduction of several 5-HT receptor agonists on the market, such as zolmitriptan and rizatriptan. The second important developmental period was observed very recently between 2018 and 2020 with the approval of drugs targeting the CGRP receptor (gepants) and the 5-HT_{1F} receptor (ditans). The latest achievements made regarding novel therapeutic agents for acute migraine reflect the recent advances made in the understanding of CGRP and 5-HT_{1F} receptor action in migraine pathogenesis. Major approvals prompting this development include rimegepant, lasmiditan and several similarly acting products.

Treatment of chronic migraine is somewhat different, and we observed the highest drug developmental activity in the most recent times. Approximately half of all drugs approved within the last 50 years have entered the market within the last decade. Our analyses show that many approvals for the treatment of chronic migraine were given to repurposed drugs that were initially approved for other indications. Drug groups falling in this category include antihypertensives such as β-adrenoceptor antagonists, anticonvulsants or, more recently, botulinum toxin A. Compounds falling in these drug groups confer their beneficial effects in migraine by targeting a relatively broad range of different molecular entities and different mechanisms, which are up to now only partly understood concerning the disease.

Drug approvals in chronic migraine made in the last 3 years are dominated by compounds targeting the CGRP system. The successful outcomes from studies with antibodies targeting CGRP or its receptor have driven pharmaceutical companies to transform the migraine drug developmental landscape towards specific anti-migraine-acting drugs. The development of new technology platforms to address endogenous soluble ligands such as CGRP as drug targets is likely to enhance this development further (Attwood et al., 2020). Furthermore, we see that the number of trials for chronic migraine is increasing. One clear aim is to widen the indication for these drugs in different demographics, for example, in children and adolescents, as well as certain migraine subtypes and usability as both acute and prophylactic treatment options.

Several new treatments have been used in clinical trials. This includes targeting the kallikrein–bradykinin system based on antisense oligo technology. Cardiovascular-acting drugs function through various MOAs, such as inhibiting calcium channels, AT_1 receptors and ASICs, and are undergoing clinical trials for their vasodilating, antihypoxic and pleiotropic effects of these drugs as beneficial mechanisms against chronic migraine. Furthermore, recent academically

driven studies have focused on the feasibility of using local and general anaesthetics in acute migraine. These trends are an indicator of current efforts to further widen the spectrum of different therapeutic options for acute and chronic migraines.

This analysis highlights the trend towards a higher number and wider spectrum of therapeutic agents tested for the treatment of acute and chronic migraines. This also reflects considerable progress in understanding the pathogenic processes underlying migraine that has been gained in recent years. Given that the non-responder rate is relatively high, even for novel anti-migraine therapeutic agents targeting the CGRP system is approximately 30% (Do et al., 2019; Wrobel Goldberg & Silberstein, 2015). Thus, consideration of a wider spectrum of drug targets and classes is important for designing individually adapted therapy for patients with migraine.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Fabbro et al., 2019; Alexander, Mathie et al., 2019).

ACKNOWLEDGEMENTS

H.B.S. was supported by the Swedish Research Foundation (Vetenskapsrådet; 2013-02892), the Swedish Brain Research Foundation (Hjärnfonden; 2019-01066) and the Novo Nordisk Foundation (Novo Nordisk Fonden; 0063805). J.M. is supported by the Svenska Läkaresällskapet (SLS-935235).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

REFERENCES

Ailani, J., Lipton, R. B., Hutchinson, S., Knievel, K., Lu, K., Butler, M., Yu, S. Y., Finnegan, M., Severt, L., & Trugman, J. M. (2020). Long-term safety evaluation of ubrogepant for the acute treatment of migraine: Phase 3, randomized, 52-week extension trial. *Headache*, *60*(1), 141–152. https://doi.org/10.1111/head.13682

Akerman, S., & Goadsby, P. J. (2005). Topiramate inhibits trigeminovascular activation: An intravital microscopy study. *British Journal of Pharmacology*, *146*(1), 7–14. https://doi.org/10.1038/sj.bjp.0706290

Akopian, A. N., Chen, C. C., Ding, Y., Cesare, P., & Wood, J. N. (2000). A new member of the acid-sensing ion channel family. *Neuroreport*, *11*(10), 2217–2222. https://doi.org/10.1097/00001756-200007140-00031

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., & Pawson, A. J. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *British Journal of Pharmacology*, *176*, S21–S141. https://doi.org/10.1111/bph.14748

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., & Southan, C. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes. *British Journal of Pharmacology*, *176*, S297–S396. https://doi.org/10.1111/bph.14752

Alexander, S. P. H., Mathie, A., Peters, J. A., Veale, E. L., Striessnig, J., Kelly, E., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Sharman, J. L. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Ion channels. *British Journal of Pharmacology*, *176*, S142–S228. https://doi.org/10.1111/bph.14749

Amery, W. K. (1987). The oxygen theory of migraine. In J. N. Blau (Ed.), *Migraine: Clinical, therapeutic, conceptual and research aspects* (pp. 403–431). Chapman & Hall.

Ansell, E., Fazzone, T., Festenstein, R., Johnson, E. S., Thavapalan, M., Wilkinson, M., & Wozniak, I. (1988). Nimodipine in migraine prophylaxis. *Cephalalgia*, *8*(4), 269–272. https://doi.org/10.1046/j.1468-2982.1988.0804269.x

Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Southan, C., Sharman, J. L., Campo, B., Cavanagh, D. R., Alexander, S. P. H., Davenport, A. P., Spedding, M., Davies, J. A., & NC-IUPHAR. (2019). The IUPHAR/BPS Guide to PHARMACOLOGY in 2020: Extending immunopharmacology content and introducing the IUPHAR/MMV Guide to MALARIA PHARMACOLOGY. *Nucleic Acids Research*, *48*(D1), D1006–D1021. https://doi.org/10.1093/nar/gkz951

Artemenko, A. R., Kurenkov, A. L., Filatova, E. G., Nikitin, S. S., Kaube, H., & Katsarava, Z. (2008). Effects of topiramate on migraine frequency and cortical excitability in patients with frequent migraine. *Cephalalgia*, *28*(3), 203–208. https://doi.org/10.1111/j.1468-2982.2007.01491.x

Attwood, M. M., Jonsson, J., Rask-Andersen, M., & Schiöth, H. B. (2020). Soluble ligands as drug targets. *Nature Reviews Drug Discovery*, *19*(10), 695–710. https://doi.org/10.1038/s41573-020-0078-4

Attwood, M. M., Rask-Andersen, M., & Schiöth, H. B. (2018). Orphan drugs and their impact on pharmaceutical development. *Trends in Pharmacological Sciences*, *39*(6), 525–535. https://doi.org/10.1016/j.tips.2018.03.003 Erratum in: Trends in Pharmacological Sciences, 2018 Dec, 39(12), 1077.

Aurora, S. K., Dodick, D. W., Turkel, C. C., DeGryse, Silberstein, S. D., Lipton, R. B., Diener, H. C., Brin, M. F., & PREEMPT 1 Chronic Migraine Study Group. (2010). OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*, *30*(7), 793–803. https://doi.org/10.1177/0333102410364676

Avcu, N., Doğan, N. Ö., Pekdemir, M., Yaka, E., Yılmaz, S., Alyeşil, C., & Akalın, L. E. (2017). Intranasal lidocaine in acute treatment of migraine: A randomized controlled trial. *Annals of Emergency Medicine*, *69*(6), 743–751. https://doi.org/10.1016/j.annemergmed.2016.09.031

Bartsch, T., & Goadsby, P. J. (2002). Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain*, *125*(7), 1496–1509. https://doi.org/10.1093/brain/awf166

Benemei, S., De Cesaris, F., Fusi, C., Rossi, E., Lupi, C., & Geppetti, P. (2013). TRPA1 and other TRP channels in migraine. *The Journal of Headache and Pain*, *14*(1), 71. https://doi.org/10.1186/1129-2377-14-71

Bolay, H., Reuter, U., Dunn, A. K., Huang, Z., Boas, D. A., & Moskowitz, M. A. (2002). Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nature Medicine*, *8*(2), 136–142. https://doi.org/10.1038/nm0202-136

Burstein, R., Noseda, R., & Borsook, D. (2015). Migraine: Multiple processes, complex pathophysiology. *The Journal of Neuroscience: The*

Official Journal of the Society for Neuroscience, *35*(17), 6619–6629. https://doi.org/10.1523/JNEUROSCI.0373-15.2015

Burstein, R., Zhang, X., Levy, D., Aoki, K. R., & Brin, M. F. (2014). Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: Therapeutic implications for migraine and other pains. *Cephalalgia*, *34*(11), 853–869. https://doi.org/10.1177/0333102414527648

Cadiou, H., Studer, M., Jones, N. G., Smith, E. S., Ballard, A., McMahon, S. B., & McNaughton, P. A. (2007). Modulation of acid-sensing ion channel activity by nitric oxide. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience.*, *27*(48), 13251–13260. https://doi.org/10.1523/JNEUROSCI.2135-07.2007

Caviness, V. S. Jr., & O'Brien, P. (1980). Current concepts. *Headache. The New England Journal of Medicine*, *302*(8), 446–450. https://doi.org/10.1056/NEJM198002213020806

Charles, A. (2013). The evolution of a migraine attack—A review of recent evidence. *Headache*, *53*(2), 413–419. https://doi.org/10.1111/head.12026

Conway, C. M., Croop, R., Dubowchik, G. M., Coric, V., & Lipton, R. B. (2019). Cardiovascular safety of rimegepant 75 mg in 3 randomized clinical trials and systematic evaluations from in vitro, ex vivo, and in vivo nonclinical assays. Retrieved from https://www.biohavenpharma.com/sites/default/files/documents/rimegepant-cv-safety-2019-ahs.pdf

Coppola, G., Di Renzo, A., Tinelli, E., Di Lorenzo, C., Di Lorenzo, G., Parisi, V., Serrao, M., Schoenen, J., & Pierelli, F. (2016). Thalamo-cortical network activity during spontaneous migraine attacks. *Neurology*, *87*(20), 2154–2160. https://doi.org/10.1212/WNL.0000000000003327

Croop, R., Ivans, A., Stock, D., Hould, J., Morris, B. A., Stringfellow, J., Jensen, C. M., Moulin, J. A., Larouche, R., Tanguay, M., & Coric, V. (2018). A phase 1 study to evaluate the bioequivalence of oral tablet and orally dissolving tablet formulations of rimegepant, a small molecule CGRP receptor antagonist. Retrieved from https://www.biohavenpharma.com/sites/default/files/documents/Rimegepant-Zydis-ODT-Bioequivalence-Phase-1-Study_AHS-2018-Late-Breaking-Poster-Presentation-1.pdf

Cuadrado, M. L., Aledo-Serrano, Á., Navarro, P., López-Ruiz, P., Fernández-de-Las-Peñas, C., González-Suárez, I., Orviz, A., & Fernández-Pérez, C. (2017). Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. *Cephalalgia*, *37*(9), 864–872. https://doi.org/10.1177/0333102416655159

Cutrer, F. M., Limmroth, V., & Moskowitz, M. A. (1997). Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia*, *17*(2), 93–100. https://doi.org/10.1046/j.1468-2982.1997.1702093.x

Dakhale, G. N., Sharma, V. S., Thakre, M. N., & Kalikar, M. (2019). Low-dose sodium valproate versus low-dose propranolol in prophylaxis of common migraine headache: A randomized, prospective, parallel, open-label study. *Indian Journal of Pharmacology*, *51*(4), 255–262. https://doi.org/10.4103/ijp.IJP_457_18

Denuelle, M., Fabre, N., Payoux, P., Chollet, F., & Geraud, G. (2007). Hypothalamic activation in spontaneous migraine attacks. *Headache*, *47*(10), 1418–1426. https://doi.org/10.1111/j.1526-4610.2007.00776.x

Depre, C., Antalik, L., Starling, A., Koren, M., Eisele, O., Lenz, R. A., & Mikol, D. D. (2018). A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache*, *58*(5), 715–723. https://doi.org/10.1111/head.13316

Derry, C. J., Derry, S., & Moore, R. A. (2014). Sumatriptan (all routes of administration) for acute migraine attacks in adults—Overview of Cochrane reviews. *The Cochrane Database of Systematic Reviews*, *2014*(5), CD009108. https://doi.org/10.1002/14651858.CD009108.pub2

Diener, H. C., Dodick, D. W., Aurora, S. K., Turkel, C. C., DeGryse, R. E., Lipton, R. B., Silberstein, S. D., Brin, M. F., & PREEMPT 2 Chronic Migraine Study Group. (2010). OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*, *30*(7), 804–814. https://doi.org/10.1177/0333102410364677

Diener, H. C., Matias-Guiu, J., Hartung, E., Pfaffenrath, V., Ludin, H., Nappi, G., & de Beukelaar, F. (2002). Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: A comparison with propranolol 160 mg daily. *Cephalalgia*, *22*(3), 209–221. https://doi.org/10.1046/j.1468-2982.2002.t01-1-00309.x

Do, T. P., Guo, S., & Ashina, M. (2019). Therapeutic novelties in migraine: New drugs, new hope? *The Journal of Headache and Pain*, *20*, 37. https://doi.org/10.1186/s10194-019-0974-3

Dodick, D. W. (2004). Indomethacin-responsive headache syndromes. *Current Pain and Headache Reports*, *8*(1), 19–26. https://doi.org/10.1007/s11916-004-0036-6

Dodick, D. W., Freitag, F., Banks, J., Saper, J., Xiang, J., Rupnow, M., Greenberg, S. J., Hulihan, J., & CAPSS-277 Investigator Group. (2009). Topiramate versus amitriptyline in migraine prevention: A 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clinical Therapeutics*, *31*(3), 542–559. https://doi.org/10.1016/j.clinthera.2009.03.020

Dohi, Y., Ohashi, M., Sugiyama, M., Takase, H., Sato, K., & Ueda, R. (2003). Candesartan reduces oxidative stress and inflammation in patients with essential hypertension. *Hypertension Research: Official Journal of the Japanese Society of Hypertension*, *26*(9), 691–697. https://doi.org/10.1291/hypres.26.691

Durley, Y., Cubberley, R. B., & Thomas, S. (1981). Antihypertensive effect of oral timolol maleate and hydrochlorothiazide once daily compared with hydrochlorothiazide once daily. *American Journal of Hospital Pharmacy*, *38*(8), 1161–1164.

Dussor, G. (2014). Serotonin, $5HT_1$ agonists, and migraine: New data, but old questions still not answered. *Current Opinion in Supportive and Palliative Care*, *8*(2), 137–142. https://doi.org/10.1097/SPC.0000000000000044

Dussor, G. (2015). ASICs as therapeutic targets for migraine. *Neuropharmacology*, *94*, 64–71. https://doi.org/10.1016/j.neuropharm.2014.12.015

Edvinsson, L. (2017). The trigeminovascular pathway: Role of CGRP and CGRP receptors in migraine. *Headache: The Journal of Head and Face Pain*, *57*(Suppl. 2), 47–55. https://doi.org/10.1111/head.13081

Edvinsson, L., Haanes, K. A., Warfvinge, K., & Krause, D. N. (2018). CGRP as the target of new migraine therapies—Successful translation from bench to clinic. *Nature Reviews Neurology*, *14*(6), 338–350. https://doi.org/10.1038/s41582-018-0003-1

Edvinsson, L., & Linde, M. (2010). New drugs in migraine treatment and prophylaxis: Telcagepant and topiramate. *Lancet*, *376*(9741), 645–655. https://doi.org/10.1016/S0140-6736(10)60323-6

Evers, S., Afra, J., Frese, A., Goadsby, P. J., Linde, M., May, A., Sándor, P. S., & European Federation of Neurological Societies. (2009). EFNS guideline on the drug treatment of migraine—Revised report of an EFNS task force. *European Journal of Neurology*, *16*(9), 968–981. https://doi.org/10.1111/j.1468-1331.2009.02748.x

Ferrari, M. D., Goadsby, P. J., Roon, K. I., & Lipton, R. B. (2002). Triptans (serotonin, $5\text{-}HT_{1B/1D}$ agonists) in migraine: Detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*, *22*(8), 633–658. https://doi.org/10.1046/j.1468-2982.2002.00404.x

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2

Giffin, N. J., Ruggiero, L., Lipton, R. B., Silberstein, S. D., Tvedskov, J. F., Olesen, J., Altman, J., Goadsby, P. J., & Macrae, A. (2003). Premonitory symptoms in migraine: An electronic diary study. *Neurology*, *60*(6), 935–940. https://doi.org/10.1212/01.wnl.0000052998.58526.a9

Goadsby, P. J., & Classey, J. D. (2003). Evidence for serotonin (5-HT)$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptor inhibitory effects on trigeminal neurons with craniovascular input. *Neuroscience*, *122*(2), 491–498. https://doi.org/10.1016/s0306-4522(03)00570-0

Goadsby, P. J., Dodick, D. W., Ailani, J., Trugman, J. M., Finnegan, M., Lu, K., & Szegedi, A. (2020). Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: A double-blind, randomised phase 2b/3 trial. *The Lancet. Neurology.*, *19*(9), 727–737. https://doi.org/10.1016/S1474-4422(20)30234-9

Goadsby, P. J., Edvinsson, L., & Ekman, R. (1990). Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Annals of Neurology*, *28*(2), 183–187. https://doi.org/10.1002/ana.410280213

Goadsby, P. J., Holland, P. R., Martins-Oliveira, M., Hoffmann, J., Schankin, C., & Akerman, S. (2017). Pathophysiology of migraine: A disorder of sensory processing. *Physiological Reviews*, *97*(2), 553–622. https://doi.org/10.1152/physrev.00034.2015

Goadsby, P. J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J. H., Zhang, F., Sapra, S., Picard, H., Mikol, D. D., & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. *The New England Journal of Medicine*, *377*(22), 2123–2132. https://doi.org/10.1056/NEJMoa1705848

Goadsby, P. J., Wietecha, L. A., Dennehy, E. B., Kuca, B., Case, M. G., Aurora, S. K., & Gaul, C. (2019). Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*, *142*(7), 1894–1904. https://doi.org/10.1093/brain/awz134

Groth, W., Blume, A., Gohlke, P., Unger, T., & Culman, J. (2003). Chronic pretreatment with candesartan improves recovery from focal cerebral ischaemia in rats. *Journal of Hypertension*, *21*(11), 2175–2182. https://doi.org/10.1097/00004872-200311000-00028

Harriott, A. M., Takizawa, T., Chung, D. Y., & Chen, S. P. (2019). Spreading depression as a preclinical model of migraine. *The Journal of Headache and Pain*, *20*(1), 45. https://doi.org/10.1186/s10194-019-1001-4

Hay, D. L. (2019). CGRP receptor biology: Is there more than one receptor? *Handbook of Experimental Pharmacology*, *255*, 13–22. https://doi.org/10.1007/164_2018_131

Hay, D. L., Garelja, M. L., Poyner, D. R., & Walker, C. S. (2018). Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. *British Journal of Pharmacology*, *175*(1), 3–17. https://doi.org/10.1111/bph.14075

Headache Classification Committee of the International Headache Society (IHS). (2018). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, *38*(1), 1–211. https://doi.org/10.1177/0333102417738202

Herd, C. P., Tomlinson, C. L., Rick, C., Scotton, W. J., Edwards, J., Ives, N., Clarke, C. E., & Sinclair, A. (2018). Botulinum toxins for the prevention of migraine in adults. *The Cochrane Database of Systemic Reviews*, *6*(6), CD011616. https://doi.org/10.1002/14651858.CD011616.pub2

Hesselager, M., Timmermann, D. B., & Ahring, P. K. (2004). pH dependency and desensitization kinetics of heterologously expressed combinations of acid-sensing ion channel subunits. *The Journal of Biological Chemistry*, *279*(12), 11006–11015. https://doi.org/10.1074/jbc.M313507200

Hill, R. G., & Salt, T. E. (1982). An ionophoretic study of the responses of rat caudal trigeminal nucleus neurones to non-noxious mechanical sensory stimuli. *The Journal of Physiology*, *327*, 65–78. https://doi.org/10.1113/jphysiol.1982.sp014220

Ho, T. W., Connor, K. M., Zhang, Y., Pearlman, E., Koppenhaver, J., Fan, X., Lines, C., Edvinsson, L., Goadsby, P. J., & Michelson, D. (2014). Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*, *83*(11), 958–966. https://doi.org/10.1212/WNL.0000000000000771

Hoffmann, U., Sukhotinsky, I., Eikermann-Haerter, K., & Ayata, C. (2013). Glucose modulation of spreading depression susceptibility. *Journal of Cerebral Blood Flow & Metabolism*, *33*(2), 191–195. https://doi.org/10.1038/jcbfm.2012.132

Holton, C. M., Strother, L. C., Dripps, I., Pradhan, A. A., Goadsby, P. J., & Holland, P. R. (2020). Acid-sensing ion channel 3 blockade inhibits durovascular and nitric oxide-mediated trigeminal pain. *British Journal of Pharmacology*, *177*(11), 2478–2486. https://doi.org/10.1111/bph.14990

Iacobucci, G. J., Visnjevac, O., Pourafkari, L., & Nader, N. D. (2017). Ketamine: An update on cellular and subcellular mechanisms with implications for clinical practice. *Pain Physician*, *20*(2), E285–E301.

Johnson, K. W., Schaus, J. M., Durkin, M. M., Audia, J. E., Kaldor, S. W., Flaugh, M. E., Adham, N., Zgombick, J. M., Cohen, M. L., Branchek, T. A., & Phebus, L. A. (1997). 5-HT$_{1F}$ receptor agonists inhibit neurogenic dural inflammation in guinea pigs. *Neuroreport*, *8*(9–10), 2237–2240. https://doi.org/10.1097/00001756-199707070-00029

Karatas, H., Erdener, S. E., Gursoy-Ozdemir, Y., Lule, S., Eren-Koçak, E., Sen, Z. D., & Dalkara, T. (2013). Spreading depression triggers headache by activating neuronal Panx1 channels. *Science*, *339*(6123), 1092–1095. https://doi.org/10.1126/science.1231897

Karsan, N., Gonzales, E. B., & Dussor, G. (2018). Targeted acid-sensing ion channel therapies for migraine. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *15*(2), 402–414. https://doi.org/10.1007/s13311-018-0619-2

Karsan, N., Palethorpe, D., Rattanawong, W., Marin, J. C., Bhola, R., & Goadsby, P. J. (2018). Flunarizine in migraine-related headache prevention: Results from 200 patients treated in the UK. *European Journal of Neurology*, *25*(6), 811–817. https://doi.org/10.1111/ene.13621

Karsan, N., Prabhakar, P., & Goadsby, P. J. (2016). Characterising the premonitory stage of migraine in children: A clinic-based study of 100 patients in a specialist headache service. *The Journal of Headache and Pain*, *17*(1), 94. https://doi.org/10.1186/s10194-016-0689-7

Kashipazha, D., Nakhostin-Mortazavi, A., Mohammadianinejad, S. E., Bahadoram, M., Zandifar, S., & Tarahomi, S. (2014). Preventive effect of greater occipital nerve block on severity and frequency of migraine headache. *Global Journal of Health Science*, *6*(6), 209–213. https://doi.org/10.5539/gjhs.v6n6p209

Kelman, L. (2007). The triggers or precipitants of the acute migraine attack. *Cephalalgia*, *27*(5), 394–402. https://doi.org/10.1111/j.1468-2982.2007.01303.x

Khazaei, M., Hosseini Nejad Mir, N., Yadranji Aghdam, F., Taheri, M., & Ghafouri-Fard, S. (2019). Effectiveness of intravenous dexamethasone, metoclopramide, ketorolac, and chlorpromazine for pain relief and prevention of recurrence in the migraine headache: A prospective double-blind randomized clinical trial. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *40*(5), 1029–1033. https://doi.org/10.1007/s10072-019-03766-x

Labastida-Ramírez, A., Rubio-Beltrán, E., Haanes, K. A., Chan, K. Y., Garrelds, I. M., Johnson, K. W., Danser, A. H. J., Villalón, C. M., & MaassenVanDenBrink, A. (2020). Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. *Pain*, *161*(5), 1092–1099. https://doi.org/10.1097/j.pain.0000000000001801

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., Feder, A., Iosifescu, D. V., Charney, D. S., & Murrough, J. W. (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry*, *76*(12), 970–976. https://doi.org/10.1016/j.biopsych.2014.03.026

Lassen, L. H., Haderslev, P. A., Jacobsen, V. B., Iversen, H. K., Sperling, B., & Olesen, J. (2002). CGRP may play a causative role in migraine. *Cephalalgia*, *22*(1), 54–61. https://doi.org/10.1046/j.1468-2982.2002.00310.x

Lauritsen, C., Mazuera, S., Lipton, R. B., & Ashina, S. (2016). Intravenous ketamine for subacute treatment of refractory chronic migraine: A case series. *The Journal of Headache and Pain*, *17*(1), 106. https://doi.org/10.1186/s10194-016-0700-3

Lauritzen, M., & Hansen, A. J. (1992). The effect of glutamate receptor blockade on anoxic depolarization and cortical spreading depression. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *12*(2), 223–229. https://doi.org/10.1038/jcbfm.1992.32

Lazreg, S., Merad, Z., Nouri, M. T., Garout, R., Derdour, A., Ghroud, N., Kherroubi, R., Meziane, M., Belkacem, S., Ouhadj, O., Baudouin, C., & Tiar, M. (2018). Efficacy and safety of preservative-free timolol 0.1% gel in open-angle glaucoma and ocular hypertension in treatment-naïve patients and patients intolerant to other hypotensive medications. *Journal Français d'Ophtalmologie*, *41*(10), 945–954. https://doi.org/10.1016/j.jfo.2018.04.012

Leo, A. A. P., & Morison, R. S. (1945). Propagation of spreading cortical depression. *Journal of Neurophysiology*, *8*(1), 33–45. https://doi.org/10.1152/jn.1945.8.1.33

Linde, M., Gustavsson, A., Stovner, L. J., Steiner, T. J., Barré, J., Katsarava, Z., Lainez, J. M., Lampl, C., Lantéri-Minet, M., Rastenyte, D., Ruiz de la Torre, E., Tassorelli, C., & Andrée, C. (2012). The cost of headache disorders in Europe: The Eurolight project. *European Journal of Neurology*, *19*(5), 703–711. https://doi.org/10.1111/j.1468-1331.2011.03612.x

Linde, M., Mulleners, W. M., Chronicle, E. P., & McCrory, D. C. (2013a). Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. *The Cochrane Database of Systematic Reviews*, *6*, CD010608. https://doi.org/10.1002/14651858.CD010608

Linde, M., Mulleners, W. M., Chronicle, E. P., & McCrory, D. C. (2013b). Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database of Systematic Reviews*, *2013*(6), CD010610. https://doi.org/10.1002/14651858.CD010610

Lipton, R. B., Goldstein, J., Baggish, J. S., Yataco, A. R., Sorrentino, J. V., & Quiring, J. N. (2005). Aspirin is efficacious for the treatment of acute migraine. *Headache*, *45*(4), 283–292. https://doi.org/10.1111/j.1526-4610.2005.05065.x

Louis, P. (1981). A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium®) in migraine. *Headache*, *21*(6), 235–239. https://doi.org/10.1111/j.1526-4610.1981.hed2106235.x

Ma, Q. P., Hill, R., & Sirinathsinghji, D. (2001). Colocalization of CGRP with 5-$HT_{1B/1D}$ receptors and substance P in trigeminal ganglion neurons in rats. *The European Journal of Neuroscience*, *13*(11), 2099–2104. https://doi.org/10.1046/j.0953-816x.2001.01586.x

MaassenVanDenBrink, A., Meijer, J., Villalón, C. M., & Ferrari, M. D. (2016). Wiping out CGRP: Potential cardiovascular risks. *Trends in Pharmacological Sciences*, *37*(9), 779–788. https://doi.org/10.1016/j.tips.2016.06.002

Maizels, M., & Geiger, A. M. (1999). Intranasal lidocaine for migraine: A randomized trial and open-label follow-up. *Headache*, *39*(8), 543–551. https://doi.org/10.1046/j.1526-4610.1999.3908543.x

Mamet, J., Baron, A., Lazdunski, M., & Voilley, N. (2002). Proinflammatory mediators, stimulators of sensory neuron excitability via the expression of acid-sensing ion channels. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *22*(24), 10662–10670. https://doi.org/10.1523/JNEUROSCI.22-24-10662.2002

Maniyar, F. H., Sprenger, T., Monteith, T., Schankin, C., & Goadsby, P. J. (2014). Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*, *137*(1), 232–241. https://doi.org/10.1093/brain/awt320

Manoukian, R., Sun, H., Miller, S., Shi, D., Chan, B., & Xu, C. (2019). Effects of monoclonal antagonist antibodies on calcitonin gene-related peptide receptor function and trafficking. *The Journal of Headache and Pain*, *20*(1), 44. https://doi.org/10.1186/s10194-019-0992-1

Marcus, R., Goadsby, P. J., Dodick, D., Stock, D., Manos, G., & Fischer, T. Z. (2014). BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*, *34*(2), 114–125. https://doi.org/10.1177/0333102413500727

Markowitz, S., Saito, K., & Moskowitz, M. A. (1987). Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. *Journal of Neuroscience*, *7*(12), 4129–4136. https://doi.org/10.1523/JNEUROSCI.07-12-04129.1987

Martella, G., Costa, C., Pisani, A., Cupini, L. M., Bernardi, G., & Calabresi, P. (2008). Antiepileptic drugs on calcium currents recorded from cortical and PAG neurons: Therapeutic implications for migraine. *Cephalalgia*, *28*(12), 1315–1326. https://doi.org/10.1111/j.1468-2982.2008.01682.x

McLean, M. J., Bukhari, A. A., & Wamil, A. W. (2000). Effects of topiramate on sodium-dependent action-potential firing by mouse spinal cord neurons in cell culture. *Epilepsia*, *41*(S1), 21–24. https://doi.org/10.1111/j.1528-1157.2000.tb02166.x

Melo-Carrillo, A., Noseda, R., Nir, R. R., Schain, A. J., Stratton, J., Strassman, A. M., & Burstein, R. (2017). Selective inhibition of trigeminovascular neurons by fremanezumab: A humanized monoclonal anti-CGRP antibody. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *37*(30), 7149–7163. https://doi.org/10.1523/JNEUROSCI.0576-17.2017

Misra, U. K., Jose, M., & Kalita, J. (2004). Rofecoxib versus ibuprofen for acute treatment of migraine: A randomised placebo controlled trial. *Postgraduate Medical Journal*, *80*(950), 720–723. https://doi.org/10.1136/pgmj.2003.012393

Mizuno, K., Niimura, S., Tani, M., Saito, I., Sanada, H., Takahashi, M., Okazaki, K., Yamaguchi, M., & Fukuchi, S. (1992). Hypotensive activity of TCV-116, a newly developed angiotensin II receptor antagonist, in spontaneously hypertensive rats. *Life Sciences*, *51*(20), PL183–PL187. https://doi.org/10.1016/0024-3205(92)90627-2

Morgan, T. (2003). Renin, angiotensin, sodium and organ damage. *Hypertension Research: Official Journal of the Japanese Society of Hypertension*, *26*(5), 349–354. https://doi.org/10.1291/hypres.26.349

Motov, S., Rockoff, B., Cohen, V., Pushkar, I., Likourezos, A., McKay, C., Soleyman-Zomalan, E., Homel, P., Terentiev, V., & Fromm, C. (2015). Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: A randomized controlled trial. *Annals of Emergency Medicine*, *66*, 222–229.e1. https://doi.org/10.1016/j.annemergmed.2015.03.004

Munkholm, T. K., & Arendt-Nielsen, L. (2017). The interaction between NGF-induced hyperalgesia and acid-provoked pain in the infrapatellar fat pad and tibialis anterior muscle of healthy volunteers. *European Journal of Pain (London, England)*, *21*(3), 474–485. https://doi.org/10.1002/ejp.941

Noseda, R., Bernstein, C. A., Nir, R. R., Lee, A. J., Fulton, A. B., Bertisch, S. M., Hovaguimian, A., Cestari, D. M., Saavedra-Walker, R., Borsook, D., Doran, B. L., Buettner, C., & Burstein, R. (2016). Migraine photophobia originating in cone-driven retinal pathways. *Brain: A Journal of Neurology*, *139*(7), 1971–1986. https://doi.org/10.1093/brain/aww119

Olesen, J., Diener, H. C., Husstedt, I. W., Goadsby, P. J., Hall, D., Meier, U., Pollentier, S., Lesko, L. M., & BIBN 4096 BS Clinical Proof of Concept Study Group. (2004). Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *The New England Journal of Medicine*, *350*(11), 1104–1110. https://doi.org/10.1056/NEJMoa030505

Olesen, J., Lauritzen, M., Tfelt-Hansen, P., Henriksen, L., & Larsen, B. (1982). Spreading cerebral oligemia in classical- and normal cerebral blood flow in common migraine. *Headache*, *22*(6), 242–248. https://doi.org/10.1111/j.1526-4610.1982.hed2206242.x

Oswald, J. C., & Schuster, N. M. (2018). Lasmiditan for the treatment of acute migraine: A review and potential role in clinical practice. *Journal*

of Pain Research, *11*, 2221–2227. https://doi.org/10.2147/JPR.S152216

Owada, K. (2004). Efficacy of candesartan in the treatment of migraine in hypertensive patients. *Hypertension Research: Official Journal of the Japanese Society of Hypertension*, *27*(6), 441–446. https://doi.org/10.1291/hypres.27.441

Parikh, S. K., & Silberstein, S. D. (2019). Current status of antiepileptic drugs as preventive migraine therapy. *Current Treatment Options in Neurology*, *21*(4), 16. https://doi.org/10.1007/s11940-019-0558-1

Parsons, C. G., Danysz, W., & Quack, G. (1999). Memantine is a clinically well tolerated *N*-methyl-D-aspartate (NMDA) receptor antagonist—A review of preclinical data. *Neuropharmacology*, *38*(6), 735–767. https://doi.org/10.1016/s0028-3908(99)00019-2

Pietrobon, D., & Moskowitz, M. A. (2013). Pathophysiology of migraine. *Annual Review of Physiology*, *75*, 365–391. https://doi.org/10.1146/annurev-physiol-030212-183717

Pietrobon, D., & Moskowitz, M. A. (2014). Chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. *Nature Reviews Neuroscience*, *15*(6), 379–393. https://doi.org/10.1038/nrn3770

Piilgaard, H., & Lauritzen, M. (2009). Persistent increase in oxygen consumption and impaired neurovascular coupling after spreading depression in rat neocortex. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *29*(9), 1517–1527. https://doi.org/10.1038/jcbfm.2009.73

Pisanu, C., Lundin, E., Preisig, M., Gholam-Rezaee, M., Castelao, E., Pistis, G., Merikangas, K. R., Glaus, J., Squassina, A., del Zompo, M., Schiöth, H. B., & Mwinyi, J. (2020). Major depression subtypes are differentially associated with migraine subtype, prevalence and severity. *Cephalalgia*, *40*(4), 347–356. https://doi.org/10.1177/0333102419884935

Pisanu, C., Preisig, M., Castelao, E., Glaus, J., Cunningham, J. L., del Zompo, M., Merikangas, K. R., Schiöth, H. B., & Mwinyi, J. (2017). High leptin levels are associated with migraine with aura. *Cephalalgia*, *37*(5), 435–441. https://doi.org/10.1177/0333102416648650

Pomeroy, J. L., Marmura, M. J., Nahas, S. J., & Viscusi, E. R. (2017). Ketamine infusions for treatment refractory headache. *Headache*, *57*(2), 276–282. https://doi.org/10.1111/head.13013

Puledda, F., Goadsby, P. J., & Prabhakar, P. (2018). Treatment of disabling headache with greater occipital nerve injections in a large population of childhood and adolescent patients: A service evaluation. *The Journal of Headache and Pain*, *19*, 5. https://doi.org/10.1186/s10194-018-0835-5

Rao, A. S., Gelaye, B., Kurth, T., Dash, P. D., Nitchie, H., & Peterlin, B. L. (2016). A randomized trial of ketorolac vs sumatripan vs placebo nasal spray (KSPN) for acute migraine. *Headache*, *56*(2), 331–340. https://doi.org/10.1111/head.12767

Rask-Andersen, M., Almén, M. S., & Schiöth, H. B. (2011). Trends in the exploitation of novel drug targets. *Nature Reviews Drug Discovery*, *10*(8), 579–590. https://doi.org/10.1038/nrd3478

Rask-Andersen, M., Zhang, J., Fabbro, D., & Schiöth, H. B. (2014). Advances in kinase targeting: Current clinical use and clinical trials. *Trends in Pharmacological Sciences*, *35*(11), 604–620. https://doi.org/10.1016/j.tips.2014.09.007

Reed, K. L., Black, S. B., Banta, C. J. 2nd, & Will, K. R. (2010). Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: Initial experience. *Cephalalgia*, *30*(3), 260–271. https://doi.org/10.1111/j.1468-2982.2009.01996.x

Rizzoli, P. B. (2014). Emerging therapeutic options for acute migraine: Focus on the potential of lasmiditan. *Neuropsychiatric Disease and Treatment*, *10*, 547–552. https://doi.org/10.2147/NDT.S25531

Russel, M. B., Rasmussen, B. K., Fenger, K., & Olesen, J. (1996). Migraine without aura and migraine with aura are distinct clinical entities: A study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia: An International Journal of Headache*, *16*(4), 239–245. https://doi.org/10.1046/j.1468-2982.1996.1604239.x

Russo, A. F. (2015). Calcitonin gene-related peptide (CGRP): A new target for migraine. *Annual Review of Pharmacology and Toxicology*, *55*, 533–552. https://doi.org/10.1146/annurev-pharmtox-010814-124701

Sánchez-Porras, R., Santos, E., Schöll, M., Stock, C., Zheng, Z., Schiebel, P., Orakcioglu, B., Unterberg, A. W., & Sakowitz, O. W. (2014). The effect of ketamine on optical and electrical characteristics of spreading depolarizations in gyrencephalic swine cortex. *Neuropharmacology*, *84*, 52–61. https://doi.org/10.1016/j.neuropharm.2014.04.018

Schulte, L. H., Jürgens, T. P., & May, A. (2015). Photo-, osmo- and phonophobia in the premonitory phase of migraine: Mistaking symptoms for triggers? *The Journal of Headache and Pain*, *16*, 14. https://doi.org/10.1186/s10194-015-0495-7

Scott, L. J. (2020). Ubrogepant: First approval. *Drugs*, *80*(3), 323–328. https://doi.org/10.1007/s40265-020-01264-5 Erratum in: Drugs, 2020 Apr, 80(5), 523.

Shepheard, S., Edvinsson, L., Cumberbatch, M., Williamson, D., Mason, G., Webb, J., Boyce, S., Hill, R., & Hargreaves, R. (1999). Possible antimigraine mechanisms of action of the $5HT_{1F}$ receptor agonist LY334370. *Cephalalgia*, *19*(10), 851–858. https://doi.org/10.1046/j.1468-2982.1999.1910851.x

Shields, K. G., & Goadsby, P. J. (2005). Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: A role in migraine? *Brain*, *128*(1), 86–97. https://doi.org/10.1093/brain/awh298

Silberstein, S., Saper, J., Berenson, F., Somogyi, M., McCague, K., & D'Souza, J. (2008). Oxcarbazepine in migraine headache: A double-blind, randomized, placebo-controlled study. *Neurology*, *70*(7), 548–555. https://doi.org/10.1212/01.wnl.0000297551.27191.70

Silberstein, S. D., Dodick, D. W., Bigal, M. E., Yeung, P. P., Goadsby, P. J., Blankenbiller, T., Grozinski-Wolff, M., Yang, R., Ma, Y., & Aycardi, E. (2017). Fremanezumab for the preventive treatment of chronic migraine. *The New England Journal of Medicine*, *377*(22), 2113–2122. https://doi.org/10.1056/NEJMoa1709038

Silberstein, S. D., & Kori, S. H. (2013). Dihydroergotamine: A review of formulation approaches for the acute treatment of migraine. *CNS Drugs*, *27*(5), 385–394. https://doi.org/10.1007/s40263-013-0061-2

Sørensen, P. S., Hansen, K., & Olesen, J. (1986). A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalalgia*, *6*(1), 7–14. https://doi.org/10.1046/j.1468-2982.1986.0601007.x

Stankewitz, A., Aderjan, D., Eippert, F., & May, A. (2011). Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(6), 1937–1943. https://doi.org/10.1523/JNEUROSCI.4496-10.2011

Steen, K. H., Reeh, P. W., Anton, F., & Handwerker, H. O. (1992). Protons selectively induce lasting excitation and sensitization to mechanical stimulation of nociceptors in rat skin, in vitro. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *12*(1), 86–95. https://doi.org/10.1523/JNEUROSCI.12-01-00086.1992

Stellar, S., Ahrens, S. P., Meibohm, A. R., & Reines, S. A. (1984). Migraine prevention with timolol: A double-blind crossover study. *JAMA*, *252*(18), 2576–2580. https://doi.org/10.1001/jama.1984.03350180030025

Stephenson, M. L., & Zamecnik, P. C. (1978). Inhibition of Rous sarcoma viral RNA translation by a specific oligodeoxyribonucleotide. *Proceedings of the National Academy of Sciences of the United States of America*, *75*(1), 285–288. https://doi.org/10.1073/pnas.75.1.285

Storer, R. J., Akerman, S., & Goadsby, P. J. (2004). Calcitonin gene-related peptide (CGRP) modulates nociceptive trigeminovascular transmission in the cat. *British Journal of Pharmacology*, *142*(7), 1171–1118. https://doi.org/10.1038/sj.bjp.0705807

Strassman, A. M., Raymond, S. A., & Burstein, R. (1996). Sensitization of meningeal sensory neurons and the origin of headaches. *Nature*, *384*(6609), 560–564. https://doi.org/10.1038/384560a0

Summ, O., Holland, P. R., Akerman, S., & Goadsby, P. J. (2011). TRPV1 receptor blockade is ineffective in different in vivo models of migraine. *Cephalalgia*, *31*(2), 172–180. https://doi.org/10.1177/0333102410375626

Takano, T., Tian, G. F., Peng, W., Lou, N., Lovatt, D., Hansen, A. J., Kasischke, K. A., & Nedergaard, M. (2007). Cortical spreading depression causes and coincides with tissue hypoxia. *Nature Neuroscience*, *10*(6), 754–762. https://doi.org/10.1038/nn1902

Tallaksen-Greene, S. J., Young, A. B., Penney, J. B., & Beitz, A. J. (1992). Excitatory amino acid binding sites in the trigeminal principal sensory and spinal trigeminal nuclei of the rat. *Neuroscience Letters*, *141*(1), 79–83. https://doi.org/10.1016/0304-3940(92)90339-9

Tepper, S. J., Krege, J. H., Lombard, L., Asafu-Adjei, J. K., Dowsett, S. A., Raskin, J., Buchanan, A. S., & Friedman, D. I. (2019). Characterization of dizziness after lasmiditan usage: Findings from the SAMURAI and SPARTAN acute migraine treatment randomized trials. *Headache*, *59*(7), 1052–1062. https://doi.org/10.1111/head.13544 Erratum in: Headache, 2019 Nov, 59(10), 1875.

Tfelt-Hansen, P., Standnes, B., Kangasneimi, P., Hakkarainen, H., & Olesen, J. (1984). Timolol vs propranolol vs placebo in common migraine prophylaxis: A double-blind multicenter trial. *Acute Neurologica Scandinavica*, *69*(1), 1–8. https://doi.org/10.1111/j.1600-0404.1984.tb07772.x

Tronvik, E., Stovner, L. J., Helde, G., Sand, T., & Bovim, G. (2003). Prophylactic treatment of migraine with an angiotensin II receptor blocker: A randomized controlled trial. *JAMA*, *289*(1), 65–69. https://doi.org/10.1001/jama.289.1.65

Turner, L. C., Molgaard, C. A., Gardner, C. H., Rothrock, J. F., & Stang, P. E. (1995). Migraine trigger factors in a non-clinical Mexican-American population in San Diego county: Implications for etiology. *Cephalalgia*, *15*(6), 523–530. https://doi.org/10.1046/j.1468-2982.1995.1506523.x

Van Reempts, J., Borgers, M., Van Dael, L., Van Eyndhoven, J., & Van De Ven, M. (1983). Protection with flunarizine against hypoxic-ischaemic damage of the rat cerebral cortex. A quantitative morphologic assessment. *Archives Internationales de Pharmacodynamie et de Thérapie*, *262*(1), 76–88.

Vinson, D. R. (2002). Treatment patterns of isolated benign headache in US emergency departments. *Annals of Emergency Medicine*, *39*(3), 215–222. https://doi.org/10.1067/mem.2002.121400

Wang, T., Chen, N., Zhan, W., Liu, J., Zhang, J., Liu, Q., Huang, H., He, L., Zhang, J., & Gong, Q. (2015). Altered effective connectivity of posterior thalamus in migraine with cutaneous allodynia: A resting-state fMRI study with Granger causality analysis. *The Journal of Headache and Pain*, *17*, 17. https://doi.org/10.1186/s10194-016-0610-4

Wang, X., Li, W. G., Yu, Y., Xiao, X., Cheng, J., Zeng, W. Z., Peng, Z., Zhu, M. X., & Xu, T. L. (2013). Serotonin facilitates peripheral pain sensitivity in a manner that depends on the nonproton ligand sensing domain of ASIC3 channel. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *33*(10), 4265–4279. https://doi.org/10.1523/JNEUROSCI.3376-12.2013

Westergaard, M. L., Lau, C. J., Allesøe, K., Gjendal, S. T., & Jensen, R. H. (2020). Monitoring chronic headache and medication-overuse headache prevalence in Denmark. *Cephalalgia*, *40*(1), 6–18. https://doi.org/10.1177/0333102419876909

Wrobel Goldberg, S., & Silberstein, S. D. (2015). Targeting CGRP: A new era for migraine treatment. *CNS Drugs*, *29*(6), 443–452. https://doi.org/10.1007/s40263-015-0253-z

Wu, L. J., Duan, B., Mei, Y. D., Gao, J., Chen, J. G., Zhuo, M., Xu, L., Wu, M., & Xu, T. L. (2004). Characterization of acid-sensing ion channels in dorsal horn neurons of rat spinal cord. *The Journal of Biological Chemistry*, *279*(42), 43716–43724. https://doi.org/10.1074/jbc.M403557200

Yoshiyama, M., Omura, T., Takeuchi, K., Kim, S., Shimada, K., Yamagishi, H., Teragaki, M., Akioka, K., Iwao, H., & Yoshikawa, J. (2001). Angiotensin blockade inhibits increased JNKs, AP-1 and NF-κB DNA-binding activities in myocardial infarcted rats. *Journal of Molecular and Cellular Cardiology*, *33*(4), 799–810. https://doi.org/10.1006/jmcc.2001.1351

Younis, S., Christensen, C. E., Toft, N. M., Søborg, T., Amin, F. M., Hougaard, A., & Ashina, M. (2019). Investigation of distinct molecular pathways in migraine induction using calcitonin gene-related peptide and sildenafil. *Cephalalgia*, *39*(14), 1776–1788. https://doi.org/10.1177/0333102419882474

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Zobdeh, F., ben Kraiem, A., Attwood, M. M., Chubarev, V. N., Tarasov, V. V., Schiöth, H. B., & Mwinyi, J. (2021). Pharmacological treatment of migraine: Drug classes, mechanisms of action, clinical trials and new treatments. *British Journal of Pharmacology*, *178*(23), 4588–4607. https://doi.org/10.1111/bph.15657