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New Entries into the Migraine Market: 2018-2021

Egilius LH Spierings* and Mancia Ko

Boston Headache Institute, Boston PainCare, Waltham, Massachusetts, USA

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***Corresponding author:** Egilius LH Spierings, Boston Headache Institute, 85 First Avenue, Waltham, MA, USA

Abstract

Migraine is a chronic condition of recurring headaches, often severe and disabling, not in the least because of the associated gastrointestinal symptoms. The focus of its treatment is pharmacological, which we traditionally divide into abortive or acute and preventive or prophylactic. In the 4-year period, 2018-2021, the United States (US) Food and Drug Administration (FDA) approved twelve new entries into the migraine market, six for abortive treatment and six for preventive treatment, including one for both. Three of them are reformulations of already marketed medications, four are CGRP antibodies, three are small-molecule CGRP-receptor antagonists or gepants, and one is a serotonin-1F receptor agonist or ditan.

In this paper, we review the twelve new migraine entries in light of the abortive and preventive migraine medications marketed prior to 2018. We present the efficacy of four of the new entries for migraine abortion – the FDA approved the remaining two based on comparable bioavailability – and of all six of the new entries for migraine prevention, focusing on 2-hour pain-free and 50%-responder rates, respectively. We conclude that preventively we have made progress if only because of the (much) better tolerability of the CGRP antibodies and gepants, in comparison to the traditional oral preventive migraine medications. In terms of efficacy, we probably have made progress as well although supported by only one randomized, double-blinded, head-to-head comparative trial. Abortively, the three new chemical entities in the classes of gepants and ditans lack vasoconstrictor activity and, hence, we can prescribe them where the ergots and triptans are contraindicated. This is a step ahead in safety while tolerability and efficacy seem similar to that of the triptans, the mainstay in abortive migraine treatment.

Keywords: Atogepant; Celecoxib; Dihydroergotamine; Eptinezumab, Erenumab; Fremanezumab; Galcanezumab; Lasmiditan; Rimegepant; Sumatriptan; Ubrogepant; Episodic migraine; Chronic migraine; 2-hour pain-free rate; 50%-responder rate; Placebo-subtracted rate

Introduction

Migraine is a chronic condition of recurring headaches, often intense and disabling, not in the least because of the associated gastrointestinal symptoms. It is a common condition with a prevalence of up to 15% of the general population and a common reason for medical and neurological consultation. The focus of its treatment is pharmacological, which we traditionally divide into abortive, also called acute, and preventive, also called prophylactic. There is an indication for pharmacological *prescription* treatment in the majority of migraineurs, certainly from an abortive perspective.

As stated, migraine headaches tend to be intense and disabling and suffering through them regularly is detrimental to physical and mental health. It also likely promotes the occurrence of headaches over time and is a known factor in the "chronification" of migraine [1]. This process causes migraine headaches to progress over time from an episodic to a chronic presentation. In the chronic presentation, migraine headaches occur frequently, often daily or almost daily. It is a challenging condition to manage, also due to its association with multiple medical and psychiatric comorbidities [2].

Effective abortive treatment is the foundation of long-term migraine management, which tends to be an uphill battle without it. Pharmacological *prescription* treatment is generally necessary to accomplish truly effective abortive treatment. Its goal is to provide *full* relief of migraine headaches, that is, reduction of headache intensity to zero, within 2 hours of initiation. Only then, we can call it truly effective. We add preventive treatment to *effective* abortive treatment depending on the frequency of the headaches. We can best establish the need for this in dialogue with the patient because it requires the regular administration of medication and, hence, compliance.

A big step ahead in the abortive treatment of migraine, we made in the 1990s and early 2000s with the marketing approval of the triptans. It subsequently took almost two decades to make a similar, if not bigger, step ahead in the preventive treatment with the marketing approval of the CGRP antibodies. These are four of

the twelve new entries into the migraine market between 2018 and 2021.

In each of the 4 years between 2018 and 2021, the United States (US) Food and Drug Administration (FDA) approved three new migraine entries. Three of them are re-formulations, one of which did not have a migraine indication yet, namely, celecoxib. As mentioned, four of them are CGRP antibodies, with CGRP standing for calcitonin gene-related peptide. Three of the new entries are small-molecule CGRP-receptor antagonists or "gepants", and one is a serotonin-1F receptor agonist of the "ditan" class.

We will further discuss these twelve new entries into the migraine market below, predominantly drawing from the FDA-approved labeling, which, for reference purposes, we list at the end of the paper.

Abortive migraine market prior to 2018

The ergots comprised the first class of medications specifically marketed for migraine treatment. Relevant to the migraine market, the class consists of three medications: ergotamine, dihydroergotamine, and methysergide. Arthur Stoll isolated ergotamine at Sandoz Laboratories in Basel, Switzerland, in 1918. Sandoz Pharmaceuticals subsequently marketed it in 1921 under the brand name, Gynergen®, an injectable, to treat postpartum hemorrhage.

Physicians used ergotamine "off label" for the abortive treatment of migraine almost as soon as it became available. Medical luminaries like Harold G. Wolff, William G. Lennox, and John R. Graham studied its migraine-related pharmacology and its use in clinical practice [3]. Based on clinical work of the latter, Sandoz marketed the medication for migraine abortion in combination with caffeine, under the brand name, Cafergot® [4].

Arthur Stoll and Albert Hoffman synthesized a better-tolerated dehydrogenated derivative of ergotamine, dihydroergotamine, in 1943. Hoffman is a Swiss chemist particularly well known for synthesizing LSD and, through self-experimentation, discovering its psychedelic effects. Sandoz marketed dihydroergotamine for the abortive treatment of migraine in 1946 as an injectable (DHE 45®) and in 1997 as a liquid nasal spray (Migranal®).

The ergots, ergotamine and dihydroergotamine, are potent nonselective vasoconstrictors, initially thought to act directly on smooth muscle to cause vasoconstriction. The development of the receptor concept led to the alpha-adrenergic receptor as their agonistic target at higher concentrations and the serotonin-1-like receptor at lower concentrations. The latter receptor, now referred to as the serotonin-1B receptor, is the predominant target of the ergot successors, the triptans. As vasoconstrictors, the triptans, due to their receptor selectivity, are much more selective than the ergots. Due to their much smaller molecular structures, they also have much better bioavailability. Finally, their half-lives are generally much shorter, conveying much shorter therapeutic benefit.

Patrick P.A. Humphrey at Allen & Hanburys, a subsidiary of GlaxoSmithKline, developed the first triptan, sumatriptan. He also developed naratriptan, which along with frovatriptan is a longer-acting triptan. In addition, he developed two serotonin-3 receptor antagonists, odansetron and alosetron, for the treatment of nausea and diarrhea-predominant irritable bowel syndrome (IBS-D), respectively.

In the 1990s and early 2000s, seven triptans received marketing approval for migraine, and the FDA approved the sumatriptan injection for cluster headache as well (Table 1). In 2009, the first nonsteroidal anti-inflammatory drug or NSAID, diclofenac, received marketing approval specifically for the abortive treatment of migraine (Cambia®).

Table 1: The seven triptans with their brand names and years of marketing approval in the US.

Sumatriptan (Imitrex®): 1992
Naratriptan (Amerge®): 1992
Zolmitriptan (Zomig®): 1997
Rizatriptan (Maxalt®): 1998
Frovatriptan (Frova®): 2001
Almotriptan (Axert®): 2001
Eletriptan (Relpax®): 2002

Already prior to 2018, sumatriptan was available in three formulations, namely, tablet, nasal spray, and subcutaneous injection. The FDA approved the tablet in 1993 under the brand name, Imitrex®, and in combination with naproxen sodium in 2008 as Treximet®. Imitrex® became available in 1997 as a liquid nasal spray and in 2016 as a powder nasal spray under the brand name, Onzetra® Xsail®. The first formulation of Imitrex® approved was the subcutaneous injection in doses of 4 mg and 6 mg (1991). In 2016, the injection became available in a 3-mg dose as well, under the brand name, Zembrace®.

Preventive migraine market prior to 2018

The marketing of methysergide (Sansert®) in 1962 introduced migraine prevention in the treatment of migraine

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(Table 2). Sandoz Laboratories in Basel, Switzerland, developed the medication, a serotonin receptor antagonist, specifically for this purpose. As a derivative of LSD, which in turn is a derivative of ergometrine, it is also an ergot. Sandoz developed it based on the understanding derived from research conducted by the Italian migraine master, Federigo Sicuteri, that a "serotonin storm" causes the migraine attack. Unfortunately, fibrotic conditions emerged as a safety issue of methysergide, which ultimately led to its withdrawal from the market.

Table 2: Approved preventive migraine medications prior to 2018 with their brand names and years of approval.

Methysergide (Sansert®): 1962
Propranolol (Inderal®): 1967
Timolol (Blocadren®): 2001
Topiramate (Topamax®): 2004
Divalproex (Depakote®): 2008
OnabotulinumtoxinA (Botox®): 2010

In the meantime, the FDA provided propranolol (Inderal®) with marketing approval for migraine prevention, which occurred in 1967. In a clinical trial in patients with angina pectoris, Rabkin et al. [5] had found the beta-blocker effective in preventing, not only attacks of angina but also those of migraine.

There is good clinical-trial evidence for six beta-blockers in the preventive treatment of migraine. Apart from propranolol, these are atenolol, bisoprolol, metoprolol, nadolol, and timolol. However, the FDA only approved two of those six for migraine prevention, and these are propranolol and timolol. What sets those six beta-blockers apart from the others, which do not prevent migraine, is a lack partial agonist or intrinsic sympathomimetic activity [6].

Anticonvulsants have been around for over a century and a half, and we have used them for the treatment of chronic pain for 80 years. They made their way into the preventive treatment of migraine after the turn of the century with the approval of topiramate (Topamax®) in 2004 and divalproex (Depakote®) in 2008. Topiramate is currently the most widely prescribed preventive migraine medication but tolerability issues, especially related to cognition, often hamper its use.

Specifically for the preventive treatment of *chronic* migraine, onabotulinumtoxinA (Botox®) received marketing approval in 2010. From a regulatory perspective and related to this particular approval, we define chronic migraine as a minimum of 8 migraine headache days per month and a total headache burden of at least 15 days per month. When the total headache burden is 14 days or less per month, we refer to the condition as episodic migraine.

New entries for abortive migraine treatment

Table 3 lists the six new entries for abortive migraine treatment in the 2018-2021 timespan. Two of them had already received marketing approval for migraine, namely, dihydroergotamine and sumatriptan. Their new approvals concern reformulations for nasal administration, with the purpose of improved pharmacokinetics.

Table 3: Abortive migraine medications approved 2018-2021 with their brand names and years of approval.

Sumatriptan (Tosymra®): 2019
Lasmiditan (Reyvow®): 2019
Ubrogepant (Ubrelvy®): 2019
Rimegepant (Nurtec®): 2020
Celecoxib (Elyxyb®): 2020
Dihydroergotamine (Trudhesa®): 2021

Dihydroergotamine was already available as a nasal spray (Migranal®) and of sumatriptan, two nasal sprays were already available, one liquid (Imitrex®) and the other powder (Onzetra Xsail®). The new dihydroergotamine formulation (Trudhesa®) utilizes a device with a propellant to deliver the liquid medication high up in the nasal cavity for improved absorption. The dose is 1.45 mg (0.725 mg in each nostril), which the patient may repeat once after 1 hour. The FDA approved the medication based on its relative bioavailability compared to Migranal® and not on its own efficacy. Hence, in the labeling, the presented efficacy is that of Migranal® and not that of Trudhesa®.

Unfortunately, the same is true for the new formulation of sumatriptan (Tosymra®), which combines the medication with a membrane permeation enhancer. However, the difference is that the sumatriptan dose in Tosymra® is half that of the Imitrex®

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nasal spray (10 mg *versus* 20 mg). The patient may repeat this dose twice with intervals of at least 1 hour, with a maximum of 30 mg. The FDA based its approval on the relative bioavailability compared to the Imitrex® 4-mg subcutaneous injection. In accordance, the labeling presents the efficacy of the Imitrex® injection but, curiously, not of the 4-mg dose but of the 6-mg dose.

The third reformulation on the list concerns a medication that the FDA had not yet but has now approved for the abortive treatment of migraine, namely, celecoxib (Elyxyb®). It is an NSAID and the only one left on the market in the class of COX-2 prostaglandin synthesis inhibitors. Although it has better gastric tolerability than the NSAIDs, it shares the class warnings despite the proposed intermittent use for migraine. Specifically for abortive migraine treatment, the formulation is that of an oral solution with self-microemulsifying technology as solubility enhancer, to improve its absorption. The dose is 120 mg, which the patient can take just once daily for abortive migraine treatment.

Of the remaining three new entries, one is a ditan and the other two are gepants. The ditan, lasmiditan (Reyvow®), is the second one developed for the abortive treatment of migraine. The company, Eli Lilly, discontinued the development of the first one because of tolerability issues [7]. As a serotonin-IF receptor agonist, lasmiditan works presynaptically and inhibits the release of neuropeptides. This includes CGRP released from nociceptive nerve fibers (*vide infra*). Uniquely, lasmiditan works peripherally as well as centrally, due to its ability to pass the blood-brain barrier and enter the central nervous system. The downside of the latter is that it creates tolerability and safety issues.

In terms of tolerability, relatively common side effects of lasmiditan are dizziness and sedation, in the labeling reported in up to 17% and 7% of patients, respectively. These side effects present a safety concern in terms of driving and operating machinery, which the FDA restricts for 8 hours after its use. The medication has some addiction potential, which caused the US Drug Enforcement Agency (DEA) to schedule it as class V. The dose of lasmiditan is 50 mg, 100 mg, or 200 mg; the patient can take any of those dosages once daily for abortive migraine treatment.

Ubrogepant (Ubrelvy®) and rimegepant (Nurtec®) are small-molecule CGRP-receptor antagonists, approved for abortive migraine treatment in 2019 and 2020, respectively. The dose of ubrogepant is 50 mg or 100 mg, which the patient may repeat once after 2 hours with a maximum of 200 mg. The dose of rimegepant is 75 mg and its formulation is that of an orally disintegrating tablet, also referred to as ODT. The patient takes rimegepant once daily for abortive migraine treatment or once every other day for preventive treatment, placed in the mouth. There, the tablet disintegrates rapidly and the patient swallows the medication down, dissolved in saliva. We need to differentiate this kind of administration from sublingual or buccal, in which the medication is absorbed in the mouth; in case of an orally disintegrating tablet, it is absorbed in the small bowel.

CGRP is a neuropeptide, synthesized in and released by the primary sensory neurons involved in pain transmission, the so-called primary nociceptive neurons. The cell bodies of those pseudo-unipolar neurons reside in the sensory ganglia, including the trigeminal ganglia. Their axons split in peripheral and central branches shortly after emerging from the cell bodies, with CGRP released at both ends but with different functions. Centrally, the neuropeptide facilitates signal transmission from the primary to the secondary nociceptive neurons. Peripherally, it mediates the vasodilatory component of neurogenic inflammation (Aδ-fibers); substance P mediates its inflammatory component (C-fibers) [8].

The migraine medications that target the CGRP pathway, that is, the gepants and CGRP antibodies, do not affect the central function of CGRP. They do not cross the blood-brain barrier and, hence, do not enter the central nervous system. Peripherally, they antagonize the vasodilatory effect of CGRP in the context of neurogenic inflammation. They do so by binding to the CGRP molecule, also referred to as the CGRP ligand, or to the CGRP receptor, either way blocking activation of the receptor and the subsequent vasodilation.

New entries for preventive migraine treatment

Four of the new entries for migraine prevention are monoclonal antibodies directed against the CGRP ligand or the CGRP receptor. The antibodies directed against the CGRP ligand are fremanezumab (Ajovy®), galcanezumab (Emgality®), and eptinezumab (Vyepti®) (Table 4). The remaining one, erenumab (Aimovig®), is an antibody directed against the CGRP receptor. Either way, they act by blocking activation of the CGRP receptor directly or indirectly and, hence, the resulting vasodilation.

Table 4: Preventive migraine medications approved 2018-2021 with their brand names and years of approval.

Erenumab (Aimovig®): 2018
Fremanezumab (Ajovy®): 2018
Galcanezumab (Emgality®): 2018
Eptinezumab (Vyepti®): 2020
Rimegepant (Nurtec®): 2021
Atogepant (Qulipta®): 2021

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We administer the antibodies subcutaneously except eptinezumab, which we administer intravenously. We dose the subcutaneously administered antibodies monthly and one of them, fremanezumab, the FDA approved for quarterly dosing as well. The intravenously administered antibody, eptinezumab, we dose quarterly. The dose of erenumab is 70 mg, which we can increase to 140 mg. The dose of fremanezumab is 225 mg when administered monthly and 675 mg when administered quarterly. The dose of galcanezumab is 120 mg with a loading dose of 240 mg, to reach steady state within the first month of treatment. The dose of eptinezumab is 100 mg, which we can increase to 300 mg.

The two remaining new entries for migraine prevention, rimegepant (Nurtec®) and atogepant (Qulipta®) also target the CGRP pathway. However, they are small molecules, as opposed to the antibodies, and we refer to them as gepants. They block the CGRP receptor and by doing so, prevent its activation and the subsequent vasodilation.

Rimegepant is the first medication to receive FDA approval for both abortive and preventive migraine treatment. For both indications, we use the 75-mg orally disintegrating tablet (ODT), taken once daily. For abortive treatment, the patient takes it as needed and for preventive treatment, in an every-other-day regimen. The dual approval provides the medication with flexibility: the patient can take it as needed when headache ensues and every other day when headaches occur frequently.

Atogepant is a standard oral preventive migraine medication that, like the traditional oral preventive migraine medications, the patient takes daily. The dose is 30 mg or 60 mg once daily, except with concomitant use of a strong CYP3A4 inhibitor or with severe renal impairment, when the dose is 10 mg once daily.

Efficacy of the new abortive migraine medications

In clinical trials conducted for the purpose of marketing approval, the so-called regulatory trials, the FDA determines efficacy of abortive migraine medications based on the percentage of subjects treating moderate or severe migraine headache and pain free 2 hours post-dose *versus* placebo. This outcome variable, or endpoint, is in line with the clinical standard of efficacy for abortive migraine treatment, which is *full* relief of headache within 2 hours of initiation of treatment.

The difference between clinical trial and clinical practice, however, is the headache intensity at which the patient can initiate treatment. In clinical trials of a regulatory nature, patients need to wait until headache intensity is moderate or severe before initiating treatment. In clinical practice, this is counterproductive and we should instruct our patients to treat their migraine headaches at mild or mild-to-moderate intensity. For this reason, the efficacy as reported in regulatory trials can be considerably lower than what we may observe in practice, when the above standard of care is applied.

In the following analysis of the new abortive migraine medications, we solely obtained data from the FDA-approved labeling listed at the end. The selected outcome measure, the 2-hour pain-free rate, we only present for the highest approved doses *versus* placebo. If more than one set of data is available, we present the most favorable one, namely, the one with the largest difference between medication and placebo response rates, that is, the placebo-subtracted difference or delta (Δ).

Comparing results across clinical trials is fraught with potential objections to the conclusions and has no scientific validity. However, in the absence of randomized, double-blinded, head-to-head comparative trials, this is the only way we can put the results into perspective. This is the case whether we perform the comparison in a simple and straightforward manner, as done here, or rely on sophisticated meta-analytic techniques. Comparing treatments that we have not compared directly in clinical trials lacks scientific validity, regardless of the way we do it and however sophisticated the comparison.

For the new abortive migraine entries, we present the 2-hour pain-free rates in Table 5 and show the placebo-subtracted differences in Figure 1. Note that the FDA-approved labeling does not contain efficacy results for Tosymra® and Trudhesa®. As aforementioned, the FDA approved these two medications based on their relative bioavailability, compared to the Imitrex® 4-mg subcutaneous injection and the Migranal® nasal spray, respectively.

In Figure 1, we show the placebo-subtracted differences or deltas, as opposed to the absolute 2-hour pain-free rates of the medications, to compensate for the differences in placebo response rates between the trials. Based on the deltas as presented, ubrogepant (Ubrelvy®) 100 mg and rimegepant (Nurtec®) 75 mg ODT are similarly effective in the abortive treatment of migraine, with the caveat that comparing across clinical trials is not scientifically valid (*vide supra*).

The efficacy as judged by the deltas and with the same caveat seems to be the highest for lasmiditan (Reyvow®) and in between for the celecoxib oral solution (Elyxyb®). However, lasmiditan comes with the tolerability and safety issues mentioned. Dizziness and sedation are relatively common side effects and present a safety concern in terms of driving and operating machinery, which the FDA has restricted for 8 hours after its use. The medication also has some addiction potential, which caused the DEA to schedule it as class V.

Efficacy of the new preventive migraine medications

In clinical trials of a regulatory nature, the FDA determines efficacy of preventive migraine medications based on the change in number of migraine headache days from prospective baseline *versus* placebo. Generally, a secondary endpoint in those trials is the 50%-responder rate, which is the percentage of patients with

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a reduction of at least 50% in the number of migraine headache days from baseline. This particular outcome variable is in line with the clinical standard of efficacy for preventive migraine treatment, and we will use it here. The difference is that in clinical trials, we use the number of migraine headache days while in clinical practice, we consider the patient's overall assessment of migraine improvement.

Table 5: The 2-hour pain-free rates and deltas of abortive migraine medications approved 2018-2021.

Medication	Study	Arms	N treated	2-Hour pain-free	Delta
Reyvow® (lasmiditan) tablet	1	100 mg	498	28.30%	13.00%
		200 mg	503	31.80%	16.50%
		Placebo	515	15.30%	
	2	50 mg	544	28.30%	7.30%
		100 mg	523	31.40%	10.40%
		200 mg	521	38.80%	**17.80%**
		Placebo	534	21.00%	
Ubrelvy® (ubrogepant) tablet	1	50 mg	422	19.20%	8.10%
		100 mg	448	21.20%	**9.40%**
		Placebo	456	11.80%	
	2	50mg	464	21.80%	7.50%
		Placebo	456	14.30%	
Nurtec® (rimegepant) ODT*		75 mg	669	21.20%	**10.30%**
		Placebo	682	10.90%	
Elyxyb® (celecoxib) oral solution	1	120 mg	284	32.40%	7.00%
		Placebo	273	25.30%	
	2	120 mg	279	35.10%	**14.10%**
		Placebo	271	21.00%	

*Orally disintegrating tablet. Please note that we only show the bolded deltas in Figure 1; also see text.

With regard to comparing across clinical trials, of course, the same applies here as stated for the abortive migraine medications. In the absence of randomized, double-blinded, head-to-head comparative trials, comparing treatments in terms of efficacy, safety, or tolerability is not scientifically valid, regardless of the way we do it. This is important to keep in mind, also when we make the comparisons in sophisticated meta-analyses, published in high-end journals.

For the new preventive migraine entries and for episodic migraine only, for which the FDA approved all six, we present the 50%-responder rates in terms of the reduction in the number of migraine headache days from baseline in Table 6 and the placebo-subtracted differences in Figure 2. Based on the deltas as presented, the CGRP antibodies seem similarly effective in the preventive treatment of *episodic* migraine, with the caveat that comparing across clinical trials is not scientifically valid (*vide supra*).

The efficacy as judged by the deltas and with the same caveat seems highest for atogepant (Qulipta®) and lowest for rimegepant (Nurtec®). Dosed 75 mg ODT every other day, rimegepant may be under-dosed, certainly when compared to atogepant 60 mg daily. Could we expect an efficacy similar to atogepant if rimegepant was dosed 75 mg ODT daily, as opposed to every other day? With the high degree of blockage of the CGRP pathway as shown for the CGRP antibodies in the approved dosages [9], is it truly possible for atogepant to be 50% more effective?

It is important to remember that the FDA only approved rimegepant (Nurtec®) and atogepant (Qulipta®) for the preventive treatment of episodic migraine, which is migraine with a total headache burden of less than half the month. In contrast, the FDA approved the CGRP antibodies for the treatment of both migraine presentations, episodic *and* chronic. As aforementioned, we define chronic migraine with at least 8 migraine headache days per month and a headache burden of more than half the month, including all headaches.

Chronic migraine is generally more difficult to treat, abortively and preventively, than episodic migraine. This is not only because of the higher frequency of the headaches but also because of its

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association with multiple medical and psychiatric comorbidities [2]. Hence, preservation of efficacy moving from episodic to chronic migraine may be an indication of higher overall efficacy, although this is certainly not an established fact and may be contentious.

Table 6: The 50%-responder rates and deltas in episodic migraine for the preventive migraine medications approved 2018-2021.

Drug	Study	Arms	Number	50%-responder rate	Delta
Aimovig® (erenumab) SQ* injection	1	70 mg	312	43.30%	16.70%
		140 mg	318	50.00%	**23.40%**
		Placebo	316	26.60%	
	2	70 mg	282	39.70%	10.20%
		Placebo	288	29.50%	
Ajovy® (fremanezumab) SQ injection	1	225 mg	287	47.70%	**19.80%**
		675 mg	288	44.40%	16.50%
		Placebo	290	27.90%	
Emgality® (galcanezumab) SQ injection	1	120 mg	210	62.00%	**23.00%**
		Placebo	425	39.00%	
	2	120 mg	226	59.00%	23.00%
		Placebo	450	36.00%	
Vyepti® (eptinezumab) IV** infusion		100 mg	221	49.80%	12.40%
		300 mg	222	56.30%	**18.90%**
		Placebo	222	37.40%	
Nurtec® (rimegepant) ODT		75 mg qod	348	49.10%	**7.60%**
		Placebo	347	41.50%	
Qulipta® (atogepant) tablet		30 mg	223	59.00%	30.00%
		60 mg	222	61.00%	**32.00%**
		Placebo	214	29.00%	

*Subcutaneous; **intravenous. Please note that we only show the bolded deltas in Figure 2; also see text.

The efficacy in terms of placebo-subtracted differences of the four CGRP antibodies, we present in Figure 3 separately for the preventive treatment of episodic and chronic migraine. It shows that the deltas of fremanezumab (Ajovy®) are similar in the two migraine presentations, while that of eptinezumab (Vyepti®) is a little better in chronic than in episodic migraine. Erenumab (Aimovig®) and galcanezumab (Emgality®), on the other hand, see a drop off in placebo-subtracted differences, galcanezumab more so than erenumab, going from episodic to chronic migraine.

If we use the above information to generate an efficacy ranking of the CGRP antibodies in migraine prevention, it would be as follows: eptinezumab, fremanezumab, erenumab, and galcanezumab. Not only does this ranking come with the caveat of comparing across clinical trials, which makes it non-scientific. It also comes with the assumption made above that preservation of efficacy going from episodic to chronic migraine is an indication of higher efficacy, which it may not be. Therefore, we should take the above CGRP antibody ranking with a big grain of salt.

Discussion

Migraine is a condition that is both underdiagnosed and undertreated and, as a result, those afflicted suffer more than is necessary. The suffering goes well beyond the actual pain that migraineurs experience and extends into the future, affecting physical and mental health. The condition is easy to diagnose because inherited, it runs in families and people are generally familiar with it. An easy and straightforward question to ask is, do you think your headaches are caused by migraine and, if so, why?

Nowadays, we can easily exclude structural neurological illness as a cause of headaches with neuroimaging, preferably

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brain magnetic resonance imaging (MRI). This is important because it is always a concern with healthcare practitioners and patients alike. Undertreatment is due to the lack of significance we give headaches, including migraine, in medical education and in medical practice, apart from it being a potential symptom of neurological illness. Although this is rarely the case, it dominates headache education and, hence, the approach to headaches in medical practice.

We have made tremendous progress with the development of brain imaging, which we once considered revolutionary but now is ubiquitously available. The question is why we have not made similar progress with the treatment of headaches, now we no longer have to worry about structural neurological illness as a potential cause.

Headache intensity is what predominantly drives medical consultation, which means that patients generally consult for severe headaches they cannot manage. Migraine is by far the most common cause of such headaches, whether it is in the community at large or in medical practice. In addition to the fact that, as mentioned, it runs in families, it should be easy to diagnose, with the next step being to secure *effective* treatment. I italicized "effective" because that is most often, where the undertreatment is evident: Migraineurs generally treat, at least abortively, but not effectively. They heavily rely on nonprescription medications, some of which have migraine in their name, often with the same ingredients as their non-migraine counterparts. The question is what effective migraine treatment is, considering it from an abortive as well as preventive perspective.

When it comes to effective abortive or preventive migraine treatment, there is no generally accepted standard, such as is the case, for example, with the treatment of hypertension or diabetes mellitus. In the context of medical care, having a treatment goal is important and is helpful in order for us to know, when we need to take further action and what that action should be. Under ideal circumstances, we share the goal with the patient, and the healthcare practitioner and patient work together towards that goal.

The advent of the triptans enabled us to set a treatment goal for migraine abortion of *full* headache relief, freedom from pain, within 2 hours of initiation. More recently, the advent of the CGRP antibodies allowed us to set a treatment goal for migraine prevention of at least 50% in terms of overall migraine improvement. If a daily headache calendar is used, we can look at the number of headache days or migraine headache days to assess the improvement. However, without such a tool, an overall assessment of migraine improvement, taking the frequency as well as intensity of the headaches into account, suffices.

The above considerations made us evaluate the efficacy of the new entries in terms of 2-hour pain-free and 50%-responder rates for abortive and preventive migraine treatment, respectively. This also happens to be the information presented in the FDA-approved labeling of the medications, the 2-hour pain-free rate as one of two co-primary endpoints and the 50%-responder rate as a secondary endpoint. The other co-primary endpoint in abortive migraine treatment is freedom from most bothersome headache-associated symptom at 2 hours. The primary endpoint in preventive migraine treatment is the change from prospective baseline in the number of monthly migraine headache days.

With regard to abortive migraine trials, it is important to realize that the FDA requires migraine headaches to be moderate or severe in intensity before patients can treat. This requirement potentially affects the efficacy of orally administered medications that rely on enteric absorption, due to slowing down of gastric emptying as headache intensity increases [10]. It is something that we needs to take into account when evaluating the results of regulatory abortive migraine trials, which consequently underestimate the benefit we may see in practice.

Of the six new entries in the category of abortive migraine medications, the labeling only provides efficacy information for four; the FDA based the approval of two on relative bioavailability. Of these four, the 2-hour pain-free rates range from 19.2% to 38.8%, with the placebo rates ranging from 10.9% to 25.3%. Due to the broad range of the placebo rates, the differences in pain-free rates *per se* do not mean anything. Hence, we used the placebo-subtracted approach in which we subtracted the placebo rates from the pain-free rates, a way of correcting for the variance in placebo rates. Although the FDA endorses this analysis technique and the placebo-subtracted rates are part of the labeling, it is not without concern as to its validity [11].

The placebo-subtracted 2-hour pain-free rates of the four new entries for which this information is available, we presented in Figure 1. With the already mentioned caveat that comparing across clinical trials is not scientifically valid, Ubrelvy® 100 mg and Nurtec® 75 mg ODT seem similarly effective. In comparison to the two gepants, Elyxyb® 120 mg seems better and Reyvow® 200 mg, much better. Whether this is, indeed, true requires randomized, double-blinded, head-to-head comparative trials. If it is true, the fact that Reyvow® has tolerability issues, particularly dizziness and sedation, tempers its superior efficacy.

For an orally administered and enterically absorbed abortive migraine medication, excellent tolerability is key. The reason is that for such a medication to be truly effective, the patient needs to take it at mild or mild-to-moderate headache intensity. An additional limitation with Reyvow® is that driving is restricted for 8 hours after its use, which affects the treatment goal of restoring normal function.

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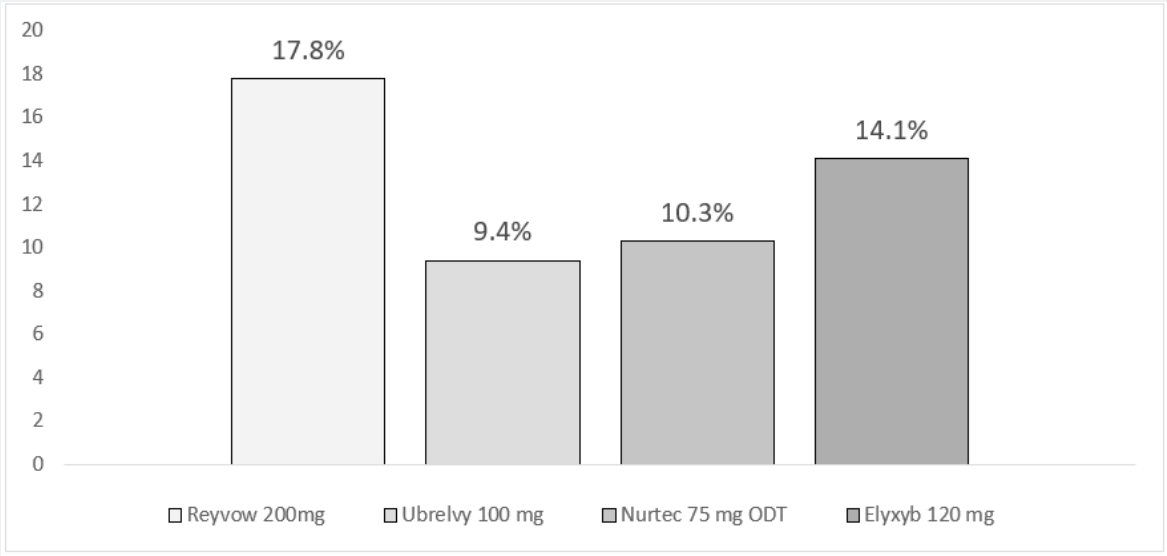

Figure 1: Placebo-subtracted differences or deltas (Δ) of the 2-hour pain-free rates for the abortive migraine medications approved 2018-2021. Note that no efficacy data are available for Tosymra® and Trudhesa® in the FDA-approved labeling.

We present the placebo-subtracted 50%-responder rates of the six new entries for migraine prevention in Figure 2. With the mentioned caveats of placebo-subtracted rates and comparing across clinical trials, the four CGRP antibodies seem similarly effective. Nurtec® 75 mg ODT every other day, on the other hand, seems less effective and Qulipta® 60 mg daily, more effective. However and as mentioned, whether this is, indeed, true requires randomized, double-blinded, head-to-head comparative trials.

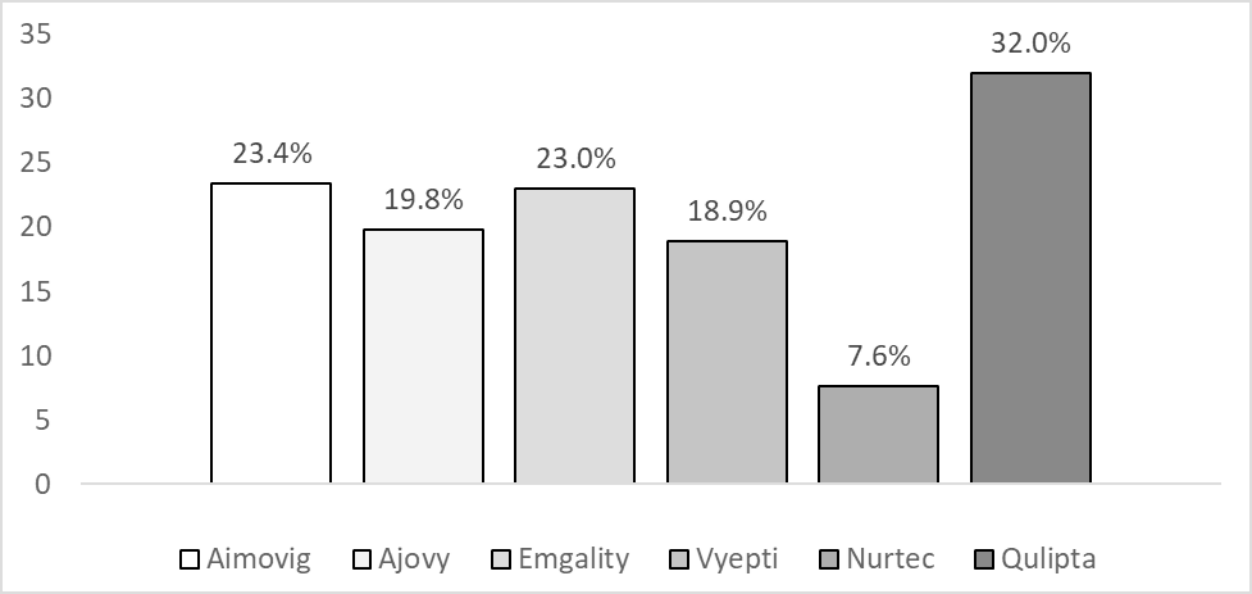

Figure 2: Placebo-subtracted differences or deltas (Δ) of the 50%-responder rates in episodic migraine for the preventive migraine medications approved 2018-2021.

The tolerability of the six new preventive migraine entries looks good, with the exception of a relatively low incidence of constipation for Aimovig® and Qulipta®. It is interesting that both medications share the CGRP receptor as their therapeutic target, as opposed to the ligand. The same is true, of course, for Nurtec® but in the approved preventive dose of 75 mg ODT every other day, we may have under-dosed it, as suggested by the lower efficacy.

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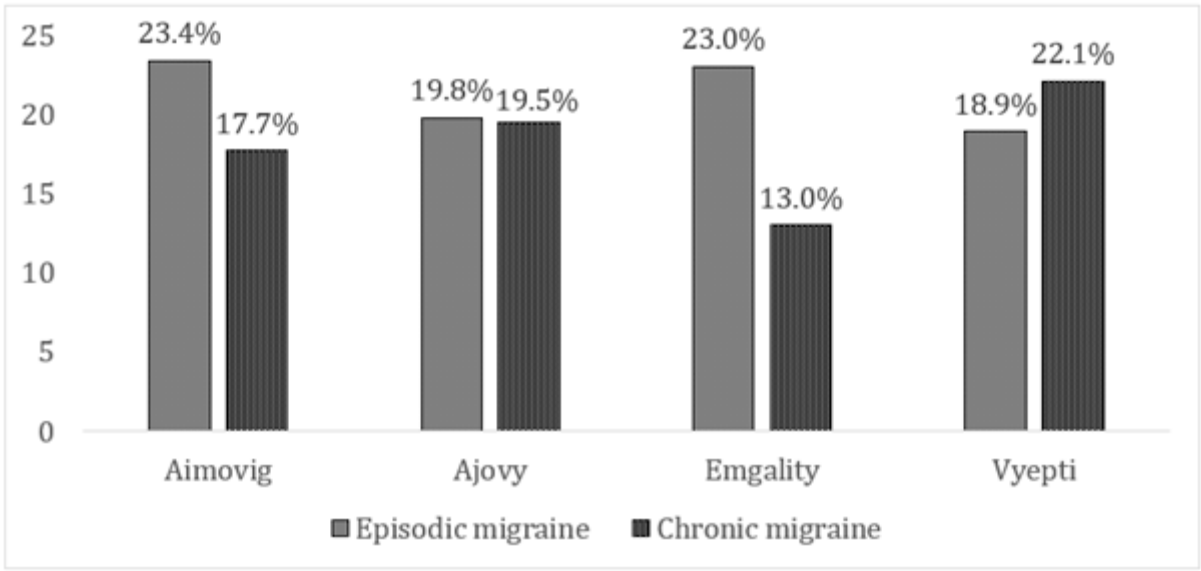

Figure 3: Placebo-subtracted differences or deltas (Δ) of the 50%- responder rates for the preventive migraine medications approved 2018-2021, separately for episodic and chronic migraine.

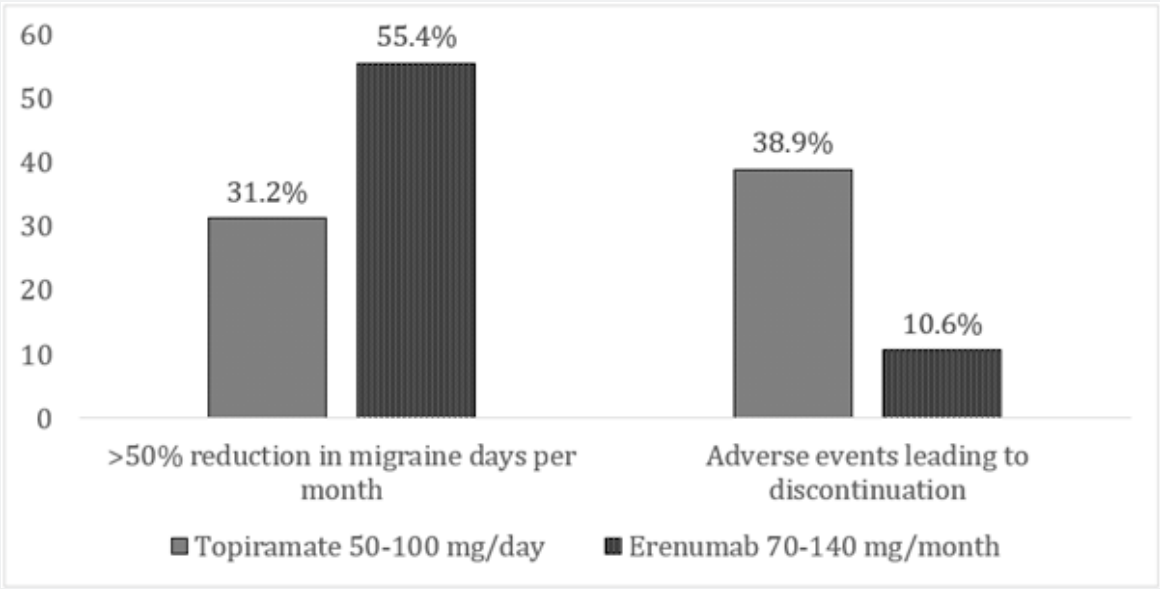

Figure 4: Efficacy and tolerability results of a randomized, double-blinded, head-to-head comparative trial in patients with episodic or chronic migraine [16].

Due to its tolerability profile, we should probably not prescribe Aimovig® or Qulipta® to patients with significant constipation or irritable bowel syndrome (IBS). The latter comes in three presentations, namely, constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and mixed IBS (IBS-M). We should be particularly careful with those medications in IBS-C and IBS-M, the latter a constipation-based condition in which the diarrhea occurs paradoxically.

An additional safety concern with Qulipta®, which also applies to the other two gepants on the market, ubrogepant (Ubrelvy®) and rimegepant (Nurtec®), is the concomitant use of a strong CYP3A4 inhibitor. For their catabolism, the gepants rely heavily on the liver CYP3A4 enzyme system and when inhibited, it amplifies their exposure with potential tolerability and safety concerns. This also relates to the ergots, ergotamine and dihydroergotamine, but not to the CGRP antibodies, because they are not metabolized by the liver but in the reticular endothelial system (RES). In addition

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and due to their vasoconstrictor activity, we consider the ergots contraindicated in patients with uncontrolled hypertension or with cardiovascular, cerebrovascular, or peripheral vascular disease, which applies to the triptans as well but not to the gepants or NSDAIDs.

A relatively new addition to the labeling of certain abortive migraine medications is "medication overuse headache; detoxification may be necessary". If present, the addition resides in the section, titled: WARNINGS AND PRECAUTIONS, and reads as follows: "Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary". Regarding the new abortive migraine entries, medication overuse headache is in the labeling of Elyxyb® (celecoxib), Reyvow® (lasmiditan), Tosymra® (sumatriptan), and Trudhesa® (dihydroergotamine).

For the approval of headache and migraine medications as well as for the content of the labeling, the FDA has come to rely heavily on the classification of headache disorders, as published by the International Headache Society [12]. They took their description of medication overuse headache from the classification, which additionally presents operational diagnostic criteria for the headache conditions listed. They geared those operational criteria towards clinical trial research, which consequently are arbitrary and represent a simplification of reality. This is also the case with the description of medication overuse headache, and there is no scientific basis for the 10-or-more-days-per-month statement therein.

Wolfson & Graham [13] were the first to recognize medication overuse headache as an increase in headache frequency with the use of ergotamine for abortive migraine treatment. Kudrow [14] subsequently identified it as a cause of decreased efficacy of preventive medications, which the labeling does not mention, however. We typically withdraw patients diagnosed with medication overuse headache from their abortive medications, before we prescribe them preventive treatment. We should expect improvement of their headaches upon abortive medication withdrawal, if medication overuse headache is, indeed, present. None of this may be an issue with the CGRP antibodies, however, as suggested by post-hoc analyses that showed similar efficacies whether medication overuse is present or not [15].

Conclusion: Have we made progress?

Preventively, it definitely seems that we have made progress if only because of the (much) better tolerability profiles of the CGRP antibodies and gepants, certainly in comparison to the traditional oral preventive migraine medications, such as topiramate, propranolol, and amitriptyline. In terms of efficacy, we probably have made progress as well although supported by only one randomized, doubled-blinded, head-to-head comparative trial, which compared erenumab (Aimovig®), 70 or 140 mg monthly, with topiramate (Topamax®), 50 to 100 mg daily [16]. The efficacy and tolerability results are presented in Figure 4, showing a 50%-responder rate for erenumab that is almost 80% better than that for topiramate. More impressive, however, is the difference in tolerability, here presented as adverse events leading to treatment discontinuation, which is almost four times better for erenumab, or more than 250%.

The biggest development in the preventive treatment of migraine, we opine, is with the CGRP antibodies. Antibodies as biologics come with two potential advantages over drugs. First, they have longer half-lives and, consequently, can be administered relatively infrequently, namely, monthly or quarterly, with the drawback that we have to administer them by injection or infusion. Second, they have a high level of target specificity and, hence, a low level of off-target activity and, consequently, they potentially have better tolerability and safety. Ultimately, the choice probably depends on the preference of the patient for daily tablet intake *versus* monthly or quarterly injections or infusions.

Regarding abortive migraine treatment, the three new chemical entities in the classes of gepants and ditans lack vasoconstrictor activity, which characterizes the ergots and triptans. Hence, we can prescribe them where we consider the latter two medication classes contraindicated, namely, in patients with uncontrolled hypertension or with cardiovascular, cerebrovascular, or peripheral vascular disease. Of course, this also applies to the chemical entity that is new to the migraine therapeutic area, which is celecoxib (Elyxyb®). This is a step ahead in safety while tolerability and efficacy seem similar to that of the triptans, the mainstay in abortive migraine treatment.

Consulted labeling information

- Aimovig® (erenumab), Amgen, 2018
- Ajovy® (fremanezumab), Teva Pharmaceuticals, 2020
- Elyxyb® (celecoxib), Dr. Reddy's Laboratories, 2021
- Emgality® (galcanezumab), Eli Lilly & Company, 2018
- Nurtec® ODT (rimegepant), Biohaven Pharmaceuticals, 2020
- Reyvow® (lasmiditan), Eli Lilly & Company, 2019
- Tosymra® (sumatriptan), Dr. Reddy's Laboratories, 2019
- Trudhesa® (dihydroergotamine), Impel NeuroPharma, 2021

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- Ubrelvy® (ubrogepant), Allergan, 2019
- Qulipta® (atogepant), Abbvie, 2021
- Vyepti® (eptinezumab), Lundbeck Seattle Biopharmaceuticals, 2020

Disclosures

Dr. Spierings is a member of the following Speaker Bureaus: Abbvie, Lundbeck Biopharmaceuticals, and Eli Lilly & Company.

References

1. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, et al. (2015) Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 84(7): 688-695.
2. Spierings ELH (2020) From headache to migraine, including episodic and chronic migraine. Open Access J Neurol Neurosurg 14(1): 1-9.
3. Spierings ELH (2004) The aura-headache connection in migraine. A historical analysis. Arch Neurol 61(5): 794-799.
4. Graham JR (1954) Rectal use of ergotamine tartrate and caffeine alkaloid for the relief of migraine. N Engl J Med 250(22): 936-938.
5. Rabkin R, Stables DP, Levin NW, Suzman MM (1966) The prophylactic value of propranolol in angina pectoris. Am J Cardiol 18(3): 370-383.
6. Turner P (1984) Beta-blocking drugs in migraine. Postgrad Med J 60(Suppl 2): 51-55.
7. Goldstein DJ, Roon KI, Offen WW, Phebus LA, Johnson KW, et al. (1999) Migraine treatment with selective 5-HT_{1F} receptor agonist (SSOFRA) LY334370. Cephalalgia 19: 318.
8. Russell FA, King R, Smillie SJ, Kodji X, Brain SD (2014) Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev 94(4): 1099-1142.
9. Buntinx L, Vermeersch S, De Hoon J (2015) Development of anti-migraine therapeutics using the capsaicin-induced dermal blood flow model. Br J Clin Pharmacol 80(5): 992-1000.
10. Boyle R, Behan PO, Sutton JA (1990) A correlation between severity of migraine and delayed gastric emptying measured by an epigastric impedance method. Br J Clin Pharmacol 30(3): 405-409.
11. Spierings ELH (1990) Therapeutic gain: a critique. Headache 39(7): 517-518.
12. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33: 629-808.
13. Kudrow L (1982) Paradoxical effects of frequent analgesic use. Adv Neurol 33: 335-341.
14. Wolfson WQ, Graham JR (1949) Development of tolerance to ergot alkaloids in a patient with unusually severe migraine. N Engl J Med 241(8): 296-298.
15. Koumprentziotis IA, Mitsikostas DD (2022) Therapies targeting CGRP signaling for medication overuse headache. Curr Opin Neurol 35(3): 353-359.
16. Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, et al. (2022) Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia 42(2): 108-118.

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