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REVIEW ARTICLE

New drugs for migraine

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Abstract After the triptans, a calcitonin gene-related peptide blocker (telcagepant) is the first acute medicine that has been developed primarily for treatment of acute migraine. Otherwise, the new drugs have been developed first for other purposes, like anticonvulsants, antihypertensives and antidepressants used for migraine prophylaxis. For acute attacks, a new way to administer a traditional drug like dihydroergotamine is under way, and documentation of efficacy in migraine has been gained for some commonly used painkillers and anti-inflammatory drugs, and for some herbal extracts. Based on insights into the basic pathophysiological mechanisms of the disorder, some drugs have been developed which seem promising in early phase II studies (NOS inhibitors and 5HT1F-receptor agonists). In the future, development and enhancements of existing medicines must be accompanied by increased efforts to develop truly new migraine drugs based on knowledge of the pathophysiology if one wishes to reduce substantially the great burden migraine poses on patients and society.

Keywords Migraine · New drugs · Randomized trials · Review · Innovation

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Introduction

Migraine is the most prevalent and probably also the most costly of the neurological disorders [1], presumably affecting 11% of the population wordwide [2], but allocation of resources for treatment [3] and research [4] for migraine and headache in general is not proportional to the societal importance of these disorders. In spite of this, the last two to three decades have seen a large progress in knowledge about the complex biology of migraine. Although many new drugs are found by serendipity, some potent new medicines are now developed de novo for migraine primarily on the basis of insight into the pathophysiology. This includes both central and peripheral mechanisms, as well as nerves and vessels. During migraine attacks, there seems to be a gradual sensitization of neurons on different levels [5], first in the periphery, around vessels and meninges, and then in the CNS, most likely in the trigeminal nucleus caudalis (TNC). Much has been learned by studying the complex innervation of the cephalic vasculature by three different types of extrinsic nerves (sympathetic, parasympathetic and sensory trigeminal) and some important transmitters [most notably calcitonin gene related peptide (CGRP), and nitric oxide (NO)] [6]. The cerebral vasculature is influenced by intrinsic cerebral pathways, stemming from serotoninergic, adrenergic, cholinergic, glutaminergic and other brainstem centres [6]. Positron emission tomography studies have shown that brainstem structures are activated during migraine attacks [7], which broadly include the pain—modulating centres in the periaqueductal grey (PAG) and the nucleus raphe magnus (NRM) [7]. A common hypothesis is that the migraine pain results from a deficiency of 5-HT in the descending pain modulating system of the brain [8]. However, the typical migraine aura cannot be directly explained by brainstem events, but rather by cortical spreading depression (CSD) [9],

Table 1 Randomized, double blind trials of topiramate for migraine prophylaxis

Study	Target population	Topiramate N (dropouts)	Maintenance period (weeks)	Mean dosage/ day (mg)	Migraine frequency (% reduction from baseline)	Therapeutic gain (% reduction vs.placebo)	Responders (Active %/ Placebo %)	Adverse events (%)
Storey [19]	MoA + MA	19 (3)	8	125	36	24	26/10	>68
Silvestrini [20]	Chronic migraine	14 (1)	8	50	61	60	71/7	36
Brandes [21]	MoA + MA	120 (58)	18	50	24	4	39/23	>34
		122 (57)		100	40	20	49/23	>50
		121 (47)		200	41	21	47/23	>49
Diener [22]	MoA + MA	139 (45)	18	100	44	24	37/22	>77
		143 (78)		200	28	8 (NS)	35/22	>81
Silberstein [23]	MoA + MA	117 (49)	18	50	24	6 (NS)	36/23	>36
		125 (42)		100	39	21	54/23	>47
		112 (67)		200	41	23	52/23	>47
Silberstein [24]	MoA + MA	138 (45)	12	161	30	10	40/34	90
Silberstein [25]	Chronic migraine	153 (73)	12	86	37	9	NA/NA	83
Diener [142]	Chronic migraine	32 (8)	12	100	23	24	22/0	75
Keskinbora [27]	MoA + MA	20 (4)	4	43	90	NA	NA/NA	40
Ashtari [28]	MoA + MA	31 (1)	8	50	70	NA	NA/NA	>23
Millan-Guerrero [29]	MoA + MA	45 (10)	12	100	46	NA	60/NA	>47
Dodick [30]	MoA + MA	172 (70)	22	91	41	NA	56/NA	67

MA migraine with aura, *MoA* migraine without aura

for which not only potassium ions and/or glutamate may play central roles, but also other ions and transmitters, including NO [10]. Migraine is clearly a genetic disorder, but the precise genetic basis for the most common forms is still unknown. In some cases of familial hemiplegic migraine, single locus mutations have been found in genes for either a brain-specific calcium channel (CACNA1A), an ATP-dependent sodium pump (ATP1A2) or a voltage-gated sodium channel (SCNA1) [11]. It is believed that also common migraine forms are channelopathies, i.e. related to some functional derangement of ion channels.

The purpose of the present review is to look at the experience we have with the new drugs introduced in this century, and to give a glimpse of the exciting new possibilities for drug treatment that may emerge in the years to come. This means that the triptans, for which extensive reviews [12] and meta-analyses [13] have been written earlier, are mostly omitted, but some old drugs may be included if there has come new evidence for effect, or novel formulations that may present a meaningful advance. We have also discussed at some length drugs which ultimately have proven to be ineffective but which have become quite extensively used based on limited evidence.

Anticonvulsants

In the 1990s, it became increasingly evident that valproate was effective for migraine prophylaxis [14], and after this many new antiepileptic drugs have been tested for migraine. A Cochrane report [15] on the use of anticonvulsants in migraine prophylaxis in adults concluded that this drug class reduced the frequency of attacks with 1–2 per month, and more than doubled the chance of having a reduction in attack frequency of more than 50% compared with placebo. Topiramate and valproate contributed most to the effect. Lamotrigine, clonazepam, vigabatrin and acetazolamide were not significantly different from placebo. A review of anticonvulsants for paediatric migraine [16] concluded that none of the drugs had adequate documentation of effect, and the paper called for new studies to establish safe and efficient migraine prophylactic drugs for children and youth. Several cerebral effects of the aniconvulsants may account for their effect in migraine, such as increase in the inhibitory transmitter GABA, antagonism of the excitatory transmitter glutamate, inhibition of sodium channels [17] and effects on calcium-channels in cortical and PAG neurons [18].

Topiramate (TPM) is probably the best documented migraine prophylactic drug in both episodic migraine (with and without aura) and in chronic migraine [19–30] (Table 1). Efficacy is well documented and placebo-subtracted reduction in migraine frequency (therapeutic gain) in most studies is around 20%. Adverse events (e.g. paresthesias, dizziness, fatigue, weight loss, memory difficulties and language disturbances) are common, but data from several controlled trials [31] indicate that TPM is generally safe for use in adult migraineurs. Although the exact mechanism of action is not known, TPM has several

pharmacological properties that may be relevant for its anti-migraine effect [32–35], such as blockade of voltage-gated sodium channels, which limits neuronal hyperexcitablility, blockade of L-type calcium channels which modulates neurogenic dural vasodilation and CGRP-induced dilatation, potentiation of GABA-mediated neurotransmission and reduction of neuronal firing in the trigeminocervical complex, suppression of glutamatergic transmission through kainate and AMPA receptors, and inhibition of carbonic anhydrase and activation of potassium currents. The sum of these effects on neuronal hyperexcitability may inhibit cortical spreading depression, pain transmission in PAG and signalling through the trigeminal system [35, 36].

With regard to gabapentin, the evidence is still inconclusive [15]. Of three randomised, controlled, double-blind trials (RCDBT) on migraine, one small study demonstrated a significant improvement of migraine with 1,200 mg gabapentin [37], with only mild side effects (somnolence, dizziness, tremor fatigue and ataxia) and no drop-outs. Another multicenter study of 145 patients, giving up to 2,400 mg for 12 weeks also showed a an effect, and also with tolerable side effects [38]. However, a third study found no effect of daily doses of 1,200 or 2,000 mg [39]. According to the Cochrane report, these studies suggest a beneficial effect, but since the two most relevant studies had methodological weaknesses it is concluded that the compound needs further evaluation. But the evidence at present is so promising that the drug may be tried in problematic migraine patients [15].

For lamotrigine, there is only one RCDBT from 1997 [40], and this study, with a high drop-out rate and change of dosing regimen during the study, failed to show superiority over placebo. Otherwise, the more recent studies are open [41, 42] or only a case report [43]. Overall, the Cochrane review concludes that the drug lacks proof of efficacy [15]. Another apparently ineffective drug is oxcarbazepine which was tried for migraine prophylaxis in a relatively large RCDBT with doses to at least 1,200mg/day [44]. Zonisamide, mostly used as add-on drug in patients with partial epilepsia, has only been tried in open studies for migraine prophylaxis [45–48], one of them in paediatric patients. All show impressive reduction in attack frequency, and tolerability is very good, although a few patients report dysphoria and concentration problems [45]. Also levetiracetam has been tested for migraine prophylaxis only in open studies, whereof two in children and adolescents [49, 50] and one in adults [51]. No serious side effects were observed, but some reported irritability and aggressiveness.

Tonabersat, which has anticonvulsive properties in experimental animal models, is a blocker of gap junctions, inhibits CSD [52] and neurogenic inflammation, and reduces NO concentrations during CSD [53]. It seems to have no contractile effect on isolated vessels or myocardium [54], but it inhibits trigeminally mediated parasympathetic reflexes on carotid vasculature [55]. A RCDBT [56] on glyceryl-trinitrate (GTN)-induced migraine attacks in migraine patients gave inconclusive results, but the study had to be terminated due to side effects, possibly from the interaction of GTN and the study drug. In another RCDBT of tonabersat 40 mg there were no significant differences in any effect parameter, although numerically all parameters favoured the substance over placebo. There were no serious adverse effects, but nausea, dizziness, and headache occurred more often in the tonabersat group [57]. In one recent RCDBT of 39 patients suffering from migraine with aura (both with and without headache, and including hemiplegic and basilar migraine), there was a significant effect of tonabersat 40 mg only on the aura attacks and aura attacks followed by headache, but not on migraine attacks without aura or headache in general [58]. If larger studies confirm this finding, tonabersat may be the first drug with a selective effect on migraine with aura.

Antihypertensive medication

Beta-blockers have been a mainstay in migraine prevention in most countries, but few new drugs in this group have been investigated for migraine during the last decade. One small RCDBT compared one for migraine established beta-blocker, metoprolol 142.5 mg, with 5 mg nebivolol, which is a third-generation beta-blocker with high β-1 selectivity, high lipid solubility to pass the blood–brain barrier, with little intrinsic activity and also a vasodilatory effect mediated by stimulation of endothelial NO production [59]. Both drugs gave a similar reduction of migraine attack frequency, but nebivolol had significantly fewer side effects [60].

The first RCDBT of a drug influencing the renin-angiotensin system (RAS) as migraine prophylactic was published in 2001, when lisinopril, an angiotensin-converting enzyme inhibitor (ACEI) [61] was shown to have a beneficial effect in a cross-over study. In 2003, a similar study demonstrated effect of candesartan, an angiotensin II, 1a-receptor blocker (ARB) [62]. Recently, an RCDBT on another ARB (telmisartan) showed effect on level with many other migraine prophylactics, but the study was inconclusive due to low power for a parallel group study [63]. The favourable side effect profile has made particularly candesartan an attractive alternative which has gained popularity in many countries in spite of the limited documentation of effect (see, e.g. [64]). For the ACEIs, coughing as a side effect may limit the use. Additional proof of efficacy of these classes of drugs in migraine is by open studies for ACEIs [65–67] and by a study on migraine among hypertensive patients for candesartan [68]. Also, there is circumstantial evidence that the effect of candesartan may be a class effect of the ARBs since a large pharmacoepidemiologic study showed decreased use of

triptans when patients started using an ACEI or an ARB of any type [69], and a meta-analysis of RCTs with ARBs used for other indications showed that headache as a side effect was lower in the ARB group than in the placebo group, irrespective of the type of ARB [70]. The mechanism for the antimigrainous action of these drugs is not known, but it is most certainly not related to decrease in the blood pressure. Interestingly, there is an intrinsic RAS of the brain within the blood brain barrier [71], and in the trigeminal ganglion [72], which has many effects that may be relevant for migraine.

Antidepressants

Considering the reasonably good evidence for the tricyclic antidepressant amitriptyline as a migraine prophylactic [73] it is notable that a Cochrane review concluded that the selective serotonin reuptake inhibitors (SSRIs) are not effective in migraine or tension-type headache [74]. There are, however, some studies that indicate preventive effect of antidepressants that inhibit reuptake of both serotonin and nor-adrenalin. A RCDBT on 60 migraine patients with venlafaxine extended release tablets showed effect of both 75 and 150 mg doses [75]. Adverse events occurred mostly on the highest dose, and they abated with time. An open-label retrospective chart review of 65 migraine patients who used duloxetine showed a modest decrease in migraine frequency after 2 months, the decrease being most marked in the subgroup with anxiety [76].

Drugs influencing the dopaminergic system

Nausea, often a disabling migraine symptom, is relieved by antiemetics like metoclopramide or domperidone which are dopamine 2 (D2) receptor antagonists. These drugs are useful not only as antiemetics but they may probably also have some effect against the migraine [77]. Dopamine receptor blockers have received relatively little attention as regular anti-migraine drugs, most likely because of the side effects, but they may be useful for the particularly severe attacks seen in patients admitted to hospital for their migraines, where the first-line medications have failed. A RCDBT of 40 patients coming to the hospital emergency room demonstrated effect of i.v. infusion of 5 mg of haloperidol, most patients being pain free within 1 h [78]. Side effects were common and included motor agitation and sedation. Another similar study of 68 patients [79] showed that chlorpromazine 0.1 mg/kg intravenously had effect after 1 h on headache and associated symptoms, the side effects being postural hypotension and drowsiness. Intramuscular droperidol, a dopamine antagonist used for induction of general anaesthesia, was tested in a RCDBT for acute migraine attacks in 305 patients [80]. There was effect with regard to headache relief at 2 h for doses 2.5–8.25 mg. Asthenia, somnolence, anxiety and acathisia were side effects related to the study drug.

One drug in this class, olanzapine, an atypical dopamine blocker with relatively low tendency to induce extrapyramidal side effects, has been explored as a potential migraine prophylactic in a retrospective study of 50 migraine patients who had used the drug, usually 5–10 mg per day [81]. Patients had a significant decrease in headache days and headache severity, but side effects, weight gain and somnolence, were bothersome.

CGRP receptor blockers

CGRP is released from trigeminal sensory neurons, and its significance for migraine was suggested in 1990 when it was shown to be increased in blood sampled from the jugular vein during ongoing headache attacks [82]. Some but not all later studies have confirmed this [83]. A further indication is that infusion of CGRP can induce attacks in migraine patients [84]. In addition to being a potent vasodilatator it has a number of other effects, like release of histamine from mast cells and increased NO production in ganglion cells [85]. CGRP receptors are present not only in vessel walls, but also in the central nervous system (cerebellum, PAG and TNC).

The proof of concept study for CGRP receptor blockade in migraine was published in 2004 [86] with olcagepant which had to be given intravenously. Later studies have been done with the orally administered telcagepant [87, 88]. CGRP receptor blockers inhibit CGRP- induced vasodilatation, but under normal circumstances they seem to have no effect on cardiovascular parameters, and particularly not on coronary arteries, and they may therefore be used in migraine patients with coronary disease. Table 2 shows some of the data from the RCDBTs comparing telcagepant with either rizatriptan 10 mg [88] or zolmitriptan 5 mg [87], and it also gives data on the different triptans from a meta-analysis [13]. There is no dose–response relationship for the doses 300–600 mg, and the response rate is not consistently higher than that of the triptans, but the number of side effects seems somewhat lower. Since the mode of action differs fundamentally from that of the triptans, it is hoped that the drug will be a valuable addition to the armamentarium of acute migraine drugs, and particularly for the large group of patients who are not satisfied with triptans due to limited efficacy, side effects or contraindications. Recently, according to the medical trials, database ClinTrials.gov (Identifier: NCT00797667) a prophylactic study with telcagepant has been terminated because of two patients with significant elevations in serum transaminases, signifying

Table 2 Efficacy and adverse events of telgacepant and triptans

Study	Type of drug	Pain relief at 2 h (%)	Pain free at 2 h (%)	2–24 h sustained pain freedom (%)	Placebo-substracted AE (%)	Adverse events (%)
Ho et al. [88]*	Telcagepant 300 mg	68.1	45.2	32.0		35.3
	Telcagepant 400 mg	48.2	24.3	22.0		36.5
	Telcagepant 600 mg	67.5	32.1	39.6		40.8
	Telcagepant 10 mg	69.5	33.4	18.4		42.0
	Placebo	46.3	14.3	11.0		36.2
Ho et al. [87]	Telcagepant 150 mg	49.8	17.2	10.7		31
	Telcagepant 300 mg	55.0	26.9	20.2.4		37
	Zolmitriptan 5 mg	56.4	31.3	18.2		51
	Placebo	27.7	9.6	5.0		32
Meta-analyses 2002	Sumatriptan 100 mg	59 (57–60)	29 (27–30)		13 (8–18)	
	Almogran 12.5 mg	58				
	Rizatriptan 10 mg	Ca. 70	37			
	Elitriptan 20 mg	Ca. 68	Ca. 40			
	Zolmitriptan 5 mg	>60	42 (36–48)			

* Only the highest doses are reported here

liver toxicity. The fate of telcagepant is therefore somewhat uncertain at the moment. Definitely, its greatest potential seems to be as acute migraine medication, and whereas liver toxicity is not expected with intermittent use, it is a common experience with most acute migraine medications that a small percent of patients will use them almost daily.

Although it is unlikely that telcagepant will be investigated for migraine prevention, there may be other ways to diminish the effect of CGRP than by receptor blockade. Currently, substances that reduce the circulating CGRP levels by acting as CGRP scavengers (antibodies and so called Spiegelmers) are under development, and these may in the future offer new possibilities of prophylactic treatment [89].

Somatostatin has been found to inhibit CGRP release, and the transmitter is also found in TNC and PAG. A somatostatin-analogue, octreotide, was tried subcutaneously in a RCDBT for migraine attacks, but with negative results [90].

Nitrogen oxide inhibitors

Intravenous infusions of the NO donor glyceryl trinitrate (GTN) tends to induce headache in all individuals, but more often in migraineurs who also get a migraine-like headache after a first phase with headache of more indeterminate nature [91]. Interestingly, NO does not seem to induce aura among patients with this migraine form, only the pain. NO is produced by degradation of L-arginin by NO synthetase (NOS) which exists in three different forms, endothelial, inducible and neuronal NOS (eNOS, iNOS and nNOS). Vascular effects of nNOS are mediated through parasympathetic fibres of the facial nerve to cephalic vessels where it mostly dilates arteries and veins but not arterioles which regulate tissue perfusion. nNOS and eNOS may both be involved in sensitisation of peripheral nerves and also central pain pathways. In view of its potentially important role in migraine, surprisingly few therapeutic studies have been performed with NOS-inhibitors. One small study with an NOS inhibitor given intravenously showed a response rate of 67% among 15 patients, in comparison to 14% among 15 patients who received placebo [92]. The study was blinded, but only 2 placebo patients were included in the study; the 14 others were historical placebo controls from another study. 3 of the 15 patients experienced some subjective side effects (pressure over the nose, tingling at the elbows and cold hands). Mean arterial pressure increased and heart rate decreased.

Hydroxocobalamin (OH-B12) is an NO scavenger, and in an open study, this compound given nasally for 3 months reduced the migraine frequency compared to the baseline period [93].

Selective 5-HT_{1D} and 5HT_{1F}-receptor agonists

Triptans act on 5-HT_{1B} and 5-HT_{1D}-receptors, and some also on 5-HT_{1F}-receptors. 5-HT_{1B}-receptors mediate vasoconstriction, whereas the 5-HT_{1D}-receptors are believed to be involved in neurogenic inflammation of the dura. The selective 5-HT_{1D}-receptor agonist PNU-142633 has been shown to block plasma extravasation induced by stimulation of the trigeminal ganglion in rodents [94]. In a small RCDBT in migraine patients there was no effect on acute attacks [95].

A selective 5-HT_{1F}-receptor- agonist (LY334370) has been tested in a small RCDBT with three different doses [96]. The two highest doses were clearly superior to placebo. Side effects were dizziness, somnolence, asthenia and paresthesia. This drug may act by blocking neurogenic inflammation or by blocking nociceptive information in the TNC. The 5-HT_{1F}-receptor- agonists seem to have no vasoconstrictor effect in the doses tried for migraine, and they may thus be safe for patients with vascular disorders [97].

Dihydroergotamine delivered by inhalation

In many countries, use of ergotamines decreased markedly when triptans were introduced, mainly due to side effects and safety concerns. However, quite recently the case has been made for a larger role for dihydroergotamine, due to its fast onset of action, relative safety and effect in particularly severe and long-lasting attacks [98]. This semisynthetic alkaloid has effects on a both adrenergic (α and β), dopaminergic and serotoninergic receptors, the latter including 5-HT_{1B} and 5-HT_{1D}. Possibly, renewed interest in this compound may be awakened by the introduction of a new device for delivering the drug by inhalation, permitting uptake through the vast and very thin barrier in the lungs. This unusual way of delivering migraine drugs has been shown to be well tolerated, with excellent pharmacokinetics on level with intravenous administration [99], and safe even in patients with asthma [100]. A recent RCDBT has shown that inhalation of dihydroergotamine mesylate gave pain relief after 2 h in 72% of patients, which is higher than most oral or intranasal triptans, and with few side effects [101], and there was a rapid onset of action, with significant relief already after 10 min. No additional effect but more side effects (mainly aftertaste) was seen for a higher dose of 1 mg.

Glutamate receptor blockers

The excitatory amino acid glutamate is believed to play an important role in CSD. In a small open study, ketamine, an antagonist of glutamate receptors of the NMDA subtype, reproducibly reduced aura symptoms with intranasal administration of the drug, but there was no effect on the headache [102]. Another drug (LY293558) is an antagonist of kainat and AMPA glutamate receptors. In a small RCDBT comparing the drug both with sumatriptan injections and placebo, LY293558 given intravenously was effective with regard to pain and accompanying symptoms of migraine [103]. The effect was somewhat smaller than with sumatriptan injections, but side effects were fewer.

Capsaicin receptor blockers

Antagonists against "capsaicin receptors", usually referred to as transient receptor potential vanilloid subfamily, member 1 (TRPV1), are currently under investigation for migraine. This receptor type is sensitive to capsaicin, which gives the burning taste of chilli peppers, and it is involved in processes causing thermal hypersensitivity. The fact that it is expressed in both central and peripheral trigeminal neurons and seems to be involved in neurogenic inflammation and sensitization makes it an interesting target for antimigraine drugs [104]. However, a series of trials of one TRPV1 antagonist, civamide, as acute migraine treatment has given disappointing results, and the trials have been terminated [105].

Drugs influencing the prostanoid system

Drugs for migraine exerting their effect through this system include acetyl salicylic acid and all the NSAIDs, which are among the most commonly used drugs for migraine. All these drugs inhibit cyclo-oxygenase (COX) which catalyses the conversion of arachidonic acid to prostaglandin H_2, a precursor of the prostanoids which are important mediators of inflammatory reactions, but which also mediate a host of other functions. COX exists in at least two forms, COX 1 which is a constitutive enzyme found in most cells, and COX 2 which is an inducible enzyme involved in inflammatory reactions found in macrophages and other cells involved in inflammation. The classical NSAIDS inhibit both COX 1 and COX 2 alike, and the gastrointestinal side effects (most notably peptic ulcer) are related to COX 1 inhibition. The selective COX 2 inhibitors seem to cause less of these side effects, but this advantage is offset by increase in cardiovascular risk, probably by lowering vascular prostacyclin production without altering platelet thromboxane levels [106].

One large RCDBT [107] has shown effect of two different doses of the COX 2 inhibitor rofecoxib 25 and 50 mg for a single migraine attack. Adverse effects were generally mild or moderate, but more common with the highest dose. Another large RCDBT has compared two doses of valdecoxib (20 and 40 mg) with placebo and sumatriptan 50 mg doses. This showed that valdecoxib was better than placebo and similar to sumatriptan, but with fewer side effects [108]. A small open-label study [109], comparing the effect of yet another COX 2 inhibitor, celecoxib 400 mg, with that of a classic NSAID (Naproxen 550 mg) for a single migraine attack, found similar efficacy for the two drugs, but significantly fewer in the celecoxib group reported epigastric pain.

Diclophenac has long been shown to have an effect on migraine attacks. Recently, a new formulation with higher water solubility (diclophenac DHEP) has demonstrated effect over placebo, and in lower doses than diclophenac potassium [110]. Another study tested diclophenac 100 mg softgel with or without caffeine 100 mg versus placebo in a triple cross over study in 46 subjects [111]. Only diclophenac + caffeine showed superiority over placebo at 60 min.

Prostaglandin E_2-receptor blockers are now under investigation for migraine. The EP4-receptor [112], which mediates some of the effect of prostaglandin E2 (PGE_2), is present in sensory dorsal root ganglia cells. PGE_2, an inflammatory mediator, is also a neuromodulator that may alter neuronal excitability and synaptic transmission [113]. The blocker BGC20-1531 can antagonise PGE_2-induced dilatation of cranial arteries, but has no effect on coronary, pulmonary and renal arteries in vitro [112]. Still, proof of concept studies are lacking for the blocker. Another blocker, CJ-023,423, has been shown to reduce thermal and mechanical hyperalgesia in animal models, and is also effective in controlling inflammatory pain [114].

Corticosteroids

These drugs are often mentioned for treating status migrainosus, but the scientific documentation has been poor [115]. A recent Cochrane review [116] identified seven randomised, placebo-controlled studies of sufficient quality, whereof five were published in 2006 or later, on its use in severe migraine in an emergency department setting [117]. All used "standard abortive therapy" and then placebo or dexamethasone intravenously or intramuscularly, in doses from 10 to 24 mg as an adjunct, with follow-up varying between 1 and 3 days. Overall, for all studies ($n = 738$) the risk of recurrence was significantly reduced by 26% in those receiving dexamethasone, with side effects similar to those in the placebo-treated group. As for oral dexamthasone, the effect of adding dexamethason 8 mg to acute treatment with phenothiazines was not significant [118], although the absolute risk reduction was 12% in the steroid treated group.

Paracetamol

For a highly prevalent disease like migraine most patients from time to time treat their attacks by over the counter medication (OTC), and the main information they get about their medication is from the package label [119]. For this reason, it is important that adequate documentation on the effect for migraine exists. One RCDBT of acetaminophen (paracetamol) 1,000 mg as attack medication documented a significant effect over placebo and there was no difference with regard to side effects [119].

Herbal extracts

As with paracetamol, the fact that many patients treat their attacks with herbal medicines has been the motivation for testing the effect of the herbs feverfew (*Tanacetum parthenium*) and butterbur (*Petastes hybridus*) which have been widely used in traditional medicine. Feverfew is known to inhibit prostaglandin production and secretion of serotonin, and to influence contractility of cephalic vessels. In a recent RCDBT on the prophylactic effect of an extract given three times daily for 3 months, it was shown to be effective with regard to frequency of attacks, with side effects on level with placebo [120]. Butterbur, which has anti-inflammatory properties, has been investigated for prophylaxis in two RCDBTs, and both have suggested a treatment effect [121, 122] with mild side effects.

Botulinum toxin

Based on the knowledge about episodic migraine pathophysiology it would seem unlikely that a substance like botulinim toxin (BTX) which blocks the release of acetylcholin in the periphery on muscle cells and sweat glands should be helpful. In pain states where BTX is effective, it seems to reduce muscle spasms causing the pain, and there is good evidence that BTX has no intrinsic antinociceptive effect in experiments on human volunteers (for review see [123]). Generally, it may be difficult to determine its effect on headaches due to the possibility of unblinding because of the visible effect on the scalp muscles and its high placebo response [123]. In spite of this, many studies have been performed in both migraine and other headache conditions. As can be seen from the overview of the six RCTs [124–129] of botulinum toxin A in Table 3, the effect on migraine is not convincing. In general, adverse events in these studies are few and not serious, mostly ptosis and diplopia in a few patients [124, 125], and usually with the highest doses. In 2006, it was, based on the negative evidence published till then, concluded that BTX as prophylactic for episodic migraine and tension-type headache had come to the end of the road [130]. A similar opinion was expressed in a more recent review since none of the six controlled studies in migraine had shown any significant effect, and three of these studies were assessed as class I evidence [131]. Also, a recent report for the American Academy of Neurology has concluded that it is ineffective for episodic migraine [132]. In the debate following the latter report [133], critics objected that this view was based on admittedly well-conducted studies

Table 3 Randomized placebo-controlled, double blind trials of botulinum toxin A for migraine prophylaxis

Study	*N*	Dose and application		Result
Silberstein [124]	122	25 and 75 U, forehead and temples	Fixed sites	25 U showed better effect than placebo, not 75 U group
Evers [125]	60	16U in forehead, 100U in forehead and neck	Fixed sites	No difference between groups
Elkind [127]	418	25 and 50 U in front and sides of head	Fixed sites	No difference between groups
Aurora [126]	369	110−260 U	"Follow the pain"	No difference between groups
Relja [128]	495	75, 150, 225 U in various head and neck muscles	Fixed sites	No difference between groups
Cady [129]	61	139 U, in various head and neck muscles	Fixed sites	No significant differences in headache frequency, but with regard to headache impact measure

but these used inadequate doses. In answer to this, the authors of the report stated that evidence-based reviews necessarily will be limited to the well-performed trials and cannot reflect all variations in dosages and injection techniques used among clinicians. Hence, it is always possible that future studies with refined techniques and measurements may yield different results, but up till now there is no good evidence to support the use of BTX in migraine.

Combination drugs

When triptans were introduced, monotherapy with these drugs supplanted in many countries the use of earlier combination pills of ergot, caffeine, tranquillizers or antiemetics. It was claimed that polypharmacy was partly responsible for side effects and medication overuse. However, it is obvious that the complex migraine pathophysiology offers multiple targets for pharmacological intervention, and today it is argued that drug combinations could give additional effects compared to monotherapy.

A large RCDBT of the combination of sumatriptan 50 mg capsules and *naproxen* 500 mg tablets against monotherapy of these same drugs [134] showed that the combination was superior to monotherapy. This was largely confirmed in two large RCDBTs, including almost 3,000 migraine patients, which compared the effect of a combination drug of sumatriptan 85 mg and naproxen 500 mg in one tablet, with monotherapy of the same drugs and doses, and with placebo [135]. An open-label safety study on 565 patients treating more than 24,000 attacks during a year showed that this combination drug was well tolerated [136]. Patients had typical triptan side effects, but few gastrointestinal problems, and there was only one serious cardiovascular event.

A RCDBT showed superiority of IndoProCaf, a combination drug given as suppositories containing prochlorperazine (a dopamine D2 receptor antagonist) 4 mg, indomethacin 25 mg and caffeine 75 mg, over sumatriptan 25 mg suppositories [137]. The number of adverse events was low and similar with the two treatments. Another RCDBT with Indoprocaf tablets (effervescent and coated) [138], with a lower prochlorperazine dose (2 mg) than the suppositories, showed similar results as with sumatriptan 50 mg tablets, with effervescent tablets being superior to coated ones.

One RCDBT compared sumatriptan 50 mg with a combination drug containing acetaminophen 500 mg, acetylsalicylic acid 500 mg and caffeine 130 mg in a RCDBT including 170 patients [139] who were advised to treat their migraine early. The combination was better than sumatriptan after both 2 and 4 h.

A RCDBT of tramadol 75 mg in combination with acetaminophen 650 mg for acute migraine attacks showed that the combination was superior to placebo for pain from 0.5 to 6 h [140].

As preventive treatment, a small RCDBT tested a combination of magnesium 300 mg with riboflavin 400 mg and feverfew 100 mg, but the combination did not show superior effect over placebo. However, since riboflavin changes the colour of the urine, the placebo had to contain 25 mg riboflavin to obtain proper blinding [141]. In that study, the placebo effect was particularly high, and it is therefore possible that the negative result was due to an active effect of the placebo.

Conclusion

The past decade has seen relatively few new medicines for migraine, and after the triptans were introduced in the 1990s, the CGRP blocker is the only drug which may soon be ready for the market and which is a truly innovative drug developed primarily for migraine, based on knowledge of the pathophysiology of the disease. Otherwise, new migraine drugs are mostly medicines that have been designed for other diseases, most notably some anticonvulsants (topiramate) and antihypertensives (ACEIs, ARBS, third generation beta-blockers). We have also obtained documentation of efficacy in migraine for some well-known painkillers and anti-

inflammatory medicines (parecetamol, NSAIDS and COX-2 inhibitors) which many patients use anyway, and the same goes for some herbal extracts. Likewise, corticosteroids and some dopamine agonists have proven their usefulness for the very severe attacks encountered in the hospital emergency room. We also see a movement towards more polypharmacy with combinations of well-known drugs. While all these developments undoubtedly represent progress, it is somewhat disquieting that development of some truly innovative substances, like NOS inhibitors and 5-HT_{1F} blockers, which have been very promising in early phase II studies, seem to have come to a halt. It is natural that low-hanging fruits are picked first, but in the long run, development and enhancement of existing drugs may be an insufficient strategy if the goal is to obtain substantial improvements for migraine patients. It is reasonable to believe that the basic science of migraine has reached such maturity that more new drugs can now be developed primarily for migraine. This can only be achieved by a focussed and concerted research effort by academia and the pharmaceutical industry. While it is considerably more expensive to manufacture a drug de novo, new effective medicines for migraine will almost certainly give payback to the developer, produce large savings for society and reduced suffering for patients.

Conflict of interest None.

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