New therapeutic approaches for the prevention and treatment of migraine

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The management of patients with migraine is often unsatisfactory because available acute and preventive therapies are either ineffective or poorly tolerated. The acute treatment of migraine attacks has been limited to the use of analgesics, combinations of analgesics with caffeine, ergotamines, and the triptans. Successful new approaches for the treatment of acute migraine target calcitonin gene-related peptide (CGRP) and serotonin (5-hydroxytryptamine, 5-HT$_{1F}$) receptors. Other approaches targeting the transient receptor potential vanilloid (TRPV1) receptor, glutamate, GABA$_A$ receptors, or a combination of 5-HT$_{1B/1D}$ receptors and neuronal nitric oxide synthesis have been investigated but have not been successful in clinical trials thus far. In migraine prevention, the most promising new approaches are humanised antibodies against CGRP or the CGRP receptor. Non-invasive and invasive neuromodulation approaches also show promise as both acute and preventive therapies, although further studies are needed to define appropriate candidates for these therapies and optimum protocols for their use.

Introduction

Migraine is the most prevalent disabling neurological disorder.[1] Until 25 years ago, neurologists had few options to treat patients with acute migraine attacks. These options included analgesics such as acetylsalicylic acid and acetaminophen (paracetamol); the combination of analgesics with caffeine; non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, ketoprofen or diclofenac;[2] and other medications with less clear mechanisms of action, such as metamizole. Ergotamine preparations, which act on serotonin receptors but also on other receptors, have also been used, with vasoconstriction presumed to be their primary mechanism of action. The triptan sumatriptan was the first drug specifically developed as an acute migraine therapy, acting with higher specificity on serotonin (5-HT$_{1B}$ and 5-HT$_{1D}$) receptors than ergotamine. Triptans are generally effective only in the acute treatment of migraine[3,4] and cluster headache;[5] although they can be highly effective in many individuals, triptans can also have substantial limitations, including recurrence of migraine symptoms after initial efficacy. Additionally, despite having only weak vasoconstrictor properties in humans, triptans are contraindicated in patients with severe vascular conditions such as myocardial infarction, angina pectoris, transient ischaemic attack or ischaemic stroke, and peripheral arterial disease, and in people with several untreated vascular risk factors.[6] Therefore, new drugs are needed to treat migraine attacks in patients in whom triptans are not effective, are initially effective but symptoms recur, are poorly tolerated, or are contraindicated. This Review provides an overview of new drugs for the acute treatment of migraine attacks, covering studies regarding clinical evidence, side effects, contraindications, and the different stages of clinical development.

Patients with frequent migraine attacks need migraine-preventive therapy. Prevention should be primarily initiated with non-medical approaches, including counselling, exercise, stress management, and relaxation techniques. If necessary, medicines for migraine prevention should be offered. Drugs classes for migraine prevention include β-blockers, anti—epileptics (topiramate and valproic acid), calcium-channel blockers (flunarizine), angiotensin II receptor antagonist inhibitors (candesartan), and antidepressants (amitriptyline and venlafaxine).[7,8] These drugs, on average, reduce migraine frequency by 50% in about 40–45% of patients. Compliance and adherence is poor because of their many adverse events.[9] As for acute therapies, new treatments are needed that are more effective, better tolerated, and without contraindications. Several new drugs are under development for the prevention of migraine attacks, and these drugs will also be covered in this Review.

In addition to drug therapies, several new neuromodulatory methods are being investigated for the acute treatment and prevention of migraine. These new treatment approaches are also discussed in this Review.

New drugs for acute treatment

Depending on what measure is used, between 40% and 70% of patients are non-responsive to a triptan at 2 h after treatment onset, or do not tolerate existing acute treatment options, including triptans (40% when headache response is defined as a transition of moderate or severe pain to mild or no pain, 2 h after intake of drug; 70% when pain free is defined as transition from severe, moderate, or mild headache pain to no pain, 2 h after intake of drugs).[4] Additionally, headache recurrence after an initial positive response is an unsolved problem in about a third of responders. Triptans are more effective if taken when the pain is mild or moderate. The efficacy of a triptan can be markedly attenuated if patients wait until the headache is severe to take the drug.[10] Several potential alternatives to triptans have been developed as acute migraine treatments (table 1).

	Status of clinical studies	Efficacy of treatment (based on primary endpoint)
Calcitonin gene-related peptide receptor antagonist		
Olcegepant (BIBN-4096BS)[11]	Development terminated because only intravenous administration was possible	Better than placebo (response 2 h after treatment: p=0·001)
Telcagepant (MK-0974)[12]	Development terminated because of increased liver enzymes[13]	Better than placebo (reduction of migraine or probable migraine days: p<0·05)
MK-3207[14]	Development terminated after emergence of delayed asymptomatic liver test abnormalities	Better than placebo (pain freedom at 2 h after 200 mg dose: p=0·001)
Rimegepant (BMS-927711)[15]	No future development plans have been announced owing to commercial decision	Better than placebo (pain freedom at 2 h after 75 mg, 150 mg, 300 mg dose p=0·002, p<0·001, p=0·002)
BI 44370 TA[16]	Development terminated for unknown reasons	Better than placebo (pain freedom at 2 h after 400mg dose: p=0·005)
MK-1602	Status unclear (NCT01613248)	Unknown
Serotonin 5-HT$_{1F}$ receptor agonist		
Lasmiditan (COL-144)[17]	Phase 2 proof of concept study	Of participants treated in the 10 mg, 20 mg, 30 mg, and 45 mg lasmiditan dose groups, 54–75% showed a 2 h headache response compared with 45% in the placebo group (p=0·0126 for the linear association between response rates and dose levels)
Lasmiditan (COL-144)[18]	Phase 3 study started in 2015 (NCT02439320)	Better than placebo in phase 2 (pain freedom at 2 h after 200 mg dose: p=0·032)
Combined serotonin (5-HT$_{1B/1D}$) receptor agonist and neuronal nitric oxide synthase (nNOS) inhibitor		
NXN-188[15]	Phase 2 study completed	Moderate effect compared with placebo (pain freedom at 2 h after dose: p=0·0801)
Transient receptor potential vanilloid (TRPV1) receptor modulators		
SB-705498[19]	Phase 2 study completed (NCT00269022)	Not better than placebo (pain freedom at 24 h: p value not stated)
Civamide[20]	Phase 2 study completed	Moderate effect on pain freedom (pain freedom at 2 h after either 20 µg or 150 µg dose: no placebo control group)
Glutamatergic targets		
Ketamine[21]	Phase 3 study completed 2012	Moderate effect in patients with aura- (reduction of aura severity: p=0·032)
Tezampanel (LY293558)[22]	Phase 2 study completed	Better than placebo but less effective than sumatriptan (headache response rate at 2 h: LY29358 p=0·017; sumatriptan p<0·01)
BGG492[23]	Development terminated owing to absence of efficacy	Not better than placebo (p=0·2)
LY466195[24]	Phase 2 study completed	Moderate effect compared with placebo but less effective than sumatriptan (p value not stated)
ADX10059[25]	Development terminated owing to increased liver enzymes	Better than placebo (pain freedom at 2 h after dose p=0·039)
Propofol		
Propofol[26]	Phase 2 study completed; phase 2/3 study in children started 2015 (NCT02485418)	Effect comparable to sumatriptan (high risk of addiction, therefore not recommended for treatment; pain intensity measure on a 11 point VAS: p= 0·53)
Benzopyran derivative		
Tonabersat[27]	Phase 2 studies completed, development terminated	Study results inconsistent

VAS=visual analogue scale.

Table 1: **New pharmacological treatments for acute migraine attacks**

Calcitonin gene-related peptide (CGRP) receptor antagonists

CGRP is produced in peripheral and central neurons, and acts as a potent vasodilatator. CGRP is also implicated in the transmission of pain signals in both the peripheral nervous system and the CNS, and is released during severe migraine attacks.[28,29] CGRP receptor antagonists have no effect on cerebral or systemic haemodynamics,[30] so they could be safe in patients with triptan contraindications, such as previous myocardial infarction, angina, or previous stroke.[6] In a proof-of-concept study,[11] olcegepant (BIBN-4096BS), a selective CGRP receptor antagonist,[31] was effective in 126 patients with migraine. The drug could only be given intravenously and was not further developed. Telcagepant (MK-0974), another CGRP receptor antagonist, underwent an extended development programme and was found effective in the treatment of acute migraine attacks.[12] In a study[13] in which telcagepant was planned to be given daily for 3 months for migraine prevention, the trial was terminated early when 13 patients showed a three or more times increase of alanine transaminase or aspartate transaminase. Interestingly, an analysis of the effect on migraine or probable migraine days showed a significant effect (telcagepant 140 mg=−2·7, 280 mg=−3·0, placebo=−1·6; p<0·05).[13] The follow-up compound MK-3207[14] displays roughly 400-times higher affinity than telcagepant for the human and rhesus monkey CGRP receptors compared with the rat receptor, but also had its development pathway terminated, most likely after emergence of asymptomatic liver test abnormalities in pharmacological studies during the phase 1 clinical trials.

Rimegepant (BMS-927711) is a potent, selective, competitive human CGRP receptor antagonist without vasoconstrictor effects.[32] In a randomised, double-blind,