EXPERT OPINION

Drug safety in acute migraine treatment

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Introduction: A number of drugs are available for acute migraine treatment, but they are not all effective for all patients and all attacks. The safety profiles of migraine drugs limit their use in patients with certain comorbid conditions, and adverse effects may also reduce the level of patient compliance.

Areas covered: The different types of acute migraine drugs are discussed, with particular regard to safety issues and potential adverse effects. The frequent use of analgesics, ergot alkaloids and triptans may result in the development of medication overuse headache (MOH).

Expert opinion: The initiation of a migraine attack is not fully understood, and therefore treatment aimed at causative factors is currently not available. The tolerability and adverse effects of the drugs available at present often limit their use. NSAIDs are frequently associated with gastrointestinal, and possibly also cardiovascular side effects. Ergot alkaloids may induce arterial vasoconstriction, while the administration of triptans is contraindicated in cardiovascular, cerebrovascular and peripheral vascular diseases. The frequent use of these drugs poses the risk of the development of MOH. There is a need for pathomechanism-based drugs, and for the future achievement of personalized medicine.

Keywords: acute treatment, efficacy, migraine, safety, tolerability

1. Introduction

Migraine is a primary headache disorder with a considerable socio-economic and personal impact. Its exact pathomechanism has not yet been fully clarified [1], and there is an ongoing debate regarding the vascular or neuronal, cortical or brainstem origin [2,3]. Most of the drugs used in migraine therapy are not disease-specific and do not target the pathobiochemical basis of the disease [4]. The primary aim of drug development is to achieve a proactive P4 medicine that is predictive, preventive, personalized and participatory [5].

The adverse events (AEs) associated with the use of different drugs are an important aspect in the daily clinical practice, because the treatment decision must take into consideration not only the efficacy but also the safety of the pharmacon. AEs, tolerability AEs and safety AEs have been defined as follows [6]: 'AEs are defined as any unusual event that follows medication use'; 'tolerability AEs are irritating to a patient, but are not significant in terms of morbidity or mortality'; and 'safety AEs are those side effects that endanger a patient.' Tolerability AEs are important as they may influence patient compliance and adherence to a medication, whereas safety AEs may lead to the hospitalization of the patient and may necessitate therapy. AEs are associated with a considerable economic impact and lead to high direct and indirect costs for the community. A multi-centre retrospective cohort study revealed that AEs in hospitals are associated with more than USD 3000 of adjusted additional average hospitalization cost per AE and with an increased length of stay in the hospital [7]. Overall direct costs related to AEs were estimated to be of

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Article highlights.

- Migraine is a primary neurovascular headache disorder, the pharmacological management of which is challenging.
- The acute treatment of migraine consists in both aspecific and specific pharmacological therapy; drugs achieving the Level A recommendations are discussed in this review.
- The safety profile of the different drugs used in the acute therapy of migraine are discussed, including NSAIDs, ergot alkaloids and triptans.
- The regular excessive use of these drugs is accompanied by the risk of development of medication overuse headache.
- Special focus is placed on the pharmacological treatment of migraine attacks during pregnancy and breastfeeding.

This box summarizes key points contained in the article.

USD 21 million per 100,000 adult inhabitants per year, which highlights the importance of AEs to the society [8].

This review addresses both common and uncommon safety issues relating to the currently available options for the acute treatment of migraine. A literature search was conducted on 1 December 2014 in databases of PubMed, Cochrane Central, Medline for articles related to acute migraine therapy. We included randomized, double-blind, placebo- and/ or active-controlled studies, case reports and reviews regarding medications used in acute migraine therapy. Priority was given to drugs with the highest level of recommendation (Level A) based on the European Federation of Neurological Societies (EFNS), the American Academy of Neurology and the American Headache Society guidelines [9-12].

2. Acute migraine therapy

Medications used to treat acute migraine attacks can be divided in two groups: non-specific and migraine-specific treatments [13]. Non-specific medications include drugs which can be used to treat any pain conditions, such as NSAIDs, opiates or combination of analgesics. Antiemetics are also widely used to treat migraine-associated symptoms; however, these treatments are also non-specific. Ergotamine, dihydroergotamine (DHE) and triptans are considered as migraine-specific medications [13].

In this review, we focus only on drugs reaching level A recommendation; however, a number of other medications are also widely used by patients and prescribed by general practitioners, including metamizole, opiates and combinations such as butalbital plus aspirin plus caffeine or butalbital plus aspirin plus caffeine plus codeine [9,14]. Notably, however, the use of these medications can be associated with several AEs; therefore, caution is needed with their used. Butalbital-containing combinations pose a risk of overuse and development of medication overuse headache

(MOH) [14]. Opioids also have a sedative effect, which may put patients at risk. American and European guidelines both suggest that the use of opioids should be limited because of limited efficacy, sedative effects and the risk of abuse [9,14,15].
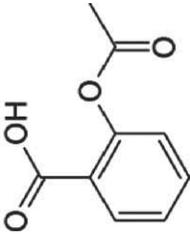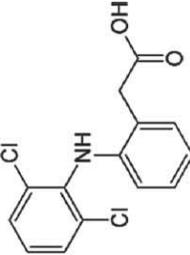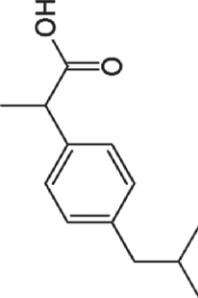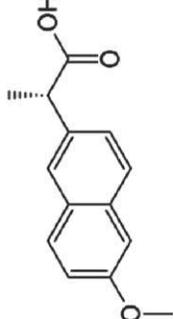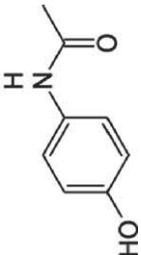
2.1 Analgesics (NSAIDs, paracetamol)

For mild-to-moderate migraine headache attacks, the drugs of first choice are analgesics [9].

2.1.1 Efficacy of NSAID monotherapy

As an irreversible COX-1 inhibitor that blocks the production of thromboxane A2, aspirin decreases platelet aggregation (**Table 1**) [16]. Aspirin is widely used as an antiplatelet drug, but it is an effective medication in acute migraine therapy as well. Evidence indicates that platelet aggregation is increased in migraineurs both ictally and interictally, which is possibly related to alterations in eicosanoid synthesis in platelets [17-19]. Aggregating platelets can lead to serotonin release, which may contribute to migraine pathomechanism [20]. Another important aspect is the increased risk of migraineurs to develop ischemic stroke and myocardial infarction, particularly in migraine with aura. The risk for ischemic stroke is especially high in women taking oral contraceptives and smoking [21,22]. Furthermore, aspirin may exert its beneficial effects in migraine through local analgesic effects, the modulation of cerebral serotonin metabolism as well as the inhibition of central trigeminal activation as demonstrated in a feline model of migraine [23]. In humans, following trigemino-nociceptive stimulation, aspirin acted on central pain processing structures such as the anterior cingular cortex and the secondary somatosensory cortex [24]. The number needed to treat (NNT) to achieve complete freedom from pain was 8.1 for 900 or 1000 mg aspirin tablets or soluble formulations, which proved to be superior to placebo [25]. The efficacy of effervescent aspirin was significantly better than that of placebo: a pain-free state at 2 h was achieved in 27.1 versus 15.1% for placebo [26,27].

Diclofenac is a phenylacetic acid derivative with a higher affinity for COX-2 inhibition than for COX-1 [28]. In addition to COX inhibition, however, acid-sensing ion channels represent another possible target of diclofenac in migraine, as the drug was able to directly inhibit their activity and expression in sensory neurons in dorsal root ganglion of rats, which mechanism can also counteract pain [29]. Accordingly, local application of diclofenac into migraine-related CNS structures, for example, thalamus, hypothalamus and nucleus raphe magnus attenuated pain transmission in experimental animals [30-32]. Its available formulations include tablets, powder and intravenous injections, which possess different pharmacokinetic parameters. In different phase clinical trials, both diclofenac potassium and epolamine were significantly more effective than placebo for the acute treatment of migraine either by relieving the pain or by diminishing the migraine-related symptoms [33-35]. Diclofenac epolamine led to a pain-free condition at 2 h in 45.8% of the patients, as

Table 1. Pharmacological and clinical data of NSAIDs and paracetamol in acute treatment of migraine.

Drug name (generic)	Aspirin	Diclofenac	Ibuprofen	Naproxen	Paracetamol
Systematic (IUPAC) name	2-(acetyloxy)benzoic acid	2-(2-(2,6-dichlorophenyl)amino)phenyl)acetic acid	(RS)-2-(4-(2-methylpropyl)phenyl) propionic acid	(+)-(S)-2-(6-methoxynaphthalen-2-yl) propionic acid	N-(4-hydroxyphenyl)ethanamide N-(4-hydroxyphenyl)acetamide
Mechanism of action	Irreversible COX-1 inhibitor	Higher affinity for COX-2 than COX-1 inhibition	Prostaglandin synthesis inhibitor	Non-selective COX-1 and COX-2 inhibitor	COX-1 and COX-2 inhibitor and mediator of the activation of descending serotoninergic pathways
Route of administration	p.o., i.v.	p.o.	p.o.	p.o.	p.o., rectal
Dosage	1000 mg (p.o.) 1000 mg (i.v.)	50-100 mg (p.o.)	200 – 800 mg	500 – 1000 mg	1000 mg (p.o.)
Chemical structure					
Pharmacokinetic parameters					
C_{max}	4.4 µg/ml (500 mg tablet)	1.071 ng/ml (50 mg tablet) 2.213 ng/ml (50 mg powder)	Ibuprofen (R-) 15.4 µg/ml (400 mg tablet) ibuprofen (S+) 16.2 µg/ml (400 mg tablet)	68.9 mg/l (500 mg tablet)	17.98 µg/ml (film-coated tablet) 20.73 µg/ml (effervescent tablet)
AUC	6.5 µg/h/ml (500 mg tablet)	1.214 ng/h/ml (50 mg tablet) 1.362 ng/h/ml (50 mg powder)	ibuprofen (R-) 44.4 µg/h/ml (400 mg tablet) ibuprofen (S+) 67.4 µg/h/ml (400 mg tablet)	786.2 mg/h/L (500 mg tablet)	52.6 µg/h/ml (powder) 56.3 µg/h/ml (tablet)
T_{max}	45 min (500 mg tablet)	0.885 h (50 mg tablet) 0.228 h (50 mg powder)	ibuprofen (R-) 1.0 h (400 mg tablet) ibuprofen (S+) 1.0 h (400 mg tablet)	2.89 h (500 mg tablet)	0.40 h (effervescent tablet) 0.88 h (film-coated tablet)
$T_{1/2}$	0.54 h (500 mg tablet)	1.03 h (50 mg tablet) 1.15 h (50 mg powder)	ibuprofen (R-) 1.6 h (400 mg tablet) ibuprofen (S+) 2.4 h (400 mg tablet)	12 – 24 h	2.65 h (film-coated tablet) 2.81 h (tablet)

AUC: Area under the plasma concentration curve; i.m.: Intramuscular; IUPAC: International Union of Pure and Applied Chemistry; i.v.: Intravenous; p.o.: Peroral; UGT: Uridine 5'-diphosphoglucuronosyltransferase.

Table 1. Pharmacological and clinical data of NSAIDs and paracetamol in acute treatment of migraine (continued).

Drug name (generic)	Aspirin	Diclofenac	Ibuprofen	Naproxen	Paracetamol
Metabolism	Hepatic CYP 2C9 UGT 1A6	Hepatic CYP 2C9	Hepatic CYP 2C9	Hepatic CYP 2C9 CYP 1A2	Hepatic CYP 2E1
Excretion	Renal (80 – 100%)	Renal (65%) biliary (35%)	Renal (95%)	Renal (70%)	Renal (85 – 90%)
Availability (USA/EU)	USA/EU	USA/EU	USA/EU	USA/EU	USA/EU
Pivotal trial(s)	[27]	[33]	[40]	[148]	[48]
Ref.	[9,25,49]	[9,28,36,37]	[9,38,54]	[9,41,45]	[9,47,56,57]

AUC: Area under the plasma concentration curve; i.m.: Intramuscular; IUPAC: International Union of Pure and Applied Chemistry; i.v.: Intravenous; p.o.: Peroral; UGT: Uridine 5'-diphosphoglucuronosyltransferase.

compared with 25.1% for placebo [35]. Diclofenac potassium powder achieved the same effect in 24.7 versus 11.7% for placebo [36]. Light hypersensitivity was reduced in 31.4%, noise hypersensitivity in 31.1%, nausea in 20.4% and vomiting in 4.9% for diclofenac epolamine, in comparison with 20.1, 14.8, 4.9 and 2.6%, respectively, for placebo. Diclofenac is considered to be an effective anti-migraine drug, especially in mild-to-moderate migraine attacks [37].

Ibuprofen represents another compound in the NSAIDs group. In addition to its antinociceptive effect achieved via COX inhibition, but experimental data indicate that ibuprofen is also capable of preventing pain behavior induced by NMDA activation [30]. Ibuprofen (R/S) has two enantiomers: the S(+) enantiomer is a strong prostaglandin synthesis inhibitor, while the R(-) enantiomer is less active [38]. A meta-analysis revealed that ibuprofen in doses of 200 or 400 mg was effective for pain relief in acute migraine: the NNT to achieve a pain-free state at 2 h for 200 mg ibuprofen was 13, and for 400 mg ibuprofen was 9 [39]. Another study confirmed that the pain was reduced to mild or none in 41.7% after 200 mg ibuprofen, and in 40.8% after 400 mg as compared with 28.1% after placebo [40].

Naproxen is a stereochemically pure NSAID of the 2-aryl-propionic acid class [41]. It is a non-selective inhibitor of COX-1 and COX-2 [26]. Naproxen is presumed to exert its effect in migraine by influencing the trigeminovascular system (TS). *In vitro* studies revealed that naproxen dose-dependently blocks the ATP receptors (P2X3) in cultured rat trigeminal neurons [42], and it was shown to inhibit the peripheral sensitization of meningeal nociceptors in rats *in vivo* [43]. In another experimental study, parenteral administration of naproxen blocked the activation of central trigeminovascular neurons in the trigeminal nucleus caudalis (TNC) in rats, indicating the potential of naproxen on central sensitization [44].

A meta-analysis revealed that naproxen sodium in a dose of 500 or 825 mg was more effective than placebo in reducing the intensity of migraine headache and in improving migraine-associated symptoms; the NNT to achieve a pain-free condition was 10, which is comparable with that of 400 mg of ibuprofen [26,45]. Naproxen was significantly better than placebo: the relative risk to achieve a pain-free response within 2 h was 4.26 for 825 mg of naproxen versus 1.83 for 500 mg [26].

2.1.2 Efficacy of paracetamol (acetaminophen)

The exact mechanism of action of paracetamol is still debated. While its inhibitory effect on the COX-1 and COX-2 metabolism is widely accepted, paracetamol also exerts a central analgesic effect is mediated through the activation of descending serotoninergic pathways, and the inhibition of thalamic nociceptive activity [46,47]. Furthermore, paracetamol is also capable of inhibiting hyperalgesia after activation of NMDA or substance P receptors [30]. A randomized placebo-controlled trial demonstrated that a paracetamol dose of 1000 mg was significantly more effective than placebo for

Table 2. Adverse events following the use of NSAIDs and paracetamol in the acute therapy of migraine.

	CNS-related AEs	Gastrointestinal-related AEs	Ref.
NSAIDs			
Aspirin	Tinnitus	Gastric ulcer	[50]
	Taste perversion	Dyspepsia	[52]
		Nausea, vomiting	[25,53]
Diclofenac	Dizziness	Nausea	[36,37]
Ibuprofen	No data	Nausea, vomiting	[40]
		Abdominal pain	[54]
Naproxen	Dizziness	Nausea	[26]
	Tinnitus	Dyspepsia	[55]
		Abdominal pain	
Paracetamol	Hyperacusis	Nausea	[56]
	Photophobia	Liver toxicity	[57]

AE: Adverse event.

Table 3. Frequency of adverse events following the administration of drugs used in the acute therapy of migraine.

	AEs > 10%	AEs 5 – 10%	AEs 1 – 5%	AEs < 1%	Ref.
NSAIDs					
Aspirin		GI-related AEs	CNS-related AEs		[25,51,52]
Diclofenac			GI-related AEs	CNS-related AEs	[36,37]
Ibuprofen	GI-related AEs				[40,54]
Naproxen			GI-related AEs		[26,55]
			GI-related AEs		
			Chest-related AEs		
Paracetamol	CNS-related AEs				[56,57]
Ergot alkaloids					
Ergotamine	CNS-related AEs	GI-related AEs			[80]
dihydroergotamine					
Triptans					
Sumatriptan		CNS-related AEs	Heaviness		[91,121]
		Skin irritation	Chest pain		
Eletriptan		GI-related AEs	CNS-related AEs		[122,123]
			Chest tightness		
Zolmitriptan	CNS-related AEs	Chest-related AEs			[99,101,124]
	GI-related AEs				
Rizatriptan			CNS-related AEs		[103]
			GI-related AEs		
Naratriptan		GI-related AEs	CNS-related AEs		[125]
Almotriptan			CNS-related AEs		[108]
			GI-related AEs		
Frovatriptan		CNS-related AEs	CNS-related AEs		[110]
			GI-related AEs		
			Skin-related AEs		
			Chest pain		
			Skeletal pain		

AE: Adverse event; GI: Gastrointestinal.

the relief of acute migraine pain and migraine-associated symptoms [48], the rate of drug-related AEs in the paracetamol-treated group was 10.2%, as compared with 14.8% in the placebo group. It reduced the migraine pain to mild or none in 2 h in 52%, as compared with 32% for placebo; the NNT was 12 [48,49].

2.1.3 *Safety and tolerability of NSAIDs and paracetamol*

The AEs of aspirin are generally mild or moderate and transient, and the most affected organ system are the gastrointestinal (GI) tract and the nervous system (Tables 2 and 3) [25]. The well-known aspirin-associated GI disturbances include

gastric ulcer, which is thought to be caused by suppression of prostaglandin synthesis by aspirin. In low-dose aspirin users, most of the gastric ulcers are asymptomatic [50]. A high single-dose (1000 mg) of aspirin for acute migraine treatment affected the GI system in 5.9% of the cases (number-needed-to-harm: 42) [51]. Data from a meta-analysis of the use of effervescent 1000 mg aspirin for the acute treatment of migraine headache demonstrated an overall AE rate of 12%, of which 3.6% were GI and 1.8% affected the nervous system [52]. Another study demonstrated that 38% of the AEs reported following a single 900 mg dose of mouth-dispersible aspirin for the treatment of migraine attack were GI disturbances on the day of treatment. Subsequent to the intake of aspirin, dyspepsia, nausea and vomiting occurred as GI symptoms [53]. The non-GI AEs observed included tinnitus, coughing and taste perversion [53]. There are data indicating that the incidence of GI AEs after aspirin administration is comparable to that following ibuprofen administration [49].

Diclofenac is associated with a low rate of side effects, which are mostly mild and transient and occur at the same rate as with placebo [37]. Among the outcomes of Phase III trials, no serious AEs were reported. The most common AEs were GI, for example, nausea (around 3%), or nervous system-related, for example, dizziness (around 1%) [36].

A randomized controlled trial demonstrated that drug-related AEs of ibuprofen 200 mg and 400 mg occurred in 27.8 and 26% of the cases, respectively. The rates of GI-related AEs were reported to be as follows: nausea 24.5% (200 mg) and 21.5% (400 mg), vomiting 4.2% (200 mg) and 4.5% (400 mg), and abdominal pain 1.4% (200 mg) and 0.4% (400 mg) [40]. Ibuprofen furnishes effective treatment for acute migraine with only mild and transient AEs [54].

The safety profile of naproxen sodium was worse than that of placebo (pooled risk ratio 1.29, 95% CI 1.04 – 1.60, p = 0.02). The observed AEs were nausea (1%), dizziness (2%), dyspepsia/abdominal pain (2%), chest tightness (2%) and tinnitus (2%) [26,55]. Although naproxen sodium is effective in reducing migraine pain and migraine-associated symptoms relative to placebo, its NNT is high; therefore, not every patient can benefit from its use. Generally, however, naproxen is safe and the associating AEs are rare.

The most common AEs of paracetamol occurred in the special senses (hyperacusis 19.2%, photophobia 15.8% and nausea 14.7%). A serious AE (liver toxicity) can emerge when paracetamol is taken regularly and in large doses (> 4 g/day) [56]. Paracetamol in a dose of 1000 mg is superior to placebo in the treatment of acute migraine, and its AEs do not differ significantly from those of placebo [57].

2.1.4 *NSAIDs in combination with caffeine*
The fixed combination of 250 mg aspirin + 200 mg paracetamol + 50 mg caffeine is effective in acute migraine treatment and is ranked Level A in the EFNS guidelines [9]. Another study demonstrated that the combination 500 mg aspirin + 500 mg paracetamol + 130 mg caffeine was superior to 400 mg ibuprofen, and to the ingredients of the combination administered alone or in dual combination for migraine pain relief (the pain was reduced to mild or none in 67% of the cases for the combination versus 62% for ibuprofen) [58,59]. Caffeine exerts its effect as an adenosine antagonist, through which it is also able to stimulate cholinergic neurons and to inhibit COX-2 protein synthesis [46]. Experimental data indicate that the combination of aspirin, paracetamol and caffeine has a synergistic effect on COX inhibition [46]. Moreover, caffeine not only potentiates the analgesic effect, but may also prevent the sedating AE of these substances, for example, the sedating effect of butalbital and codeine in the fixed drug combination of aspirin+butalbital+codeine+caffeine [60,61]. On the other hand, a dose of over 200 – 300 mg caffeine may induce dysphoria, vomiting or motor unrest [62]. Another important aspect of the potentiating effect caffeine is that it can permit the reduction of analgesic dose, which may also reduce the risk of potential AEs such as liver toxicity induced by paracetamol. GI AEs are well-known risks of analgesics, and clinical studies indicated that the combination of paracetamol + aspirin + caffeine was associated with a higher risk of GI complaints than either ibuprofen or sumatriptan. However, these AEs were generally mild, and no serious AEs have been reported [59,63]. The presence of caffeine does not increase renal toxicity, and there is no evidence of a greater risk of MOH or physical dependence in a combination with analgesics than for caffeine alone [46,64]. The multicomponent drugs may be generally more effective than the single substances and are generally not associated with a higher risk of AEs.

2.1.5 *NSAIDs in combination with antiemetics*
NSAIDs such as aspirin, diclofenac, ibuprofen, naproxen and paracetamol are often combined with antiemetics with the aim of diminishing acute migraine headache. Antiemetics may increase the extent of NSAID absorption from the GI tract. Metoclopramide and domperidon are suggested for the purpose of Level B recommendation [9]. Various routes of administration of metoclopramide are available, for example, oral, suppository, intramuscular, intravenous and subcutaneous. Metoclopramide is usually well tolerated and is generally associated with mild side effects such as drowsiness, restlessness or bowel disturbances [65]. Metoclopramide is an antagonist of central dopaminergic receptors; therefore, especially at higher doses, extrapyramidal side effects may develop such as tardive dyskinesia, drug-induced parkinsonism and akathisia [66,67]. Interestingly, tardive dyskinesia was more severe in diabetic patients compared to non-diabetics [66]. In patients with renal impairment, the risk of developing extrapyramidal side effects is higher; therefore the dose of metoclopramide has to be reduced [68]. Rapid intravenous administration of metoclopramide may induce cardiac arrest, representing a rare but serious AE [69]. Domperidone, another antiemetic, has a better safety profile as it does not cross the

blood–brain barrier, and therefore, extrapyramidal side effects do not develop in adults [70].

2.1.6 NSAIDs and cardiovascular risk

There has been no systematic review of cardiovascular AEs following the use of NSAIDs in migraine treatment. The relationship between the administration of NSAIDs and cardiovascular AEs is still debated. Awareness of the potential cardiovascular risks of NSAID users were highlighted by the VIGOR study in 2000, which reported that rofecoxib increased the risk of myocardial infarction [71]. A large UK meta-analysis led to the conclusion that the vascular risk of high-dose diclofenac and possibly ibuprofen was comparable to that of selective COX-2 inhibitors (coxibs), while high-dose naproxen had less vascular risk than that with other NSAIDs [72]. Major coronary events were more frequent with coxibs, diclofenac and ibuprofen, whereas major vascular events were associated only with coxibs and diclofenac. Naproxen did not increase the risk of vascular death, major coronary events or major vascular events as serious AEs in comparison with coxibs and diclofenac [72]. The risk of heart failure was higher in diclofenac, ibuprofen and naproxen. Neither NSAID was associated with an increased risk of stroke [72]. In spite of these data, the US FDA has recently (February 2014) reported that the current data did not indicate that naproxen had a lower risk of thrombotic events than other NSAIDs [73].

The relative risks or odds ratios (OR) associated with NSAIDs to develop cardiovascular events are below 2 [74]. Randomized clinical trials and observational studies have suggested that the risk of cardiovascular events related to the use of NSAIDs is clearly dose- and duration-dependent [75].

2.1.7 Summary of NSAIDs

In general, the use of NSAIDs is associated with low rates of AEs, generally manifesting in nausea, peptic ulcer, dizziness, tinnitus, hepatotoxicity and nephropathy as the most common. The contraindications of the administration of NSAIDs are peptic ulcer, bowel diseases, hemorrhagic stroke and the third trimester of pregnancy [76]. However, the first-line use of NSAID/aspirin medication proved to be 10% among diagnosed gastroesophageal reflux disease (GERD) patients. In one study, 22% of migraineurs reported the existence of GERD [77]. The risk of developing NSAID-related GI complications is significantly higher in older patients, in case of pre-existing gastric ulcer, in case of concomitant use of oral anticoagulants or corticosteroids, among alcoholics or smokers, as well as in patients with Helicobacter pylori infection [78]. Non-selective NSAIDs pose a significantly higher risk of GI toxicity than COX-2-selective ones, and their toxic effect increases with dose. The risk of dying of peptic ulcer bleeding is estimated to be around 5% in Europe, US and Asia as well [79]. The presence of gastric ulcer represents an absolute contraindication for NSAIDs. In the presence of other risk factors, the use of these medications needs to be

carefully considered, and caution is recommended. Among the other GI-related AEs, nausea and vomiting are most frequently associated with the use of ibuprofen, and less frequently with naproxen and diclofenac.

In patients with high cardiovascular risk, caution is needed when considering NSAID therapy. In such a case, naproxen is probably a better choice than diclofenac or ibuprofen. Cardiovascular risk related to NSAIDs is most likely dose-dependent; therefore, if low doses are used to treat a migraine attack, the associating risk of developing major vascular events is low. The overuse of NSAIDs involves a low risk of transformation from an episodic state to a chronic form of migraine [76].
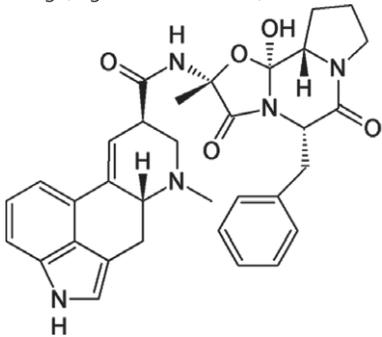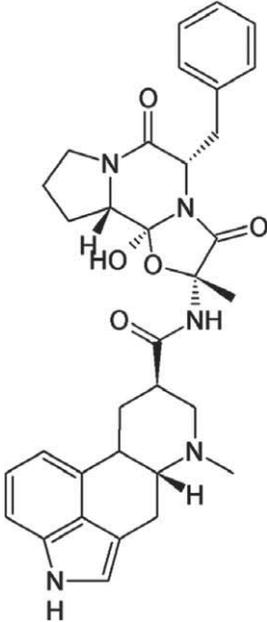
2.2 Ergot alkaloids

One of the oldest groups of medication for the treatment of migraine attack are the ergot alkaloids. The first publication relating to the use of ergotamine tartrate for migraine therapy dates from 1934 and the administration of DHE was reported in 1945 [80]. DHE and ergotamine display broad monoaminergic receptor affinity (e.g., 5-hydroxytryptamine [5-HT$_{1B/1D/1A}$] agonists, dopamine D$_2$ agonists and epinephrine agonists) (Table 4). Ergotamine was capable of blocking neurogenic inflammation by preventing plasma extravasation in the dura mater of rats [81]. Regarding DHE, evidence indicates that it is able to influence the pain-processing nuclei in the brainstem [82]. The various routes of administration available for DHE include intravenous, intramuscular, intranasal, subcutaneous and orally inhaled. Oral DHE tablets are not available because of the poor bioavailability [80,83].

DHE administered by the intravenous, intramuscular, subcutaneous, intranasal route or orally inhaled is more effective than placebo for the treatment of a migraine attack [80,84,85]. Orally inhaled administration of DHE was achieved at 2 h pain relief in 59% of the migraine patients compared to 35% in placebo group [80,84,85]. Ergotamine is also an effective therapeutic option for diminishing migraine pain [86]. In one prospective clinical trial, the AEs following intravenous DHE administration were nausea (72%), light-headedness (33%) and leg cramps (23%) (Tables 3 and 5) [80]. Subsequent to an intranasal DHE formulation, the commonly observed AEs were rhinitis (26%), nausea (10%) and an altered sense of taste (8%) [80]. One the other and, frequent use of ergotamine has been associated with the development of pericardial, pulmonary and retroperitoneal fibrosis. These rare complications are suggested to be serotonergic-related idiosyncratic responses. Fibrotic AEs have been reported in connection with DHE only in rare cases [80].

Serious AEs after the use of DHE are relatively rare. Vasoconstrictive AEs are not common after any DHE formulation, comparatively, arterial vasoconstriction was frequent when ergotamine was used [80]. This difference can be explained by their different pharmacological properties, as DHE is a less potent arterial vasoconstrictor than ergotamine, even though they induce venoconstriction in a similar level [80].

Table 4. Pharmacological and clinical data of ergot alkaloids in acute treatment of migraine.

Drug name (generic)	Ergotamine	DHE
Systematic (IUPAC) name	(6aR,9R)-N-((2R,5S,10aS,10bS)- 5-benzyl-10b-hydroxy-2-methyl- 3,6-dioxooctahydro-2H-oxazolo[3,2-a] pyrrolo[2,1-c]pyrazin-2-yl) -7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg] quinoline-9-carboxamide	(2R,4R,7R)-N-[(1S,2S,4R,7S)-7-benzyl-2-hydroxy-4-methyl-5,8-dioxo-3-oxa-6,9-diazatricyclo[7.3.0.0^{2,6}]dodecan-4-yl]-6-methyl-6,11-diazatetracyclo[7.6.1.0^{2,7}.0^{12,16}]hexadeca-1(16),9,12,14-tetraene-4-carboxamide
Mechanism of action	5-HT$_{1B/1D/1A}$ receptor agonist dopamine D2 receptor agonist epinephrine receptor agonist	5-HT$_{1B/1D/1A}$ receptor agonist dopamine D2 receptor agonist epinephrine receptor agonist
Route of administration	p.o., rectal	Nasal, orally inhaled, s.c., i.m., i.v.
Dosage	2 mg (ergotamine tartrate)	3 mg (DHE mesylate)
Chemical structure		

Pharmacokinetic parameters

	Ergotamine	DHE
C_{max}	454 pg/ml (2 mg rectal) 21 pg/ml (2 mg p.o.)	45.289 pg/ml (1 mg i.v.) 1.145 pg/ml (1 mg orally inhaled)
AUC	3.91 ng/h/ml (0.25 mg i.v.)	610 pg/h/ml (1 mg i.v.) 175 pg/h/ml (1 mg orally inhaled)
T_{max}	69 min (2 mg p.o.)	6 min (1 mg i.v.) 12 min (1 mg orally inhaled)
$T_{1/2}$	2 h	11.8 h (1 mg i.v.) 10.7 h (orally inhaled)
Metabolism	Hepatic CYP 3A	Hepatic CYP 3A4
Excretion	Biliary (90%)	Biliary
Availability (USA/EU)	EU	USA
Pivotal trial(s)	[86]	[85]
Ref.	[80]	[80,83,84]

5-HT: 5-hydroxytryptamine; AUC: Area under the plasma concentration curve; DHE: Dihydroergotamine; i.m.: Intramuscular; IUPAC: International Union of Pure and Applied Chemistry; i.v.: Intravenous; p.o.: Peroral; s.c.: Subcutaneous.

Table 5. Adverse events following the use of ergot alkaloids and triptans in the acute therapy of migraine.

	CNS-related AEs	Gastrointestinal-related AEs	Skin-related AEs	Any AEs	Ref.
Ergot alkaloids					
Ergotamine DHE	Light-headedness Leg cramps Altered sense of taste	Nausea	No data	Arterial vasoconstriction	[80]
Triptans					
Sumatriptan	Fatigue Paraesthesia Disgeusia Sedation	No data	Flushing Skin irritation	Heaviness Chest pain	[121] [89]
Eletriptan	Dizziness Somnolence	Asthenia Nausea	No data	Chest tightness	[122]
Zolmitriptan	Dizziness Paresthesia Somnolence	Nausea	No data	Chest tightness	[99] [101] [124]
Rizatriptan	Dizziness Somnolence	Asthenia Nausea	No data	No data	[103]
Naratriptan	Tingling	Nausea Vomiting	No data	No data	[125]
Almotriptan	Dizziness Somnolence Paraesthesia	Nausea Vomiting	No data	Chest tightness	[108]
Frovatriptan	Dizziness Fatigue Paraesthesia	Dry mouth Dyspepsia	Flushing	Skeletal pain Chest pain	[110]

AE: Adverse event; DHE: Dihydroergotamine.

Ergotamine is therefore contraindicated in cases of vertebro-basilar migraine or prolonged aura [80]. A recent systematic review of observational studies revealed that the pooled OR of serious ischemic events was 2.28 (95% CI 1.18 – 4.41) for ergotamine compounds (ergotamine or DHE) administered for acute migraine treatment [87]. The risk of developing ischemic stroke is elevated in women with migraine with aura, especially if they smoke or take hormonal contraceptives [88,89]. Therefore, in those women suffering from migraine with aura who smoke and take hormonal contraceptives at the same time, ergotamine and DHE are not recommended.

Ergotamine is more likely to cause MOH [80]. This difference can be explained the different pharmacokinetic profiles of DHE and ergotamine, The elimination of DHE is biphasic and has a long elimination half-life [80]. The availability of the various routes of administration of DHE is favorable for the daily clinical practice, and DHE is effective and well tolerated in the treatment of migraine attacks.

2.3 Triptans

Triptans are the drugs of first choice for the acute treatment of moderate-to-severe migraine headaches [9]. Seven different triptans are currently available: sumatriptan, eletriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan and frovatriptan (**Table 6**).

2.3.1 *Efficacy of triptan monotherapy*

Sumatriptan is a selective 5-HT$_{1B/1D/1F}$ receptor agonist, and it also has a potency to influence serotonergic

neurotransmission in the brainstem, predominantly in the dorsal raphe nucleus (**Table 6**) [90]. Oral sumatriptan proved to be more effective than placebo, and the Cochrane Database reviews reported that sumatriptan by any route of administration was superior to placebo as concerns the efficacy outcome [91,92]. Oral 50 mg sumatriptan provided complete pain relief in 28% of the patients, as compared with 11% for placebo [91]. The most effective dose of sumatriptan for pain relief at 2 h was 100 mg orally (NNT 3.5), 6 mg subcutaneously (NNT 2.1), 20 mg intranasally (NNT 3.5) or 25 mg rectally (NNT 2.4) [91]. The efficacy results from clinical trials of the iontophoretic sumatriptan patch revealed that the freedom from pain at 2 h was NNT 11.1 [93,94].

Eletriptan is a selective 5-HT$_{1B/1D/1F}$ receptor agonist and in preclinical studies has been demonstrated to modulate the activation of the TS [95]. Eletriptan is more lipophilic than other triptans and readily reaches the CNS. It demonstrates significant efficacy in the acute treatment of migraine to achieve complete pain relief in 2 h in doses of 40 and 80 mg versus placebo (27, 27 and 4%, respectively) [96,97]. Zolmitriptan, a member of the tryptamine-based drug family, binds to 5-HT$_{1B/1D}$ and 5-HT$_{1A/1F}$ receptors, and it is also influences trigeminal pain processing, as indicated by the inhibition of the nociceptive blink reflex response [98,99]. It is available as an oral formulation (2.5 and 5 mg tablets) and a nasal spray (5 mg). Zolmitriptan is effective relative to placebo in the acute treatment of migraine [99-101]. Oral zolmitriptan in a dose of 2.5 or 5 mg achieved complete headache

relief at 2 h, with the same efficacy as sumatriptan 50 mg (66, 67 and 68%, respectively).

Rizatriptan is a potent agonist with high affinity for the $5HT_{1B/1D}$ receptor, and it exerts inhibitory effects on nociceptive neurotransmission in the TNC and on the activation of the nucleus raphe magnus after trigeminal activation [102]. Oral 5 and 10 mg tablets and a disintegrating wafer formulation containing 10 mg are available [103]. Rizatriptan proved more effective than placebo in migraine attack therapy (pain-free 40 – 42 vs 7 – 10% for placebo) [103,104].

Naratriptan has high affinity for $5\text{-HT}_{1B/1D/1F}$ receptors exerting its beneficial effect on trigeminovascular neurons [105]. Naratriptan has higher bioavailability than those of other orally administered triptans [106]. Naratriptran is effective relative to placebo in the acute treatment of migraine: the headache relief at 2 h was 52 versus 31% with placebo [107].

Almotriptan acts on the $5\text{-HT}_{1B/1D/1F}$ receptors. Almotriptan in a dose of 12.5 mg is superior to placebo for the acute treatment of migraine: the relative risk to achieve complete pain relief was 2.15 compared to placebo [108,109].

Frovatriptan exerts potent effects on the $5\text{-HT}_{1B/1D}$ receptors, while it has moderate affinity for $5\text{-HT}_{1A/1F}$ receptors [110]. The efficacy of oral frovatriptan to achieve pain relief within 2 h in acute migraine therapy was better than that of placebo: 37 – 46 versus 21 – 27% [111-114].

2.3.2 Combination of triptans and NSAIDs

The combined administration of sumatriptan with naproxen represents an effective treatment of migraine attacks, providing better pain relief than either of the two drugs applied alone in the same dose, and exhibiting good tolerability at the same time [115]. Furthermore, in migraineurs who displayed poor response to triptans administered alone, this combination was significantly more effective than placebo [116]. This combination was generally well tolerated, with the most frequent AE being chest pain, but no serious AEs were reported [116]. Similarly, combinations of rizatriptan plus rofecoxib, almotriptan plus aceclofenac or frovatriptan plus dexketoprofen all exhibited better efficacy than the listed drugs alone, while the frequency of AEs was not significantly different for either combination compared to the corresponding triptan alone [117-120]. The good efficacy of frovatriptan plus dexketoprofen was also proved in menstrually related migraine [117]. These studies all confirmed that the combination of triptans with NSAIDs is superior to the monotherapy in case of each of these medications, while the tolerability and safety profiles are comparable.

2.3.3 Safety and tolerability of triptans

Sumatriptan-associated AEs vary with the formulation. AEs were generally found to be infrequent after oral administration and included fatigue (6%), paraesthesia (5%), heaviness (4%) and chest pain (3%) (**Tables 3** and 5). Following the intranasal form, taste disturbances and disgeusia occurred in up to 30% of the cases, while after the subcutaneous form,

local reactions and flushing were most common [121]. Use of the transdermal patch was associated with skin irritation (8%), pain (23%) and paraesthesia (12%). The suppository form has been reported to cause sedation in 6% of the cases [121]. The AEs tend to be more common following administration via the injectable route and following oral or intranasal administration of higher doses [91].

The AEs of eletriptan are dose-related: following the 20 mg dose, they were equivalent to those after the placebo, the 40 mg dose led to only a slightly higher frequency (2%) than after the placebo, while the 80 mg dose resulted in increased rates of AEs (1 – 7%) [122]. The most frequent AEs were asthenia (20 mg: 4%; 40 mg: 5%; 80 mg: 12%), nausea (20 mg: 5%; 40 mg: 7%; 80 mg: 10%), dizziness (20 mg: 3%; 40 mg: 5%; 80 mg: 7%), chest tightness (20 mg: 1%; 40 mg: 2%; 80 mg: 5%) and somnolence (20 mg: 3%; 40 mg: 5%; 80 mg: 6%) [122,123]. Eletriptan has a very high safety and tolerability profile [122].

The AEs observed following a 5 mg dose of zolmitriptan were asthenia (14%), nausea (12%), paraesthesia (11%), dizziness (11%), somnolence (10%) and chest tightness (7%) [99,124].

The most common (fewer than 10% of the migraine patients) dose-related AEs of 10 mg rizatriptan were nausea (4%), somnolence (4%), dizziness (2%) and asthenia/fatigue (2%) [103]. The AE profile of naratriptan includes mainly mild AEs, indicating that naratriptan is well tolerated [106,111]. The most frequent AEs of 2.5 mg naratriptan: nausea (7%) vomiting (7%) and tingling (3%) [125].
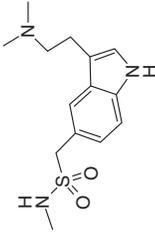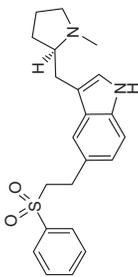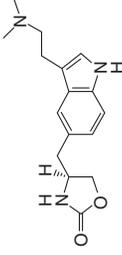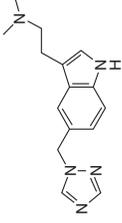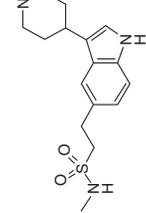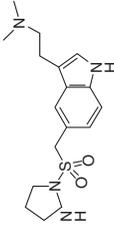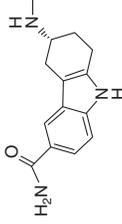
Almotriptan (12.5 mg) does not differ significantly in any AE from placebo, for example, dizziness (2.7%), paraesthesia (2.7%), nausea (1.9%), somnolence (1.6%) and vomiting (1.6%) [108].

The most frequent treatment-emergent AEs of 2.5 mg frovatriptan were dizziness (8%), fatigue (5%), paraesthesia (4%), flushing (4%), skeletal pain (3%), dry mouth (3%), chest pain (2%) and dyspepsia (2%) [110].

2.3.4 Summary of triptans

All the triptans have attained the level A recommendation in acute migraine therapy. The chest-related AEs are chest pain, chest tightness, chest heaviness and chest pressure [126]. The explanation of the observed chest pain (3 – 5% of the triptan users) without ECG abnormalities is still unknown. The relevant hypotheses include an oesophageal spasm, an intercostal muscle spasm, pulmonary vasoconstriction and even anxiety [76]. Subcutaneous sumatriptan has been associated with 25% more AEs than placebo, whereas naratriptan and almotriptan displayed similar rates of AEs as in the case of placebo [126]. The AEs of triptans are generally mild and transient, for example, dizziness, somnolence, tiredness, dry mouth, impaired concentration, paraesthesia, a warm sensation, palpations, a facial flush and chest tightness [76]. The contraindications to triptans are hemiplegic and brainstem migraine, a transient ischemic attack, ischemic stroke,

Table 6. Pharmacological and clinical data of triptans in acute treatment of migraine.

Drug name (generic)	Sumatriptan	Eletriptan	Zolmitriptan	Rizatriptan	Naratriptan	Almotriptan	Frovatriptan
Systematic (IUPAC) name	1-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methanesulfonamide	(R)-3-[(1-methylpyrrolidin-2-yl)methyl]-5-(2-phenylsulfonylethyl)-1H-indole	(S)-4-({3-[2-(dimethylamino)ethyl]-1H-indol-5-yl}methyl)-1,3-oxazolidin-2-one	N,N-dimethyl-2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethanamine	N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]ethanesulfonamide	N,N-dimethyl-2-[5-(pyrrolidin-1-ylsulfonylmethyl)-1H-indol-3-yl]-ethanamine	(+)-(R)-3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole
Mechanism of action	5-HT$_{1B/1D}$ receptor agonist	5-HT$_{1B/1D/1F}$ receptor agonist	5-HT$_{1B/1D/1A/1F}$ receptor agonist	5-HT$_{1B/1D}$ receptor agonist	5-HT$_{1B/1D/1F}$ receptor agonist	5-HT$_{1B/1D/1F}$ receptor agonist	5-HT$_{1B/1D/1A/1F}$ and 5-HT$_7$ receptor agonist
Dosage	25, 50, 100 mg (p.o.) 25 mg (rectal) 10, 20 mg (nasal) 6 mg (s.c.)	20, 40 mg (p.o.)	2.5, 5 mg (p.o.) 2.5, 5 mg (nasal)	10 mg (p.o.)	2.5 mg (p.o.)	12.5 mg (p.o.)	2.5 mg (p.o.)
Route of administration	p.o., nasal, s.c., rectal, transdermal	p.o.	p.o., nasal	p.o.	p.o.	p.o.	p.o.
Chemical structure							
Pharmacokinetic parameters							
C_{max}	54 ng/ml (50 – 100 mg tablet)	188 – 234 ng/ml (80 mg tablet)	5.6 – 9 ng/ml (5 mg tablet)	15.7 ng/ml (10 mg tablet)	8.0 ng/ml (2.5 mg tablet)	52.4 ng/ml (12.5 mg tablet)	2.44 ng/ml (2.5 mg tablet)
AUC	202 ng*h/ml (100 mg tablet)	1194 – 1514 ng/h/ml (80 mg tablet)	30 – 54 ng*h/ml (5 mg tablet)	72.1 ng/h/ml (10 mg tablet)	74.6 ng/h/ml (2.5 mg tablet)	339.2 ng/h/ml (12.5 mg tablet)	40.8 ng/h/ml (2.5 mg tablet)
T_{max}	1.5 h (50 – 100 mg tablet)	1.8 – 2.5 h (80 mg tablet)	1.5 h (5 mg tablet)	2.3 h (10 mg tablet)	4 h (2.5 mg tablet)	1.9 h (12.5 mg tablet)	2.7 h (2.5 mg tablet)
$T_{1/2}$	2.3 h (50 – 100 mg tablet)	4 – 7 h (80 mg tablet)	2.7 h (5 mg tablet)	3.2 h (10 mg tablet)	4.9 h (2.5 mg tablet)	5.1 h (12.5 mg tablet)	29.3 h (2.5 mg tablet)
Metabolism	Hepatic MAO	Hepatic CYP 34A	Hepatic CYP 1A2	Hepatic MAO	Hepatic CYP 1A2	Hepatic MAO-A CYP 2D6 CYP 3A4	Hepatic CYP 1A2
Excretion	Renal (60%) fecal (40%)	Hepatic (90%)	Renal (65%) fecal (35%)	Renal (82%) fecal (12%)	Renal	Renal (90%)	Renal
Availability (USA/EU)	USA/EU	USA/EU	USA/EU	USA/EU	USA/EU	USA/EU	USA/EU
Pivotal trial(s)	[92]	[97]	[100]	[104]	[107]	[109]	[113,114]
Ref.	[91,121]	[122,123]	[99,101]	[103]	[106]	[111]	[110,112]

5-HT: 5-hydroxytryptamine; AUC: Area under the plasma concentration curve; i.m.: Intramuscular; IUPAC: International Union of Pure and Applied Chemistry; i.v.: Intravenous; MAO: Monoamine oxidase; p.o.: Peroral; s.c.: subcutaneous.

ischemic heart disease, Prinzmetal's angina, peripheral vascular disease (e.g., Raynaud's disease), uncontrolled hypertension, pregnancy, lactation, the use of ergot alkaloids, the use of monoamine oxidase inhibitors, association with selective serotonin re-uptake inhibitors, severe renal or liver failure, and hypersensitivity to triptans [9,76]. Postmarketing surveillance data and the experience of physicians suggest that in real-life practice triptans reach very good or good ranges of efficacy and safety among a broad spectrum of migraine patients [127].

3. Pregnancy and breastfeeding in women with migraine

The safe and efficacious treatment of pregnant and breastfeeding migraineurs poses a considerable challenge. The possible AEs and therefore the recommendations are different for the periods of pregnancy and lactation.

For acute migraine treatment, only paracetamol is allowed during all three trimesters of pregnancy. NSAIDs can be given in the second trimester and should be avoided in the third trimester [9,128]. The administration of NSAIDs during the third trimester causes an increased risk of constriction of the ductus arteriosus Botalli [129]. Following the use of aspirin in first trimester pregnancy, gastroschisis was confirmed as a malformation [128]. The intake of antiemetics such as metoclopramide during pregnancy does not increase the risk of birth defects. Ergotamine and DHE are contraindicated during pregnancy due to their vasoconstrictive and uterine-contracting activities [128]. Later, triptans were launched, but they are also contraindicated in all trimesters of pregnancy according to the manufacturers' instruction [9,15]. However, most recent studies concluded that triptan redemption during pregnancy was not associated with major congenital malformations or prematurity [130,131]. Therefore, in daily clinical practice, the risk/benefit ratio should be carefully assessed for both the mother and the fetus before initiating triptan therapy.

Drug safety for breastfeeding mothers is rated according to the Hale lactation risk categories and American Academy of Pediatrics recommendations [132,133]. The Hale's criteria range from L1 (the safest) to L5 (contraindicated). During breastfeeding, aspirin is considered to be safe in low doses, while in higher doses it is contraindicated, because it reaches high levels in infants, and can also be associated with Reye's syndrome [132-134]. Other possible AEs related to the use of aspirin include haemorrhage and metabolic acidosis [133]. Ibuprofen is detectable in only low concentrations in the maternal milk after a dosage of 400 mg, and is therefore considered safe. Although < 1% of naproxen is excreted into the human milk, it has a long half-life and its use has been reported to be associated with bleeding abnormalities in the newborn; other NSAIDs are therefore preferable (L4 possibly hazardous) [133]. Diclofenac is probably compatible because it is excreted in only low levels in the maternal milk, but it achieved only the L2 grade (safer) on the Hale

scale. Only acetaminophen and ibuprofen reached the L1 category, considered safest and compatible with breastfeeding [132,134]. Several analgesics are combined with caffeine, which is generally regarded as safe (L2). However, in high doses it may cause sleep disturbances in the infant, and its use by mothers should therefore be restricted [132,134].

Metoclopramide passes into the maternal milk and could elicit extrapyramidal side effects or methemoglobinemia in the newborn [133]. Its use should be avoided during lactation [128]. Ergot alkaloids should be avoided during lactation, because the level excreted in the maternal milk is unknown, and some data have indicated that they may inhibit prolactin production and lactation [128,132,135].

No data are available for most triptans; only eletriptan and sumatriptan have been reported to be in low levels of maternal milk and cause no AEs in infants, but only in small numbers of women [132,134,136]. Rizatriptan has been reported to pass into the milk only in low levels in rodents; however, human data are at present not available [134].

The recommendation of the American Academy of Pediatrics helps the physician in counseling a nursing mother the safest drug during breastfeeding. According to its recommendations, aspirin and ergotamine can be recommended with caution, whereas acetaminophen, caffeine, ibuprofen, naproxen and sumatriptan are usually compatible with breastfeeding [137].

4. Medication overuse headache

MOH is a secondary headache disorder with a worldwide prevalence of 1 – 2% [138]. The diagnosis of MOH can be established if a patient has headache on at least 15 days/month for > 3 months, and the headache can be linked to regular overuse of a headache medication [139]. The criteria of chronic migraine are very similar (headache present for 15 days or more per month for at least 3 months); however, in this case at least eight attacks have to fulfill the criteria of migraine headache as well. Chronic migraine can occur either in association with or independently of MOH [139]. The fact that medication withdrawal in MOH is generally followed by symptomatic improvement and a decrease in headache frequency represents an important difference, as in case of chronic migraine drug withdrawal does not help [139]. It is still controversial whether medication overuse is a consequence of chronic headache or vice versa, generally it cannot be decided until medications are discontinued [138]. The uncertainty is due to the observation that not all headache patients who overuse medication will develop MOH. MOH can develop following the intake of simple analgesics on 15 days/month, whereas for triptans and ergotamines it develops after an intake on 10 days/month [139]. The risk of MOH is higher for triptans, which cause MOH faster and after less intake than other pharmacons used in the treatment of acute migraine attacks. The average time for the development of MOH is around 2 years in the case of triptan administration,

while for analgesics it is ~ 5 years [138]. The American Migraine Prevalence and Prevention study proved that the extent of risk of migraine chronification depends on the different medications used, with triptans posing the highest risk for developing chronic migraine. Interestingly, the effect of NSAIDs depends on the number of days with headache: in patients with < 10 headache days/month, the use of NSAIDs decrease the risk of chronic migraine, whereas in those patients with above 10 headache days, they even increase this risk. Combined use of NSAIDs plus triptans was not associated with an increased risk of chronic migraine compared to that seen in triptan monotherapy. Opioids and barbiturates dose-dependently increase the risk of migraine chronification with an observable gender difference: the risk of chronification for opioids is higher in men, whereas barbiturate use associates with an increased risk in women. Caffeine-containing combinations also increase the risk of chronification, but not the risk of MOH [140,141]. The types of overused medications changed over the last decades. Nowadays, triptans and NSAIDs are the most frequently used drugs for acute migraine treatment; therefore, they became the drugs that are the most frequently associated with MOH, with a frequency exceeding that for ergots and butalbital combinations, which used to represent the most frequent causes of MOH in the past [142]. A large population-based study revealed that the regular use of tranquilizers increases the risk of developing MOH even 11 years later [143]. Besides medications, several other risk factors have been identified such as depression, anxiety, smoking and physical inactivity [138,143]. However, the exact pathomechanism of the initiation of MOH still not fully elucidated.

5. Conclusion

Among the pharmacons currently used for the acute treatment of migraine, several NSAIDs, ergot alkaloids and all triptans have reached the level A recommendation on the basis of their efficacy. These drugs all have distinct safety profiles and may be associated with various AEs. NSAIDs have a low ratio of AEs, gastric intolerance being the most frequent. Among the ergot alkaloids, DHE is generally better tolerated and poses a lower risk than ergotamine. Triptans are widely used, effective medication to counter migraine attacks, and their AEs are generally mild and transient. Caution is recommended with triptans in patients with severe cardiovascular disease, peripheral vascular disease or cerebrovascular disease. As concerns MOH, NSAIDs present a lower risk than those of ergots and triptans. The only drug which can be used in all trimesters of pregnancy and during lactation is paracetamol.

6. Expert opinion

The widely accepted criterion for effective migraine pharmacological treatment is the achievement of complete relief of pain within 2 h. Other important requirements of the therapy are safety and tolerability, which can additionally determine the patient compliance. The pathomechanism of migraine, the initiation of the attacks and the genetic background have not yet been fully clarified, and the currently used pharmacons are in the main not aimed at causative factors. The use of NSAIDs in migraine is supported by the neurogenic inflammation concept, whereas ergot alkaloids and particularly triptans target the TS, the activation and sensitization of which represents another widely accepted hypothesis concerning the pathomechanism of migraine. Most of the available drugs do not (or only partly) meet the above criteria. The development of novel pharmacons is delayed by the lack of adequate animal models, and by the fact that there are no migraine-specific biomarkers in humans. Another important point involved in drug development is that there are no adequate methods with which to predict drug safety in different patients.

The currently available medications do not satisfy all requirements of acute migraine treatment. Several AEs can lead to loss of patient compliance, whereas the use of several medications require special caution in light of the comorbid conditions. In a number cases, the therapeutic decision is difficult, for example, when a concomitant disease contraindicates the use of a drug class while other medications cannot be tolerated or are not effective. In daily clinical practice, special focus has to be placed on the concomitant presence of cardiovascular and GI disorders, as they may limit the use of triptans or NSAIDs. As young women represent a significant proportion of migraine patients, pregnancy and breastfeeding are common situations that narrow the therapeutic options.

For patients who experience frequent attacks with mild or moderate headache severity, NSAIDs are currently recommended, because the risk of MOH is relatively low for this group of anti-migraine medications. Caution is needed in patients with GI disorders, where NSAID administration may worsen the GI symptoms; in this patient subgroup, triptans must be considered. There is still insufficient evidence regarding the cardiovascular risk following NSAID use in migraine. More studies are needed to clarify the possible relationships between NSAIDs and cardiovascular events.

Triptans are recommended for patients with for patients with more severe migraine pain, but the risk of development of MOH is higher after triptans than after NSAIDs. Interestingly, although triptans are very effective for acute migraine treatment, a 12-year Danish study revealed that the use of triptans did not decrease the duration of absence from work [144]. Triptans generally induce only modest side effects and have a well-established safety record. However, there is also evidence that 1000 mg of aspirin has the same efficacy as 50 mg of sumatriptan, and aspirin has a better side effect profile [52]. Among the seven triptans, almotriptan seems to be the best tolerated [108]. The tolerability of triptans cannot be predicted from their pharmacokinetic profile [76]. Postmarketing surveys have demonstrated an acceptable benefit-risk ratio of triptans, which justifies the prescription of these drugs

for the acute treatment of migraine, and furthermore the patients wish to continue this type of therapy.

Ergot alkaloids are currently not the drugs of first choice; they are mainly used in patients who do not benefit from triptans or who cannot tolerate them. Importantly, the development of MOH is very rare among DHE users, but frequent with ergotamine [9]. In patients with migraine with aura or with vascular risk factors, ergots are also not recommended.

The safety profile of different medications is different for pregnancy and lactation. During pregnancy, triptans and ergots are contraindicated, so NSAIDs are during the third trimester of pregnancy. Paracetamol is the only drug that can be recommended during pregnancy, whereas during lactation paracetamol and ibuprofen are applicable.

The future goal of drug development must be the creation of potent drugs with a favourable safety profile, which are well tolerated. In recent years, a number of different new formulations have been developed, for example, a transdermal iontophoretic patch, a needle-free subcutaneous device, rapidly disintegrating oral formulations, oral inhalation forms, orodispersible granules, effervescent tablets and micronized tablets. These administration routes may be associated with better tolerability profiles. Although such formulations are as yet available for only a few pharmacons, in the near future they should be made available for more of the drugs currently used in the acute therapy of migraine.

The ultimate goal in the next 5 years of treatment is the attainment of personalized medicine, that is, pharmacotherapy tailored to the individual migraineur. To achieve this, the pathomechanism and genetic background must be clearly elucidated, and reliable biomarkers must be established. As the currently utilized drugs do not address the pathomechanism

perfectly, novel targets must be identified for drug development. Calcitonin gene-related peptide receptors appear to be good targets for the acute treatment of migraine, but the safety profile is not yet favorable. Another novel option would be the application of neurally acting anti-migraine agents, but the currently available drugs frequently result in AEs in the CNS. Future investigations are necessary to overcome these limitations.

Recent preclinical data point to the possible roles of the kynurenine system as well as pituitary adenylate-cyclase activating polypeptide and its receptor [145-147]. They are promising targets for the development of novel pharmacons, which may also have a beneficial safety profile.

Future research addressing these outstanding issues will hopefully promote progress in the daily clinical practice through the determination of beneficial pharmacotherapy for the individual migraine patient.

Declaration of interest

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