Antimigraine Agents, Triptans Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
almotriptan (Axert®)	Ortho-McNeil	Acute treatment of migraine attacks with or without aura in adults
eletriptan (Relpax™)	Pfizer	
frovatriptan (Frova™)	Endo	
naratriptan (Amerge®)	GlaxoSmithKline	
rizatriptan (Maxalt®)	Merck	
sumatriptan (Imitrex®)	GlaxoSmithKline	Acute treatment of migraine attacks with or without aura in adults (oral, nasal spray, injection) Injection: Acute treatment of cluster headache episodes in adults
sumatriptan/naproxen (Treximet™)	GlaxoSmithKline	Acute treatment of migraine attacks with or without aura in adults
zolmitriptan (Zomig®)	AstraZeneca	Acute treatment of migraine attacks with or without aura in adults (oral, nasal spray)

Overview

Headache is one of the most common complaints by patients when presenting to a physician. Migraine accounts for 10 to 20 percent of all headaches in adults.[1] The American Migraine Study 2 showed that there are 27.9 million Americans who suffer from migraines.[2] Migraine causes decreased productivity and absenteeism from work for many patients, which creates a large economic impact for the nation. Sixty-four percent of physician-diagnosed patients who experience migraines, and 41 percent of undiagnosed migraine sufferers reported severe impairment or the need for bed rest due to their migraine symptoms. In addition, a recent count showed 17.2 percent of females and six percent of males to be migraine sufferers, an epidemiologic profile that has remained stable over many years.[3] Approximately 85 percent of patients with migraine headaches suffer less than three to four attacks per month.[4] The median frequency of migraine attacks among migraine sufferers is one and one-half per month.[5]

Migraine headache must be differentiated from tension-type headache. Criteria for the diagnosis of migraine headache includes an episodic headache lasting from four to 72 hours with at least two of the following symptoms: unilateral pain, throbbing, aggravation of pain upon moving, pain of moderate to severe intensity accompanied by nausea, vomiting, photophobia, or phonophobia.[6] Treatment of acute migraine attacks includes acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and the ergot alkaloids. Due to well-established efficacy, the "triptans" have become the drugs of choice for treating actual migraine attacks.

Pharmacology

Drug	High Binding Affinity	Weak Binding Affinity
almotriptan (Axert)	5-HT_{1B}, 5-$HT_{1D,}$ 5-HT_{1F}	5-HT_{1A}, 5-HT_{7}
eletriptan (Relpax)	5-HT_{1B}, 5-$HT_{1D,}$ 5-HT_{1F}	5-HT_{1A}, 5-HT_{1E}, 5-HT_{2B}, 5-HT_{7}
frovatriptan (Frova)	5-HT_{1B}, 5-HT_{1D}	--
naratriptan (Amerge)	5-HT_{1B}, 5-HT_{1D}	--
rizatriptan (Maxalt)	5-HT_{1B}, 5-HT_{1D}	5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{7}
sumatriptan (Imitrex, Treximet)	5-HT_{1D}	5-$HT_{1A,}$ 5-$HT_{5A,}$ 5-HT_{7}
zolmitriptan (Zomig)	5-HT_{1B}, 5-HT_{1D}	5-HT_{1A}

Migraine pain is believed to result from activity within the trigeminovascular system. This activity results in a release of vasoactive neuropeptides with subsequent vasodilation, dural plasma extravasation, and perivascular inflammation. The therapeutic activity of the triptan derivatives can be attributed to agonist effects on the vascular and neuronal serotonin (5-hydroxytripamine, 5-HT_1) receptor subtypes in the trigeminal system. Relief of migraine headache may result from (1) intracranial vessel constriction via stimulation of vascular 5-HT_{1B} receptors; (2) inhibition of vasoactive neuropeptide release through stimulation of presynaptic 5-HT_{1D} receptors; and (3) interruption of pain signal transmission within the brainstem through stimulation of 5-HT_{1D} receptors.

All seven serotonin agonists are selective 5-HT_1 receptor agonists, acting at subsets 5-HT_{1B} and 5-HT_{1D}. When activated, these receptors are believed to mediate the symptoms associated with a migraine attack.[7,8]

Naproxen, an NSAID, inhibits the synthesis of inflammatory mediators and has analgesic properties.

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hrs)	Tmax (hrs)	Metabolites	Excretion (%)
almotriptan (Axert)[9]	70	3-4	1-3	2 metabolites, inactive	Urine: 75 Feces: 13
eletriptan (Relpax)[10]	50	4	1.5-2	1 major active metabolite (N-demethylated metabolite)	Predominantly non-renal
frovatriptan (Frova)[11]	20 in men 30 in women	26	2-4	4 metabolites, 1 with minor activity	Urine: 32 Feces: 62
naratriptan (Amerge)[12]	70	6	3-4	Many metabolites, all inactive	Urine: 80
rizatriptan (Maxalt)[13]	45	2-3	1-1.5* 1.6-2.5**	5 metabolites, 4 inactive; N-monodesmethyl-rizatriptan (activity similar to parent)	Urine: 82 Feces: 12
sumatriptan oral (Imitrex)[14]	15	2.5	1.5	1 major metabolite, inactive	Urine: 60 Feces: 40
sumatriptan injection (Imitrex)[15]	97	1.9	12 minutes	1 major metabolite, inactive	Urine: 60
sumatriptan nasal spray (Imitrex)[16]	17	2	--	1 major metabolite, inactive	Urine: 45
sumatriptan naproxen (Treximet)[17]	15 95	2 12-19	1 6	1 major metabolite, inactive extensively metabolized to 6-0-desmethyl naproxen	Urine: 60 Feces: 40 Urine: 95
zolmitriptan (Zomig)[18]	40	3	1.5* 3**	3 metabolites, 2 inactive; N-desmethyl metabolite (potency is 2 to 6 times that of the parent)	Urine: 65 Feces: 30
zolmitriptan nasal spray (Zomig)[19]	102 versus oral tablet	3	3	3 metabolites, 2 inactive; N-desmethyl metabolite (potency is 2 to 6 times that of the parent)	Predominantly renal

*Regular tablets **Orally disintegrating tablets

Contraindications/Warnings

Hypersensitivity to any component of the triptan formulations is a contraindication to its use.

While the incidence is rare, the triptans have been associated with angina, including Prinzmetal's variant angina, myocardial infarction, cardiac arrhythmias, hypertension, or stroke, particularly when they were used in patients with vascular risk factors. For this reason, they should be used with extreme caution in these patients or those with a suspected history of coronary artery disease. These medications should not be used in patients with uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, or cerebrovascular disease. Patients with other significant underlying cardiovascular diseases should not receive sumatriptan/naproxen (Treximet), nor should patients who have undergone coronary artery bypass graft surgery.

Triptans should not be used in patients with severe hepatic impairment or diseases that impair absorption, metabolism and excretion of these products.

In Public Health Advisory, the FDA cautioned that serotonin syndrome could occur if triptans are used in combination with selective serotonin reuptake inhibitor or selective serotonin/norepinephrine reuptake inhibitor antidepressants.[20]

NSAIDs such as naproxen can cause serious gastrointestinal inflammation, bleeding, ulceration, and perforation. Long-term administration of NSAIDs can also lead to renal dysfunction, skin reactions such as Stevens-Johnson syndrome, and premature closure of the ductus arteriosus in late pregnancy.

Drug Interactions

All agents from this class should not be given within 24 hours of ergot alkaloids or another triptan.

Rizatriptan (Maxalt), sumatriptan (Imitrex, Treximet), and zolmitriptan (Zomig) should not be given within two weeks of a monoamine oxidase inhibitor (MAO).

Eletriptan (Relpax) should not be used within 72 hours of the following CYP450 3A4 inhibitors: ketoconazole (Nizoral®), itraconazole (Sporanox®), nefazodone, clarithromycin (Biaxin®), ritonavir (Norvir®), nelfinavir (Viracept®), or any other known potent CYP450 3A4 inhibitor.[21]

Rizatriptan (Maxalt) dose must not exceed 5 mg (up to a maximum of three doses in any 24-hour period) when administered concurrently with propranolol (Inderal®, Innopran XL®).[22]

Adverse Effects[23]

Drug	Paresthesia	Pain and pressure sensations	Flushing/ Palpitations	Nausea	Dizzi-ness	Somnolence	Unusual taste/ Nasal irritation
almotriptan (Axert)[24] 12.5 mg	1	< 1	< 1	2	< 1	< 1	nr
eletriptan (Relpax)[25] 40 mg	3	2	2	5	6	6	nr
frovatriptan (Frova)[26] 2.5 mg	4	2-3	4	> 2	8	> 2	nr
naratriptan (Amerge)[27] 2.5 mg	2	4	nr/ < 1	5	2	2	nr
rizatriptan (Maxalt)[28] 10 mg	4	9	> 1 / > 1	6	9	8	nr
sumatriptan (Imitrex)[29] 50 mg oral	5	6	> 1	> 1	> 1	> 1	nr
sumatriptan (Imitrex)[30] 6 mg injection	4.6	7.1	6.6 / < 1	1.3	11.9	2.7	nr
sumatriptan (Imitrex)[31] 20 mg nasal spray	1.4	< 1	< 1	13.5	1.4	< 1	24.5 / 3.8
sumatriptan/ naproxen (Treximet)[32]	2	3	>1	3	4	3	nr
zolmitriptan (Zomig)[33] 5 mg oral	9	22	nr/ 2	6	10	8	nr
zolmitriptan (Zomig)[34] 5 mg nasal spray	10	10	nr/ >1 - 2	4	3	4	21 / 3

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative.
nr = not reported.

Special Populations[35,36,37,38,39,40,41,42,43,44,45]

Pediatrics

None of the available products in this class have been approved for use in pediatric populations (<18 years of age).

sumatriptan (Imitrex)

A randomized, double-blind, placebo-controlled, single-attack study was conducted in 653 patients aged 12 to 17 years who had at least a six-month history of migraine.[46] The primary efficacy endpoint was headache relief two hours post-dose with sumatriptan (Imitrex) nasal spray 20 mg or placebo. Headache relief one-hour post-dose was significantly greater for patients using 20 mg of sumatriptan nasal (56 percent) compared with placebo (41 percent). Headache relief two hours post-dose approached statistical significance for 20 mg (63 percent) compared with placebo (53 percent, $p<0.05$). Complete relief two hours post-dose was significantly greater for patients using 20 mg of sumatriptan nasal compared with placebo (36 versus 25 percent, respectively, $p<0.05$). Sumatriptan 20 mg was superior to placebo with respect to the cumulative percentages of patients first reporting headache relief within two hours of dosing ($p<0.05$). Photophobia and phonophobia were significantly reduced two hours post-dose for sumatriptan nasal 20 mg, compared with placebo (36 versus 48 percent and 25 versus 44 percent, respectively). A similarly designed study in 83 patients had the same conclusions.[47]

Another study in adolescents was conducted.[48] This was a randomized, placebo-controlled, double-blind, parallel-group study of 738 adolescent subjects with at least a six-month history of migraine. Patients self-treated a single attack of moderate or severe migraine with sumatriptan 5 or 20 mg nasal spray or placebo. The primary endpoints were headache relief at one hour and sustained relief from one to 24 hours. Sumatriptan 20 mg provided greater headache relief than placebo at 30 minutes (42 versus 33 percent, respectively; $p=0.046$) and two hours (68 versus 58 percent; $p=0.025$) postdose, but did not reach statistical significance at one hour (61 versus 52 percent; $p=0.087$) or for sustained headache relief from one to 24 hours ($p=0.061$). Significant differences ($p<0.05$) in favor of sumatriptan 20 mg over placebo were observed for several secondary efficacy endpoints including sustained relief from two to 24 hours. In general, sumatriptan 5 mg percentages were slightly higher than placebo, but the differences did not reach statistical significance. Both doses of sumatriptan were well tolerated.

One study in patients aged six to 17 years using rizatriptan (Maxalt) showed possible efficacy.[49]

Pregnancy

All products in this review are Pregnancy Category C.

Nursing Mothers

Eletriptan and sumatriptan are excreted in human breast milk. Infant exposure can be minimized by avoiding breast-feeding for twelve hours after treatment with sumatriptan tablets. Caution should be exercised when administering eletriptan to nursing women.

It is not certain whether almotriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan are excreted in human milk. Caution should be employed when the products in this class are administered to women who are breast-feeding.

Geriatric Use

Use of naratriptan and sumatriptan is not recommended in elderly populations due to the potential of decreased hepatic/metabolic activity, increased risk of coronary artery disease and hypertension.

For almotriptan, clinical studies did not include sufficient numbers of subjects over sixty-five to determine whether they respond differently from younger subjects. In general, dose selection for elderly patients should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or drug therapy.

For eletriptan, there is little clinical experience in patients sixty-five year and older. There were no apparent differences in efficacy or adverse events between the elderly and non-elderly patients. A statistically significant increased half-life is seen in elderly subjects compared to younger adult subjects.

For frovatriptan, mean blood concentrations in elderly subjects were one and one-half to two times higher than those seen in younger adults. Because migraines occur infrequently in the elderly, clinical experience with frovatriptan is limited in such patients.

For rizatriptan, pharmacokinetics are similar between the elderly and younger populations. As migraines are less common in the elderly, there is little clinical experience in such patients. In clinical trials there was no apparent difference in efficacy or overall adverse experience rates between patients under sixty-five years of age and those sixty-five and above.

For zolmitriptan, while the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger patients, there is no information about the safety and effectiveness of zolmitriptan in this population because patients over sixty-five were excluded from controlled clinical trials.

Dosages

Drug	Availability	Single Initial Dose	Minimum Time Before Repeat Dose (hr)	Maximum Dose in 24 Hours (mg)	Package Size
almotriptan (Axert)	6.25, 12.5 mg tablets	6.25 mg or 12.5 mg	2	25	6, 12 (12.5 mg only)
eletriptan (Relpax)	20, 40 mg tablets	20 mg or 40 mg	2	80	6, 12 (40 mg only)
frovatriptan (Frova)	2.5 mg tablet	2.5 mg	2	7.5	9
naratriptan (Amerge)	1, 2.5 mg tablets	1 mg or 2.5 mg	4	5	9
rizatriptan (Maxalt, MLT)	5, 10 mg tablets	5 mg or 10 mg	2	30	Tablets: 12 MLT: 12 (4 x unit of use carrying case of 3 ODTs)
sumatriptan (Imitrex)	25, 50, 100 mg tablets	25 mg to 100 mg	2	200	9
sumatriptan injectable (Imitrex)	4 mg or 6mg SC	4, 6 mg SC (single dose vial available for doses ≤6 mg, maximum single dose)	1	12	2 injections, 5-vial cartons (6 mg injections only)
sumatriptan nasal spray (Imitrex)	5, 20 mg per spray	5 or 10 mg (1-2 sprays) or 20 mg (1 spray)	2	40	6
sumatriptan/ naproxen (Treximet)	85 mg/500 mg tablets	one tablet	2	two tablets	9
zolmitriptan (Zomig, ZMT)	2.5, 5 mg tablets	2.5 mg or 5 mg	2	10	3 (5 mg only), 6 (2.5 mg only)
zolmitriptan nasal spray (Zomig)	5 mg per spray	5 mg	2	10	6

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Randomized, controlled comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

almotriptan (Axert) and sumatriptan (Imitrex)

A randomized, double-blind trial comparing the efficacy and safety of almotriptan 12.5 mg and oral sumatriptan 50 mg enrolled 1,173 patients with migraine.[50] Efficacy was evaluated at two hours for headache relief (decrease in pain to little or no pain), headache freedom (decrease to no pain), use of rescue medications, and headache recurrence. At two hours, almotriptan and sumatriptan provided headache relief in 58 percent and 57.3 percent of patients, respectively. Almotriptan provided headache freedom in 17.9 percent of patients, and 24.6 percent of the sumatriptan group reported headache freedom (p=0.005). All other efficacy variables were similar for both treatment groups. Adverse effects were reported less frequently in the almotriptan group (15.2 percent) compared to the sumatriptan group (19.4 percent, p=0.06).

In a study to evaluate patient satisfaction with antimigraine therapy, 1,173 patients were randomized to almotriptan 12.5 mg or sumatriptan 50 mg oral in a double-blind manner.[51] Diaries were evaluated for satisfaction of pain relief, side effects, functional status, and health-related quality of life (HRQOL). No difference was seen between the groups for satisfaction with pain relief, functional status, or HRQOL results. Almotriptan patients reported being less bothered by side effects.

In a randomized, single-dose, placebo-controlled, double-blind study, almotriptan and sumatriptan were compared for efficacy and safety in the treatment of migraine.[52] Patients (n=668) were randomized to almotriptan 12.5 or 25 mg, sumatriptan 100 mg, or placebo and evaluated for pain relief at two hours following dosing. All active therapies had equivalent response rates that were significantly superior to placebo. Almotriptan was tolerated best and similar to placebo. Almotriptan 25 mg and sumatriptan 100 mg had similar incidence of adverse effects.

almotriptan (Axert) and zolmitriptan (Zomig)

In a multicenter, double-blind, randomized trial, 532 adult migraineurs received almotriptan 12.5 mg and 530 adult migraineurs received zolmitriptan 2.5 mg for the treatment of a single migraine attack.[53] For blinding purposes, both drugs were encapsulated. The primary endpoint was sustained pain-free patients with no adverse events. Other endpoints included pain relief,

and pain-free at several time points, sustained pain free, headache recurrence, use of rescue medication, functional impairment, time lost because of migraine, treatment acceptability, and overall treatment satisfaction. No significant differences were seen in the percentage of patients that were sustained pain-free with no adverse events (almotriptan 29.2 percent and zolmitriptan 31.8 percent, p=0.357) or the other efficacy endpoints measured including pain-relief and pain-free at two hours. The incidence of triptan-associated adverse events and triptan-associated central nervous system adverse events was significantly lower for patients receiving almotriptan compared to zolmitriptan (p=0.03).

eletriptan (Relpax) and sumatriptan (Imitrex)

In a randomized, double-blind, parallel-group trial, eletriptan and sumatriptan were compared for efficacy, safety, and tolerability in the acute treatment of migraine in 692 patients.[54] Patients were randomized to placebo, sumatriptan 100 mg, eletriptan 20 mg, 40 mg, or 80 mg. At two hours, headache response rates were 24 percent for placebo, 55 percent for sumatriptan, 54 percent for eletriptan 20 mg, 65 percent for eletriptan 40 mg, and 77 percent for eletriptan 80 mg. At two hours, there was a difference between sumatriptan 100 mg and eletriptan 80 mg in headache response rate (p<0.001). All doses of eletriptan were significantly different from placebo for headache response rate (p<0.001). Headache-free rates at two hours for eletriptan 80 mg were superior to sumatriptan 100 mg (37 versus 23 percent; p<0.05). All therapies were well tolerated. Eletriptan 80 mg is not currently available in the US, nor is the 80 mg dose FDA-approved.

Eletriptan and sumatriptan were compared in a single migraine attack study enrolling 2,113 patients.[55] Patients were randomized to eletriptan 40 mg, sumatriptan 100 mg, or placebo in the double-blind, parallel-group trial involving patients with moderate migraine headaches. After two hours, the headache response rate was 67 percent for eletriptan, 59 percent for sumatriptan, and 26 percent for placebo, both statistically significant differences in favor of eletriptan (p<0.001, p<0.0001). Eletriptan patients also reported less nausea, photophobia, and phonophobia compared with sumatriptan after two hours. Overall, the incidence of adverse effects was low for the two active treatment groups, with nausea being the most commonly reported in all groups.

Eletriptan and sumatriptan were compared for efficacy in the acute treatment of migraine in 1,008 patients.[56] Patients were randomized in a double-blind manner to placebo, eletriptan 40 mg or 80 mg, or sumatriptan 50 mg or 100 mg to treat up to three attacks. The sumatriptan doses were encapsulated in the study. The primary endpoint of the study was the one-hour headache response which was 12 percent for placebo, 24 percent for sumatriptan 50 mg, 27 percent for sumatriptan 100 mg, and 30 and 37 percent for eletriptan 40 and 80 mg, respectively. Two-hour response rates were 31 percent for placebo, 50 percent for sumatriptan 50 mg, 53 percent for sumatriptan 100 mg, 64 percent for eletriptan 40 mg, and 67 percent for eletriptan 80 mg. For the two-hour response rate, all doses of eletriptan were superior to sumatriptan for headache response and complete pain relief (p<0.05). All treatments were well tolerated.

eletriptan (Relpax) and naratriptan (Amerge)

In a randomized, double-blind, placebo-controlled study, migraine patients (n=548) were randomized to treat a single migraine attack with either eletriptan 40 mg, naratriptan 2.5 mg, or placebo.[57] Headache response rates at two hours and four hours, respectively, were 56 and 80 percent for eletriptan, 42 and 67 percent for naratriptan (p<0.01 for both time-points), and 31 and 44 percent for placebo (p<0.0001 versus both active drugs at both time-points). Eletriptan showed a greater pain-free response at two hours (35 versus 18 percent; p<0.001) as well as

lower use of rescue medication (15 versus 27 percent; p<0.01) and higher sustained headache response at 24 hours (38 versus 27 percent; p<0.05) compared with naratriptan.

eletriptan (Relpax) and zolmitriptan (Zomig)

In a multicenter, double-blind, double-dummy, parallel-groups trial, 1,587 outpatients with migraine were randomized in a 3:3:3:1 ratio to eletriptan 80 mg, eletriptan 40 mg, zolmitriptan 2.5 mg, or placebo.[58] Of these, 1,312 treated a single migraine attack and were included in the intention-to-treat population. For the primary efficacy endpoint of headache response at two hours, rates were 74 percent for eletriptan 80 mg, 64 percent for eletriptan 40 mg, 60 percent for zolmitriptan (p<0.0001 versus eletriptan 80 mg), and 22 percent on placebo (p<0.0001 versus all active treatments). Eletriptan 40 mg had similar efficacy to zolmitriptan 2.5 mg and significantly (p<0.05) lower recurrence rate and need for rescue medication past 24 hours. All treatments were well tolerated, and on patients' global ratings of treatment, both eletriptan doses scored significantly better than zolmitriptan.

frovatriptan (Frova)

Three randomized, placebo-controlled, double-blind, parallel-group trials enrolling 2,676 patients were performed to confirm the clinical efficacy of frovatriptan 2.5 mg for the acute treatment of migraines.[59] Headache response two hours after frovatriptan dosing was significantly greater than placebo in all three trials (p<0.001). There was approximately a two-fold measure of effect over placebo for headache response at both the two- and four-hour measurement. The incidence of 24-hour headache recurrence was low (10 to 25 percent). In patients with migraine-associated nausea, photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms in frovatriptan-treated patients.

There are currently no peer-reviewed comparative trials evaluating efficacy of other triptans with frovatriptan. Tolerability and safety of frovatriptan 2.5 mg and sumatriptan 100 mg were compared in a trial with a 12-month open-label extension that enrolled 1,554 patients.[60] Fewer adverse events were observed with frovatriptan compared to sumatriptan (36 versus 43 percent, p=0.03).

naratriptan (Amerge) and rizatriptan (Maxalt)

In a randomized, double-blind, placebo-controlled study, 522 patients treating a single migraine attack were given either rizatriptan 10 mg, naratriptan 2.5 mg, or placebo.[61] Rizatriptan provided earlier headache relief (p<0.001), acting as early as 30 minutes following a dose. More patients were pain-free at two hours versus naratriptan (44.8 versus 20.7 percent, p<0.001). Both treatments were effective compared to placebo.

naratriptan (Amerge) and sumatriptan (Imitrex)

A randomized, double-blind, placebo-controlled trial compared naratriptan and sumatriptan for the acute treatment of migraine.[62] Patients (n=643) were randomized to naratriptan 1, 2.5, 5, 7.5, or 10 mg or sumatriptan 100 mg or placebo per attack. Efficacy was determined at two hours post-dose for headache relief. Naratriptan response (52 to 69 percent) and sumatriptan response (60 percent) were superior to placebo (31 percent, p<0.05). Over the course of 24 hours, efficacy as determined by sustained headache relief without need for rescue medication or recurrence was reported more frequently with naratriptan and sumatriptan than placebo. Adverse effects were similar among naratriptan 1, 2.5, or 5 mg doses and placebo. Naratriptan 5, 7.5, and 10 mg doses and sumatriptan had a similar incidence of adverse effects.

A randomized, double-blind study evaluated headache recurrence between naratriptan 2.5 mg and sumatriptan 100 mg in 253 patients with known history of recurrent migraine headaches.[63]

Recurrence was defined as recurrence of headache following a pain-free interval of at least 24 hours between attacks. No difference was observed in the incidence of recurrent headache pain during four to 24 hours after treatment for naratriptan (45 percent) and sumatriptan (57 percent, p=NS). Pain relief after the second attack was achieved more frequently with sumatriptan (57 percent) than naratriptan (41 percent, p=0.005). Side effects were similar in both treatments with no difference in incidence following the second dose.

rizatriptan (Maxalt) and sumatriptan (Imitrex)

Patients who had migraine with or without aura were randomized to receive 10, 20, or 40 mg doses of rizatriptan or sumatriptan 100 mg or placebo.[64] This was a double-blind outpatient trial enrolling 449 patients. The proportion of patients with headache relief at two hours was 18 percent for placebo, 46 percent for sumatriptan, 52 percent for rizatriptan 10 mg, 56 percent for rizatriptan 20 mg, and 67 percent for rizatriptan 40 mg. All differences with placebo were statistically significant (p<0.001). Rizatriptan 40 mg was superior to sumatriptan (p=0.001). The recurrence of headache within 24 hours was found to be equal across all treatment groups at approximately 40 percent. Adverse events occurred more frequently after rizatriptan 40 mg compared to other treatments. Rizatriptan doses of 20 and 40 mg exceed the current FDA approved labeling.

Rizatriptan 5 and 10 mg and sumatriptan 25 and 50 mg were compared in a double-blind, placebo-controlled, crossover study for efficacy and safety in two migraine attacks.[65] Patients (n=1,329) were randomized to rizatriptan 5 mg/sumatriptan 25 mg; sumatriptan 25 mg/rizatriptan 5 mg; rizatriptan 10 mg/sumatriptan 50 mg; sumatriptan 50 mg/rizatriptan 10 mg; or placebo/placebo. At two hours, more patients had pain relief with rizatriptan 5 mg than sumatriptan 25 mg (68 versus 62 percent, p<0.05), and more patients were pain free (33 versus 28 percent, respectively; p<0.05). With the higher doses, rates of pain relief (72 versus 68 percent) and pain-free (41 versus 37 percent) status were similar between rizatriptan 10 mg and sumatriptan 50 mg. Safety was similar among all groups.

In a double-blind single migraine attack study, 1,268 patients were randomized to rizatriptan 5 or 10 mg, sumatriptan 100 mg, or placebo and evaluated after two hours for headache relief.[66] Headache relief at one hour with rizatriptan 10 mg (37 percent) was significantly higher than with sumatriptan (28 percent, p=0.01). At two hours, all groups had similar rates of headache relief (60 percent for rizatriptan 5 mg, 67 percent for rizatriptan 10 mg, and 63 percent for sumatriptan 100 mg) and were superior to placebo ($p \leq 0.001$). Significantly fewer adverse events were reported with rizatriptan 10 mg (33 percent) compared to sumatriptan 100 mg (41 percent, p=0.014).

rizatriptan (Maxalt) and zolmitriptan (Zomig)

Rizatriptan 10 mg and zolmitriptan 2.5 mg were compared in a randomized, double-blind, placebo-controlled, single migraine attack study with 766 patients.[67] Both drugs had a similar pain relief response at two hours (70.5 versus 66.8 percent) although pain-free response (43.2 versus 35.6 percent, p=0.041) and return to normal function (45.4 versus 37 percent, p<0.05) were greater with rizatriptan. Headache recurrence was similar among the groups. All therapies were well tolerated.

sumatriptan (Imitrex) 4 mg injection

In the randomized, double-blind, placebo-controlled study, 577 subjects received either sumatriptan 4 mg SC or placebo SC for a migraine attack with headache pain of moderate to severe intensity.[68] The primary efficacy measurement was pain relief, reported by way of questioning and observation of subjects at two hours. At 120 minutes post-administration, sumatriptan 4 mg SC was associated with a greater proportion of patients experiencing pain

relief (70 versus 22 percent; p<0.001) or who were pain free (50 versus 11 percent; p<0.001). There were statistically significant differences in favor of sumatriptan 4 mg SC compared to placebo for multiple secondary end points, including pain relief as early as 10 and 30 minutes post-administration.

sumatriptan/naproxen (Treximet)

Two randomized, double-blind, single-attack, parallel-group studies were conducted among 1,461 and 1,495 patients who were diagnosed as having migraine and received treatment for a moderate or severe migraine attack.[69] Patients were randomized to receive a sumatriptan/naproxen tablet, sumatriptan 85 mg, naproxen 500 mg, or placebo after onset of a migraine with moderate to severe pain. Primary outcome measures included the percentages of patients with headache relief two hours after dosing, absence of photophobia, absence of phonophobia, and absence of nausea for the comparison between sumatriptan/naproxen and placebo, and the percentages of patients with sustained pain-free response for the comparison between sumatriptan/naproxen and each monotherapy. Sumatriptan/naproxen was more effective than placebo for headache relief at two hours after dosing (study one, 65 versus 28 percent; p<0.001 and study two, 57 versus 29 percent; p<0.001), absence of photophobia at two hours (58 versus 26 percent; 50 versus 32 percent; both p<0.001), and absence of phonophobia at two hours (61 versus 38 percent; 56 versus 34 percent; both p<0.001). The absence of nausea two hours after dosing was higher with sumatriptan/naproxen than placebo in study one (71 versus 65 percent; p=0.007), but not in study two (65 versus 64 percent; p=0.71). For two- to 24-hour sustained pain-free response, sumatriptan/naproxen was superior (25 and 23 percent in studies one and two, respectively; all p<0.01) to sumatriptan (16, 14 percent), naproxen (10, 10 percent), and placebo (8, 7 percent). The incidence of adverse events was similar between sumatriptan/naproxen and sumatriptan.

zolmitriptan (Zomig) and sumatriptan (Imitrex)

A total of 1,522 patients were randomized in a double-blind trial to receive zolmitriptan 2.5 mg or 5 mg or sumatriptan 50 mg for the treatment of up to six moderate to severe migraine attacks.[70] The two-hour headache response was 62.9, 65.7, and 66.6 percent, respectively. No significant differences were seen with the percentage of patients achieving headache response at one or two hours throughout the six attacks. All treatments were well tolerated.

Zolmitriptan and sumatriptan were compared for efficacy in the treatment of migraine headaches in 1,445 patients over six months.[71] In the double-blind study, patients were randomized to zolmitriptan 2.5 or 5 mg, sumatriptan 25 or 50 mg, and were permitted to administer a second dose of study medication for recurrent headache at least four hours after the first dose. Headache response was determined at two hours after dosing and was 67.1 percent for zolmitriptan 2.5 mg, 64.8 percent for zolmitriptan 5 mg, 59.6 percent for sumatriptan 25 mg, and 63.8 percent for sumatriptan 50 mg. Statistically significant differences were observed at two hours between zolmitriptan 2.5 mg and 5 mg and sumatriptan 25 mg (odds ratio=1.47 and 1.54; both p<0.001) and 50 mg doses (odds ratio=1.17, p=0.021; odds ratio=1.22, p=0.005). Similar headache response rates at two hours were seen with zolmitriptan 5 mg and sumatriptan 50 mg. All therapies were well tolerated.

In a triptan-naïve patient population of 1,058, zolmitriptan 5 mg and sumatriptan 100 mg were compared in a multicenter, double-blind, placebo-controlled trial for efficacy in a single migraine attack.[72] Patients were randomized and evaluated for headache response at one and two hours after dosing. Zolmitriptan and sumatriptan had similar rates of response at one and two hours; pain-free (complete) responses at two hours were 39 percent for zolmitriptan, 38 percent for sumatriptan, and 32 percent for placebo. Adverse reactions were similar between the triptan groups.

zolmitriptan (Zomig) nasal spray

In a randomized, double-blind study, zolmitriptan nasal spray was evaluated for efficacy and safety over a one-year period.[73] Patients (n=1,093) were randomized to zolmitriptan 0.5, 1, 2.5, or 5 mg dose or placebo with the availability of a second dose at least two hours after the first. The first portion of the study identified that zolmitriptan 5 mg was the most effective dose in reducing migraine headache pain at two hours post-dose (73.2 percent response rate). Over the one-year period, the response rate at two hours for zolmitriptan nasal spray remained 72 to 74.6 percent. The second portion of the study focused on adverse effects and tolerability, and all patients received zolmitriptan 5 mg for up to one year. Zolmitriptan nasal spray was well tolerated with only 1.9 percent of patients discontinuing therapy due to adverse effects. Adverse effects, which were mostly mild and transient, were reported in 22.1 percent of treated attacks.

Meta-analysis

A recent meta-analysis evaluated the relative efficacy and safety of zolmitriptan in the treatment of acute migraine attacks.[74] A total of 24 randomized controlled trials with 15,408 patients with acute migraine attacks were included. Zolmitriptan 2.5 mg had similar efficacy for pain-free response at two-hours postdose compared to almotriptan 12.5 mg, eletriptan 40 mg, and sumatriptan 50 mg, and being more effective than naratriptan 2.5 mg. Zolmitriptan 2.5 mg was also as effective as rizatriptan 10 mg in terms of headache relief and pain-free response but less effective in terms of sustained pain-free response. Zolmitriptan 5 mg was as effective as sumatriptan 50 mg and 100 mg in two-hour pain-free rates. Zolmitriptan 2.5 mg was associated with a higher risk of adverse effects than naratriptan 2.5 mg and rizatriptan 10 mg. Demonstrating a dose-response relationship, zolmitriptan 5 mg was superior to zolmitriptan 2.5 mg in achieving two-hour pain-free response.

Summary

There are several products with various dosage forms: rizatriptan (Maxalt) is available as an oral tablet and a rapidly disintegrating oral tablet; sumatriptan (Imitrex) is available as an oral tablet, nasal spray, and injection; and zolmitriptan (Zomig) is available as an oral tablet, rapidly disintegrating oral tablet, and nasal spray. No studies are available comparing zolmitriptan (Zomig) nasal spray with sumatriptan (Imitrex) nasal spray. Nasal irritation can occur, and unpleasant taste is common. Both often begin to produce relief in 15 minutes. Subcutaneous administration of sumatriptan (Imitrex) can have an onset of pain relief as soon as 10 minutes following a dose. Sumatriptan (Imitrex) has undergone a formulation revision to a rapid-release system that disperses the drug quicker than the conventional tablets. One study reported that sumatriptan (Imitrex) measured more effective than placebo, with relief beginning 17 to 25 minutes following administration of the 100 mg rapid-release tablet.[75]

The US Headache Consortium, the American Academy of Family Physicians, and the American College of Physicians – American Society of Internal Medicine have recognized that the triptans are effective agents for the acute treatment of migraine.[76,77] It is, however, possible for migraine patients to exceed manufacturer and Consensus Panel recommendations for use. The safety in treating more than four headaches in a thirty-day period has not been established for almotriptan, frovatriptan, naratriptan, sumatriptan and zolmitriptan nasal spray. Additionally, the safety in treating more than three headaches in a thirty day period has not been established for eletriptan or zolmitriptan tablets. Patients who experience more than four migraines a month may be considered candidates for preventative therapy.

NSAIDs are recommended as first-line therapy for those patients with mild to moderate migraine pain. Migraine-specific agents (triptans, dihydroergotamine [DHE]) should be used in patients

whose migraine attacks do not respond to NSAIDs. A nonoral route of administration should be selected when nausea or vomiting present early as significant components of migraine attacks. Sumatriptan/naproxen (Treximet) is available for patients whose relief requires multiple mechanisms of action.

These groups recognized the fact that naratriptan (Amerge) has a slightly delayed onset of pain relief compared to the other triptans. Data reviewed for the guidelines did not demonstrate that any one triptan was superior. Frovatriptan (Frova) and eletriptan (Relpax) were not available at the time of publication of the guidelines. These groups indicated that therapy with any triptan for a patient with moderate to severe migraine pain in whom no contraindications exist is appropriate. If a patient does not experience adequate relief or experiences intolerable adverse reactions with one triptan, treatment with another agent in the class can be effective.[78,79,80,81]

Frovatriptan (Frova) has the longest half-life of the products. Theoretically, patients should not need to redose as frequently with this product; however, it may take longer for the product to begin to work. The other triptans have similar half-lives and durations of action. Almotriptan (Axert) may have fewer side effects that are bothersome compared to the other agents. A meta-analysis of 53 clinical trials of the triptans collected data on 24,089 patients with migraines and evaluated comparative efficacy and tolerability data.[82] In light of the findings of this meta-analysis, differences among the triptans are in general relatively small, but clinically relevant for individual patients. Sumatriptan (Imitrex) features the longest clinical experience and the widest range of formulations. Almotriptan (Axert) 12.5 mg and rizatriptan (Maxalt) 10 mg may have the highest likelihood of reliable clinical success.

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