Drug Class Review: **Oral $5HT_1$ Receptor Agonists**

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Objectives

To review the efficacy, safety, and administration of currently available oral dosage forms of the $5HT_1$ receptor agonists (triptans) in the management of migraine headaches. There are injectable and nasal forms available but are not included in this review.

Table 1: Currently Available Oral $5HT_1$ Receptor Agonists[1]

Generic Name	Trade Name	Available oral tablets	Manufacturer
Sumatriptan	Imitrex®	25,50,100 mg	Glaxo Wellcome
Rizatriptan	Maxalt® and Maxalt MLT®	Tablets and orally disintegrating tablets 5,10 mg	Merck
Naratriptan	Amerge®	1, 2.5 mg	Glaxo Wellcome
Zolmitriptan	Zomig® and Zomig-ZMT®	Tablets 2.5,5 mg Orally disintegrating tablet 2.5, 5 mg	Astra-Zeneca
Almotriptan	Axert™	6.25, 12.5 mg	Pharmacia
Frovatriptan	Frova™	2.5 mg	Elan

Another agent, eletriptan will not be included in this review. Eletriptan is not currently available in the United States.

I. Introduction[2-7]

Migraine can be a painful and debilitating disorder, affecting approximately 28 million persons in the United States. While precise estimates vary, migraines may be responsible for millions of reduced-activity days per year, in addition to billions of dollars in medical costs and lost productivity.[2] Recent experiences with health related quality of life measures suggest patients with migraine may suffer a greater degree of functional status and well being impairment than patients with arthritis, depression or diabetes.[3]

A combination of vascular, muscular, and biochemical changes likely explains the pathophysiology of migraines. Migraine pain is believed to come from activation of the trigeminovascular system. Activity in the trigeminovascular system is regulated by serotonin. The $5HT_1$ presynaptic autoreceptors ($5HT_{1D}$) modulate neurotransmitter release and release of vasoactive neuropeptides. The post-synaptic receptors ($5HT_{1B}$) constrict blood vessel walls. The serotonin agonists (triptans) are specific for the $5HT_{1B}$ and $5HT_{1D}$ autoreceptors. It seems that levels of serotonin in the blood fall at the onset of headache but are normal between attacks.

Migraine therapy can be divided into three general categories of treatment: acute pharmacologic therapy, prophylactic pharmacologic therapy, and nonpharmacologic approaches. Acute pharmacologic therapy (also referred to as abortive therapy) can be further subdivided into nonspecific and specific migraine therapy. Nonspecific therapy relies on several classes of analgesics, anxiolytics and barbiturates. Specific therapy refers to drugs targeted against the pathophysiology of the migraine itself, and includes serotonin receptor agonists, both selective and nonselective.

II. Pharmacology[8,9]

The $5\text{-}HT_{1B/1D}$ receptor agonists appear to mediate effects on the $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors. These receptors are both peripheral and central. Cranial vessels contain $5\text{-}HT_{1B}$ receptors with stimulation resulting in vasoconstriction. The trigeminal nerves contain $5\text{-}HT_{1D}$ receptors and their activation results in neuronal inhibitory effects. Centrally, the trigeminal nucleus contains $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors. Stimulation of these receptors is responsible for interruption of nociceptive transmission within the brainstem. Since the etiology of migraine is a mixed interaction of systems, the relative contribution of both central and peripheral agonist activity in providing relief of migraine pain is not known.

III. Indications[10-15]

All of the agents under discussion are approved for the acute treatment of migraine attacks with or without aura. None are indicated for the treatment of hemiplegic or basilar migraine. The only agent indicated for cluster headache is the subcutaneous formulation of sumatriptan.

IV. Pharmacokinetics[10-15]

Table 2: Pharmacokinetics of oral triptans

Characteristic	Sumatriptan	Naratriptan	Zolmitriptan	Rizatriptan	Almotriptan	Frovatriptan
Oral Bioavailability (%)	14-15	70	40-48	45	70	20-30
Protein Binding (%)	10-21	28-31	25	14	35	15
Vol. Of Distribution	2.4-3.3 L/kg	2.4 L/kg	7.0 L/kg	140 L (male) 110 L (female)	180-200L	3.0L/kg (female) 4.2L/kg (male)
Metabolism	MAO -A	CYP-450	CYP 1A2, MAO-A	MAO-A	MAO, CYP2D6, CYP3A4	P450, 1A2
Active metabolites	No	No	Yes	Yes	no	no
Excretion	Urine (57%) Feces (38%)	Urine	Urine (65%) Feces (30%)	Urine	Urine 40% Feces 13%	Renal 40%
Half-life (hrs)	2	6 (mean)	3	2	3-4	26
Onset	30-60 min	1-3 hrs	45 min	30 min-2 hrs	1-3hrs	1-2 hrs
Duration of Action	Short	Long	Short	Short	Short	long
Tmax (hrs)	2.5	3-4	2-3	1-1.5	1-3	2-4

V. Clinical Efficacy

Review of placebo controlled studies

A number of randomized, double blind, placebo-controlled trials have been performed with each of these agents to determine its efficacy vs. placebo. The results of these studies are outlined in Table 3.

Table 3: Efficacy of oral triptans vs. placebo for the treatment of migraine headache

Drug	Efficacy at 2hrs (% of pts with HA improvement from 2-3 to 0-1)	Efficacy at 4hrs (% of pts with HA improvement from 2-3 to 0-1)	Pain free at 2hrs	Pain free at 4hrs	Headache recurrence (within 24hrs of study med) [4]
Sumatriptan[16,17]	46-68% (25-100 mg)	65-78% (25-100 mg)	21-23% (25-10 mg)	45-50% (25-100 mg)	40%
Rizatriptan[118,19]	52-77% (5-10 mg)*	79-84% (2.5-10 mg)	25-44% (2.5-10 mg)	Not done	41%
Naratriptan[20, 21]	Not done	60-68% (2.5 mg)	Not done	33-45% (2.5 mg)	27% (2.5 mg)
Zolmitriptan[22-24]	59-67% (2.5-10 mg)*	Not done	9-47% (1-20 mg)	Not done	30%
Almotriptan[25]	59.9-70.3% (6.25-12.5mg)	Not done	29.9-38.8% (6.25-12.5mg)	Not done	28.7-30.1% (6.25-12.5mg)
Frovatriptan[15]	37-46%	Not done	Not reported	Not done	Not reported

* FDA-approved maximum daily doses are 30mg for rizatriptan and 10mg for zolmitriptan

Review of head to head trials[26-31]

There is no single measure considered to be the standard for determining the optimal agent to use in the abortive treatment of migraine headache. Several outcome measures have been used to assess the efficacy of 5-HT$_{1B/1D}$ receptor agonists in the treatment of migraine attacks. The most clinically relevant outcomes focus on percentage of patient's pain free at 2 hrs, headache recurrence and decrease in headache severity at 2 hrs. Direct comparisons of the available 5-HT$_{1B/1D}$ receptor agonists have been conducted in a limited number of clinical trials. Table 4 summarizes these trials.

Table 4: Head to head studies comparing efficacy of oral triptans

Author	Drugs and strengths compared	Design	N	Efficacy @ 2 hours	Pain Free @ 2 hours	Headache recurrence at or before 24 hours
Visser et al[26]	Rizatriptan 10mg, 20mg, 40mg, sumatriptan 100mg, placebo	R, DB, PC, parallel group, outpt trial	449, male and female, 18-55 y/o	PL-18%, R10-52%, R20-56%, R40-67%, S100-46% (all p<0.001 vs. PL, R40 vs. S100, p< 0.01)	Not done	PL-36%, R10-41%, R20-53%, R40-42%, S100-41% (no stat testing done)
Tfelt-Hansen et al[27]	Rizatriptan 5mg, 10mg, sumatriptan 100mg, placebo	R, DB, PC, triple-dummy, parallel-group	1,268, male and female, 18-65 y/o	PL-40%, R5-60%, R10-67%, S100-62% (all p<0.001 vs. PL)	PL-9%, R5-25%, R10-40%, S100-33% (all p<0.001 vs. PL, R10 vs.	PL-20%, R5-48%, R10-35%, S100-32% (no stat testing done)

		group			PL, R10 vs. S100, p<0.05)	done)
Goldstein et al[28]	Rizatriptan 5mg, 10mg, sumatriptan 25mg, 50mg, placebo	DB, PC, crossover	1,329, male and female, 18-91 y/o	PL-38%, R5-68%, R10-72%, S25-62%, S50-68% (all p=NS except R5 vs. S25, p<0.05)	PL-9%, R5-33%, R10-41%, S25-28%, S50-37% (all p=NS except R5 vs. S25, p< 0.05)	PL-32%, R5-33%, R10-35%, S25-32%, S50-31% (no stat testing done)
Block et al[29]	Rizatriptan 5mg, 10mg, standard therapy (ST)	R, multi-center	1,831, male and female, 18-65 y/o	R5-80%, R10-90%, ST-70% (R5 and R10 vs. ST, p<0.001)	R5-35%, R10-50%, ST-29% (R10 vs. R5 and ST, p<0.016)	~30% with R5 and R10 (no stat testing done)
Bornhof et al[30]	Rizatriptan 10mg, naratriptan 2.5mg, placebo	R, PC, double-masked, double-dummy	522, male and female, 18-65 y/o	PL-22%, R10-69%, N2.5-48% (R10 vs. N2.5, p<0.001)	PL-8%, R10-45%, N2.5-21% (R10 vs. N2.5, p<0.001)	PL-25%, R10-33%, N2.5-21% (no stat testing done)
Spierings, et al[31]	Almotriptan 12.5 mg Sumatriptan 50 mg	R, DB, MC, parallel group	1255, male and female, 18-65 y/o treated 1173	A 58%, S 57.3%	A 17.9%, S 24.6% (p<0.005)	A 27.4% S 24.0%

Further analysis of available data

The tremendous variability in the effectiveness of the placebo arms in these studies makes it impossible to draw valid conclusions by directly comparing the reported efficacies. Two recent meta-analyses attempted to overcome this problem by comparing the "number needed to treat (NNT)" for the medication in each study.[32,33] This is calculated using the equation 1/(proportion benefiting from the experimental intervention minus the proportion benefiting from the control intervention), which corrects for control group variability. The NNT is defined as 1 divided by the absolute risk reduction (ARR), which equals the number of patients to be treated to avoid or cure the studied event, in this case, aborting a migraine headache. The results of these analyses are presented in Table 5.

Table 5: Efficacy of oral triptans based on number needed to treat

Drug	Dose (mg)	# Studies	# Patients	NNT (95% CI)
Zolmitriptan	5	2	407	2.8 (2.2 to 3.9)
Rizatriptan	10	3	1,143	2.9 (2.5 to 3.5)
Sumatriptan	100	12	2,890	3.0 (2.8 to 3.4)
Zolmitriptan	10	1	369	3.1 (2.4 to 4.6)
Zolmitriptan	2.5	2	651	3.5 (2.7 to 4.7)
Rizatriptan	5	2	954	3.8 (3.1 to 4.9)
Naratriptan	2.5	1	249	8.8 (4.3 to no benefit)
Almotriptan	6.25 mg	2	782	5.7-7.4

Almotriptan	12.5 mg	2	790	4.2-8.9

This analysis suggests that with the exception of naratriptan there is no evidence of a difference in the ability of the available oral triptans at the studied doses to relieve headache at 2 hours since the NNT for each agent is almost identical and the confidence intervals around those values overlap significantly. The relatively high NNT for naratriptan may be attributable to its delayed onset on action.

VI. Safety and Adverse Effects Safety

Contraindications[1,10-15]

All triptans are contraindicated in patients with ischemic heart disease (angina, history of MI, documented silent ischemia), Prinzmetal's variant angina, or other significant cardiovascular disease, coronary artery spasm, or uncontrolled hypertension. They should not be used concurrently (or within 24 hours of) another triptan or ergot alkaloid (see drug interactions), or concurrently or within 2 weeks of discontinuation of a MAO-A inhibitor (except naratriptan). All the triptans are contraindicated in patients with uncontrolled hypertension.

Their use is contraindicated for the management of hemiplegic or basilar migraine, and in patients with demonstrated hypersensitivity to the drug.

Naratriptan is contraindicated in patients with cerebrovascular or peripheral vascular syndromes, severe renal impairment (< 15 ml/min) or severe hepatic impairment (Child Pugh grade C).

Zolmitriptan is contraindicated in patients with symptomatic Wolff-Parkinson-White (WPW) syndrome or arrhythmias associated with other cardiac accessory conduction disorders.

Rare but Serious Side Effects

Relatively few patients in clinical trials have experienced the side effects of chest pain/tightness/angina/coronary vasospasm and hypertension:[34,35] . Triptans should not be prescribed to patients who are at risk for coronary artery disease (CAD) without prior cardiac evaluation. This includes postmenopausal women, males over 40 years, and/or patients with other American Heart Association cardiac risk factors (hypertension, hyperlipidemia, obesity, diabetes, smoking, strong family history). There have been rare reports of significant cardiovascular events including death (39 deaths within 24 hours of sumatriptan/100,000,000 doses of sumatriptan from 1991-1996) in patients with a history of cardiovascular disease or significant cardiovascular risk factors.[34] This is most likely related to coronary artery vasoconstriction that occurs with all of these agents.[36]

Other Side Effects

Rebound headaches [37,38] Medication-overuse (rebound) headaches result from frequent use of acute medications to abort migraine headaches. Rebound headaches are associated with acute withdrawal of analgesics or abortive agents. There is no universal agreement on which agents cause rebound or medication-overuse headache. Implicated agents include ergotamine, opiates, triptans, NSAIDs, a[illegible]thers. Patients requiring abortive treatment more often than this should be evaluated for preventive therapies (i.e. [illegible] blockers, amitriptyline, divalproex).

Binding to melanin-containing tissues[15] Studies conducted in animal models(pigmented rats) have suggested that frovatriptan may bind to the melanin of the eye. This may result in accumulation of the drug in these areas with prolonged use. The clinical effects of this are not known.

Special Populations

Age: No alterations in pharmacokinetics have been reported in the elderly. Safety and efficacy have not been established in pediatrics.

Hepatic function impairment: The liver plays an important role in the presystemic (first pass) clearance of all triptans. Bioavailability of triptans may be increased in patients with liver disease. Zolmitriptan should be used with

caution in patients with severe hepatic impairment. Providers are advised to prescribe ≤2.5mg/dose and a maximum daily dose of 5mg/24 hours. Naratriptan is contraindicated in severe hepatic impairment (Child-Pugh grade C). In patients with mild/moderate hepatic impairment, recommended maximum dose is 2.5mg/day. Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentration of 30%. Sumatriptan doses should not exceed 50 mg as single dose in presence of liver disease. It is contraindicated in severe hepatic impairment. The use of almotriptan in patients with severe hepatic impairment is not contraindicated, but a maximum dose of 12.5 mg per 24 hours and starting dose of 6.25 mg is recommended.

Renal function impairment: Naratriptan is contraindicated in patients whose creatinine clearance is less than 15 ml/min. The clearance of naratriptan is reduced by 50% in patients with moderate renal impairment (creatinine clearance < 20-25 ml/min); the recommended maximum dose is 2.5mg/day for these patients.
Rizatriptan should be used with caution in dialysis patients due to decreased clearance of the drug. Rizatriptan clearance is reduced by more than 40% in patients with severe renal impairment, but no specific dosage adjustment is recommended in this population.

Pregnancy – Category C. There have been reports of fetal abnormalities and death in animals. There are no adequate and well-controlled studies in pregnant women. These agents should be used in pregnancy only when the benefits outweigh the risks.

Drug Interactions[10-15]

Rizatriptan and propranolol: The area under the curve (AUC) of rizatriptan increases 70% in patients on concurrent propranolol therapy (prophylaxis). The manufacturer recommends starting with the 5 mg dose in patients taking propranolol. Although the clinical significance is not stated, it appears reasonable to expect a greater incidence of adverse effects if the dose of rizatriptan is not adjusted in this population.

Triptans and MAO inhibitors: MAO-A inhibitors can significantly increase systemic levels of the triptans (except naratriptan). Naratriptan is not contraindicated with concurrent MAO inhibitors since it is metabolized through a different metabolic pathway.[4, 7] MAO-A inhibitors significantly increase the AUC of 5HT1 agonists (i.e. triptans) when combined with or given within 2 weeks of discontinuation of an MAO inhibitor, especially an MAO-A isoenzyme inhibitor. There is no appreciable effect when concurrent treatment with an MAO-B inhibitor such as selegiline (Eldepryl®) is given. The greatest interaction is seen with oral dosage forms, then nasal, then subcutaneous. Because MAO is only involved to a limited extent in almotriptan's metabolism, concurrent use of an MAO-inhibitor or within 2 weeks of initiation of almotriptan is not contraindicated.

Triptans and ergot alkaloids: These drugs should not be used within 24 hours of each other. Prolonged vasospastic reactions have occurred with this combination.

Triptans and other triptans: Concomitant use of more than one triptan as well as use within 24 hours of using another triptan is contraindicated. All the triptan package inserts contain this contraindication because of a concern that the adverse effects of these agents, especially the vasoconstriction, may be additive. Although some providers have suggested using a short acting triptan (i.e. sumatriptan) and then a longer acting triptan (i.e. naratriptan) to give quick relief and prevent recurrent headaches, these combinations are not recommended. The safety, efficacy, and tolerability have not been thoroughly evaluated although small, preliminary studies in healthy volunteers did not show significant adverse events.

Zolmitriptan and cimetidine Because zolmitriptan is metabolized through the cytochrome P-450 1A2 (CYP 1A2) system and cimetidine is a specific inhibitor of this isoenzyme, this combination caused a doubling of the half life and AUC of zolmitriptan. The clinical effect of this interaction is undetermined. Although naratriptan is metabolized through a wide variety of cytochrome P-450 (CYP) isoenzymes, there are no active metabolites. The other available triptans (rizatriptan and sumatriptan) are not metabolized through the CYP enzyme systems.

Triptans and SSRIs: Patients on this combination require close observation. Combinations of a triptan and an SSRI have shown rare instances of a serotonin-like syndrome to include weakness, hyperreflexia, and incoordination.

In published clinical trials, all the oral triptans are generally well tolerated. Most adverse reactions were mild and transient and did not require discontinuation. The incidence of side effects appeared to increase with dose.

Differences in patient populations, methods of collecting patient complaints, the duration of the trials, and the level of suspicion of clinical investigators could cause wide variance in reported incidence and discontinuation rates. This is raw, pooled data and not adjusted by, or corrected with, placebo dropout rates. Caution should be exercised when comparing one triptan to another based on adverse events reported during clinical trials.

VII. Dosage and Administration

Table 6: Dosing of oral triptans[10-15]

Drug (Manufacturer)	Trade Name	Dosage form	Oral Dose	Maximum Oral Dose
Sumatriptan (Glaxo-Wellcome)	Imitrex®	25mg tab, 50mg tab, 100mg tab	25-50mg may repeat q2 hrs	100mg/dose, 200mg/day
Naratriptan (Glaxo-Wellcome)	Amerge®	1mg tab 2.5mg tab	1-2.5mg may repeat once in ≥ 4 hrs	5mg/day
Zolmitriptan (AstraZeneca)	Zomig®	2.5mg tab 5mg tab	2.5mg, may repeat in > 2 hrs	5mg/dose, 10mg/day
Rizatriptan (Merck)	Maxalt® Maxalt-MLT®	5mg tab 10mg tab 5mg oral disintegrating tab 10mg oral disintegrating tab	5-10mg, may repeat in > 2 hrs	30mg/day
Almotriptan (Pharmacia)	Axert™	6.25 and 12.5 mg tablets	6.25-12.5 mg, may repeat after 2hrs	25 mg/24 hrs
Frovatriptan (Elan)	Frova™	2.5 mg tablets	2.5 mg may repeat after 2 hrs	7.5 mg/ 24hrs

VIII. Conclusions and Recommendations

All the oral triptans are efficacious in treating migraine headache with and without aura. A meta-analysis of several studies suggests that with the exception of naratriptan there is no evidence of a difference in the ability of the available oral triptans to relieve headache at 2 hours. The most recent meta analysis of available trials reported that rizatriptan 10 mg and almotriptan 12.5 mg provided the most consistent success.[39] Rizatriptan 10mg may be slightly more effective in relieving headache at 2 hours compared to zolmitriptan or sumatriptan. Headache recurrence rates appear similar. All these agents are generally well tolerated. Side effects are very similar. Differences in patient populations, methods of collecting patient complaints, and the duration of the trials could cause wide variance in reported incidence of adverse drug reactions. There is insufficient evidence available to conclude that the incidence of other adverse events differs significantly between the triptans. There are slight differences in drug-drug interactions and dosage adjustments based on renal and hepatic function.

There should be one oral triptan on the VA National Formulary. Naratriptan would not be the preferred agent due to its longer onset of action. The agent chosen should be sumatriptan, zolmitriptan, almotriptan or rizatriptan. The alternate forms of sumatriptan (injectible, intranasal) should be available for those patients who require treatment in a non-oral route. There is insufficient evidence to demonstrate the rapidly dissolving dosage forms offer more advantages than the standard oral tablet.

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