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Triptans in Migraine

A Comparative Review of Pharmacology, Pharmacokinetics and Efficacy

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Contents

Abstract

Triptans are a new class of compounds developed for the treatment of migraine attacks. The first of the class, sumatriptan, and the newer triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan and frovatriptan) display high agonist activity at mainly the serotonin 5-HT_{1B} and 5-HT_{1D} receptor subtypes. As expected for a class of compounds developed for affinity at a specific receptor, there are minor pharmacodynamic differences between the triptans.

Sumatriptan has a low oral bioavailability (14%) and all the newer triptans have an improved oral bioavailability and for one, risatriptan, the rate of absorption is faster. The half-lives of naratriptan, eletriptan and, in particular, frovatriptan (26 to 30h) are longer than that of sumatriptan (2h). These pharmacokinetic improvements of the newer triptans so far seem to have only resulted in minor differences in their efficacy in migraine.

Double-blind, randomised clinical trials (RCTs) comparing the different triptans and triptans with other medication should ideally be the basis for judging their place in migraine therapy. In only 15 of the 83 reported RCTs were 2 triptans compared, and in 11 trials triptans were compared with other drugs. Therefore, in all placebo-controlled randomised clinical trials, the relative efficacy of the triptans was also judged by calculating the therapeutic gain (i.e. percentage response for active minus percentage response for placebo). The mean therapeutic gain with subcutaneous sumatriptan 6mg (51%) was more than that for all other dosage forms of triptans (oral sumatriptan 100mg 32%; oral sumatriptan 50mg 29%; intranasal sumatriptan 20mg 30%; rectal sumatriptan 25mg 31%; oral zolmitriptan 2.5mg 32%; oral rizatriptan 10mg 37%; oral eletriptan 40mg 37%; oral almotriptan 12.5mg 26%). Compared with oral sumatriptan 100mg (32%), the mean therapeutic gain was higher with oral eletriptan 80mg (42%) but lower with oral naratriptan 2.5mg (22%) or oral frovatriptan 2.5mg (16%). The few direct comparative randomised clinical trials with oral triptans reveal the same picture. Recurrence of headache within 24 hours after an initial successful response occurs in 30 to 40% of sumatriptan-treated patients. Apart from naratriptan, which has a tendency towards less recurrence, there appears to be no consistent difference in recurrence rates between the newer triptans and sumatriptan. Rizatriptan with its shorter time to maximum concentration (t_{max}) tended to produce a quicker onset of headache relief than sumatriptan and zolmitriptan.

The place of triptans compared with non-triptan drugs in migraine therapy remains to be established and further RCTs are required.

The triptans are a new class of compounds known as serotonin (5-hydroxytryptamine; 5-HT) 5-$HT_{1B/1D}$, previously 5-HT_1-like/5-HT_{1D},[1,2] receptor agonists. The first of this family, sumatriptan, is undoubtedly a significant advance in migraine therapy.[3-9] Despite its great utility in migraine treatment, sumatriptan has certain limitations: for example, low oral bioavailability; high headache recurrence (for definition, see section 5.1.5), possibly due to a short half-life; and contraindication in patients with coronary artery disease. Therefore, a number of newer triptans with agonist activity at 5-$HT_{1B/1D}$ receptors have been developed. Several such compounds (zolmitriptan, rizatriptan and naratriptan) are already on the market, while others (eletriptan, almotriptan and frova-

triptan) are in advanced stages of clinical development (for chemical structures, see figure 1). Despite the efficacy of avitriptan,[10,11] BMS-181885[12] and the non-triptan alniditan[13] in the treatment of migraine, these compounds are no longer in clinical development. In this review, we discuss the pharmacology and pharmacokinetics of these triptans, the randomised placebo-controlled clinical trials with triptans demonstrating their efficacy and evaluating the optimum dose, randomised clinical trials (RCTs) comparing triptans, and RCTs comparing triptans with other treatments.

1. Pharmacological Effects of Triptans

1.1 Receptor Binding Profile

Sumatriptan and the newer triptans display high affinities at 5-HT_1 receptor subtypes, mainly the 5-HT_{1B} and 5-HT_{1D} receptors (table I).[14-22] There are no profound differences in affinities at the 5-HT_{1B} and 5-HT_{1D} receptors. These compounds also interact with 5-HT_{1A} and 5-HT_{1F} receptors, but rizatriptan appears to be more selective for 5-$HT_{1B/1D}$ receptors. However, it must be said that

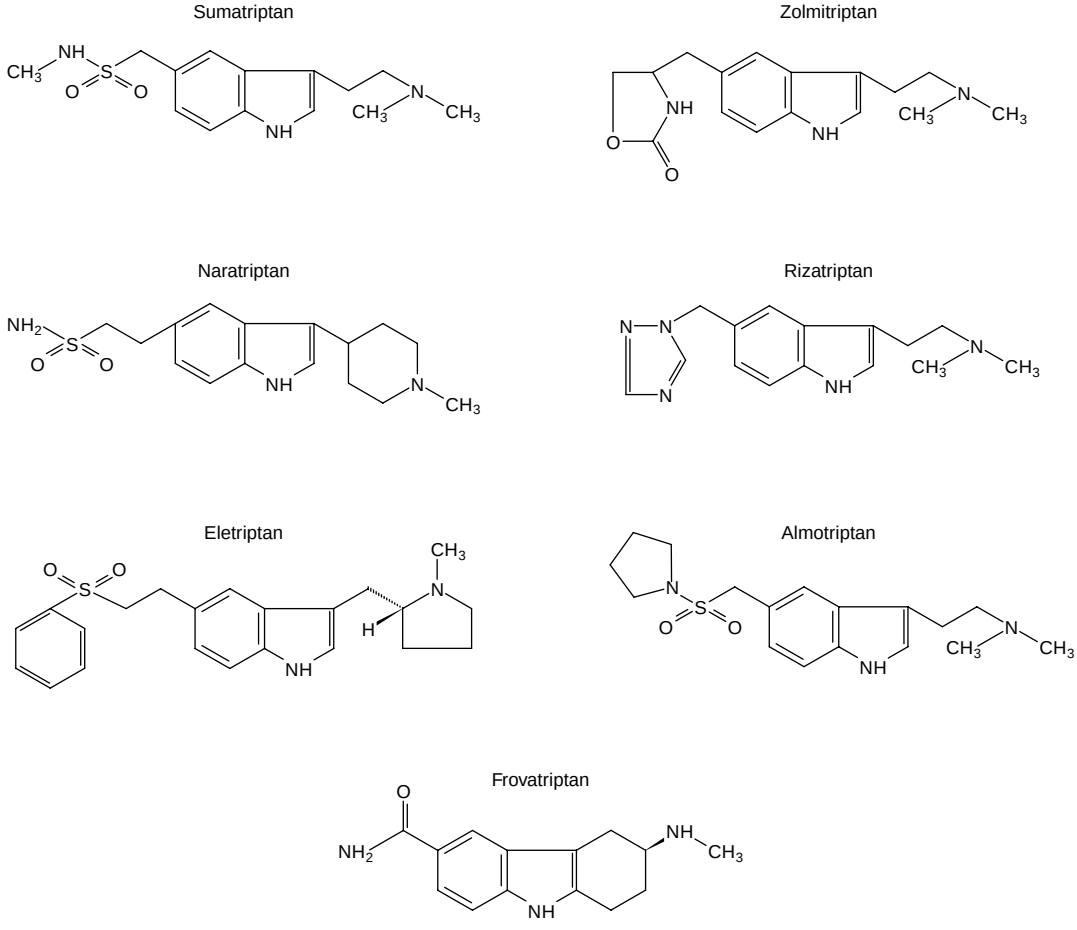

Fig. 1. Chemical structures of sumatriptan and second generation triptans.

Table I. Receptor affinities (pK_i values) of triptans at 5-HT receptors; all values refer to the human receptor, except when stated otherwise

Receptor	Triptan						
	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Eletriptan	Almotriptan	Frovatriptan
5-HT_{1A}	6.4[14]	6.5[16]	7.6[15]	6.4[18]	7.4[18]	6.3[19]	7.3[20]
	6.9[15]		7.1 (rat)[17]				
			7.1[18]				
5-HT_{1B}	7.8[14]	8.3[16]	8.7[17]	6.9[18]	8.0[18]	8.0[19]	8.6[20]
			8.1[18]	8.1[a]			
				7.7[21]			
5-HT_{1D}	8.5[14]	9.2[16]	8.3[17]	7.9[18]	8.9[18]	8.0[19]	8.4[20]
			8.4[18]	8.6[a]			
5-ht_{1E}	5.8[14]	7.7[18]	7.7[18]	6.8[18]	7.3[18]		<6.0[20]
5-ht_{1F}	7.9[14]	7.2[16]	8.2[18]	6.8[18]	8.0[18]		7.0[20]
	7.9[18]	7.5[18]					
5-HT_{2A}	<5.0 (pEC_{50})[14]	<5.5[18]	<5.5[18]	<5.5[18]	<5.5[18]		<5.3[20]
5-HT_{2B}	6.9[b]	7.2[b]		6.6[b]			
5-HT_{2C}	<5.0 (pEC_{50}, pig)[14]	F4.1 (guinea-pig)[16]	<5.5[18]	<5.5[18]	<5.5[18]		<5.3[20]
Mouse 5-HT_3	<5.0 (pEC_{50})[14]	<5.5[18]	<5.5[18]	<5.5[18]	<5.5[18]		<6.0[20]
Guinea-pig 5-HT_4	<5.0 (pEC_{50})[14]	<5.5[18]	<5.5[18]	<5.5[18]	<5.5[18]		
5-ht_{5A}	5.5[a]; <5.5 (rat)[18]	6.4 (rat)[b]	5.5 (rat)[18]	5.3 (rat)[18]	5.8 (rat)[18]		
5-ht_6	<5.5[18]	<5.5[18]	<5.5[18]	<5.5[18]	6.3[18]		
5-HT_7	5.9[18]	7.0[18]	<5.5[18]	5.7[18]	6.7[18]	<6.5[19]	6.70[20]

a Pauwels PJ, personal communication.

b Gupta P, personal communication.

pEC_{50} = concentration eliciting 50% inhibition.

the non-triptan compound, alniditan, which has shown efficacy in migraine,[13] has little if any affinity at the 5-HT_{1F} receptor.[14]

Sumatriptan, zolmitriptan, eletriptan and frovatriptan display a micromolar affinity at the 5-HT_7 receptor, which mediates smooth muscle relaxation.[1,23]

1.2 Cardiovascular Effects

1.2.1 Systemic Haemodynamics

Human volunteer studies show that sumatriptan,[24,25] zolmitriptan[26] and rizatriptan[27] slightly increase arterial blood pressure (BP). This hypertensive response, which has little clinical relevance, is probably related to peripheral vasoconstriction. Interestingly, in anaesthetised animals, high intravenous doses of sumatriptan,[28,29] eletriptan[30] and rizatriptan[29] decrease BP, which appears to be due to reduction of sympathetic outflow. It is known that hypotension can be mediated via an agonist action at 5-HT_{1D} and/or 5-HT_{1A} receptors.[29,31,32]

1.2.2 Carotid Haemodynamics

Sumatriptan increases internal carotid and middle cerebral artery blood flow velocity in patients with migraine.[33-35] Although this is yet to be established, on the basis of similar pharmacological properties, other triptans are likely to have comparable effects. This effect is probably caused by constriction of intracranial arteries, consistent with findings in animal models (see section 1.2.3).

As shown in table II,[17,19,28,30,36-40] sumatriptan and the other triptans decrease carotid artery blood flow in anaesthetised animals. The apparent rank order of agonist potency in decreasing canine carotid blood flow was as follows [with dose eliciting 50% effect (ED_{50}) in μg/kg], intravenously administered frovatriptan (0.4)[39] > zolmitriptan (2.3)[36] > eletriptan (12)[38] = naratriptan (19)[17] ≥ rizatriptan (30)[37] = sumatriptan (39).[17] Almotriptan[19]

potently reduces carotid blood flow in the cat. Using intracarotid administration of radiolabelled microspheres, it has also been shown that the carotid vasoconstriction by sumatriptan,[28,41] zolmitriptan[36] and eletriptan[30] is confined to arteriovenous anastomoses, which may dilate during migraine headaches.[42,43] Similarly, sumatriptan (infused into the brachial artery) is able to decrease human forearm blood flow by a selective vasoconstrictor action on arteriovenous anastomoses.[44] The extracerebral blood flow increases in response to 5-$HT_{1B/1D}$ receptor agonists,[28,30,41] although with zolmitriptan a decrease has been reported.[36] Interestingly, cerebral blood flow does not seem to be affected by triptans, as shown with sumatriptan[28,41] and even with the much more lipophilic, brain-penetrant compounds zolmitriptan,[36] eletriptan[30] and rizatriptan.[40]

1.2.3 Constriction of Isolated Blood Vessels

As shown in table III, a number of isolated blood vessels from several species contract in response to triptans.[16,17,19,20,45-54] This effect is more marked on cranial vessels where, unlike in most peripheral arteries, 5-HT_{1B} rather than 5-HT_2 receptors are predominant.[55,56] All compounds resemble sumatriptan in their action and potency, but naratriptan appears to be more efficacious [higher maximum effect (E_{max})] than sumatriptan in the canine basilar artery.[17] Moreover, eletriptan seems to behave as a partial agonist in the dog saphenous vein,[51] whereas zolmitriptan shows a somewhat lower maximal contraction in the rabbit saphenous vein than sumatriptan.[16]

1.2.4 Coronary Vascular Effects

In the human coronary artery, 5-HT_2 receptors are more important in mediating vasoconstriction, but about 20 to 30% response is mediated by 5-HT_1 receptors.[55,56] Accordingly, sumatriptan moderately constricts the human coronary artery, both *in vivo*[24] and *in vitro* (table III). Other triptans for which data are available are slightly more potent (except eletriptan), but show similar efficacy (fig. 2a and b).[45,49,50,53] Figure 2c[49,50,53] presents the ratio between the unbound peak plasma concentration (C_{max}) after administration of clinically effective doses and the EC_{50} value of the compounds in contracting the human isolated coronary artery. A C_{max}/EC_{50} ratio of 1 indicates that the drug (active metabolite excluded)[53] would elicit 50% of its E_{max} in a clinical situation. Since in each case the C_{max}/EC_{50} ratio is well below 0.4 (zolmitriptan and eletriptan even below 0.05), the triptans are expected to cause only a little coronary constriction at therapeutic doses in patients with migraine without any coronary artery disorder. However, in patients with coronary artery disease (stenosis or hyperreactivity), the second generation triptans may still cause myocardial ischaemia (for details see MaassenVanDenBrink et al.[53]).

1.3 Inhibitory Effects on the Trigeminovascular System

1.3.1 Peripheral Trigeminal Neuronal Inhibition

As shown in table IV,[16,17,19,38,57-65] the triptans (although this has yet to be established for frovatriptan) inhibit dural plasma protein extravasation following electrical stimulation of the trigeminal nerve.[16,17,19,38,58] Since sumatriptan was

Table II. Decrease in carotid blood flow with triptans expressed as ED_{50} (g/kg IV)

	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Eletriptan	Almotriptan	Frovatriptan
Total (↓)	39 (dog)[17]	2.3 (dog)[36]	19 (dog)[17]	30 (dog)[37]	12 (dog)[38]	10 (cat)[19]	0.4 (dog)[39]
	30-100 (pig)[28]	1.0 (cat)[36]			30-100 (pig)[30]		
AVA(↓)	<30 (pig)[28]	<10 (cat)[36]			30-100 (pig)[30]		
Extracerebral	↑ (pig)[28]	↓ (dog)[36]			↑ (pig)[30]		
Cerebral	= (pig)[28]	= (dog)[36]		= (dog)[40]	= (pig)[30]		

AVA = arteriovenous anastomoses; **ED_{50}** = dose eliciting 50% effect; **IV** = intravenous; ↓ indicates decrease; ↑ indicates increase; = indicates no change.

Table III. Contraction of isolated blood vessels by triptans, expressed as pEC_{50} values; if known, the intrinsic activity relative to serotonin (serotonin = 1) is given in parentheses

	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Eletriptan	Almotriptan	Frovatriptan
Human basilar artery	6.93 (1.11)[45]					5.46[19]	7.86 (1.25)[45]
Dog basilar artery	6.16 (0.63)[46]	6.63 (0.61)[46]	6.96 (1.05)[17]		7.20 (0.77)[47]		
	6.80 (0.89)[47]						
Primate basilar artery	6.46 (0.48)[16]	6.92 (0.56)[16]					
Rabbit basilar artery	6.00[20]						7.20[20]
Dog middle cerebral artery	7.80 (1.08)[a]		7.15 (1.14)[17]				
Human middle meningeal artery	7.15 (0.66)[48]			7.05 (0.83)[48]	7.30 (0.79)[49]	7.52[19]	
Human saphenous vein	6.14 (0.54)[50]				5.91 (0.48)[50]		
Dog saphenous vein	6.10 (0.85)[51]				6.30 (0.57)[51]		
Rabbit saphenous vein	6.48 (0.97)[16]	6.79 (0.77)[16]		6.64 (0.90)[52]			
Human coronary artery	6.10 (0.24)[53]	6.32 (0.20)[53]	6.77 (0.17)[53]	6.35 (0.17)[53]	5.37 (0.33)[49]		7.38 (0.42)[45]
	6.70 (0.35)[16]	7.30 (0.37)[16]	6.77 (0.33)[17]	5.99 (0.22)[54]			
	6.14 (0.21)[17]						
	6.20 (0.43)[54]						

a Yocca FD, personal communication.

pEC_{50} = concentration eliciting 50% inhibition.

ineffective in 5-HT_{1B} receptor knockout mice, this effect seems to involve the 5-HT_{1B} receptor.[66] Similarly, this receptor mediates the effects of sumatriptan in the guinea-pig dura mater,[66,67] where the 5-HT_{1F}[68,69] as well as a novel[66,67] receptor also play an important role. In the rat, the inhibition of plasma protein extravasation involves non-5-HT_{1B} receptors, possibly 5-HT_{1D} receptors and/or another CP-122288–sensitive receptor.[57] Importantly, it should be noted that inhibition of plasma protein extravasation alone is not consistent with antimigraine activity, since CP-122288 (in doses devoid of vasoconstrictor effect) was ineffective in migraine.[70] Moreover, May et al.[71] recently questioned the involvement of plasma extravasation in migraine, mainly on the basis of the lack of retinal permeability changes during migraine attacks.

Sumatriptan[59] and zolmitriptan[60] have been shown to inhibit neuropeptide release (mainly calcitonin gene-related peptide; CGRP) elicited by trigeminal ganglion stimulation. Moreover, sumatriptan and rizatriptan, but not CP-122288, inhibit neurogenically induced dural vasodilatation, an effect which, at least in rats, seems to be mediated by the 5-HT_{1B} receptor.[57]

1.3.2 Central Trigeminal Neuronal Inhibition

More recently, Goadsby and colleagues have shown that intravenous administration of zolmitriptan[62] as well as naratriptan[64] inhibits action potentials generated in the trigeminal nucleus caudalis after superior sagittal sinus stimulation in cats. Similarly, in rats, intravenous rizatriptan inhibits such potentials evoked by dural stimulation.[65] Thus, these drugs exhibit a central inhibitory effect within the trigeminal system, which may partly contribute to their therapeutic effect in migraine. However, because of its poor central penetration, intravenous sumatriptan did not affect *c-fos* mRNA expression in the trigeminal nucleus caudalis following trigeminal ganglion stimulation in rats.[61] This raises the question whether central trigeminal inhibition is predictive of antimigraine potential. On the other hand, it remains to be clarified whether during migraine headaches the blood-brain barrier is partly disrupted. Indeed, after disruption of the blood-brain barrier by infusion of hyperosmolar mannitol, sumatriptan did inhibit *c-fos* mRNA expression.[61]

The central trigeminal inhibitory effects of naratriptan in the cat, being susceptible to blockade by GR-127935, are mediated by 5-$HT_{1B/1D}$ recep-

tors.[64] Since ketanserin displaced zolmitriptan from its binding sites in the cat brain stem, the involvement of 5-HT_{1D} receptors is likely.[72] Also, in rats, the central trigeminal antinociceptive action by zolmitriptan is mediated by 5-HT_{1D} but not 5-HT_{1B} receptors.[63]

2. Possible Mechanisms of Action

The theoretically possible mechanisms of action of triptans in migraine are constriction of dilated cranial blood vessels, inhibition of neurogenic inflammation around the blood vessels,[73]

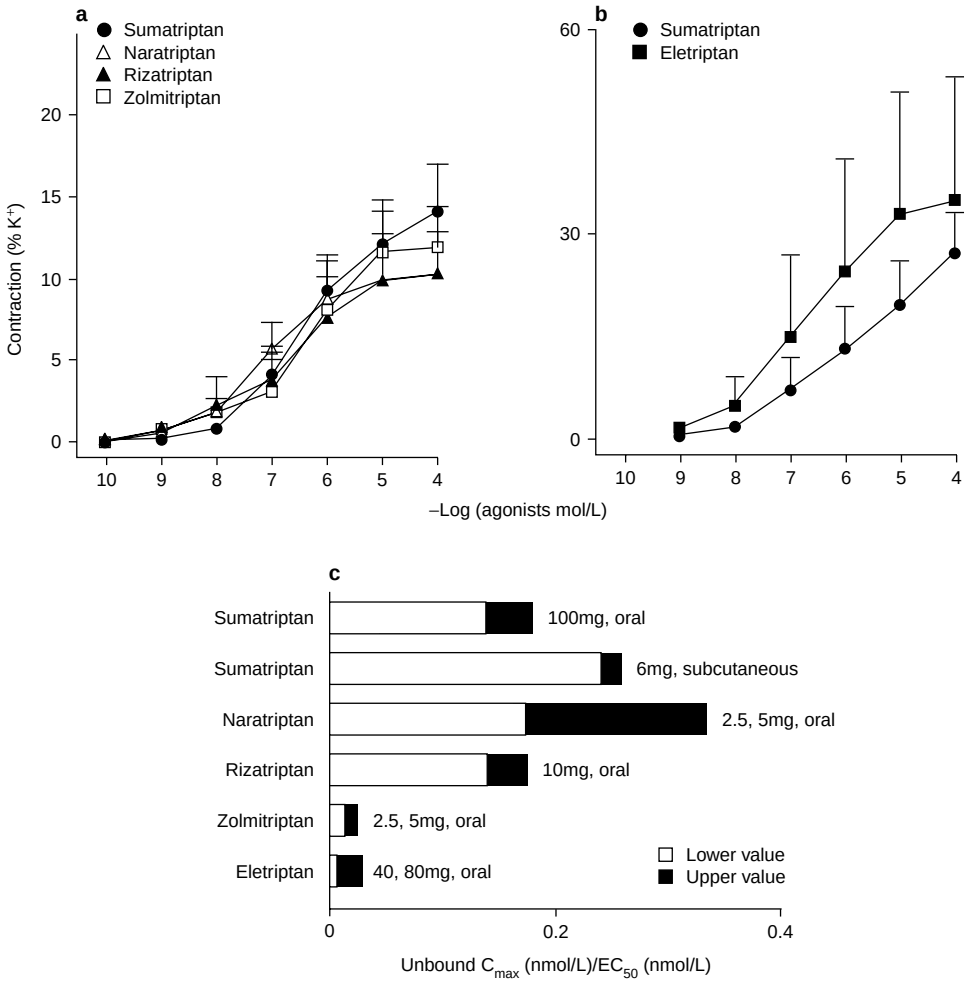

Fig. 2. Coronary effects of triptans. Concentration-response (expressed as percentage of response to 100 mmol/L K^+) curves in human isolated coronary arteries obtained with sumatriptan, naratriptan, rizatriptan and zolmitriptan (**a**: n = 9, data taken from MaassenVanDenBrink et al.[53]) and sumatriptan and eletriptan (**b**: n = 9, data from MaassenVanDenBrink et al.[49]). (**c**): Relationship between reported peak plasma concentration (C_{max}; corrected for plasma protein binding) in patients and EC_{50} (dose eliciting 50% effect) values in contracting human isolated coronary artery. Frovatriptan, which also constricts the human coronary artery,[45] has not been included because the exact therapeutic dose and plasma protein binding level are not known.

Table IV. Trigeminal neuronal inhibition by triptans (no data available for frovatriptan) expressed as ED_{50} (g/kg IV)

Study	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Eletriptan	Almotriptan
Inhibition of plasma protein extravasation after trigeminal ganglion stimulation	4 (rat)[17] 31 (rat)[57]	10-30 (guinea-pig)[16]	4.1 (rat)[17]	31 (rat)[58]	30-300 (rat)[38]	200 (guinea-pig)[19]
Inhibition of CGRP release after cat trigeminal ganglion stimulation	Yes[59]	Yes[60]				
Inhibition of dural vasodilatation after rat trigeminal ganglion stimulation	1000-10 000[57]			1000-3000[58]		
Inhibition of activity in trigeminal nucleus caudalis after stimulation[a]	Inactive (rat)[61]	100 (cat)[62] 300-1000 (rat)[63]	30-100 (cat)[64]	1000-3000 (rat)[65]		

a Stimulation of the superior sagittal sinus in cats or dural meninges in rats.

CGRP = calcium gene-related peptide; **ED_{50}** = dose eliciting 50% effect; **IV** = intravenously.

and inhibition of impulse transmission centrally within the trigeminovascular system.[74,75] In our view, the main action of triptans in migraine is to constrict dilated cranial extracerebral blood vessels, most likely via 5-HT_{1B} receptors.[3,76-78] Thus, in one study,[33] during migraine attacks the middle cerebral artery was found dilated on the headache side, and this was reversed by intravenous sumatriptan. In 2 other studies,[34,35] an increase in middle cerebral artery blood flow velocity was observed after administration of subcutaneous sumatriptan during migraine attacks, although not correlated to the efficacy on migraine pain in one of the studies.[35] In addition, the triptans can reduce neuropeptide release and plasma protein extravasation across dural vessels[73] and inhibit impulse transmission centrally within the trigeminovascular system.[74,79] However, the possible contribution of the neuronal effect of triptans mediated via the 5-HT_{1D} receptor has been put in doubt because PNU-142633F, a selective 5-HT_{1D} receptor agonist, has not proved ineffective in the treatment of migraine.[80]

3. Pharmacokinetics

The pharmacokinetic characteristics of triptans have been studied in healthy volunteers and in patients with migraine (table V).[27,81-98] Subcutaneous sumatriptan (6mg) is quickly absorbed, with a time to maximum plasma concentration (t_{max}) of approximately 10 minutes and an average bioavailability of 96%.[81,82] After oral administration of therapeutic doses (100mg) of sumatriptan, however, the t_{max} is substantially longer (1.5h) and, more importantly, the bioavailability is rather low (≈14%).[81,83] Intranasal or rectal administration of sumatriptan does not seem to improve these parameters much.[82,84,99] The oral bioavailability of newer triptans, especially naratriptan and almotriptan, is much improved. This can be partly attributed to the more lipophilic nature of these drugs. Interestingly, the t_{max} after oral administration of zolmitriptan,[100,101] naratriptan,[87,88] eletriptan,[91-93] almotriptan[94,95] and frovatriptan[97] is not similar to or longer than that of sumatriptan, whereas rizatriptan[27,90] seems to reach C_{max} more quickly than sumatriptan. The faster oral absorption of rizatriptan than sumatriptan is supported by a comparative study where the median t_{max} was 1.3 (range 1 to 3) hours for rizatriptan and 2.5 (range 1 to 4) hours ($p < 0.001$) for sumatriptan.[27] It may be noted that the unbound C_{max} values (C_{max} corrected for plasma protein binding) of newer triptans are lower than that of sumatriptan. This is apparently due to 2

main factors: lower therapeutic concentrations are needed, as these drugs have a higher affinity at 5-$HT_{1B/1D}$ receptors (see table I), and these drugs have been better titrated.

With the exception of rizatriptan, the newer triptans are degraded more slowly than sumatriptan. Frovatriptan, particularly, has a plasma half-life ($t_{½}$) of 26 to 30 hours,[97] and, in view of the putative relationship of this parameter with headache recurrence, the results of clinical trials comparing sumatriptan and frovatriptan are awaited with interest. In contrast to sumatriptan and naratriptan, active metabolites have been reported for zolmitriptan,[101] rizatriptan[89] and eletriptan.[92] It is not known whether, and if so, to what extent, the metabolites contribute towards therapeutic activity. We are not aware of whether the metabolism of almotriptan or frovatriptan results in the formation of active metabolites.

The possible interaction of triptans with drugs used for migraine prophylaxis or drugs likely to be coadministered with a triptan in the treatment of migraine attacks has mainly been investigated in healthy volunteers. The pharmacokinetic profile of sumatriptan was not influenced by concomitant administration of propranolol, pizotifen, flunarizine, dihydroergotamine, paroxetine, butorphanol or naratriptan.[9]

There were no clinically significant changes in the pharmacokinetics of zolmitriptan after concomitant administration of dihydroergotamine, propranolol, pizotifen, fluoxetine, metoclopramide or paracetamol (acetaminophen).[102] The pharmacokinetic parameters of naratriptan were not influenced significantly by coadministration of ergotamine[103] and dihydroergotamine.[104] The mean plasma concentrations of rizatriptan were increased by 70% by administration of a high dose of propranolol,[105] but this interaction appears to be unique to propranolol, because nadolol and metoprolol had no such effect on plasma concentrations of rizatriptan.[105] As a safety precaution, rizatriptan 5mg is recommended for patients taking propranolol. Paroxetine did not affect the plasma concentrations of rizatriptan.[105,106] Rizatriptan did not

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Table V. Pharmacokinetic parameters of triptans in healthy volunteers and in patients with migraine

Drug	Dose (mg) and route of administration	t_{max} (h)	C_{max} (mg/L)	Bioavailability (%)	$t_{½}$ (h)	AUC (mg/L • h)	Active metabolites	Plasma protein binding (%)	CL_R (ml/min)	Log $D_{pH7.4}$	References
Sumatriptan	6 SC	0.17	72	96	2	90	–	14-21	220	–1.5	81,82
	100 PO	1.5	54	14	2	158			260		81,83
	20 IN	1.5	13	15.8	1.8	48			210		82
	25 PR	1.5	27	19.2	1.8	78			200		82,84
Zolmitriptan	2.5 PO	1.5	3.3/3.8[a]	39	2.3/2.6[a]	18/21[a]	+	25[b]	193	–1.0	85
	5 PO	1.5	10	46	3.0	42			193		86
Naratriptan	2.5 PO	2	12.6	74	5.5	98	–	20[b]	220	–0.2	87,88
Rizatriptan	10 PO	1.0	19.8	40	2.0	50	+	14[b]	414	–0.7	27,89,90
Eletriptan	40 PO	1.8[b]	82[b]	50[b]			+	85[b]	597[b]	+0.5	91-93
	80 PO	1.4	246	50	6.3	1661					91-93
Almotriptan	12.5 PO	2.5	49.5	80	3.1	266					94,95
	25 PO	2.7	64	69	3.6	443					96
Frovatriptan	2.5 PO	3.0	4.2/7.0[a]	29.6	25.7	94		15[c]			97
	40 PO	5.0	24.7/53.4[a]	17.5	29.7	881					
	0.8 IV		18.6/24.4[a]	100	23.6	104			132		

a Value for men and women, respectively.

b McHarg A, personal communication.

c Besides plasma protein binding, about 60% of frovatriptan is bound to red blood cells (Buchan, personal communication).

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma concentration; **CL_R** = renal clearance; **IN** = intranasal; **IV** = intravenous; **Log$D_{pH7.4}$** = measure of lipophilicity with increasing numbers indicating greater lipid solubility;[98] **PO** = oral; **PR** = rectal; **SC** = subcutaneous; **$t_{½}$** = plasma half-life; **t_{max}** = time to C_{max}; **+** indicates yes; **–** indicates no.

affect plasma concentrations of ethinylestradiol and norethisterone (norethindrone) [oral contraceptive pills].[105] In contrast, administration of the monoamine oxidase (MAO)-A selective inhibitor moclobemide increased plasma concentrations of sumatriptan, zolmitriptan and rizatriptan.[9,102,105]

4. Efficacy in the Acute Treatment of Migraine

Ideally, to define their place in migraine therapy according to evidence-based medicine, all triptans and administration forms of triptans should be compared in recommended doses in placebo-controlled RCTs, and all triptans in different administration forms should be compared with relevant alternative standard treatments. We identified a total of 83 double-blind, RCTs (many not yet published in full) with a triptan. So far, however, only 15 RCTs comparing the second generation triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan and almotriptan) with oral sumatriptan, and rizatriptan with naratriptan and zolmitriptan, have been performed (table VI),[107-121] and triptans have been compared with other drugs in only 11 RCTs (table VII).[122-132] In addition to comparative RCTs, one must therefore also search for information about the relative efficacy of the different triptans and administration forms of triptans from trials with a placebo control. In the following sections we review results from RCTs with a placebo control, from comparative trials with triptans, and from trials comparing a triptan with other drugs.

Headache relief with triptans in current randomised clinical trials is defined as a decrease from an initial moderate or severe headache to none or mild[6] after a certain time (1, 2 or 4 hours). We consider here as primary responses for active drugs and placebo only the response rates at 1 hour after injections and at 2 hours after other routes of administration. Four-hour response rates are generally disregarded, since it is not, in our opinion, satisfactory to ask patients to wait 4 hours for an effect on migraine headache. These response rates vary considerably in different trials, for example from 56 to 88% at 1 hour after subcutaneous sumatriptan,[133] most likely because of a variable placebo response. Therefore, the results of the trials are given as the therapeutic gain (percentage response for active drug minus percentage response for placebo) with 95% confidence intervals (CI). In comparative trials the results are also given as differences with 95% CI.

5. Efficacy Compared with Placebo

5.1 Sumatriptan

5.1.1 Subcutaneous Sumatriptan

Subcutaneous sumatriptan has a reasonably well defined dose-response curve, with 1mg being the minimum effective dose and 6mg being the optimum dose, and with no benefit in increasing to 8mg.[4] Subcutaneous sumatriptan 6mg has been evaluated against placebo in 13 double-blind, placebo-controlled RCTs[129,134-145] where headache relief was reported after 1 hour. As shown in figure 3, subcutaneous sumatriptan 6mg [based on 2108 patients treated with sumatriptan (headache relief in 70%) and 1307 patients treated with placebo (headache relief in 19%)] has a mean therapeutic gain of 51% (95% CI 48 to 53%) after 1 hour.[133] After 2 hours in 10 of these trials, the therapeutic gain was the same [52% (95% CI 40 to 56%)] as after 1 hour (Tfelt-Hansen, personal observation), indicating that the response to subcutaneous sumatriptan should be evaluated after 1 hour. In 2 trials with subcutaneous sumatriptan in which headache relief was reported after 1½ hours,[146,147] the mean therapeutic gain was 45% (95% CI 34 to 56%). Sumatriptan 6mg was superior to placebo in producing headache relief after 10 minutes, the first time point recorded.[133]

In 11 of these trials, the incidence of adverse events reported was 64% (930/1456) after sumatriptan and 31% (290/890) after placebo. There were thus 33% (95% CI 29 to 37%) more adverse events after subcutaneous sumatriptan than after placebo. Most of these adverse events were, however, mild to moderate and short lasting.

Table VI. Randomised, controlled clinical trials comparing triptans (percentage in parenthesis are 95% confidence interval)

Drug and dose (mg)	Number of patients	Success rate[a] (%)	Therapeutic gain[b] (%)	Pain free[c] (%)	Recurrence[d] (%)	Adverse events (%)	Comparative efficacy (%)[a,b]
Geraud et al.[107]e							
PL	55	44		13	25	23	Success rates: ZO 5 *vs* SU 100 –2% (–8 to +4%); pain free: ZO 5 *vs* SU 100 –1% (–7 to +5%)
ZO 5	491	59	15	29	26	58	
SU 100	498	61	17	30	28	57	
Gallagher[108]							
ZO 2.5	295	67, 83[f]		?	?[g]	?	Success rates: Across up to 6 attacks ZO 2.5 > SU 25 and SU 50 (2 hours)
ZO 5	305	65, 84[f]		?	?[g]	?	
SU 25	306	60, 76[f]		?	?[g]	?	
SU 50	306	64, 81[f]		?	?[g]	?	
Diener et al.[109]h							
PL	146	29		10	26	21	Success rates: ZO 2.5 *vs* RI 10 –4% (–11 to +4%)
ZO 2.5	289	67	38	36	29	39	
RI 10	292	70	41	43	28	31	
Havanka et al.[110]							
PL	91	31, 39[f]			36	23	Success rates: NA 2.5 *vs* SU 100 –8% (–23 to +6%); success rates at 4 hours: NA 2.5 *vs* SU 100 –16% (–29 to –3%); recurrence rates: NA 2.5 *vs* SU 100 –27% (–42 to –13%)
NA 1	85	58, 64[f]	27		31	20	
NA 2.5	87	52, 63[f]	21		17	21	
NA 5	93	54, 65[f]	23		32	32	
NA 7.5	93	68, 80[f]	37		30	37	
NA 10	96	69, 80[f]	38		29	35	
SU 100	98	60, 80[f]	29		44	26	
Bates and Winter[111]							
PL	104	22, 27[f]			10	29	Success rate: NA 2.5 *vs* SU 100 –9% (–18 to +1%); sucess rates at 4 hours: NA 2.5 *vs* SU 100 –9% (–18 to –1%); Recurrence rates: NA 2.5 *vs* SU 100 –17% (–27 to –7%)
NA 0.1	207	30, 36[f]	8		30	29	
NA 0.25	214	29, 36[f]	7		43	26	
NA 1	208	38, 52[f]	18		42	29	
NA 2.5	199	50, 66[f]	28		19	32	
SU 100	229	59, 76[f]	37		36	48**	
Göbel et al.[112]i							
NA 2.5	215	76[f]			43[h]	22	Success rates at 4 hours: NA 2.5 *vs* SU 100 –8% (–15 to 0%); recurrence rates: NA 2.5 *vs* SU 100 –14% (–24 to –3%)
SU 100	216	84[f]			57	33	
Bornhof et al.[113]h							
PL	107	22		8	25	23	Success rates: NA 2.5 *vs* RI 10 –20% (–30 to –11%); pain free: NA 2.5 *vs* RI 10 –24% (–33 to –15%); recurrence rates: NA 2.5 *vs* RI 10 –12% (–23 to –1%)
NA 2.5	213	48	26	21	21	29	
RI 10	201	69	47	45	33	39*	
Visser et al.[114]							
PL	85	18		3	36	36	Success rates: RI 10 *vs* SU 100 +6% (–10 to +21%) RI 40 *vs* SU 100 +21% (+7 to +35%); pain free: RI 10 *vs* SU 100 +4% (–10 to +17%) RI 40 *vs* SU 100 +27% (+14 to +40%)
RI 10	89	52	34	26	41	48	
RI 20	82	56	38	35	53	67	
RI 40	120	67	49	49	42	83**	
SU 100	72	46	28	22	43	46	

Continued over page

Table VI. Contd

Drug and dose (mg)	Number of patients	Success rate[a] (%)	Therapeutic gain[b] (%)	Pain free[c] (%)	Recurrence[d] (%)	Adverse events (%)	Comparative efficacy (%)[a,b]
Lines et al.[115]							
PL	80	23		3	33	20	Success rates: RI 5 *vs* SU 50 –4% (–11 to +3%); pain free: RI 5 *vs* SU 50 –6% (–12 to +2%)
RI 5	352	63	40	27	38	33	
SU 50	356	67	44	32	34	37	
Goldstein et al.[116]h							
PL	141	38		9	32	35	Success rate: RI 10 *vs* SU 50 +4% (–3 to +11%) RI 5 *vs* SU 25 +6% (–2 to +14%); pain free: RI 10 *vs* SU 50 +4% (–4 to +12%) RI 5 *vs* SU 25 +6% (–1 to +13%)
RI 5	294	68	30	33	33	44	
RI 10	305	72	34	41	35	45	
SU 25	297	62	24	27	32	46	
SU 50	291	68	30	37	31	46	
Tfelt-Hansen et al.[117]h							
PL	159	40		9	20	32	Success rates: RI 10 *vs* SU 100 +5% (–2 to +12%); pain free: RI 10 *vs* SU 100 +7% (+1 to +14%)
RI 5	164	60	20	25	48	39	
RI 10	385	67	27	40	35	47	
SU 100	387	62	22	33	32	52	
Jackson,[118] Pitman et al.[119]							
PL	126	24		6	23	17	Success rates: EL 20 *vs* SU 100 –1% (–13 to +12%) EL 40 *vs* SU 100 +10% (–2 to +23%); EL 80 *vs* SU 100 +22% (+11 to 34%); pain free: EL 20 *vs* SU 100 –4% (–14 to +6%) EL 40 *vs* SU 100 +6% (–6 to +17%); EL 80 *vs* SU 100 +14% (+2 to +25%)
EL 20	129	54	30	19	27	34	
EL 40	117	65	41	29	33	35	
EL 80	118	77	53	37	32	51	
SU 100	115	55	31	23	33	40	
Pitman et al.[119]							
PL	80	31		4	25	32	Success rates: EL 40 *vs* SU 50 +14% (+4 to +24%) EL 40 *vs* SU 100 +11% (0 to +21%); EL 80 *vs* SU 50 +17% (+6 to +27%) EL 80 *vs* SU 100 +14% (+3 to +24%); pain free: EL 40 *vs* SU 50 +12% (+3 to +21%) EL 40 *vs* SU 100 +13% (+3 to +22%); EL 80 *vs* SU 50 +18% (+9 to +28%) EL 80 *vs* SU 100 +19% (+9 to +28%)
EL 40	169	64	33	31	19	43	
EL 80	160	67	36	37	16	51*	
SU 50	176	50	19	19	26	33	
SU 100	160	53	22	18	27	38	
Pitman et al.[119]							
PL	86	40		9	19	34	Success rates: EL 40 *vs* SU 25 + 10% (–1 to +20%) EL 40 *vs* SU 50 +6% (–4 to +17%); EL 80 *vs* SU 25 +17% (+7 to +28%) EL 80 *vs* SU 50 +14% (+4 to +24%); pain free: EL 40 *vs* SU 25 +2% (–6 to +11%) EL 40 *vs* SU 50 +1% (–7 to +10%); EL 80 *vs* SU 25 +10% (+1 to +18%) EL 80 *vs* SU 50 +8% (–0.5 to +17%)
EL 40	175	62	22	19	6	39	
EL 80	170	70	30	26	8	53**	
SU 25	171	53	13	17	14	36	
SU 50	175	56	16	18	6	34	
Cabarrocas et al.[120]							
PL	99	42			20	10	Success rates: AL 12.5 *vs* SU 100 –7% (–17 to +3%) AL 25 *vs* SU 100 –7% (–17 to +3%); subcutaneous administration
AL 12.5	184	57	15		18	11*	
AL 25	191	57	15		15	21	
SU 100	194	64	22		25	24	

Landscape table VI to be placed here

In 1 placebo-controlled trial,[145] subcutaneous sumatriptan has also been shown to reduce productivity loss during a migraine attack.

5.1.2 Oral Sumatriptan

The lower part of the dose-response curve for oral sumatriptan was until recently[148] not well established.[4] The minimum effective dose of sumatriptan was 25mg[116,148] and the optimal dose 50 to 100mg; when the dose was increased to 200 to 300mg, there was no gain in efficacy, but more adverse events were reported.[4,149]

Oral sumatriptan 100mg has been evaluated against placebo in 20 double-blind, placebo-controlled RCTs.[107,110,111,114,117,119,120,124,125,148-155] Oral sumatriptan 100mg [based on 2928 patients treated with sumatriptan (headache relief in 59%) and 1653 patients treated with placebo (headache relief in 28%)] had a mean therapeutic gain of 32% (95% CI 29 to 34%) after 2 hours (fig. 3). The response rate of sumatriptan 100mg was superior to that of placebo after 30 minutes.[133]

In 11 of these trials, the incidence of adverse events reported was 40% (708/1786) after sumatriptan and 24% (270/1148) after placebo. There were thus 16% (95% CI 13 to 19%) more adverse events after oral sumatriptan 100mg than after placebo. Most of these adverse events were, however, mild and short lasting.

The lower doses of oral sumatriptan, 25 and 50mg, have been investigated only in 5 and 7 clinical trials, respectively. For sumatriptan 50mg [based on 1599 patients treated with sumatriptan (headache relief in 59%) and 653 patients treated with placebo (headache relief in 30%)], the mean therapeutic gain was 29% (95% CI 25 to 33%).[116,119,148,152,153,156] Thus, the therapeutic gain was similar to that with sumatriptan 100mg (fig. 3). In 2 direct comparative trials, the efficacy of the 2 doses of sumatriptan was quite comparable.[148,157] The response rate with sumatriptan 50mg was superior to that of placebo at 30 minutes.[116,148,156] The incidence of adverse events reported was 35% (357/1034) after sumatriptan 50mg versus 32% (164/509) after placebo (NS) between the two.[116,148,152,153,156] In the 2 comparative tri-

Dahlöf et al.[121]							
PL	63	41		17	35	22	Success rates: NA 5 *vs* SU 6 +5% (–7 to +17%) NA 10 *vs* SU 6 +2% (–11 to +15%); pain free: NA 5 *vs* SU 6 +24% (+4 to +44%) NA 10 *vs* SU 6 +33% (+15 to +51%)
NA 0.5	60	65	24	30	39	33	
NA 1	55	75	34	44	41	29	
NA 2.5	42	83	42	60	49	43	
NA 5	34	94	53	79	22	59	
NA 10	34	91	50	88	29	71	
SU 6	47	89	48	55	45	53	

a A decrease in headache from severe or moderate to mild or none at 2 hours.
b Percentage success with active drug minus percentage success with placebo.
c At 2 hours.
d Percentage of patients with an initial success who had an increase in headache to moderate or severe within 24 hours.
e Secondary efficacy parameter.[107]
f Success rate at 4 hours.
g Both doses of zolmitriptan were superior to both doses of sumatriptan in providing pain relief over 24 hours across 6 attacks, see Gallagher.[108]
h The primary effect parameter was time to headache relief or time to pain free within 2 hours.
i Patients selected as having frequent recurrences (≥50% of attacks treated with any medication).

AL = almotriptan; **EL** = eletriptan; **NA** = naratriptan; **PL** = placebo; **RI** = rizatriptan; **SU** = sumatriptan; **ZO** = zolmitriptan; * = statistically significant difference at $p < 0.05$ *vs* comparator; ** = statistically significant difference at $p < 0.01$ *vs* comparator.

Table VII. Randomised, clinical trials comparing sumatriptan and eletriptan with standard treatments for migraine attacks (percentage in parenthesis are 95% confidence interval)

Drugs and dose (mg)	No. of patients	Success rate (%)		Recurrence[a] (%)	Adverse events (%)	Comparative efficacy (%)
		at 2h	at 4h			
Oral administration						
Multinational Oral Sumatriptan and Cafergot Comparative Study Group[122]						
SU 100	220	66**		41**	45	Success rates: SU 100 *vs* E 2 + C 200 +18% (+9 to +27%)
E 2 + C 200	246	48		30	39	
Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group[123]						
SU 100	133	56		42	42**	Success rates: SU 100 *vs* A 900 + M 10 +11% (–1 to +23%)
A 900 + M 10	138	45		33	29	
Tfelt-Hansen et al.[124]						
PL	124	24		30	13	Success rates: SU 100 *vs* L-ASA 1620 + M 10 –4% (–17 to +8%)
SU 100	119	53[b]		38	28**	
L-ASA 1620 + M1	133	57[b]		18	36	
Myllylä et al.[125]						
PL	41	29		25	19	Success rates: SU100 *vs* RTA 200 + RTA 200 +2% (-17 to +20%)
RTA 200 + RTA 200	43	77[b]		23	30	
SU 100	42	79[b]		22	41	
The Diclofenac-K/Sumatriptan Migraine Study Group[126]						
PL	131			19	20	Differences in VAS: SU 100 *vs* DIC-K 50 –3% (–9 to +4%); differences in VAS: SU 100 *vs* DIC-K 100 –4% (–11 to +3%)
DIC-K 50	131	-17[c]		22	19	
DIC-K 100	122	-19[c]		24	15	
SU 100	130	-15[c]		26	26	
Subcutaneous sumatriptan						
Touchon et al.[127]						
SU 6	266	80**		31**	43**	Success rates: SU 6 *vs* DHEn1 + DHEn1 +30% (+19 to +41%)
DHEn1 + DHEn1	266	50		17	22	
Winner et al.[128]						
SU 6	150	85***	83	45**	?	Success rates (2h): SU 6 *vs* DHEs1 + DHEs1 +12% (+3 to +21%); success rates (4h): SU 6 *vs* DHEs1 + DHEs1 –3% (–11 to +5%)
DHEs1 + DHEs1	145	73	86	18	?	
Diener et al.[129]						
SU 6	114	91[b]**			33**	Success rates: SU 6 *vs* L-ASA 1000 + 17% (+8 to +27%)
L-ASA 1800	119	74[b]			8	
PL	42	24			9	
Intranasal sumatriptan						
Boureau[130]						
SU 20	327	63				Success rates: SU 20 *vs* DHEn1 + DHEn1 + 12% (+4 to +20%)
DHEn1 + DHEn1	327	51				
Rectal sumatriptan						
Medical Products Agency[131][d]						
SU 25	241	63		22*	2e	Success rates: SU 25 *vs* E 2 + C 100n + E 2 + C 100 – 10% (–18 to –2%)
E 2 + C 100	241	73*		11	14[e]**	
+E 2 + C 100						

Table VII. Contd

Drugs and dose (mg)	No. of patients	Success rate (%)		Recurrence[a] (%)	Adverse events (%)	Comparative efficacy (%)
		at 2h	at 4h			
Oral eletriptan						
Reches[132]						
PL	102	21		44		Success rates: EL 40 *vs* E 2 + C 200 +21% (+11 to +30%); EL 80 *vs* E2 + C 200 +35% (+26 to +44%)
EL 40	206	54[b]**		21		
EL 80	209	68[b]**		22		
E2 + C200	197	33[b]		8		

a Recurrence rate definition varied (see individual papers).

b Statistically significant difference from placebo at $p < 0.01$.

c Difference from placebo in mm on a 100mm visual analogue scale at 2 hours.

d 44% preferred sumatriptan and 37% preferred E+C in this crossover trial (NS).

e Only nausea and/or vomiting are given as adverse events.

A = aspirin; **C** = caffeine; **DHEn** = intranasal dihydroergotamine; **DHEs** = subcutaneous dihydroergotamine; **DIC-K** = diclofenac-potassium; **E** = ergotamine; **EL** = eletriptan; **L-ASA** = lysine acetylsalicylate; **M** = metoclopramide; **PL** = placebo; **RTA** = rapid release tolfenamic acid; **SU** = sumatriptan. * = statistically significant difference at $p < 0.05$ *vs* comparator; ** = statistically significant difference at $p < 0.01$ *vs* comparator.

als[148,157] sumatriptan 50mg caused fewer adverse events than sumatriptan 100mg.

The mean therapeutic gain for sumatriptan 25mg was 24% (95% CI 18 to 29%) [based on 1113 patients treated with sumatriptan (headache relief in 56%) and 428 patients treated with placebo (headache relief in 32%); fig. 3].[116,148,152,153] In 2 direct comparative trials[148,157] sumatriptan 25mg was found to be inferior to sumatriptan 50mg and 100mg. In 1 trial,[116] sumatriptan 25mg was superior to placebo after 30 minutes. After sumatriptan 25mg, 38% (273/714) of patients experienced the same incidence of adverse events as after placebo – 37% (132/353).

Concerning oral sumatriptan, one can conclude that the 50 and 100mg doses are equally efficacious and are superior to the 25mg dose. Fewer adverse events are reported with the 25 and 50mg doses than the 100mg dose, and no more adverse events than placebo are seen with either of the lower doses. Based on these results, 50mg should be the optimum dose of sumatriptan. Even though 100mg caused more adverse events than 50mg in 1 crossover trial,[157] almost the same percentage of patients (35 and 31%, respectively) preferred the 2 higher doses of sumatriptan, whereas only 21% preferred the 25mg dose. This could be due to the fact that more patients on 100mg than on 50mg reported complete relief of pain.[157] Some patients seem to prefer a more effective dose and will endure the cost of more – transient and often mild – adverse events.

5.1.3 Intranasal Sumatriptan

In randomised clinical trials the minimum effective dose of intranasal sumatriptan was 5mg; 10mg was also effective, but less so than 20mg.[9] Intranasal sumatriptan 20mg was the optimum dose,[9] with no benefit in increasing the dose to 40mg.[9,158]

Intranasal sumatriptan 20mg has been evaluated against placebo in 7 trials.[158-162] Intranasal sumatriptan 20mg [based on 1205 patients treated with sumatriptan (headache relief in 61%) and 701 patients treated with placebo (headache relief in 31%)] had a mean therapeutic gain of 30% (95% CI 25 to 34%) after 2 hours (fig. 3). Intranasal sumatriptan 20mg was superior to placebo after 15 minutes.[133] There were 21% (95% CI 16 to 26%) more adverse events reported with intranasal su-

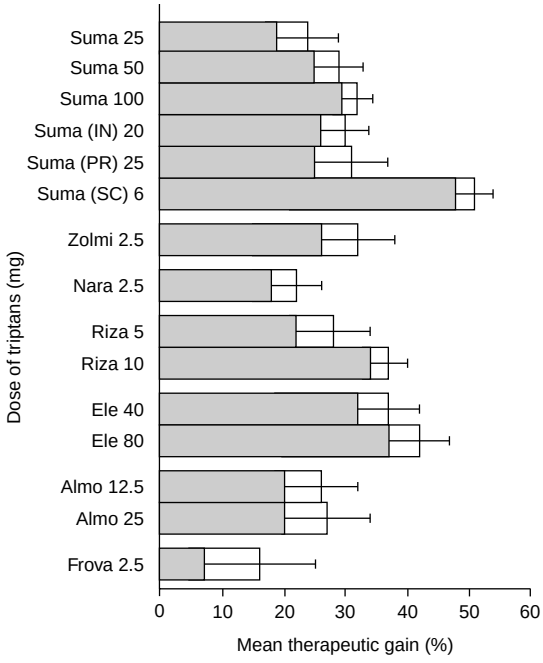

Fig. 3. Mean therapeutic gain (proportion of patients responding to active drug minus proportion of patients responding to placebo) and 95% confidence intervals for different doses of sumatriptan (Suma), zolmitriptan (Zolmi), naratriptan (Nara), rizatriptan (Riza), eletriptan (Ele), almotriptan (Almo) and frovatriptan (Frova). All triptans were administered orally, except for sumatriptan, where intranasal (IN), rectal (PR) and subcutaneous (SC) routes were also used. For the number of patients treated with each agent and placebo, see text. Note that the therapeutic gain was determined with most certainty for sumatriptan 100mg, subcutaneous sumatriptan 6mg and rizatriptan 10mg (approximately 4500, 3000 and 3500 patients, respectively).

matriptan 20mg than with placebo;[163] the most common adverse event was taste disturbance.[158-162]

In 1 trial, 37% (73/200) of patients treated with intranasal sumatriptan 20mg had headache relief after 30 minutes (primary efficacy parameter), compared with 22% (45/207) of patients treated with oral sumatriptan 100mg.[164] Intranasal sumatriptan thus had a therapeutic gain over oral sumatriptan of 15% (95% CI 6 to 23%) after 30 minutes. Similar therapeutic superiority of intranasal sumatriptan was also found at 15 minutes, and at 45 and 60 minutes. After 4 hours, oral sumatriptan was almost superior to intranasal sumatriptan [9% difference in response (95% CI –0.2 to +19%)]. For the second and third attacks treated, no superiority of intranasal over oral sumatriptan could be demonstrated from 15 to 120 minutes, and oral sumatriptan was superior to intranasal sumatriptan after 4 hours ($p < 0.01$).

5.1.4 Rectal Sumatriptan

Two trials comparing the recommended 25mg rectal dose of sumatriptan have been published.[165,166] In addition, 2 trials have been presented as posters.[167,168] Rectal sumatriptan 25mg [based on 426 patients treated with sumatriptan (headache relief in 70%) and 403 patients treated with placebo (headache relief in 39%)] had a mean therapeutic gain of 31% (95% CI 25 to 37%) after 2 hours (fig. 3). Rectal sumatriptan 25mg was significantly superior to placebo from 30[165] to 60 minutes.[166,167] In these clinical trials,[165-167] the incidence of adverse events reported was 25% (76/301) after sumatriptan versus 14% (24/171) after placebo. There were thus 11% (95% CI 4 to 18%) more adverse events with rectal sumatriptan 25mg than with placebo. Higher doses of 50 and 100mg did not increase the efficacy compared with 25mg,[166] and 12.5mg can be considered as the minimum effective dose.[165-168]

5.1.5 Special Randomised Clinical Trials

The question of whether a second dose of sumatriptan increases efficacy has been investigated in 4 placebo-controlled clinical trials.[134,135,169,170] In 2 trials, subcutaneous sumatriptan 6mg or placebo was given 1 hour after the first dose of sumatriptan to patients without headache relief. There was no difference in headache response at 2 hours between the 6mg plus 6mg of sumatriptan and the 6mg of sumatriptan plus placebo regimens.[134,135] In 2 trials, patients initially took oral sumatriptan 100mg, which was followed at 2[169] or 4[170] hours by either another dose of sumatriptan 100mg or placebo in a double-blind fashion. Headache relief rates at 4[169] and 8[170] hours after the initial, nonblind dose of sumatriptan were 80 and 77% for the 100mg plus 100mg of sumatriptan group[169] and 85 and 84% for the 100mg of sumatriptan plus placebo group.[170] Taken together, these 4 trials demonstrate that neither a second dose of sumatriptan

to patients not responding to the first dose nor the routine use of a second dose increases the efficacy of sumatriptan.

Headache recurrence (significant worsening of headache within 24 to 48 hours after an initial successful response at, for example, 2 hours) is a problem with all triptans and also with other acute migraine treatments (see tables VI and VII). With sumatriptan, it occurs in 20 to 40% of primary successfully treated patients in controlled clinical trials. It is also a major problem in clinical practice; about 75% of patients are reported to experience headache recurrence in at least some attacks and up to 40% in most of their attacks.[171]

Oral sumatriptan has been evaluated for the prevention of recurrence by administering 100mg 2[169] or 4[170] hours after oral sumatriptan 100mg, or 4 hours after subcutaneous sumatriptan 6mg.[172] In all 3 trials, the patients were first given nonblind sumatriptan and then either sumatriptan 100mg or placebo. In none of these studies did sumatriptan 100mg decrease the incidence of headache recurrence compared with placebo. Prevention of recurrence with a second dose of sumatriptan is thus not recommended.[169,170,172]

The efficacy of sumatriptan in treating recurrent headache (after it has occurred) has been investigated in 3 trials.[169,170,173] In all 3 trials, sumatriptan was superior to placebo. Oral sumatriptan 100mg seems to have the same efficacy in the treatment of headache recurrences [mean therapeutic gain after 2 hours of 32% (95% CI 18 to 45%)][169] as in the treatment of migraine attacks (see above and fig. 3). In the second trial[170] with oral sumatriptan, the therapeutic gain was approximately 37% after 4 hours. In the third trial,[173] subcutaneous sumatriptan 6mg had a 84% response rate compared with 50% for placebo for the first attack. The therapeutic gain was thus 34% (95% CI 15 to 52%). In conclusion, a second dose of sumatriptan is effective in the treatment of headache recurrence, as is a second dose of rizatriptan (see section 5.4).

Subcutaneous sumatriptan was compared with placebo during the aura phase in 1 trial.[174] 88 patients treated themselves with sumatriptan 6mg and 83 patients received placebo during a typical aura. The median duration of aura was 25 minutes after sumatriptan and 30 minutes after placebo (NS). The proportion of patients who developed a moderate or severe headache after administration of test drugs was similar in the 2 groups (68% after sumatriptan and 75% after placebo). The reasons for the lack of effect of sumatriptan administered during the aura phase on the subsequent development of headache remain obscure.

5.2 Zolmitriptan

Zolmitriptan has a well established dose-response curve, with 1mg being the minimum effective dose and 2.5mg being the optimum dose.[175] Doses up to 25mg zolmitriptan have been evaluated[176-180] and generally no increase in efficacy was observed above the 2.5 to 5mg dose but an increase in adverse effects was noticeable.[175,176] An exception is the high therapeutic gain of 58% (95% CI 47 to 68%) for zolmitriptan 20mg in 1 trial,[180] a result normally seen only after subcutaneous sumatriptan (fig. 3).

The recommended dose of zolmitriptan 2.5mg has been compared with placebo in 3 trials.[109,177,179] Zolmitriptan 2.5mg [based on 742 patients treated with zolmitriptan (headache relief in 65%) and 367 patients treated with placebo (headache relief in 33%)] had a mean therapeutic gain of 32% (95% CI 26 to 38%) after 2 hours (fig. 3). After 1 hour, the mean therapeutic gain was 15% (95% CI 10 to 21%).[109,177,179] Zolmitriptan 2.5mg was superior to placebo after 1 hour in 2 trials.[109,179] In all 3 trials,[109,177,179] adverse events occurred in 43% (341/802) of patients treated with zolmitriptan and in 26% (102/393) of patients treated with placebo. The use of zolmitriptan 2.5mg thus resulted in 17% (95% CI 11 to 22%) more adverse events than placebo.

A recurrence rate of 22% after zolmitriptan 2.5mg was reported in 1 trial,[177] and in another trial[109] it was 29%. The overall recurrence rate in dose-ranging studies was 31% with zolmitriptan 2.5mg or 5mg.[175]

5.3 Naratriptan

Oral naratriptan has been evaluated in a wide dose range from 0.1 to 10mg,[110,111,181,182] with sumatriptan 100mg as control treatment in 2 trials[110,111] (see table VI). The minimum effective dose was 1mg and naratriptan 2.5mg was chosen as the dose resulting in no more adverse events than placebo.[183] Higher oral doses of naratriptan 7.5 and 10mg were quite comparable in efficacy to 100mg sumatriptan in 1 trial.[110,111]

Oral naratriptan 2.5mg, the recommended dose, has been evaluated against placebo in 5 trials.[110,111,113,181,182] Naratriptan 2.5mg [based on 1223 patients treated with naratriptan (headache relief in 48%) and 1019 patients treated with placebo (headache relief in 27%)] had a mean therapeutic gain of 22% (95% CI 18 to 26%) after 2 hours (fig. 3). Escape medication could first be taken after 4 hours, and at this time the mean therapeutic gain was 33% (95% CI 29 to 37%).[110,111,181,182] Naratriptan 2.5mg was superior to placebo in producing headache relief after 60 minutes.[113,183] Recurrence rates for naratriptan 2.5mg were 17%,[181] 19%,[182] 21%,[110] 27%[111] and 28%.[113]

In 1 early, relatively small dose-ranging study (see table VI), subcutaneous naratriptan in the dose range of 0.5 to 10mg was compared with placebo and subcutaneous sumatriptan 6mg.[121] After 2 hours, all doses of naratriptan were superior to placebo, with response rates of 65% (0.5mg), 75% (1mg), 83% (2.5mg), 94% (5mg) and 91% (10mg) versus 41% for placebo. The response rate for sumatriptan was 89%. Naratriptan 2.5mg (and higher doses) was thus quite comparable to sumatriptan 6mg but, as shown by the wide 95% CI (see table VI), the trial is too small to demonstrate comparability. The recurrence rates were 45% for sumatriptan and comparable to those with the lower doses of naratriptan (38%, 0.5mg; 41%, 1mg; and 49%, 2.5mg), whereas the 5 and 10mg doses resulted in lower, but not significantly different, recurrence rates of 22 and 29%, respectively.

5.4 Rizatriptan

The minimum effective dose for rizatriptan is 5mg, with the optimum dose being 10mg.[105] A dose of rizatriptan 2.5mg was ineffective,[184] whereas the high 40mg dose had a therapeutic gain of 49%,[114] but it caused too many adverse events (83% of patients).

Rizatriptan 10mg has been evaluated in 8 placebo-controlled trials.[109,113,114,116,117,184-186] Rizatriptan 10mg [based on 2470 patients treated with rizatriptan (headache relief in 69%) and 1097 patients treated with placebo (headache relief in 32%)] had a mean therapeutic gain of 37% (95% CI 34 to 40%) after 2 hours (fig. 3). Rizatriptan 10mg was superior to placebo after 30 minutes (Tfelt-Hansen personal observation).[116] In 6 of these trials,[109,113,114,116,117,185] the incidence of adverse events reported was 42% (718/1705) after rizatriptan versus 27% (234/88120) after placebo. There were thus 16% (95% CI 12 to 29%) more adverse events after 10mg rizatriptan than after placebo.

The 5mg dose of rizatriptan, recommended for use in patients on propranolol, has been evaluated in 5 controlled trials.[115-117,184,185] Rizatriptan 5mg [based on 1397 patients treated with rizatriptan (headache relief in 62%) and 749 patients treated with placebo (headache relief in 34%)] had a mean therapeutic gain of 28% (95% CI 23 to 32%) after 2 hours (fig. 3). Rizatriptan 5mg was superior to placebo after 30 minutes in 1 trial.[116] In 4 of these trials,[115-117,185] the incidence of adverse events reported was 35% (448/1268) after rizatriptan and 27% (188/686) after placebo. There were thus 8% (95% CI 4 to 12%) more adverse events after rizatriptan 5mg than after placebo.

A rapidly dissolving wafer of rizatriptan has been compared with placebo in 2 trials (Merck & Co. Inc., data on file).[187] Rizatriptan 10mg as a wafer [based on 288 patients treated with rizatriptan (headache relief in 70%) and 265 treated with placebo (headache relief in 34%)] had a mean therapeutic gain of 37% (95% CI 29 to 45%); the same therapeutic gain as 10mg rizatriptan tablets (see above). Rizatriptan 5mg as a wafer (headache relief

in 62% of 271 patients) had a mean therapeutic gain of 28% (95% CI 20 to 36%). Rizatriptan 10mg as a wafer was superior to placebo after 30 minutes with a small therapeutic gain of 11% (95% CI 3 to 18%).[187]

In 1 trial,[185] rizatriptan 10mg was superior to placebo in the treatment of headache recurrence with a therapeutic gain of 38% (95% CI 23 to 52%) after 2 hours, whereas rizatriptan 5mg was not significantly superior to placebo in the treatment of recurrence.

5.5 Eletriptan

So far, no peer-reviewed paper on eletriptan has been published. An early dose-finding study evaluating doses from 5 to 30mg eletriptan found only minor difference from the placebo response.[188] From 4 placebo-controlled trials,[118,119,132,189] the mean therapeutic gain for eletriptan 80mg [based on 894 patients treated with eletriptan (response rate 68%) and 524 patients treated with placebo (response rate 25%)] was 42% (95% CI 37 to 47%) after 2 hours (fig, 3). For eletriptan 40mg, the mean therapeutic gain was 37% (95% CI 32 to 42%) after 2 hours.[119,132,189] Both the 40 and 80mg doses of eletriptan were superior to placebo in producing headache relief after 30 minutes.[189]

In the trial programme for eletriptan, adverse events were reported to occur in 50, 42 and 31% of patients treated with eletriptan 80 and 40mg and placebo, respectively.[190] Asthenia was the common adverse event occurring in 5% of patients treated with eletriptan 40mg and 10% of patients treated with eletriptan 80mg.[190]

5.6 Almotriptan

No peer-reviewed papers on almotriptan have been published. The first efficacy trial demonstrated that subcutaneous almotriptan 6 and 10mg were superior to placebo.[191] A meta-analysis[192] of placebo-controlled trials reported that the mean therapeutic gain with almotriptan 12.5mg [based on 719 on patients treated with almotriptan (response rate 61%) and 355 patients treated with placebo (response rate 35%)] was 26% (95% CI 20 to 32%). The mean therapeutic gain with almotriptan 25mg [based on 386 patients treated with almotriptan (response rate 63%) and 210 patients treated with placebo (response rate 39%)] was 24% (95% CI 16 to 33%) [fig. 3]. The 6.25mg dose of almotriptan had a mean therapeutic gain of 20% (95% CI 14 to 26%)[192] and was thus the minimum effective dose. Almotriptan 12.5mg was superior to placebo after 30 minutes in 1 trial.[96] Higher doses up to 150mg almotriptan were not superior to the 25mg dose.[193] The incidence of adverse events was similar after almotriptan 12.5mg and after placebo, whereas there were more adverse events with almotriptan 25mg than placebo (odds ratio versus placebo: 2.0).[192] A recurrence rate of 15% was reported in 1 trial.[120]

5.7 Frovatriptan

Based on only 2 placebo-controlled trials, published as abstracts,[194,195] the mean therapeutic gain for frovatriptan 2.5mg [225 patients treated with frovatriptan (response rate 40%) and 214 patients treated with placebo (response rate 24%)] was 16% (95% CI 8 to 25%) after 2 hours (fig. 3). Higher doses up to frovatriptan 40mg were not superior to the 2.5mg dose[194] and lower doses were not superior to placebo.[195] Recurrence rates of 11%[194] and 14%[195] were reported for frovatriptan 2.5mg, but comparative trials are lacking.

5.8 Other 5-$HT_{1B/1D}$ Receptor Agonists

Avitriptan (BMS-180048) 75mg had a mean therapeutic gain of 22% (95% CI 9 to 36%) in 2 trials,[10,11] but the development programme for avitriptan has been stopped because of hepatic toxicity.

Subcutaneous alniditan, a non-triptan 5-$HT_{1B/1D}$ receptor agonist, had a therapeutic gain of 45% (95% CI 26 to 65%) at a dose of 1.4mg after 1 hour in 1 trial.[13] A decrease in recurrence rate with increasing dose of alniditan was observed,[13] but as alniditan did not result in fewer recurrences than sumatriptan (Jansen, data on file), the development of alniditan was stopped.

5.9 Consistency of Response in Multiple Attacks

In patients treating 3 migraine attacks with sumatriptan 100 to 300mg, 47% responded to all 3 treatments compared with 8% responding to placebo in all 3 attacks.[149] This trial was, however, not designed to investigate consistency of response.

Consistency of response to subcutaneous sumatriptan 6mg was investigated in 120 patients treating 3 migraine attacks with sumatriptan and 1 attack with placebo in a double-blind, randomised crossover trial.[147] Relief rates were 78, 85, 84 and 84% at 60 minutes postdose for the first to fourth attacks, indicating that the efficacy of sumatriptan did not diminish with repeated use. 73% of patients responded to all sumatriptan-treated attacks. In a another double-blind, crossover trial, consistency of response to sumatriptan 100mg was evaluated by letting 154 migraine patients treat up to 9 attacks with sumatriptan and up to 3 attacks with placebo.[155] Patients were randomised to receive sumatriptan or placebo in a 3 : 1 ratio for three 4-attack blocks. The response to sumatriptan (49 to 50%; mean of 3 attacks) and placebo (16 to 20%) was quite similar for each of the three 4-attack blocks. In a subset of patients who treated 9 moderate or severe attacks, 62% experienced headache relief in 7 of 9 attacks.

The consistency of the effect of rizatriptan 10mg was investigated in 1 placebo-controlled trial[186] in which 407 patients treated up to 4 attacks in a special crossover design. The percentages of patients responding at 2 hours to rizatriptan 10mg were consistent (75 to 80%) over the 4 attacks, whereas the response to placebo varied somewhat (28 to 54%). Of the 315 patients who treated at least 3 migraine attacks with rizatriptan, 272 (86%) had relief in at least 2 of the attacks.

Apart from these 3 trials, consistency of response to a triptan has been claimed but not proven in nonblind long term studies with sumatriptan,[196,197] zolmitriptan,[198] naratriptan,[199] and rizatriptan;[200] for discussion, see Saxena & Tfelt-Hansen[75] and Tfelt-Hansen.[201]

6. Comparative Trials versus Other Triptans

The second generation triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan and almotriptan) have been compared with oral sumatriptan in 13 double-blind RCTs and, in addition, rizatriptan has been compared with zolmitriptan and naratriptan in 1 trial each (see table VI). Furthermore, 1 trial compared subcutaneous naratriptan, an administration form of naratriptan not developed for clinical use, with subcutaneous sumatriptan[121] (table VI). Rizatriptan 40mg was superior to sumatriptan 100mg for success rate at 2 hours,[114] but this dose was later reduced because of a high incidence of adverse events. Eletriptan 80mg was superior to sumatriptan 100mg[119] and 25 and 50mg,[119] in most cases also for the clinically more relevant parameter of being pain free after 2 hours.[202] Eletriptan 40mg was superior[119] or comparable to sumatriptan 100mg,[119] whereas this dose of eletriptan was not superior to sumatriptan 25 or 50mg in 1 trial with a rather high placebo response of 40%.[119] For zolmitriptan 5mg,[107] rizatriptan 5[115,116] and 10mg,[116,117] eletriptan 20mg,[119] and almotriptan 12.5 and 25mg,[120] the results at 2 hours were similar to those with the comparative sumatriptan dose (table VI). Zolmitriptan 5mg was comparable to sumatriptan 50 and 100mg in 2 trials[107,108] and marginally better than sumatriptan 25mg in 1 trial[108] (table VI). The 2.5mg dose of zolmitriptan was also marginally better than sumatriptan 25 and 50mg,[108] and it was comparable to rizatriptan 10mg for headache relief but inferior for being pain free in 1 trial[109] (table VI). Naratriptan in oral doses of 7.5 and 10mg was comparable to sumatriptan 100mg.[110] However, the 2.5mg oral dose of naratriptan, which was chosen for clinical use based on incidence of adverse events being comparable to that with placebo,[183] was inferior to sumatriptan 100mg in 3 trials for the chosen primary efficacy parameter, headache relief after 4 hours.[110-112] As would be expected, naratriptan 2.5mg was inferior to rizatriptan 10mg in 1 trial.[113] Subcutaneous naratriptan in doses

from 2.5 to 10mg was comparable to subcutaneous sumatriptan 6mg.[121]

The recurrence rates for sumatriptan 100mg varied considerably among trials (see table VI). In 1 trial[119] with generally extremely low recurrence rates for all drugs it was as low as 6%. In patients who were recurrence-prone, it was predictably high, at 57%.[112] In the other 8 trials, the recurrence rates for sumatriptan 100mg were between 27 and 44%. This variability demonstrates that recurrence rates for 2 drugs can be compared only in comparative trials. Apart from naratriptan, there are no consistent differences in recurrence rates between the new triptans and sumatriptan (table VI). Naratriptan 2.5mg resulted in fewer recurrences than sumatriptan 100mg in 2 trials[110,111] and this was also the case in patients with recurrence-prone migraine in 1 trial.[112] In addition, in 1 trial,[113] naratriptan 2.5mg resulted in fewer recurrences (21%) than rizatriptan 10mg (33%). Thus, even if there are statistical concerns about comparing recurrence rates in 2 groups of patients responding to 2 different drugs,[203] these results strongly indicate that the longer half-life of naratriptan compared with sumatriptan and rizatriptan (see table VI) results in fewer recurrences. However, this is not always the case, as illustrated by the high recurrence rates after some of the subcutaneous naratriptan doses[121] (table VI). That recurrence rates can also depend on factors other than the half-lives of drugs is indicated by the lower recurrence rates with ergot alkaloids than with triptans (see section 7); this is most likely due to differences in the kinetics of drug-receptor interaction.

On the basis of the more rapid absorption of rizatriptan compared with sumatriptan (see section 3), 2 trials[116,117] compared the speed of onset of headache relief between oral rizatriptan and oral sumatriptan with time to headache relief analysis up to 2 hours. One analysis[116] suggests that approximately 15% more patients are likely to achieve headache relief within 2 hours after rizatriptan 5 and 10mg than after sumatriptan 25 and 50mg, respectively. In the other trial,[117] the sumatriptan-treated group was marginally but significantly older than the rizatriptan group, and older age was correlated with better response. After correction for age imbalance, the results suggest that 21% more patients are likely to achieve headache relief within 2 hours after rizatriptan 10mg than sumatriptan 100mg.[117] More patients treated with rizatriptan 10mg (40%) than with sumatriptan 100mg (33%) were pain free after 2 hours (table VI). A post hoc analysis of the results suggests that 29% more patients are likely to be pain free within 2 hours after rizatriptan 10mg than after sumatriptan 100mg.

In addition, rizatriptan 10mg was compared with zolmitriptan 2.5mg for time to being pain free within 2 hours[109] and with naratriptan 2.5mg for time to headache relief within 2 hours.[113] Rizatriptan 10mg was more effective than the clinically used low dose of naratriptan 2.5mg after 2 hours (see section 5.3 and figure 3). Therefore, as expected, both analysis of time to headache relief (62% more likely to be relieved with rizatriptan than with naratriptan) and analysis of time to being pain free (2.5 times more likely to be pain free with rizatriptan than with naratriptan) demonstrated the superiority of rizatriptan ($p < 0.0001$).[113] Patients treated with rizatriptan 10mg were 26% more likely to be pain free within 2 hours than those treated with zolmitriptan 2.5mg ($p = 0.075$).[109] When analysed for time to sustained pain-free status through the 2-hour period, a pre-planned analysis, the difference became statistically significant ($p = 0.041$). Similar results were found for time to headache relief.[109] Patients treated with rizatriptan 10mg had a normal function at 2 hours significantly more often (45%) than those treated with zolmitriptan 2.5mg (37%).[109]

7. Comparative Trials with Drugs other than Triptans

Sumatriptan, the first triptan, is the only one that has been compared with several standard treatments for migraine attacks. In addition, eletriptan has been compared with ergotamine (ergotamine tartrate) 2mg plus caffeine 200mg (ergotamine/caffeine) in 1 clinical trial.[132] A brief summary of

these 11 randomised, double-blind clinical trials is shown in table VII. Oral sumatriptan 100mg was superior to ergotamine/caffeine, with a quicker onset of action, but with more recurrences (41 *vs* 30%) within 48 hours.[122] Sumatriptan 100mg was not significantly superior to a combination of aspirin (acetylsalicylic acid) 900mg and metoclopramide 10mg for the first treated migraine attack, the primary efficacy parameter, but was superior for the second and third treated attacks, and for other parameters.[123] A combination of a highly soluble aspirin salt, lysine acetylsalicylate 1620mg (equivalent to 900mg aspirin), and metoclopramide 10mg was equivalent to sumatriptan 100mg.[124] Diclofenac-potassium, 50 and 100mg, was equivalent to sumatriptan 100mg,[126] but the primary efficacy parameter used – changes in head pain on a visual analogue scale – makes it difficult to compare the results with those of other trials with triptans. Apparently, a rapidly soluble form of tolfenamic acid, given in a dose of 200mg plus 200mg, was comparable to sumatriptan 100mg,[125] but as demonstrated by the wide 95% CI (see table VII), this finding needs confirmation in a larger trial.

Subcutaneous sumatriptan 6mg was considerably superior to dihydroergotamine (dihydroergotamine mesylate) nasal spray (1mg + 1mg), with superiority being already evident at 15 minutes.[127] Recurrence of headache occurred less often after dihydroergotamine (17%) than after sumatriptan (31%).[127] Compared with subcutaneous dihydroergotamine (1mg + optional 1mg), subcutaneous sumatriptan was superior for the first 2 hours, but after 3 and 4 hours the effects of both treatments were similar.[128] After dihydroergotamine there were significantly fewer recurrences than after sumatriptan (18 *vs* 45%). Subcutaneous sumatriptan 6mg was superior to intravenous lysine acetylsalicylate 1800mg (corresponding to 1000mg aspirin).[129]

Intranasal sumatriptan 20mg was superior to intranasal dihydroergotamine (1mg + optional 1mg) from 45 to 120 minutes after administration,[130] but there were fewer recurrences after dihydroergotamine (13%) than after sumatriptan (23%). Rectal sumatriptan 25mg was inferior to the ergotamine/caffeine suppositories (ergotamine 2mg plus caffeine 100mg) taken by two-thirds of the patients twice within 30 minutes, and there were fewer recurrences after ergotamine/caffeine (11%) than after sumatriptan (22%).[131] However, because of adverse events, 44% of patients preferred sumatriptan and 37% preferred ergotamine/caffeine in this crossover study (NS). Both eletriptan 40 and 80mg were superior to ergotamine 2mg/caffeine 200mg and placebo.[132]

Sumatriptan 100mg produced more adverse events than aspirin plus metoclopramide[123] and lysine acetylsalicylate plus metoclopramide,[124] and more adverse events were seen with subcutaneous sumatriptan 6mg than intranasal dihydroergotamine (1mg + optional 1mg)[127] and intravenous lysine acetylsalicylate.[129] Rectal sumatriptan 25mg produced less nausea and/or vomiting than ergotamine 2mg/caffeine 100mg suppositories[131] (table VII). In most cases, the adverse events were mild to moderate, but 1 case of atrial fibrillation after sumatriptan 100mg necessitated hospitalisation.[124]

An interesting observation is that in all 5 trials[122,127,128,130,131] comparing sumatriptan with either ergotamine or dihydroergotamine, the recurrence rate was lower after the ergot alkaloid than after sumatriptan (table VII). A similar tendency was observed for ergotamine versus eletriptan.[132] This is most probably because of the long duration of the vascular effects of a single dose of an ergot alkaloid.[204,205]

8. Conclusions

Second generation triptans do not seem to differ much from sumatriptan in their pharmacodynamic properties apart from being more lipophilic (see table V), with a resultant potential effect on central parts of the trigeminovascular system. However, they show improved pharmacokinetics. Thus, all second generation triptans have a higher oral bioavailability than the 14% observed for sumatriptan (table V). Oral bioavailability is 46% for zolmitriptan, 74% for naratriptan, 40% for rizatriptan, 50% for eletriptan, 80% for almotriptan and 30%

for frovatriptan. Oral rizatriptan is absorbed more quickly than oral sumatriptan, whereas the other triptans are absorbed at the same rate as or more slowly than sumatriptan. The half-life of the newer triptans is either approximately comparable (zolmitriptan 3 hours, rizatriptan 2 hours and almotriptan 3 hours) to the 2 hours for sumatriptan, or longer (naratriptan 5.5 hours, eletriptan 6 hours and frovatriptan 30 hours).

Do these relatively minor pharmacodynamic and considerable pharmacokinetic differences compared with sumatriptan result in clinically relevant increased efficacy compared with oral sumatriptan? And what is the relative efficacy of the second generation triptans? To answer these questions definitively, a wide range of RCTs comparing the triptans is needed. So far, only 15 such comparative clinical trials (13 trials involving a newer triptan and sumatriptan) have been performed.

In addition to comparative trials, all triptans have therefore been compared with placebo (also in this review) by calculating mean therapeutic gains for headache relief (fig. 3). However, this kind of analysis should be used with caution, since it is not based on randomisation of patients to treatments. In our view, only definitely outstanding results should be judged as most likely to be clinically relevant. This analysis thus indicates that, with respect to headache relief at 2 hours, eletriptan 80mg is superior to sumatriptan 100mg, and that naratriptan 2.5mg and frovatriptan 2.5mg are inferior to sumatriptan 100mg. All other triptans or doses of oral triptans seem roughly equivalent to sumatriptan 50 to 100mg. Intranasal and rectal sumatriptan seem equivalent to oral sumatriptan, whereas subcutaneous sumatriptan is superior to all clinically used oral doses of triptans (fig. 3).

A review of the relatively few comparative trials (table VI) provides the same conclusions for headache relief. Eletriptan 80mg is superior to sumatriptan 100mg, and naratriptan 2.5mg is inferior to this dose of sumatriptan, whereas the other recommended oral doses of the second generation triptans are comparable to sumatriptan 100mg. No comparative trial with frovatriptan has been published so far. Apart from efficacy, headache relief after 2 hours, speed of onset of action (a feature highly valued by the patients[206]), and recurrence or secondary treatment failure have been investigated in a few comparative trials. Thus, patients treated with rizatriptan 10mg are slightly more (15 to 26%) likely to achieve headache relief within 2 hours than patients treated with sumatriptan 50 or 100mg[116,117] or zolmitriptan 2.5mg.[109] Patients treated with naratriptan 2.5mg had, in most studies, fewer recurrences than those treated with sumatriptan 100mg (table VI).

Finally, how do the triptans compare with non-triptan drugs? Relatively few comparative trials, some of them unpublished, have been performed (table VII). Oral sumatriptan 100mg and oral eletriptan 40 and 80mg were superior to the widely used oral ergotamine 2mg/caffeine 200mg. Oral sumatriptan 100mg was marginally better than or comparable to the combination of metoclopramide and aspirin, tolfenamic acid or diclofenac potassium. Subcutaneous sumatriptan was superior to intranasal dihydroergotamine and intravenous lysine acetylsalicylate, and comparable to subcutaneous dihydroergotamine. Intranasal sumatriptan was superior to intranasal dihydroergotamine, and rectal sumatriptan was marginally inferior to rectal ergotamine. There is clearly a need for more comparative trials with the second generation triptans and current non-triptan drugs to definitively establish the place of triptans in migraine therapy.

References

1. Saxena PR, De Vries P, Villalón CM. 5-HT_1-like receptors: a time to bid goodbye. Trends Pharmacol Sci 1998; 19: 311-6
2. De Vries P, Villalón CM, Saxena PR. Pharmacology of triptans. Emerg Drugs 1999; 4: 107-25
3. Humphrey PPA, Feniuk W. Mode of action of the anti-migraine drug sumatriptan. Trends Pharmacol Sci 1991; 12: 444-6
4. Tfelt-Hansen P. Sumatriptan for the treatment of migraine attacks – a review of controlled clinical trials. Cephalalgia 1993; 13: 238-44
5. Plosker GL, McTavish D. Sumatriptan. A reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs 1994; 47: 622-51
6. Pilgrim AJ. Methodology of clinical trials of sumatriptan in migraine and cluster headache. Eur Neurol 1991; 31: 295-9
7. Wilkinson M, Pfaffenrath V, Schoenen J, et al. Migraine and cluster headache – their management with sumatriptan: a critical review of the current clinical experience. Cephalalgia 1995; 15: 337-57

8. Dechant KL, Clissold SP. Sumatriptan. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs 1992; 43: 776-98
9. Perry CN, Markham A. Sumatriptan. An updated review of its use in migraine. Drugs 1998; 55: 889-922
10. Ryan Jr RE, Elkind A, Goldstein J. Twenty-four-hour effectiveness of BMS 180048 in the acute treatment of migraine headaches. Headache 1997; 37: 245-8
11. Couch JRJ, Saper J, Meloche JP. Treatment of migraine with BMS180048: response at 2 hours. North American BMS180048 Study Group. Headache 1996; 36: 523-30
12. Yocca FD, Gylys JA, Smith DW, et al. BMS-181885: a clinically effective migraine abortive with peripherovascular and neuronal 5-HT_{1D} agonist properties. Cephalalgia 1997; 17: 404
13. Goldstein J, Dahlöf CG, Diener H-C, et al. Alniditan in the acute treatment of migraine attacks: a subcutaneous dose-finding study. Cephalalgia 1996; 16: 497-502
14. Leysen JE, Gommeren W, Heylen L, et al. Alniditan, a new 5-hydroxytryptamine$_{1D}$ agonist and migraine-abortive agent: ligand-binding properties of human 5-hydroxytryptamine$_{1D\alpha}$, human 5-hydroxytryptamine$_{1D\beta}$, and calf 5-hydroxytryptamine$_{1D}$ receptors investigated with [^{3}H]5-hydroxytryptamine and [^{3}H]alniditan. Mol Pharmacol 1996; 50: 1567-80
15. Newman-Tancredi A, Conte C, Chaput C, et al. Agonist activity of antimigraine drugs at recombinant human 5-HT_{1A} receptors: potential implications for prophylactic and acute therapy. Naunyn Schmiedebergs Arch Pharmacol 1997; 355: 682-8
16. Martin GR, Robertson AD, MacLennan SJ, et al. Receptor specificity and trigemino-vascular inhibitory actions of a novel 5-$HT_{1B/1D}$ receptor partial agonist, 311C90 (zolmitriptan)®. Br J Pharmacol 1997; 121: 157-64
17. Connor HE, Feniuk W, Beattie DT, et al. Naratriptan: biological profile in animal models relevant to migraine. Cephalalgia 1997; 1997: 145-52
18. Napier C, Stewart M, Melrose H, et al. Characterisation of the 5-HT receptor binding profile of eletriptan and kinetics of [^{3}H]eletriptan binding at human 5-HT_{1B} and 5-HT_{1D} receptors. Eur J Pharmacol 1999; 368: 259-68
19. Bou J, Domenech T, Gras J, et al. Pharmacological profile of almotriptan, a novel antimigraine agent. Cephalalgia 1997; 17: 421
20. Brown A, Parsons AA, Raval P, et al. SB 209509 (VML 251), a potent constrictor of rabbit basilar artery with high affinity and selectivity for human 5-HT_{1D} receptors. Br J Pharmacol 1996; 119: 110P
21. Wurch T, Palmier C, Colpaert FC, et al. Recombinant saphenous vein 5-HT_{1B} receptors of the rabbit: comparative pharmacology with human 5-HT_{1B} receptors. Br J Pharmacol 1997; 120: 153-9
22. Wainscott DB, Johnson KW, Phebus LA, et al. Human 5-HT_{1F} receptor-stimulated [^{35}S]GTPgammaS binding: correlation with inhibition of guinea pig dural plasma protein extravasation. Eur J Pharmacol 1998; 352: 117-24
23. Eglen RM, Jasper JR, Chang DA, et al. The 5-HT_7 receptor: orphan found. Trends Pharmacol Sci 1997; 18: 104-7
24. MacIntyre PD, Bhargava B, Hogg KJ, et al. Effect of subcutaneous sumatriptan, a selective $5HT_1$ agonist, on the systemic, pulmonary, and coronary circulation. Circulation 1993; 87: 401-5
25. Tfelt-Hansen P, Sperling B, Winter PDO. Transient additional effect of sumatriptan on ergotamine-induced constriction of peripheral arteries in man. Clin Pharmacol Ther 1992; 51: 149
26. Dixon RM, Meire HB, Evans DH, et al. Peripheral vascular effects and pharmacokinetics of the antimigraine compound, zolmitriptan, in combination with oral ergotamine in healthy volunteers. Cephalalgia 1997; 17: 639-46
27. Sciberras DG, Polvino WJ, Gertz BJ, et al. Initial human experience with MK-462 (rizatriptan): a novel 5-HT_{1D} agonist. Br J Clin Pharmacol 1997; 43: 49-54
28. De Vries P, Heiligers JPC, Villalón CM, et al. Blockade of porcine carotid vascular response to sumatriptan by GR127935, a selective 5-HT_{1D} receptor antagonist. Br J Pharmacol 1996; 118: 85-92
29. Pagniez F, Valentin JP, Vieu S, et al. Pharmacological analysis of the haemodynamic effects of 5-$HT_{1B/D}$ receptor agonists in the normotensive rat. Br J Pharmacol 1998; 123: 205-14
30. Willems E, De Vries P, Heiligers JP, et al. Porcine carotid vascular effects of eletriptan (UK-116,044): a new 5-$HT_{1B/1D}$ receptor agonist with anti-migraine activity. Naunyn Schmiedebergs Arch Pharmacol 1998; 358: 212-9
31. Humphrey PP, Feniuk W, Perren MJ, et al. The pharmacology of the novel 5-HT_1-like receptor agonist, GR43175. Cephalalgia 1989; 9: 23-33
32. Dreteler GH, Wouters W, Saxena PR. Comparison of the cardiovascular effects of the 5-HT_{1A} receptor agonist flesinoxan with that of 8-OH-DPAT in the rat. Eur J Pharmacol 1990; 180: 339-49
33. Friberg L, Olesen J, Iversen HK, et al. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet 1991; 338: 13-7
34. Caekebeke JF, Ferrari MD, Zwetsloot CP, et al. Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks. Neurology 1992; 42: 1522-6
35. Limmroth V, May A, Auerbach P, et al. Changes in cerebral blood flow velocity after treatment with sumatriptan or placebo and implications for the pathophysiology of migraine. J Neurol Sci 1996; 138: 60-5
36. MacLennan SJ, Cambridge D, Whiting MV, et al. Cranial vascular effects of zolmitriptan, a centrally active 5-$HT_{1B/1D}$ receptor partial agonist for the acute treatment of migraine. Eur J Pharmacol 1998; 361: 191-7
37. Shepheard SL, Williamson DJ, Baker R, et al. In vivo pharmacology of the novel 5-HT_{1D} receptor agonist MK-462. Cephalalgia 1995; 15: 204
38. Gupta P, Brown D, Butler P, et al. Pre-clinical in vivo pharmacology of eletriptan (UK-116,044): a potent and selective partial agonist at '5-HT_{1D}-like' receptors. Cephalalgia 1996; 16: 386
39. Parsons AA, Parker SG, Raval P, et al. Comparison of the cardiovascular effects of the novel 5-$HT_{(1B/1D)}$ receptor agonist, SB 209509 (VML251), and sumatriptan in dogs. Cardiovasc Pharmacol 1997; 30: 136-41
40. Sperling B, Tfelt-Hansen P, Lines C. Lack of effect of MK-462 on cerebral blood flow in humans. Cephalalgia 1995; 15: 206
41. De Vries P, Willems EW, Heiligers JPC, et al. Investigation of the role of 5-HT_{1B} and 5-HT_{1D} receptors in the sumatriptan-induced constriction of porcine carotid arteriovenous anastomoses. Br J Pharmacol 1999; 127: 405-12
42. Heyck H. Pathogenesis of migraine. Res Clin Stud Headache 1969; 2: 1-28
43. Saxena PR. Cranial arteriovenous shunting, an *in vivo* animal model for migraine. In: Olesen J, et al. (editors). Experimental headache models. Philadelphia: Lippincott-Raven, 1995: 189-98
44. Van Es NM, Bruning TA, Camps J, et al. Assessment of peripheral vascular effects of antimigraine drugs in humans. Cephalalgia 1995; 15: 288-91
45. Parsons AA, Raval P, Smith S, et al. Effects of the novel high-affinity 5-$HT_{(1B/1D)}$ receptor ligand frovatriptan in human iso-

lated basilar and coronary arteries. J Cardiovasc Pharmacol 1998; 32: 220-4
46. Martin GR. Inhibition of the trigemino-vascular system with 5-HT_{1D} agonist drugs: selectively targeting additional sites of action. Eur Neurol 1996; 36: 13-8
47. Gupta P, Napier CM, Scatchard J, et al. Further characterization of the in vitro pharmacology of eletriptan. Cephalalgia 1997; 17: 413
48. Longmore J, Razzaque Z, Hargreaves RJ, et al. Rizatriptan selectively contracts human middle meningeal over coronary artery: comparison with sumatriptan. Cephalalgia 1997; 17: 388-9
49. MaassenVanDenBrink A, Van Den Broek RWM, De Vries R, et al. Human middle meningeal and coronary artery contraction to eletriptan and sumatriptan. Cephalalgia 1999; 19: 398
50. Van Den Broek RWM, MaassenVanDenBrink A, De Vries R, et al. Pharmacological analysis of contraction to eletriptan and sumatriptan in human isolated coronary artery and saphenous vein. Cephalalgia 1999; 19: 399
51. Gupta P, Scatchard J, Shepperson N, et al. In vitro pharmacology of eletriptan (UK-116,044) at the '5-HT_{1D}-like' receptor in the dog saphenous vein. Cephalalgia 1996; 16: 386
52. Beer MS, Middlemiss DN, Stanton JA, et al. *In vitro* pharmacological profile of the novel 5-HT_{1D} receptor agonist MK-462. Cephalalgia 1995; 15: 203
53. MaassenVanDenBrink A, Reekers M, Bax WA, et al. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation 1998; 98: 25-30
54. Longmore J, Boulanger CM, Desta B, et al. 5-HT_{1D} receptor agonists and human coronary artery reactivity in vitro: cross-over comparisons of 5-HT and sumatriptan with rizatriptan and L-741,519. Br J Clin Pharmacol 1996; 42: 431-41
55. Connor HE, Feniuk W, Humphrey PPA. 5-Hydroxytryptamine contracts human coronary arteries predominantly via 5-HT_2 receptor activation. Eur J Pharmacol 1989; 161: 91-4
56. Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D et al. 5-HT receptors mediating contractions of the isolated human coronary artery. Eur J Pharmacol 1993; 239: 203-10
57. Shepheard SL, Williamson DJ, Beer MS, et al. Differential effects of 5-$HT_{1B/1D}$ receptor agonists on neurogenic dural plasma extravasation and vasodilation in anaesthetized rats. Neuropharmacology 1997; 36: 525-33
58. Williamson DJ, Shepheard SL, Hill RG, et al. The novel antimigraine agent rizatriptan inhibits neurogenic dural vasodilation and extravasation. Eur J Pharmacol 1997; 328: 61-4
59. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 1993; 33: 48-56
60. Goadsby PJ, Edvinsson L. Peripheral and central trigeminovascular activation in cat is blocked by the serotonin (5HT)-$_{1D}$ receptor agonist 311C90. Headache 1994; 34: 394-9
61. Shepheard SL, Williamson DJ, Williams J, et al. Comparison of the effects of sumatriptan and the NK_1 antagonist CP-99,994 on plasma extravasation in dura mater and c-fos mRNA expression in trigeminal nucleus caudalis of rats. Neuropharmacology 1995; 34: 255-61
62. Goadsby PJ, Hoskin KL. Inhibition of trigeminal neurons by intravenous administration of the serotonin $(5HT)_{1B/D}$ receptor agonist zolmitriptan (311C90): are brain stem sites therapeutic target in migraine? Pain 1996; 67: 355-9
63. Cumberbatch MJ, Hill RG, Hargreaves RJ. The effects of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor agonists on trigeminal nociceptive neurotransmission in anaesthetized rats. Eur J Pharmacol 1998; 362: 43-6
64. Goadsby PJ, Knight Y. Inhibition of trigeminal neurones after intravenous administration of naratriptan through an action at 5-hydroxytryptamine (5-$HT_{1B/1D}$) receptors. Br J Pharmacol 1997; 122: 918-22
65. Cumberbatch MJ, Hill RG, Hargreaves RJ. Rizatriptan has central antinociceptive effects against durally evoked responses. Eur J Pharmacol 1997; 328: 37-40
66. Yu XJ, Waeber C, Castanon N, et al. 5-Carboxamido-tryptamine, CP-122,288 and dihydroergotamine but not sumatriptan, CP-93,129, and serotonin-5-O-carboxymethyl-glycyl-tyrosinamide block dural plasma protein extravasation in knockout mice that lack 5-hydroxytryptamine$_{1B}$ receptors. Mol Pharmacol 1996; 49: 761-5
67. Yu XJ, Cutrer FM, Moskowitz MA, et al. The 5-HT_{1D} receptor antagonist GR-127,935 prevents inhibitory effects of sumatriptan but not CP-122,288 and 5-CT on neurogenic plasma extravasation within guinea pig dura mater. Neuropharmacology 1997; 36: 83-91
68. Phebus LA, Johnson KW, Zgombick JM, et al. Characterization of LY344864 as a pharmacological tool to study 5-HT_{1F} receptors: binding affinities, brain penetration and activity in the neurogenic dural inflammation model of migraine. Life Sci 1997; 61: 2117-26
69. Johnson KW, Schaus JM, Durkin MM, et al. 5-HT_{1F} receptor agonists inhibit neurogenic dural inflammation in guinea pigs. Neuroreport 1997; 8: 2237-40
70. Roon K, Diener HC, Ellis P, et al. CP-122,287 blocks neurogenic inflammation, but is not effective in aborting migraine attacks: results of two controlled clinical trials. Cephalalgia 1997; 17: 245
71. May A, Shepheard SL, Knorr M, et al. Retinal plasma extravasation in animals but not in humans: implications for the pathophysiology of migraine. Brain 1998; 121: 1231-7
72. Mills A, Rhodes P, Martin GR. [^{3}H]311C90 binding sites in cat brain stem: implications for migraine treatment. Cephalalgia 1995; 15: 116
73. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. Trends Pharmacol Sci 1992; 13: 307-11
74. Goadsby PJ. Current concepts of the pathophysiology of migraine. Neurol Clin 1997; 15: 27-42
75. Saxena PR, Tfelt-Hansen P. Triptans, 5-$HT_{1B/1D}$ receptor agonists in the acute treatment of migraine. In: Olesen J, et al. (editors). The headaches. Philadelphia: Lippincott, Williams & Wilkins, 2000: 411-38
76. Saxena PR, Ferrari MD. 5-HT_1-like receptor agonists and the pathophysiology of migraine. Trends Pharmacol Sci 1989; 10: 200-4
77. Ferrari MD, Saxena PR. Clinical and experimental effects of sumatriptan in humans. Trends Pharmacol Sci 1993; 14: 129-33
78. Humphrey PPA, Goadsby PJ. The mode of action of sumatriptan is vascular? A debate. Cephalalgia 1994; 14: 401-10
79. Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. Headache 1991; 31: 365-71
80. Cutler NR, Gomez-Mancilla B, Lebowitz M, et al. A study of safety and efficacy in patients with acute migraine, using PNU-142633, a selective 5-HT_{1D} agonist. Cephalalgia 2000; 20: 268
81. Fowler PA, Lacey LF, Thomas M, et al. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. Eur Neurol 1991; 31: 291-94
82. Duquesnoy C, Mamet JP, Sumner D, et al. Comparative clinical pharmacokinetics of single doses of sumatriptan following

subcutaneous, oral, rectal and intranasal administration. Eur J Pharm Sci 1998; 6: 99-104
83. Lacey LF, Hussey EK, Fowler PA. Single dose pharmacokinetics of sumatriptan in healthy volunteers. Eur J Clin Pharmacol 1995; 47: 543-8
84. Kunka RL, Hussey EK, Shaw S, et al. Safety, tolerability, and pharmacokinetics of sumatriptan suppositories following single and multiple doses in healthy volunteers. Cephalalgia 1997; 17: 532-40
85. Seaber EJ, Peck RW, Smith DA, et al. The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers. Br J Clin Pharmacol 1998; 46: 433-9
86. Peck RW, Seaber EJ, Dixon RM, et al. The pharmacodynamics and pharmacokinetics of the 5HT$_{1B/1D}$-agonist zolmitriptan in healthy young and elderly men and women. Clin Pharmacol Ther 1998; 63: 342-53
87. Kempsford RD, Baille P, Fuseau E. Oral naratriptan (2.5-10 mg) exhibit dose-proportional pharmacokinetics. Cephalalgia 1997; 17: 408
88. Fuseau E, Baille P, Kempsford RD. A study to determine the absolute oral bioavailability of naratriptan. Cephalalgia 1997; 17: 417
89. Goldberg MR, Lee Y, Vyas KP, et al. Rizatriptan, a novel 5-HT1B/1D agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. J Clin Pharmacol 2000; 40: 74-83
90. Cheng H, Polvino WJ, Sciberras D, et al. Pharmacokinetics and food interaction of MK-462 in healthy males. Biopharm Drug Dispos 1996; 17: 17-24
91. Milton KA, Buchanan TJ, Haug-Pihale G, et al. The pharmacokinetics, safety and tolerability of oral eletriptan in subjects with impaired hepatic function. Cephalalgia 1998; 18: 411-2
92. Hyland R, Jones BC, McCleverty P, et al. In vitro metabolism of eletriptan in human liver microsomes. Cephalalgia 1998; 18: 404
93. Morgan P, Rance D, James G, et al. Comparative absorption and elimination of eletriptan in rat, dog and human. Cephalalgia 1997; 17: 414
94. Robert M, Warrington SJ, Zayas JM, et al. Electrocardiographic effects and pharmacokinetics of oral almotriptan in healthy subjects. Cephalalgia 1998; 18: 406
95. Cabaroccas X, Salva M. Pharmacokinetic and metabolic data on almotriptan, a new antimigraine drug. Cephalalgia 1997; 17: 421
96. Fernandez FJ, Cabaroccas X, Zayas JM, et al. Oral almotriptan in the treatment of migraine. A dose finding study. Cephalalgia 1999; 19: 362-3
97. Buchan P. The pharmacokinetics of frovatriptan (VML 251/SB 209509), a potent selective 5-HT$_{1B/1D}$agonist, following single dose administration by oral and intravenous routes to healthy male and female volunteers. Headache 1998; 38: 376
98. Rance D, Clear N, Dallman L. Physicochemical comparison of eletriptan and other 5-HT$_{1D}$-like agonists as a predictor of oral absoption potential. Headache 1997; 37: 328
99. Moore KHP, Hussey EK, Shaw S, et al. Safety, tolerability, and pharmacokinetics of sumatriptan in healthy subjects following ascending single intranasal doses and multiple intranasal doses. Cephalalgia 1997; 17: 541-50
100. Dixon R, On N, Posner J. High oral bioavailability of the novel 5-HT$_{1D}$ agonist 311C90. Cephalalgia 1995; 15: 218
101. Dixon R, Gillotin C, Gibbens M, et al. The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers. Br J Clin Pharmacol 1997; 43: 273-81
102. Rolan PE, Martin GR. Zolmitriptan: a new acute treatment for migraine. Exp Opin Invest Drugs 1998; 7: 633-52
103. Kempsford RD, Nicholls B, Lam R, et al. A study to investigate the potential interaction of naratriptan and ergotamine. Cephalalgia 1997; 17: 416
104. Kempsford RD, Nicholls B, Lam R, et al. A study to investigate the potential interaction of naratriptan and dihydroergotamine. Cephalalgia 1997; 17: 416
105. Dahlöf C, Lines C. Rizatriptan: a new 5-HT$_{1B/1D}$receptor agonist for the treatment of migraine. Exp Opin Invest Drugs 1999; 8: 671-86
106. Goldberg MR, Lowry RC, Musson DG. Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine. Br J Clin Pharmacol 1999; 39: 1-8
107. Geraud G, Olesen J, Pfaffenrath V, et al. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. Cephalalgia 2000; 20: 30-8
108. Gallagher RM. Comparison of zolmitriptan and sumatriptan for the acute treatment of migraine. Cephalalgia 1999; 19: 358
109. Diener HC, Pascual J, Vega P. Comparison of rizatriptan 10 mg versus zolmitriptan 2.5 mg in migraine. Headache 1999; 39: 351
110. Havana H, Dahlof C, Pop PH, et al. Efficacy of naratriptan tablets in the acute treatment of migraine: a dose-ranging study: Naratriptan S2WB2004 Study Group. Clin Ther 2000; 22: 970-80
111. Bates D, Winter P. Efficacy and tolerability of naratriptan tablets (0.1-2.5 mg) in the acute treatment of migraine. Eur J Neurol 1998; 5: S48-S9
112. Göbel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients: Naratriptan International Recurrence Study Group. Clin Ther 2000; 22: 981-9
113. Bornhof MK, Legg N, Paz J. Comparison of rizatriptan 10 mg vs naratriptan 2.5 mg in migraine. Headache 1999; 39: 344
114. Visser WH, Terwindt GM, Reines SA, et al. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Arch Neurol 1996; 53: 1132-7
115. Lines C, Visser WH, Vandormael K, et al. Rizatriptan 5 mg versus sumatriptan 50 mg in the acute treatment of migraine. Headache 1997; 37: 319-20
116. Goldstein J, Ryan R, Jiang K, et al. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Headache 1998; 38: 737-47
117. Tfelt-Hansen P, Teall J, Rodriguez F, et al. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Headache 1998; 38: 748-55
118. Jackson NC, on behalf of the Eletriptan Steering Committee. Clinical measures of efficacy, safety and tolerability for the acute treatment of migraine: a comparison of eletriptan (20-80 mg), sumatriptan (100 mg) and placebo. Neurology 1998; 50: A376
119. Pitman V, Forster E, Jackson N. Comparison of the efficacy of oral eletriptan and oral sumatriptan for the acute treatment of migraine: combined analysis across three clinical trials. Headache 1999; 39: 374
120. Cabarrocas X, Zayas JM, Suris M, et al. Equivalent efficacy of oral almotriptan, a new 5-HT$_{1B/1D}$ agonist, compared with sumatriptan 100 mg. Headache 1998; 38: 377-8
121. Dahlöf C, Hogenhuis L, Olesen J, et al. Early clinical experience with subcutaneous naratriptan in the acute treatment of migraine: a dose-ranging study. Eur J Neurol 1998; 5: 469-77
122. Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan in the acute treatment of migraine. Eur Neurol 1991; 31: 314-22

123. Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. Eur Neurol 1992; 32: 177-84
124. Tfelt-Hansen P, Henry P, Mulder K, et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet 1995; 346: 923-6
125. Myllylä V, Havanka H, Herrala L, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. Headache 1998; 38: 201-7
126. The Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a non-steroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. Cephalalgia 1999; 19: 232-40
127. Touchon J, Bertin L, Pilgrim AJ, et al. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. Neurology 1996; 47: 361-5
128. Winner P, Ricalde O, Le Force B, et al. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol 1996; 53: 180-4
129. Diener HC. for the ASASUMAMIG Study Group. Efficacy and safety of intravenous acerylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, parallel group study. Cephalalgia 1999; 19: 581-8
130. Boureau F, Kappos L, Schoenen J, et al. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. Int J Clin Pract 2000; 54: 281-6
131. Swedish Medical Products Agency. Monography on sumatriptan suppositories [online]. Available from: http://www.mpa.se/lakemedel/nn_lakeindex.html [Accessed 2000 Oct 24]
132. Reches A, on behalf of the Eletriptan Steering Committee. Comparison of the efficacy, safety and tolerability of oral eletriptan and Cafergot® for the acute treatment of migraine. Cephalalgia 1999; 19: 355
133. Tfelt-Hansen P. Efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment: a systemic review based on number needed to treat. Cephalalgia 1998; 18: 532-8
134. Cady RK, Wendt JK, Kirchner JR, et al. Treatment of acute migraine with subcutaneous sumatriptan. JAMA 1991; 265: 2831-5
135. Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. N Engl J Med 1991; 325: 316-21
136. Sumatriptan Auto-Injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Eur Neurol 1991; 31: 323-31
137. Gross MLP, Kay J, Turner AM, et al. Sumatriptan in acute migraine using a novel cartridge system self-injector. Headache 1994; 34: 559-63
138. Jensen K, Tfelt-Hansen P, Hansen EW, et al. Introduction of a novel self-injector for sumatriptan. A controlled clinical trial in general practice. Cephalalgia 1995; 15: 423-9
139. Bousser MG, d'Allens H, Richard A, et al. Efficacy of subcutaneous sumatriptan in the acute treatment of early-morning migraine: a placebo-controlled study. J Intern Med 1993; 234: 211-6
140. Henry P, d'Allens H, and the French Migraine Network Bordeaux-Lyon-Grenoble. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. Headache 1993; 33: 432-5
141. Mathew NT, Dexter J, Couch J, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. Arch Neurol 1992; 49: 1271-6
142. Russel MB, Holm-Thomsen OE, Nielsen MR, et al. A randomized, double-blind, placebo-controlled crossover study of subcutaneous sumatriptan in general practice. Cephalalgia 1994; 14: 291-6
143. Facchinetti F, Bonellie G, Kangasneimi P, et al. The efficacy and safety of sumatriptan in the acute treatment of menstrual migraine. Obstet Gynecol 1995; 86: 911-6
144. Mushet GR, Cady RK, Baker CC, et al. Efficacy and tolerability of of subcutaneous sumatriptan administered using the IMITREX®_STATdose™ system. Clin Ther 1996; 18: 687-99
145. Cady RC, Ryan R, Jhingran P, et al. Sumatriptan injection reduces productivity loss during a migraine attack. Results of a double-blind, placebo-controlled trial. Arch Intern Med 1998; 158: 1013-8
146. Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. Ann Emerg Med 1995; 25: 464-9
147. Cady RK, Dexter J, Sargent JD, et al. Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. Neurology 1993; 43: 1363-8
148. Pfaffenrath V, Cunin G, Sjonell G, et al. Efficacy and safety of sumatriptan tablets (25mg, 50mg, 100mg) in the acute treatment of migraine: defining the optimum doses of oral sumatriptan. Headache 1998; 38: 184-90
149. Oral Sumatriptan Dose-defining Study Group. Sumatriptan – an oral dose-defining study. Eur Neurol 1991; 31: 300-5
150. Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. Eur Neurol 1991; 31: 306-13
151. Goadsby PJ, Zagami AS, Donnan GA, et al. Oral sumatriptan in acute migraine. Lancet 1991; 338: 782-3
152. Cutler N, Mushet GR, Davis R, et al. Oral sumatriptan for the acute treatment of migraine: Evaluation of three dosage strengths. Neurology 1995; 45: S5-S9
153. Sargent J, Kirchner JR, Davis R, et al. Oral sumatriptan is effective and well tolerated for the acute treatment of migraine: Results of a multicenter study. Neurology 1995; 45: S10-S14
154. Nappi G, Sicuteri F, Byrne M, et al. Oral sumatriptan compared with placebo in the acute treatment of migraine. J Neurol 1994; 41: 138-44
155. Rederich G, Rapoport A, Cutler N et al. Oral sumatriptan for the long-term treatment of migraine: clinical findings. Neurology 1995; 45: S15-S20
156. Savani N, Brautaset NJ, Reunanen M, et al. A double-blind placebo-controlled study assessing the efficacy and tolerability of sumatriptan 50-mg tablets in the acute treatment of migraine. Int J Clin Pract 1999; Suppl. 105: 7-15
157. Salonen R, Ashford EA, Hassani H. and The S2BM11 Study Group. Patients preference for oral sumatriptan 25, 50 or 100 mg in the acute treatment of migraine: a double-blind, randomized, crossover study. Int J Clin Pract 1999; Suppl. 105: 16-24
158. Salonen R, Asford E, Dahlöf C, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol 1994; 241: 463-9
159. Dahlöf C. Sumatriptan nasal spray: a review of data from multinational clinical trials. Funct Neurol 1996; 11: 150

160. Ryan R, Elkind A, Baker CC, et al. Sumatriptan nasal spray for the acute treatment of migraine. Results of two clinical studies. Neurology 1997; 49: 1225-30
161. Diamond S, Elkind A, Jackson T, et al. Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine. Arch Fam Med 1998; 7: 234-40
162. Peikert A, Becker WJ, Ashford EA, et al. Sumatriptan nasal spray: a dose-ranging study in the acute treatment of migraine. Eur J Neurol 1999; 6: 43-9
163. Ashford E, Salonen R, Saiers J, et al. Consistency of response to sumatriptan nasal spray across patient subgroups and migraine types. Cephalalgia 1998; 18: 273-7
164. Swedish Medical Products Agency. Monograph on sumatriptan nasal spray. Available from: http://www.mpa.se/lakemedel/nn_lakeindex.html [Accessed 2000 Oct 24]
165. Tepper SJ, Cochran A, Hobbs S, et al. Sumatriptan suppositories for the acute treatment of migraine. Int J Clin Pract 1998; 52: 31-5
166. Göbel H, on behalf on the Study Group. A placebo-controlled, dose-defining study of sumatriptan suppositories in the acute treatment of migraine. In: Olesen J, et al. (editors). Headache treatment: trial methodology and new drugs. Philadelphia: Lippincott-Raven, 1997: 203-6
167. Henriksson A, on behalf of the Study Group. Safety and efficacy of sumatriptan suppositories in the acute treatment of migraine attacks. Cephalalgia 1995; 15: 235
168. Klassen AC, Gabriel H, Hobbs S, et al. Safety and efficacy of sumatriptan suppositories in the acute treatment of migraine attacks. Cephalalgia 1995; 15: 234
169. Ferrari MD, James MH, Bates D, et al. Oral sumatriptan: effect of a second dose, and treatment of headache recurrence. Cephalalgia 1994; 14: 330-8
170. Scott RJ, Aitchison WRC, Barker PR, et al. Oral sumatriptan in the acute treatment of migraine and migraine recurrence in general practice. Q J Med 1996; 89: 613-22
171. Visser WH, de Vriend RH, Jaspers MW, et al. Sumatriptan in clinical practice: a 2-year review of 453 migraine patients. Neurology 1996; 47: 46-51
172. Rapoport A, Visser WH, Cutler NR, et al. Oral sumatriptan in preventing headache recurrence after treatment of migraine attacks with subcutaneous sumatriptan. Neurology 1995; 45: 1505-9
173. Cull RE, Price WH, Dunbar A. The efficacy of subcutaneous sumatriptan in the treatment of recurrence of migraine headache. J Neurol Neurosurg Psychiat 1997; 62: 490-5
174. Bates D, Ashford E, Dawson R, et al. Subcutaneous sumatriptan during migraine aura. Neurology 1994; 44: 1587-92
175. Schoenen J, Sawyer J. Zolmitriptan (Zomig™, 311C90), a novel dual central and peripheral $5HT_{1B/1D}$ agonist: an overview of efficacy. Cephalalgia 1997; 17: 28-40
176. Ferrari MD. 311C90: Increasing the options for therapy with effective acute antimigraine 5HT1B/1D receptor agonists. Neurology 1997; 48: S21-S4
177. Solomon GD, Cady RK, Klapper JA, et al. The clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. Neurology 1997; 49: 1219-25
178. Visser WH, Klein KB, Cox RC, et al. 311C90, a new central and peripherally acting 5-HTiD receptor agonist in the acute oral treatment of migraine: a double-blind, placebo-controlled, dose-range finding study. Neurology 1996; 46: 522-6
179. Rapoport AM, Ramadan NM, Adelman JU, et al. Optimizing the dose of zolmitriptan (ZomigTM, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. Neurology 1997; 49: 1210-8
180. Dahlöf C, Diener H-C, Goadsby PJ, et al. Zolmitriptan, a 5-HT receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. Eur J Neurol 1998; 5: 535-43
181. Mathew NT, Asgharnejad M, Peykamian M, et al. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled crossover study. Neurology 1997; 49: 1485-90
182. Klassen A, Elkind A, Asgharnejad M, et al. Naratriptan is effective and well-tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. Headache 1997; 37: 640-5
183. Gunasekara NS, Wiseman LR. Naratriptan. CNS Drugs 1997; 8: 402-8
184. Gijsman H, Kramer MS, Sargent J, et al. Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK-462) in the acute treatment of migraine. Cephalalgia 1997; 17: 547-651
185. Teall J, Tuchman M, Cutler N, et al. Rizatriptan (MAXALT®) for the acute treatment of migraine and migraine recurrence. Headache 1998; 38: 281-7
186. Kramer M, Matzura-Wolfe D, Polis A, et al. A placebo-controlled crossover study of rizatriptan in the treatment of multiple attacks. Neurology 1998; 51: 773-81
187. Ahrens SP, Visser WH, Jiang K, et al. Rizatriptan RPD™ for the acute treatment of migraine. Eur J Neurol 1998; 5: S52
188. Färkkilä M, Diener H-C, Dahlöf C, et al. A dose-finding study of eletriptan (UK-116,044) (5-30 mg) for the acute treatment of migraine. Cephalalgia 1996; 16: 387
189. Hettiarachichi J, on behalf of the Eletriptan Steering Committee. Efficacy, safety and tolerability of oral eletriptan versus placebo in the acute treatment of migraine: a phase III randomised trial. Headache 1999; 39: 358-9
190. Hettiarachichi J, on behalf of the Eletriptan Steering Committee. Adverse event profile of oral eletriptan: review of clinical trial experience. Cephalalgia 1999; 19: 355
191. Cabarrocas X, on behalf of the Almotriptan Subcutaneous Study Group. First efficacy data on subcutaneous almotriptan, a novel $5HT_{1D}$ agonist. Cephalalgia 1997; 17: 420-1
192. Martinez E, Cabarrocas X, Peris F, et al. Meta-analysis of the efficacy and safety of almotriptan in the treatment of migraine. Cephalalgia 1999; 19: 362
193. Cabarrocas X, on behalf of the Almotriptan Oral Study Group. Efficacy data on oral almotriptan, a novel $5HT_{1B/1D}$agonist. Headache 1998; 38: 377
194. Ryan R, Keywood C, on behalf of the US Multi-center Study ofVML251. A preliminary study of VML251 (SB209509) a novel $5HT_{1B/1D}$agonist for the treatment of migraine attacks. Cephalalgia 1997; 17: 418
195. Goldstein J, Keywood C. A low dose range finding study of frovatriptan, a potent selective $5\text{-}HT_{1B/1D}$agonist for the treatment of migraine. Funct Neurol 1998; 13: 178
196. Tansey MJB, Pilgrim AJ, Martin PM. Long-term experience with sumatriptan in the treatment of migraine. Eur Neurol 1993; 33: 310
197. Gross MLP, Kay J, Turner AM, et al. Long-term efficacy of subcutaneous sumatriptan using a novel self-injector. Headache 1995; 35: 601-6
198. The International 311C90 Long-term Study Group. The long-term tolerability and efficacy of oral zolmitriptan (Zomig, 311C90) in the acute treatment of migraine. An international study. Headache 1998; 38: 173-83
199. Bomhof MAM, Heywood J, Pradalier A, et al. The tolerability and efficacy of naratriptan tablets with long-term treatment (6 months). Cephalalgia 1998; 18: 33-7

200. Block GA, Goldstein J, Polis A, et al. Efficacy and safety of rizatriptan versus standard care during long-term treatment for migraine. Headache 1998; 38: 764-71
201. Tfelt-Hansen P. Pitfalls in long-term studies assessing acute migraine therapy. Cephalalgia. in press
202. Massiou H, Tzourio C, El Amrani M, et al. Verbal scales in the acute treatment of migraine: semantic categories and clinical relevance. Cephalalgia 1997; 17: 37-9
203. Ferrari MD. How to assess and compare drugs in the management of migraine: success rates in term of response and recurrence. Cephalalgia 1999; 19: 2-8
204. Tfelt-Hansen P, Eickhoff JH, Olesen J. The effect of single dose ergotamine tartrate on peripheral arteries in migraine patients: methodological aspects and time effect curve. Acta Pharmacol Toxicol 1980; 47: 151-6
205. Aellig WH, Rosenthaler J. Venoconstrictor effects of dihydroergotamine after intranasal and intramuscular administration. Eur J Clin Pharmacol 1986; 30: 581-4
206. Göbel H, Petersen-Braun M, Heinze A. Which properties do patients expect of new and improved drugs in the treatment of primary headache disorders? In: Olesen J, et al. (editors). Headache treatment: trial methodology and new drugs. Philadelphia: Lippincott-Raven, 1997: 93-7

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