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PHENYLEPHRINE FOR PSEUDOEPHEDRINE IN OTC COLD MEDICINES: AN EQUAL EXCHANGE?

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During the peak of cough and cold season millions, of Americans find themselves searching through the cold medicine section of the neighborhood store in an attempt to relieve nasal stuffiness and sinus pressure. Until recently, the choice included with the ingredient pseudoephedrine found in over 700 cough and cold remedies. Pseudoephedrine (Sudafed®), phenylpropanolamine, and phenylephrine were three of the oral decongestants deemed safe and effective by the US Food and Drug Administration in 1976 for the relief of nasal congestion caused by the common cold, allergic rhinitis, and sinusitis.[1] After a large, multi-centered trial in 2000 confirming the link between phenylpropanolamine use and hemorrhagic stroke in women, all pharmaceutical manufacturers voluntarily removed it from their products.[2] The FDA estimates that phenylpropanolamine caused between 200 and 500 strokes a year among 18 to 49 year-old users.[2]

More recently, after passing the USA Patriot Act (HR 3889, Title VII) in September of 2006, all stores are required to keep pseudoephedrine containing products behind the counter requiring purchasers to show photo identification and sign a log book prior to purchase. These changes are part of a nation-wide effort to reduce home-based "meth labs" that create methamphetamine, a highly addictive street drug derived from pseudoephedrine. Fearing customers would shy away from pharmacists to ask for these products, Pfizer introduced a replacement product containing 10 mg phenylephrine (Sudafed-PE®) that cannot be converted to methamphetamine and has no restrictions. This conversion has left the consumer with a package that looks indistinguishable from the previous product, but with unproven efficacy.

Pharmacology and Pharmacokinetics

Phenylephrine is a potent vasoconstrictor that stimulates α-receptors with minimal effect on β-receptors of the heart. It is chemically related to epinephrine. Phenylephrine increases both systolic and diastolic blood pressure in a dose-dependent manor, but because it has little affinity for β-receptors, heart rate and contractility are generally unaffected.[3,4] However, reflex bradycardia is sometimes seen following the use of phenylephrine.[6] Pseudoephedrine is a stereoisomer of ephedrine and exerts its effects both directly through α-receptor agonism and indirectly via release of norepinephrine from storage sites.[5,6,7]

Sympathomimetics, such as pseudoephedrine and phenylephrine, carry a risk of cardiovascular side effects. However, nasal blood vessels are approximately 5 times more sensitive than the heart to

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circulating catecholamines.[8] This explains why pseudoephedrine in OTC products in a low dose causes effective nasal congestion relief with minimal cardiac effects.

Despite the fact that both pseudoephedrine and phenylephrine cause vasoconstriction of the nasal mucosa, little evidence substantiates the effectiveness of oral phenylephrine in its 10 mg dosage form. This difference in efficacy is most likely due to the metabolism of each compound. Both phenylephrine and pseudoephedrine are well absorbed in the gut. Phenylephrine, however, undergoes extensive presynaptic metabolism by monoamine oxidase in the gut wall.[9,10] As a result, less than 40% of phenylephrine actually reaches systemic circulation. Pseudoephedrine is resistant to the actions of monoamine oxidase resulting in over 90% of the drug remaining unchanged in the body. Pseudoephedrine also lacks the hydroxyl group on the benzene ring increasing its lipid solubility; thus, increasing CNS stimulant effects. The tolerability of phenylephrine as an oral nasal decongestant is likely to be due to its poor access to the systemic circulation rather than to its pharmacological profile.[11]

Efficacy

The efficacy of pseudoephedrine as a nasal decongestant has been documented in several trials. Pseudoephedrine reduces airway resistance in patients suffering from nasal congestion.[12-15] Pseudoephedrine is also an effective treatment for nasal congestion associated with the common cold when administered in multiple doses over several days.[12,16] Phenylephrine on the other hand, has conflicting data supporting its efficacy as an oral dosage form for the relief of nasal decongestion. The limited evidence the FDA used to accept phenylephrine as an effective oral decongestant is derived from five in-house studies provided by the pharmaceutical companies.[17] These unpublished studies demonstrated either a minor improvement or no difference in airway resistance as compared to placebo. Despite the concern expressed about the efficacy of phenylephrine as an oral decongestant, the FDA maintained its approval for phenylephrine as an effective nasal decongestant and phenylephrine was accepted as an effective oral nasal decongestant in the FDA's final conclusions on nasal decongestants published in 1994.[18]

A summary of studies comparing the efficacy of phenylephrine and pseudoephedrine in patients suffering from nasal congestion is located in **Table 1**. This is not meant to be an exhaustive list of all pseudoephedrine and phenylephrine trials, but rather a summary of a few of the better designed randomized, double-blinded, placebo-controlled clinical trials.

Safety

When oral pseudoephedrine and phenylephrine are used as indicated (including the dosing, length of time used, and medications to avoid), they are safe for use without medical supervision. Because most formulations of these OTC products contain analgesics or antihistamines, it is difficult to ascertain whether or not adverse events are associated with the drug or its combination ingredients. Nevertheless, millions of people have used pseudoephedrine and phenylephrine containing products for years without trends pointing to adverse events.

As with all sympathomimetics, pseudoephedrine and phenylephrine should be avoided in patients with hypertension, hyperthyroidism or heart disease as their vasoconstrictive properties could exacerbate these conditions.[23-25] Also, patients suffering from Raynaud's syndrome or taking medicines that inhibit monoamine oxidase should consult their doctor before taking phenylepherine.

Phenylephrine and pseudoephedrine may cause urinary retention in patients with prostatic hypertrophy. Pseudoephedrine is associated with an increased incidence of CNS adverse events compared with phenylephrine, but when taken in OTC doses, the most commonly reported side effect of pseudoephedrine is insomnia.[16]

Federal impact of pseudoephedrine regulations

Because of the recent restrictions surrounding the sale of pseudoephedrine containing OTC products, it is expected that fewer methamphetamine arrests and hospital admissions will occur. Numerous governments have regulated methamphetamine precursor chemicals to help limit the production and availability of methamphetamine.[26] In 2005, Cunningham et al[27] concluded that methamphetamine arrests declined 31% to 45% when large scale manufactures were regulated. Regulation targeting smaller-scale products had very little effect on the number of arrests.

Similar results were found among hospital

Table 1. Clinical trial summaries on the efficacy of pseudoephedrine and phenylephrine

Source	Demographics	Design	Oral Dose	N	Results
Taverner et al.[13]	Previously healthy patients who had the common cold for 5 days or less with moderate to severe nasal congestion	DB, PC, R	PDE 60 mg	54	Symptoms of congestion improved at times 60, 90,120, and 150 minutes after dose of PDE. NAR decreased significantly (p= 0.018, p=0.003 respectively)
Eccles et al.[12]	Patients suffering from nasal congestion associated with common cold	DB, PC, R	PDE 60mg	238	PDE had significantly lower area under the NAR curve than placebo (p=0.006) and on day 3 after multiple doses (p= 0.001)
Roth et al.[14]	Patients suffering from acute or chronic nonsuppurative rhinitis	DB, PC, R	PDE 60 mg	64	Reduction in NAR occurred within 30 min and was maintained for at least 4 hours (p=0.04)
Benson et al.[15]	Patients suffering from nasal congestion associated with a common cold	DB	PDE 60mg	112	PDE showed a decrease in NAR (p=0.001) when compared to placebo.
Mclaurin et al.[19]	Patients with nasal congestion from a variety of causes	DB, PC, R, CO	PE 10mg	88	10 mg of phenylephrine was no more effective than placebo in decreasing either NAR or subjective symptom scores
Bickerman et al.[20]	Patients with chronic nasal stuffiness	R, DB, CO	PDE 60mg, PP 40mg, PE 10mg	20	Nasal stuffiness declined significantly within 30 minutes and was maintained for 4 hours with PDE (p=0.01), but not with PP or PE (p > 0.05)
Huntingdon et al.[21]	Patients with elevated flow/resistance (F/R) measurements from colds	R, DB, PC, CO	PE 10, PE 25mg	32	NAR was not reduced in either 10mg or 25mg
Elizabeth et al.[22]	Patients with "head colds"	R, DB, PC, CO	PE 5mg, PE 15mg, PE 25mg	33	No significant reduction in airway resistance for all three doses of PE

N= number of patients, NAR= nasal airway resistance, DB= double-blind, R= randomized, PC= placebo-controlled, CO= cross-over, PE= phenylephrine, PDE= pseudoephedrine, PP= phenylpropanolamine

admissions in California, Arizona and Nevada when pseudoephedrine regulations were established.[28] Reductions in methamphetamine-related hospital admissions dropped 35% to 71% during the study period. However, these reductions only occurred when large-scale bulk powder regulations were enacted. Restrictions of small-scale ephedrine and pseudoephedrine combination products had little to no impact on hospital admissions.[28]

Alternative Therapies

Patients suffering from nasal congestion caused by the flu or the common cold are encouraged to ask the pharmacist for the pseudoephedrine-containing products located behind the pharmacy counter. Another alternative for patients suffering from congestion are topical nasal decongestants, such as oxymetazoline hydrochloride (Afrin®), phenylephrine (Neo-Synephrine®), and xylometazoline (Otrivin®), which are available over-the-counter in the United States. These agents work very quickly to open nasal passages by constricting blood vessels in the lining of the nose.[29,30] With prolonged use, these types of sprays can damage the delicate

mucous membranes in the nose, ironically causing an increased inflammatory effect known as rhinitis medicamentosa, or the "rebound effect".[31] As a result, decongestant nasal sprays are advised for short-term use only. Short-term use (3-4 days) can be advantageous for nasal congestion relief as most cold symptoms usually last fewer than three days

Saline sprays are a common and safe alternative to decongestants. A mist of saline solution helps to moisturize dry or irritated nostrils, but will have little effect on decreasing nasal resistance.

A future approach to treating nasal congestion may involve targeting α_2-receptors. Alpha$_2$-receptor agonists (yohimbine and BHT-920) have been shown to contract the nasal mucosa of several different species (dog, pig, monkey) and elicit decongestion without the side effects seen with other sympathomimetic agents (hypertension, increased heart rate, insomnia, nervousness).[32] These studies have not been performed in humans and currently there is no FDA approved α_2-adrenoceptor agonist available for treatment of nasal congestion.

Summary

Pseudoephedrine has been used safely and effectively for many years to relieve nasal congestion associated with the common cold. The effectiveness of pseudoephedrine (60 mg orally) has been well documented in several trials.[12-16] However, there is little evidence supporting the use of oral phenylephrine as a decongestant.[19-22] There has been a reduction in the number of methamphetamine-related hospital admissions and arrests when strict regulations are applied to bulk manufactures of pseudoephedrine, but no evidence showing a decline when small-scale, combination products are restricted.

In an attempt to reduce the number of clandestine “meth” labs by restricting all pseudoephedrine containing OTC products, the FDA has pulled the only effective oral decongestant from the shelves. Its replacement, phenylephrine, has similar packaging with dissimilar, unproven efficacy. Lack of sales of the “hidden” or behind-the-counter products may force pharmacies to reduce inventory of these pseudoephedrine-containing cold medicines depriving the public of a safe and effective nasal decongestant.

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OVERVIEW OF TRIPTANS IN THE MANAGEMENT OF ACUTE MIGRAINE

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Migraine headache is a debilitating chronic condition affecting approximately 18% of women and 7% of men. At this prevalence, migraine affects 30 million people in the US.[1] The prevalence of migraine varies by geographic location, age, gender, race, and socioeconomic status.[2] Currently, the rationale behind relief of acute migraine is rooted in vasoconstriction versus a vasodilatory approach desired in prophylaxis treatment. Triptans were developed to mimic serotonin's ability to cause vasoconstriction, which diminishes migraine attacks. Triptans were also designed to be more selective at receptor subtypes in order to decrease unwanted side effects and increase tolerability.[3] The triptans, as a class of drugs, have a FDA indication for acute treatment of migraine with or without aura. The original triptan, sumatriptan, also has an indication for cluster headaches.[4]

In clinical guidelines, the triptans are generally held as migraine-specific medications reserved for those who have failed NSAID therapy. The U.S. Headache Consortium Recommendations place the triptans as first line therapy for patients with severe migraine and as second-line therapy for those who respond poorly to analgesics.[5] The American College of Physicians-American Society of Internal Medicine recommend using triptans in those patients who fail to respond to NSAIDS.[6] This paper will review the pharmacodynamics, pharmacokinetics, clinical trials, adverse effects, and cost of triptans in the treatment of acute migraine.

Pharmacology/Pharmacokinetics

The mechanism of action of triptans is specific for the treatment of migraine pain; the pathophysiology of which is believed to involve both neural and vascular mechanisms. The triptans are serotonin $(5\text{-HT})_{1B/1D}$ receptor agonists with three mechanisms contributing to their antimigraine activity. The first targets the vascular pathophysiology of migraine. Activation of the sensory trigeminovascular

system leads to vasoactive substance release from trigeminal nerve terminals. This in turn causes an inflammatory reaction, including vasodilation, plasma protein extravasation, and platelet activation.[7] The dilation of these intracranial extracerebral vessels generates the pain of migraine headaches. Serotonin$_{1B}$ receptors are expressed on neuronal tissue and vascular smooth muscle cells and evidence suggests that these receptors are responsible for vascular smooth muscle contraction. When triptans bind these receptors, they cause vasoconstriction of the vasculature, resulting in reduction of painfully vasodilated vessels.[8]

A secondary mechanism of action includes stimulation of the 5-HT$_{1D}$ receptors. Peripherally, this causes inhibition of trigeminal nerves and prevents release of vasoactive neuropeptides, which during migraine contribute to the manifestation of head pain. Centrally, stimulation of 5-HT$_{1D}$ receptors works to decrease pain signal transmission by inhibiting the release of neurotransmitters.[8]

The first triptan developed, sumatriptan, proved to be a useful tool in treating patients with migraine. However, it possessed some limiting pharmacokinetic parameters such as low bioavailability, short plasma half-life, and low lipidsolubility. These limitations provided other companies an opportunity to improve on the pharmacokinetics of newer triptan formulations.[8] A concise summary of the available triptans and their specific pharmacokinetics is presented in **Table 1**.

Clinical Trials

There is an abundance of primary literature on the use of triptans in the treatment of acute migraine. Although there are many trials, meta-analyses, and guidelines to evaluate the benefit of triptans vs. placebo and other anti-migraine medications, this article will focus on comparison trials with other triptans.[9] Some acute migraine treatment outcomes include therapeutic gain (defined as reduction of moderate-severe pain to mild-moderate pain at 2 hours post-dose), percent of patients pain free at 2 hours post-dose, percent of patients requiring rescue medication 2 hours post-dose, and percent of patients with headache recurrence 24 hours post-dose.[2]

Some differences among products have been elucidated, and even though they seem to be small, clinical response and tolerability to these products vary.[10] This is best demonstrated by a meta-analysis of 53 trials conducted by Ferrari et al. in 2001.[11] For this meta-analysis, they collected raw data of double-blind (DB), randomized (R), controlled clinical trials involving triptans. This included trials of triptan vs. placebo and triptan comparison trials. There were 22 eligible comparison trials of triptan vs. triptan similar to those outlined in **Table 2**.

In trials comparing sumatriptan (SU) 100 mg against other triptans for efficacy endpoints and adverse reactions: zolmitriptan (ZO) 5 mg showed no difference (p=0.7); naratriptan (NA) 2.5 mg showed lower efficacy at 4 hours (p<.001, p=.03) and lower adverse effects (AE) overall (p<.05) in two trials;

Table 1. Pharmacokinetics of triptans[12]

Parameter	Sumatriptan 100mg	Almotriptan 12.5mg	Eletriptan 80mg	Frovatriptan 2.5mg	Naratriptan 2.5mg	Rizatriptan 10mg	Zolmitriptan 2.5mg
C_{max} (ng/ml)	54.0-78.4	49.5	107-190	4.2-7.0	7.8-14.4	20mg	1.3-4.7
t_{max} (h)	1.5-2.3	1.4-3.8	1.0-1.5	2-4	0.8-4.1	1-3	0.5-6.0
$t_{½}$ (h)	2.0	3.0-3.7	3.6-6.9	25	4.5-6.6	1.8-3	1.5-3.6
Bioavailability (%)	14	70-80	50	24-30	63-74	40-45	40-49
Protein binding	14-21	NR	NR	NR	28-31	14	25
Major metabolic enzyme	MAO-A	CYP3A MAO-A	CYP3A4	NR	CYP450	MAO-A	CYP 1A2 MAO-A
Volume of Distribution (L/kg)	2.4-3.3	2.5	2.4	3-4	2.4-2.9	1.3-2.5	7.0-2.3
Clearance (ml/min/kg)	3.5-3.9	8.6	6.6	1.9-3.1	2.7-3.8	3.2-5.3	2.0-3.1
Lipid solubility	Low	NR	High	Low	High	High	High

Table 2. Clinical trials comparing triptans

Trial	Design	Drug/Dose	Results		Conclusion
			Response at 1 h	**Response at 2 h**	
Eletriptan vs. Sumatriptan[14]	DB, PC N =1008	EL 40mg	30%; p<.005 vs. placebo	64%; p<.05 vs. SU100mg	Both doses of EL showed significantly higher rates of sustained response than SU
		EL 80mg	37%; p<.05 vs. SU 50mg	67%; %; p<.05 vs. SU 100mg	Both SU and EL are well tolerated and efficacious for the treatment of acute migraine
		SU 50mg	24%; p<.05 vs. placebo	50%; p<.01 vs. placebo	
		SU 100mg	27%; p=.053 vs. EL 80mg	53%; p<.01 vs. placebo	
Rizatriptan vs. Sumatriptan[19]	R, DB, PC, XO N = 1447	RI 5mg	36.4%; p=0.1 vs. SU 25mg	65.7%; p=.004 vs. SU 25mg	Response at 1 hour was superior in RI 10mg vs. SU 50mg
		RI 10mg	40.5%; p=.04 vs. SU 50mg	68%; p=.29 vs. SU 50mg	Response at 2 hours was superior in RI 5mg vs. SU 25mg
			Second dose required for same headache	**Headache recurrence 4-24 hours after initial dosing**	
Naratriptan vs. Sumatriptan[18]	R, DB, XO N = 253	NA 2.5mg	40%; p < .001 vs SU	45%; NS vs SU	NA showed a difference in the ability to use only one dose for one single acute attack
		SU 100mg	57%	57%	NA was not different from SU in reducing headache recurrence
			Relief at 2 hours	**Headache freedom at 2 hours**	
Almotriptan vs. Sumatriptan[16]	R, DB, PC N = 1255	AL 12.5mg	58%; NS	17.9%; p = .005 vs SU	AL and SU are similarly effective at treating migraine
		SU 50mg	57.3%	24.6%	
			Relief at 2 hours	**Relief at 4 hours**	
Zolmitriptan vs. Sumatriptan[17]	R, DB, PC N = 1445	ZO 2.5mg	67.1%; p<.05 vs. SU 50mg	p<.05 vs. SU 25mg	Both doses of ZO were as effective as both doses of SU
		ZO 5mg	64.8%; p=.064 vs. SU 50mg	p=.01 vs. SU 50mg	ZO 2.5mg was superior to SU 50mg at both 2 and 4 hours

N = number of patients EL=eletriptan, SU=sumatriptan, RI=rizatriptan, NA=naratriptan, AL=almotriptan, DB=double-blind, PC=placebo-controlled, R=randomized, XO=crossover study, NS = not statistically significant

Table 3. Efficacy and tolerability in direct comparison trials [12]

Comparison	Response[a,b]	Pain free[a,c]	Sustained pain free [a,d]	Any-AE [a,e]	CNS-AE [a,f]	Chest-AE [a,g]	Primary endpoint
NA 2.5 mg vs. ZO 2.5mg	1% (-15, 17)	1% (-12, 15)	-	-23% (-37, -8)	-10% (-20, 1)	-9% (-16, -2)	N/A [h]
RI 10 mg vs. ZO 2.5mg	4% (-4, 11)	8% (-0, 15)	9% (1, 16)	-8% (-15, 0)	-6% (12, -0)	-1% (-4, 1)	p=.075
RI 10 mg vs. NA 2.5mg	20% (11, 30)	24% (15, 33)	12% (4, 20)	10% (1, 19)	11% (4, 18)	1% (-2, 4)	p<.001

[a] Direct difference (95% CI); [b] patients with headache response at 2 h; [c] patients with pain free at 2 h; [d] patients with sustained freedom from pain; [e] patients with at least one adverse event (AE); [f] patients with at least one CNS AE; [g] patient with at least one chest AE; [h] comparison not done

rizatriptan (RI) 10 mg was superior in one of 2 studies (p=.03); eletriptan (EL) 40 mg showed superiority in all parameters (p<.05) when two studies were combined; EL 80 mg was superior in two trials on all parameters (p<.01) and when combined (p<.05), but showed more AE when two studies were combined (p<.05); and finally almotriptan (AL) 12.5 mg showed no difference in efficacy.[11-13] Comparing SU 50 mg against other triptans: ZO 2.5 mg is superior in the primary endpoint in one of two trials (p=.02); ZO 5 mg showed no difference in two trials (p=0.8, p=0.6); RI 5 mg showed no difference in three studies except for slightly more AEs; RI 10 mg was significant for the primary endpoint alone (p=.046) in one of two trials; EL 40 mg was superior when two trials were combined (p<.05), but caused more AEs in the combination of trials (p<.05); EL 80 mg was superior in the combination of two trials for all parameters (p<.05), but showed more AEs (p<.05). The meta-analysis evaluated placebo-controlled trials of each triptan product. When the placebo effect was subtracted, the effect of each triptan was remarkably similar to the direct comparison trial results.[11-13]

There are a few trials in the literature which

Table 4. Currently available FDA approved triptans

Generic	Manufacturer	Brand	Formulations	Standard dosing
Sumatriptan	GlaxoSmith-Kline	Imitrex®	Tablets	25-100 mg (Max dose 200 mg daily)
			Nasal spray	5-20 mg (Max dose 40 mg daily)
			Subcutaneous injection	6 mg (Max dose two 6 mg injection in 24-48 hours)
Zolmitriptan	AstraZeneca	Zomig®	Tablets	Up to 2.5 mg per dose (Max dose 10 mg daily)
		Zomig-ZMT®	Orally disintegrating tablets	Up to 2.5 mg per dose (Max dose 10 mg daily)
		Zomig®	Nasal spray	5 mg daily (Max dose 10 mg daily)
Rizatriptan	Merck	Maxalt®	Tablets	5-10 mg per dose (Max dose 30 mg daily)
		Maxalt-MLT®	Orally disintegrating tablets	5-10 mg per dose (Max dose 30 mg daily)
Naratriptan	GlaxoSmith-Kline	Amerge®	Tablets	1 or 2.5 mg per dose (Max dose 5 mg daily)
Almotriptan	Ortho-McNeil Neurologics	Axert®	Tablets	6.25-12.5 mg daily (Max dose 25 mg daily)
Eletriptan	Roerig Division of Pfizer	Relpax®	Tablets	20 or 40 mg per dose (Max dose 80 mg daily)
Frovatriptan	Endo Pharmaceuticals	Frova™	Tablets	2.5 mg per dose (Max dose 7.5 mg daily)

Table 5. Cost of triptans per dose

Pharmacy	SU 50mg	SU 100mg	ZO 2.5mg	ZO 5mg	RI 5mg	RI 10mg	NA 2.5mg	AL 12.5mg	EL 40 mg	FR 2.5mg
Chain	$23.50	$24.30	$15.70	$16.60	$23.10	$23.10	$24.50	$21.30	$25.10	$24.30
Discount	$23.45	$23.45	$21.03	$22.94	$22.44	$22.44	$26.67	$21.73	$22.14	$22.54
Independent	$22.62	$22.62	$25.81	$25.89	$29.97	$29.97	$27.50	$28.40	$25.54	$23.72
Average	$23.19	$23.46	$20.85	$21.81	$25.17	$25.17	$26.22	$23.81	$24.26	$23.52

compare triptans, where the comparator is not sumatriptan. ZO 2.5 mg was compared to NA 2.5mg and found to be comparable in relief at 4 hours. RI 10 mg did not reach statistical significance in response against ZO 2.5 mg. However, RI 10 mg was superior to NA 2.5 mg in all parameters, but caused more AEs (**Table 3**).[12]

Based on triptan comparison trials, recurrence rates, adverse effect profiles, or quicker time to relief may differ between agents. However, this usually comes at a cost.[2] For instance, eletriptan has one of the highest rates of efficacy, but it also has a slightly higher rate of treatment-related adverse events.[14]

Adverse Reactions

Overall, the triptans as a class are well tolerated. Most patients who discontinue triptans do not do so due to adverse reactions. The more common adverse reactions include fatigue, dizziness, paresthesias, warm sensations, and chest, neck, and throat tightness.[8] However, there is a safety concern with triptans in heart disease. Triptans may cause significant coronary vasoconstriction in patients with coronary artery disease, uncontrolled hypertension, or those with other cardiac risk factors. Triptans have been used extensively in the last decade, and history has shown that this risk is minimal. The 5-HT_{1B} receptors are present at a higher density in the meningeal arteries than the coronary arteries, which produces the differential vasoconstrictive selectivity of the triptans. There is no safe triptan in the presence of significant vascular disease; however, in the absence of vascular disease, the triptans appear to be relatively safe.[15, 20]

Dosing

Standard dosing for each product is listed in **Table 4**.

Cost

All triptans, which are migraine-specific agents, are effective treatment options in acute migraine. However, since some differences amongst agents have been noted, price should also be included in this analysis. Price was solicited from three different types of pharmacies: chain retail, discount, and independent. The price at each location for a dose and the average of all three locations for each triptan is listed in **Table 5**.

Summary

Triptans have been used for nearly a decade, and have proven to be a valuable asset in treating patients with acute migraine. This class of drugs is typically used to treat migraine in patients who have not responded to traditional analgesics. They work to combat the pathogenesis of acute migraine by stimulating 5-$HT_{1B/1D}$ receptors to produce vasoconstriction of severely dilated cranial blood vessels, decrease release of vasoactive neuropeptides, and inhibit pain transmission centrally. Clinical trials comparing triptans show some statistically significant results for one product over another for certain endpoints; however, there is not enough consistent evidence to suggest that any one triptan is superior.

As noted earlier, each product has its own clinical strengths and weaknesses, and selecting a triptan should be patient specific and tailored to optimize these differences.

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