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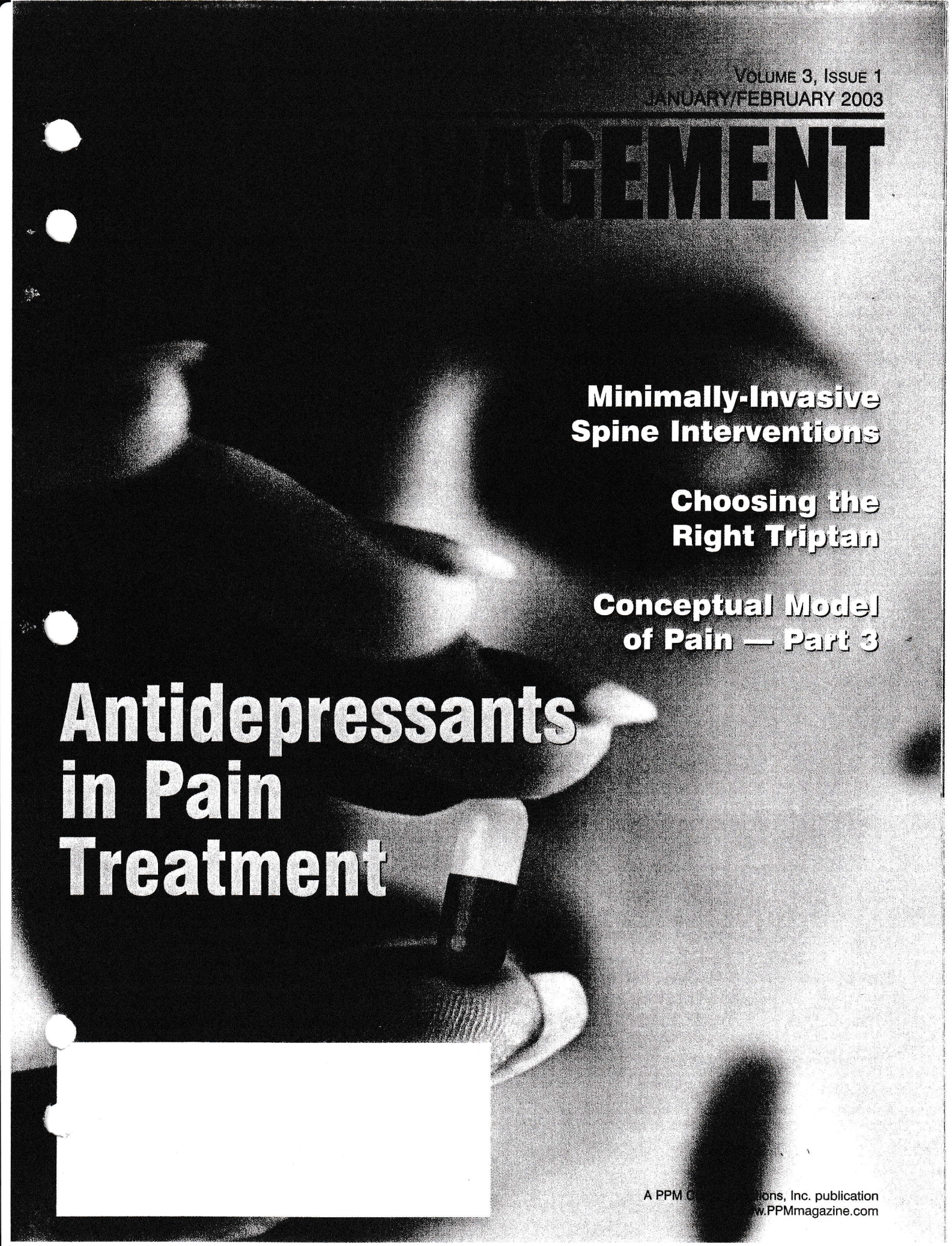

Minimally-Invasive Spine Interventions

Choosing the Right Triptan

Conceptual Model of Pain — Part 3

Antidepressants in Pain Treatment

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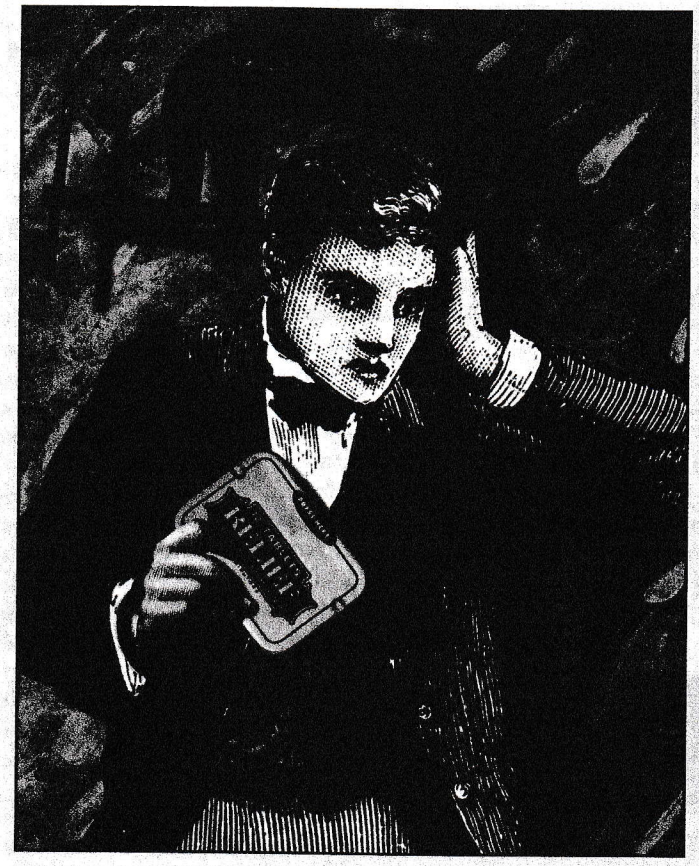

CHOOSING THE RIGHT TRIPTAN

Discussion of current triptan options in the treatment of migraine.

by Randall Lee Oliver, MD and
April Taylor, RN, BSN

Five years have elapsed since the advent of triptan options as the treatment of choice for migraine.[1,2] With the vast clinical experience gained over this period, it is useful to review triptan delivery, efficacy, and dosage for the wide variety of migraine presentations.

There are currently six triptans available on the US market. They are — in the order of their introduction — Imitrex, Maxalt, Zomig, Axert, Frova, and Amerge. Available dosages and manufacturers are listed in Table 1.

Available in Europe, and possibly soon in the U.S., is eletriptan in 80mg tablets from Pfizer.

With the notable exception of Imitrex nasal spray and Imitrex injectable, which have an increased percentage of efficacy over any pill, the efficacy rates between all of the pills — comparing dose to dose — are roughly the same with only minor variation. In general, when one combines most of the studies done on various triptans in comparing equal doses of the oral agents, they all seem to work in the 40 to 60% range. While most triptans seem to work with statistically equal efficacy, there does seem to be a variance in the individual preference for triptans.

The triptan class contains three categories: the ultra fast or immediate acting, the fast acting, and the slow acting/long lasting triptans (see Table 2).

Imitrex injectable is the only ultra-fast acting triptan and has a 70% response rate. The fast acting triptans are the traditional triptans: Imitrex tablet and nasal spray, Maxalt, Zomig, and Axert. The slow acting/long lasting triptans are Amerge and Frova. We now have a wide range of treatment options for the many presentations of migraine. Imitrex injectable is for the migraine that needs to be stopped as quickly and completely as possible. Frova and Amerge are for the long lasting migraine and the traditional triptans for the rest.

Following are discussions of clinical observations for each of the triptans identified above.

Imitrex

Imitrex has the advantage of coming with the most widely diverse dosage forms and delivery systems. The nasal spray and the injectable offer alternatives for the nauseated or migraine patient with actual emesis. There is certainly no doubt that the subcutaneous form of Imitrex is the triptan that works the quickest and is most generally effective. It has a 70% efficacy at a one hour response rate compared to a two-hour response rate for all the others. Another advantage is that you can move between the dosage forms. There is allowance for individual migraine variation between individual patients. For instance, one can use an Imitrex tablet for mild headaches or headaches having slow onset with the option of switching to an Imitrex nasal spray if the headache onset accelerates or has more nausea associated with it. Imitrex injectable can be used if the headache is coming on rapidly, the patient is vomiting, or if a break-through headache occurs with tablet use. When Imitrex pill or nasal spray is used as a starting dose, Imitrex allows the option of a follow-up with Imitrex injectable in the event that the headache does not respond or worsens. Note however that the FDA has not approved mixing Imitrex injectable with any other triptan so that Imitrex injectable is not an option if a different triptan was used as the starting dose. The only option in this case is to utilize

Triptans Available on the US Market		
Name	**Company**	**Available Dosages**
Imitrex (sumatriptan)	Glaxo-Smith Kline	25mg, 50mg and 100mg tablets 5mg and 20mg nasal spray 6 mg subcutaneous injectable
Maxalt (rizatriptan)	Merck	5mg or 10mg tablets orally-dissolving tablet
Zomig (zolmitriptan)	Astra Zeneca	2.5mg and 5mg tablets orally- dissolving tablet
Axert (almotriptan)	Pharmacia	6mg and 12.5mg tablets
Frova (frovatriptan)	Elán	2.5mg tablets
Amerge (naratriptan)	Glaxo Wellcome	1mg and 2.5 mg tablets

TABLE 1.

Triptan Categories and Uses		
Category	**Usage**	**Triptan**
Immediate acting/ultra fast	Quick onset; severe pain	Imitrex Injectable
Fast acting	Moderate onset; moderate pain	Imitrex nasal/oral Axert Maxalt oral/melt Zomig oral/melt Eletriptran
Slow onset/long acting	Slow onset; long duration; menstrual; prodrome	Frova Amerge

TABLE 2.

medication outside of the triptan class. Disadvantages of Imitrex include side effects and recurrence rate. The side effects, however, typically last only 30 minutes. The Imitrex pill has a 40% chance of side effects, which is greater than other triptans with the exception of eletriptan 80 mg. The recurrence rate of the Imitrex injection is 35-50% and for the Imitrex oral is 25-40%. Table 3 summarizes the advantages/disadvantages of Imitrex.

Maxalt

Maxalt does show some evidence of having a somewhat quicker onset of action than Zomig and Imitrex oral. (Some response at 30 minutes) However, it is still much slower than the Imitrex injectable. This may be due to its quicker T_{max}. This, however, may lead to a greater incident of headache recurrence. All triptans combined have a recurrence rate of 20-45%, while Maxalt has a 29-47% recurrence rate.[3] There is some confusion surrounding the oral dissolving preparation. Some physicians and patients think it is absorbed in the buccal surface and has a faster onset. Actually both the orally absorbing tablet and the pill are absorbed through the GI tract. There is some evidence that the orally dissolving tablet has a slower onset of action than the non-dissolving tablet. The benefit of the melt tablets is convenience. It is easier to use if the patient is nauseated or does not have water available to follow the pill. Of interest is that sniffing with the Imitrex nasal spray, while also contributory to the bad taste effect, changes the absorption to the GI route. This slows the onset of efficacy compared to the nasal route. Table 4 summarizes the advantages/disadvantages of Maxalt.

Zomig

Zomig offers some diversity in that it is offered in a pill, melt and soon in a nasal spray. On the other hand, Zomig offers no advantage in side effect profile, onset of action or recurrence rate. When initially released, Zomig was characterized as being able to cross the blood/brain barrier easier than Imitrex or Maxalt, and as a result, might have a greater efficacy or speed of efficacy. This effect has proven not clinically significant in studies. Reasons for this may be two-fold. First, crossing the blood/brain barrier may not be important in control of migraines. Action at the $5HT_{1B}$ receptor is in the blood vessels.[4] The $5HT_{1D}$ receptor is located on the intracranial branch of the trigeminal nerve. A recent study tested a drug that only agonized the $5HT_{1D}$ receptor[3] and it showed no effect on migraine. Hence, action at the trigeminal nerve (across the blood/brain barrier) may not be as important. Secondly, the blood/brain barrier seems to change during the migraine attack making all triptans equally effective at crossing the blood/brain barrier during the actual migraine event.[5] Table 5 summarizes advantages/disadvantages for Zomig.

Axert

Axert has a quick onset and action similar to Maxalt and eletriptan with a response time of 30 minutes. It also has a low incidence of side effects, particularly a much less incidence of chest pain. It should be mentioned that the chest pain associated with triptans is usually non-cardiac. It is either due to abnormalities in the chest wall or the esophagus, but not due to any process involving the heart. However, Axert may be a good alternative for a patient's piece of mind. Axert also does seem to have some decreased incidence of recurrence as compared to all three of the above and is available in 6 mg and 12.5 mg doses. Table 6 summarizes the advantages/disadvantages of Axert.

Eletriptan

Eletriptan has a fast onset similar to Axert and Maxalt with response within 30 minutes. It has superior efficacy to Imitrex 100mg at 40 and 80mg doses. Its mode of elimination means one must be careful in

IMITREX	
Subcutaneous Fastest onset Most effective	Most side effects
Nasal/Oral Can be combined with injectable Nasal spray used in nausea	

TABLE 3.

MAXALT	
Quickest pill onset Melt for nausea or convenience	Recurrence Propanolol warning

TABLE 4. *Summary of advantages and disadvantages of Maxalt.*

ZOMIG	
Melt for nausea or convenience	none noted

TABLE 5. *Summary of advantages and disadvantages of Zomig.*

AXERT	
Quickest onset Low recurrence Low side effects	none noted

TABLE 6. *Summary of advantages and disadvantages of Axert.*

ELETRIPTAN	
Low recurrence	Side effects Medication interaction

TABLE 7. *Summary of advantages and disadvantages of Eletriptan.*

FROVA	
Extremely long half-life Low recurrence Prophylactic use Early onset use Low side effects	Slower onset Lower overall efficacy

TABLE 8. *Summary of advantages and disadvantages of Frova.*

AMERGE	
Low recurrence Prophylactic use Early onset use Low side effects	Slower onset Lower overall efficacy

TABLE 9. *Summary of advantages and disadvantages of Amerge.*

mixing it with certain medications such as erythromycin antibiotics and certain antifungals. It has the greatest amount of side effects of any of the triptan pills, even greater than Imitrex 100mg. Side effects at 20 mg occur in 34% of patients; at 40mg, 35%; and at 80mg, 51%. It is essentially a faster, more effective Imitrex with more side effects and medication interactions. Table 7 summarizes the advantages/disadvantages of Eletriptan.

Frova

Frova's main advantage is its extremely long half-life of twenty-four hours. The negative side is its speed of onset. It is slow (about 3 hours)[3] compared to Imitrex, Maxalt, Zomig, Axert, and Eletriptan. When it finally does kick in, there seems to be a decreased recurrence rate. However, when compared in at least one head to head study with Amerge, there was no difference in recurrence rate. While, it may still offer some advantage in the patient for whom recurrence is a factor, it is most appropriate for the patient having a slow onset of headache. It may also have a place in the treatment of migraine with prodrome. Frova might show a benefit, if taken prior to the actual headache, for those migraineurs who have a warning or sense of an imminent migraine.[6] At least one study also shows benefit in menstrual migraine.[6] Frova's nitch is the slow onset, long lasting, recurring headache or the early-on predictable migraine (prodrome). Table 8 summarizes the advantages/disadvantages of Frova.

Amerge

Amerge was specifically developed to have a low incidence of side effects. Because the dose that causes low incidence of side effects also causes slower onset of action, it is generally one of the least effective triptans, yet, similar to Frova, it is an option when a slow onset/long acting triptan is indicated. It has lower recurrence rate (17-28%) than any of the above except for Frova, making it a good agent to use where recurrence is a problem. Because of its long duration of activity (approximately twelve hours) it can also be used in a prophylactic manner. For patients who wake up with early morning headaches, it can be taken at bedtime to help ward these off.[6] For certain people with long acting headaches such as a menstrual migraine; it can be taken every twelve hours for three to four days during this cycle to help decrease these long acting migraines. It can also be used in migraine with prodrome or advanced warning. A recent study comparing Frova and Amerge, both given at bedtime in advance of migraine, showed efficacy in decreasing migraine intensity and frequency the following day. The patients generally preferred Amerge to Frova for decreasing both migraine incidence and severity the following day.[6] Amerge, however will generally be little help for migraines having moderate of quick onset or moderate or severe intensity. Table 9 summarizes the advantages/dis-

Triptans Available on the US Market								
	Imitrex Injectable	Imitrex	Maxalt	Axert	Electripan	Zomig	Amerge	Frova
Speed of Onset	▲▲▲	▲	▲▲	▲▲	▲▲	▲	●	●
Recurrence	▲▲▲	▲▲	▲▲▲	▲▲	▲▲	▲▲	●	●
Side Effects	▲▲▲	▲▲	▲	●	▲▲▲	▲▲	●	●
Forms	injectable	pill, melt, nasal	pill, melt	pill	pill	pill, melt	pill	pill
Interactions			propanolol		erthromycins, antifungals, Claritan			
▲▲▲ most ▲▲ significant ▲ minor ● least								

Table 10.

Equipotent Dosing of the Triptans						
Imitrex	Maxalt	Axert	Electripan	Zomig	Amerge	Frova
6mg injectable	—	—	—	—	—	—
20mg NS	—	—	—	—	—	—
100mg	—	—	80mg	—	—	—
50mg	10mg	12.5mg	40mg	5mg	2mg	2.5mg
25mg	5mg	6mg	20mg	2.5mg	1mg	2.5mg

Table 11.

advantages of Axert.

Discussion

Triptan attributes vary from one formulation to another. The variety allows selection of a triptan that works best for a particular patient with a particular migraine presentation. Table 10 summarizes triptan attributes relative to speed of onset, recurrence, side effects, dosage forms, and drug interactions. It has been found that a migrainer, having failed one, two, or even three of the available triptans on the market, may still find success with the one of the remaining triptans. It is advisable to try each of the available triptans before a patient is deemed "triptan failure."

A stratified approach versus the step approach is preferable.[8] The Disability in Strategies of Care (DISC) Study showed that physicians should choose a drug according to MIDAS scores[9] and accordingly prescribe migraine treatments according to severity. This is opposed to attempting OTC's, then metoclopramide, and then oral triptans and eventually working up to the Imitrex injectable. The stratified approach skips the early steps in a person that clearly meets criteria for a triptan and possibly the injectable form and avoids the frustration of the physician and patient when the initial inadequate medication fails.

"Most migraine specialists will relate instances where they have tried several oral triptans without success, but found a third or fourth triptan, which did give the patient relief."

It is important to use equipotent dosages when comparing triptans and, before a particular triptan can be considered a failure, use the maximum dose and most effective route (see Table 11). Certainly do not deem the patient a triptan failure until having tried the "Gold Standard" which is the Imitrex injectable form.

In evaluating different triptans for efficacy, it is necessary that a single triptan be utilized for a minimum of two or three headaches[10] for accurate assessment. Such trials should be initially matched to a migraine's particular presentation (speed of onset, severity, etc.) and applied at the appropriate stage in the course of a migraine. For example, trying any one of the oral tablets with a severe headache late in its course is not going to be comparable to Imitrex injectable early in the course of a mild migraine. Research has shown that early treatment in the migraine, possibly even with prodrome, means the patient is more likely to achieve complete relief and no recurrence.[6,10]

Summary

The current choice of triptans gives the practitioner multiple options in addressing varying migraine presentation and patient preference.

Imitrex may be used for a patient who has both slow onset and quick onset of migraines. One might use Imitrex prepara-

(continued on page 37)

(continued from page 18)

tions for a patient for whom a pill sometimes works but often times needs rescuing with Imitrex injectable. For patients preferring an orally dissolving tablet, Maxalt or Zomig are options. Among the oral preparations, Maxalt, Axert and Eletriptan may have the possible advantage of fastest onset. Axert, Frova and Amerge have the advantage of offering the lowest side effect profile in patients with side effect problems. Frova and Amerge offer advantages if the patient has problem with recurrence and if the headaches have slow onset. Both might also have advantages in prophylactic settings or migraines with prodrome.

There are some unpredictable or idiosyncratic differences among the triptans. A recent study comparing Maxalt MLT to Zomig ZMT (orally dissolvable preparations) found equal patient preference between the two. Of the patients that expressed a preference of one or the other, the preference was not necessarily based on an identifiable reason such as speed of onset, general efficacy or side effect pattern. In short, there was no singular identifiable trait that patients preferred between them. Rather the individual triptan preference seemed to be totally random, although roughly equal.[7]

Most migraine specialists will relate instances where they have tried several oral triptans without success, but found a third or fourth triptan, which did give the patient relief. A small study of Imitrex oral-failure patients were given Maxalt or Zomig. Researchers found a response rate of 70-80% of the 30% who failed Imitrex. Therefore, while any one triptan has a total response rate of 70%, combining all triptans yields a total response rate in the range of 90%. ■

Dr. Oliver is Medical Director of the Oliver Headache & Pain Clinic, a regional pain center in Evansville, IN, and President of the Indiana Pain Academy. He regularly lectures, writes, does research and conducts seminars on multidisciplinary pain management. He can be contacted at Oliverclinic@cs.com.

April Taylor is a research writer on multiple projects for Dr. Oliver. She is also a diabetes nurse educator for critical cardiac care patients at Methodist Hospital, Indianapolis, Indiana.

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