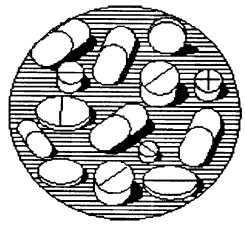
OREGON DUR BOARD NEWSLETTER



Vol. 1 No. 2 October 1998

NEW DRUGS: ACUTE MIGRAINE THERAPY REVIEWED

By: Myke Green and Ann Hamer, Pharm.D. Candidates
Dean Haxby, Pharm.D., Michele Koder, Pharm.D.

Five new products have recently become available for the abortive treatment of moderate to severe migraine headaches. Zolmitriptan (Zomig, *Zeneca*), naratriptan (Amerge, *Glaxo-Wellcome*), and rizatriptan (Maxalt, *Merck*) are oral selective serotonin receptor agonists that are structurally similar to sumatriptan (Imitrex®, *Glaxo-Wellcome*). In addition, two nasal spray formulations of older drugs, sumatriptan (Imitrex) and dihydroergotamine (Migranal, *Novartis*) are now available. The purpose of this article is to provide a brief review of these new products and evaluate their place in abortive migraine therapy.

Mechanism of Action – Zolmitriptan, naratriptan, and rizatriptan have the same mechanism as sumatriptan and bind selectively to 2 distinct serotonin (5-HT) receptors, specifically 5-HT1B and 5-HT1D. Agonism of these serotonin receptors results in vasoconstriction of dilated cranial vessels and inhibition of inflammatory neuropeptide release. Dihydroergotamine (DHE) has a similar mechanism, but it is a non-selective 5-HT1 receptor agonist that also binds to alpha and beta adrenergic receptors and dopamine receptors. The clinical significance of binding to the other receptors is not substantial, but may explain a reduced effect on alleviating nausea associated with migraine headaches.

Effectiveness – All of these new products are significantly more effective than placebo. Table 1 presents effectiveness data from various clinical trials with these new products. Since there is limited data from comparative clinical trials, caution is warranted when interpreting and comparing effectiveness results from different clinical trials as presented in Table 1. While there does not appear to be important differences in peak effectiveness among these products, there are differences in onset, time to peak effect, and recurrence of headache within 24 hours of dosing.

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—— DUR Board Vacancies ——

The Oregon Drug Use Review (DUR) Board has three immediate openings. The DUR Board meets quarterly to review and make recommendations on the Prospective and Retrospective drug use review programs administered by the Office of Medical Assistance Programs (OMAP).

Interested persons need expertise in one or more of the following: 1.) clinically appropriate prescribing of outpatient drugs covered by the medical assistance program; 2.) clinically appropriate dispensing and monitoring of outpatient drugs covered by the medical assistance program; 3.) drug use review, evaluation and intervention; or 4.) medical quality assurance.

Interested persons may inquire by phone (503) 494-1589, or submit a CV to Kathy L. Ketchum at:

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LIMITING GI COMPLICATIONS ASSOCIATED WITH NSAID USE

By Ann Hamer, Pharm. D. Candidate

Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed daily for about 1% of the population.[1] They are one of the most commonly prescribed groups of drugs. These drugs are associated with a large percentage of reported adverse drug reactions.[2] The Oregon RetroDUR program has noted an increase in the numbers of GI diagnoses associated with patients prescribed multiple NSAIDs or on extended NSAID therapy.

The types of injury associated with NSAID use include buccal ulceration, reflux esophagitis, esophageal strictures, non-ulcer dyspepsia, and peptic ulcer. Ulcers were noted to form in the stomach, duodenum, jejunum, ileum, and colon. Endoscopic studies show gastric ulcers occur more frequently than duodenal ulcers. Ulcers develop in as many as 20% of NSAID users.[3] It is reported that NSAID users have a three-fold greater risk of developing severe adverse GI events (bleeding or perforation) than nonusers.[2,4] Risk factors for NSAID-induced GI damage are shown in Table 1.

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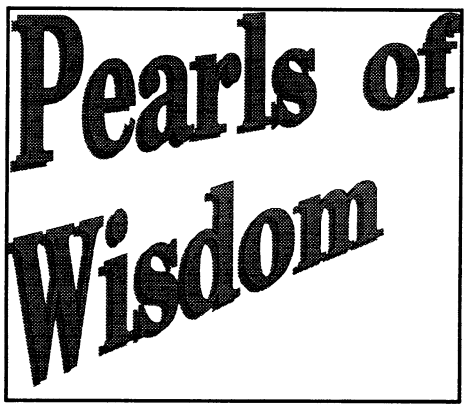

PHARMACIST COUNSELING THE DIABETIC PATIENT ON BETA-BLOCKERS

By Cynthia Wong, Pharm.D. Candidate

The Oregon DUR Board recently reviewed drug interaction ProDUR criteria for beta-blockers and decided to retain the insulin/beta-blocker alert for non-selective beta-blockers. At issue was the recognition that beta-blockers are largely under-utilized in the diabetic population. The Board considered this an excellent opportunity for pharmacists to counsel insulin-dependent diabetic patients on this clinically important interaction.

Systemic and topical (ophthalmic) beta-blockers are capable of "masking" or "blunting" the adrenergic response to hypoglycemia. Beta-blockers alter some symptoms of hypoglycemia caused by the release of catecholamines.[1] The symptoms of hypoglycemia (i.e. increased heart rate, palpitations, shakiness, tremors, and nervousness) can be attenuated by beta-blockers. Thus, the insulin-dependent diabetic patient may not be aware of the low blood glucose until they are dangerously hypoglycemic. Other signs (i.e. irritability, nausea, and hunger) are unlikely to be affected by beta-blockers. Sweating and hypertension may actually increase on beta-blockers.[1]

The cardioselective beta-blockers (i.e. atenolol) are preferred over the non-selective beta-blockers (i.e. propranolol) because they affect heart rate, blood pressure, and duration of hypoglycemia to a lesser degree. However, even the cardioselective beta-blockers attenuate some of the symptoms of hypoglycemia. While the reactions are rare, they can be severe, and counseling the non-insulin and insulin-dependent diabetic patient on what to expect while taking a beta-blocker is definitely warranted. ■

Reference

1. Mills, GA, Horn, JR. B-Blockers and Glucose Control. Drug. Intell Clin Pharm 1985;19:246-251.

Important Counseling Tips:

1) Use this opportunity to remind patients on the importance of regular monitoring of their blood glucose levels.

2) Help the patient distinguish between symptoms of hypoglycemia and hyperglycemia. Ask them how they feel when either occurs. This will increase their awareness and help them determine their unique responses to hypoglycemia or hyperglycemia.

3) Individual patient responses during hypoglycemic episodes vary, as do the responses to beta-blockers. Tell patients that they may or may not experience an increase in heart rate, palpitations, shakiness, tremors, and nervousness once started on a beta-blocker. If they usually get irritable, diaphoretic, hungry, or nauseated tell them that these symptoms are usually NOT attenuated by beta-blockers.

4) Suggest to the patient to increase their awareness of how they feel when they record "low" glucose levels which would have been symptomatic before they started the beta-blocker. And, insure the patient knows when and how to treat hypoglycemia.

5) Be sure to counsel patients with any change or dose increase of beta-blockers. Cardioselective beta-blockers at increased doses start to lose selectivity. Remember, ophthalmic beta-blockers are often systemically active.

■ **NSAID Use**, continued from page 1

TABLE 1.

Risk Factors for NSAID-Induced GI Damage

- Use of multiple NSAIDs
- Male Gender
- Smoking
- Alcohol
- Age >60 years
- History of GI bleed or Peptic Ulcer Disease
- Concurrent use of corticosteroids

GI injury is the result of two distinct mechanisms. The first is local irritation caused by back diffusion of acid into the GI mucosa that can induce tissue damage.

The second mechanism is via the inhibition of prostaglandin synthesis and occurs with both the parenteral and oral administration of these drugs. [5] Damage can be correlated to the biosynthetic inhibition of GI prostaglandins, especially PGI2 and PGE2. These prostaglandins are cytoprotective agents in the GI mucosa.

GI damage caused by NSAIDs can be minimized with preventive measures (Table 2). High risk patients should be dissuaded from using alcohol and smoking cigarettes. Patients should use the lowest effective dose of NSAID. Multiple NSAID use is not advised. There is no advantage gained by using different drugs within this class at lower doses. OTC use by patients should be addressed. Treatment duration should be minimized. [5,6]

TABLE 2.

Preventive Measures to Reduce NSAID-Induced GI Damage

- *Decrease use of alcohol and cigarettes*
- *Use a single agent rather than multiple NSAIDs*
- *Use lowest effective dose of NSAID*
- *Add prophylactic therapy*

The efficacy of prophylactic therapy to prevent GI events is disputable. The studies generally use endoscopic endpoints rather than actual events (bleeding or perforation). Misoprostol, a synthetic prostaglandin, is dosed at 400 - 800 micrograms daily. Its use is limited by abdominal side effects including diarrhea and abdominal cramps. Side effects may be limited by using the lower dosage, but so may its efficacy.[1]

Other potential prophylactic treatments include H2-blockers and proton pump inhibitors. Anti-secretory therapy with H2-blockers to prevent NSAID-induced ulcers requires high doses and is not conclusively proven effective.[1,6,7] Prophylactic use of proton pump inhibitors continue to be studied.[8,9]

In comparative studies, there is little evidence that one NSAID is more effective than another. The deciding factor becomes the relative risk of inducing GI damage. Several studies have been done to determine the toxicity potential of various NSAIDs, but they have been largely inconsistent or inconclusive.[10]

NSAIDs work by inhibiting cyclooxygenase (COX), a critical group of enzymes in the biosynthesis of prostaglandins. The majority of NSAIDs are reversible, non-selective, competitive inhibitors of COX activity. Two isoforms of COX exist, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is found in blood vessels, stomach, and kidney tissue and has maintenance functions. COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators. Theoretically, selective inhibitors of COX-2 will play a role in the prevention of inflammation while preserving the protective functions of COX-1.[4] This hypothesis, however, has yet to be proven with the currently available drugs.

Over 70 million prescriptions for NSAIDs are written each year in the United States. This widespread exposure makes NSAID-induced GI mucosal injury one of the leading drug-induced adverse effects.[10] Until better options are available, avoiding all NSAID use in high-risk patients is advisable. If acetaminophen or salsalate are not viable alternatives for high-risk patients, the use of preventive measures (limited NSAID exposure) may reduce the risk of developing GI side effects. Prophylactic therapies may be tried if the other options have failed. ■

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SUGGESTIONS FOR MANAGING INSOMNIA

By Michele Koder, Pharm.D.

Three questions need to be asked when considering drug therapy for insomnia. First, is there a true indication for drug therapy? Second, is the drug dosed appropriately and is the dose adjusted when indicated? Third, is there an indication to treat longer than four weeks?

To address the first question, it is essential to rule out potential secondary causes of insomnia including concurrent medical conditions or their treatment; the use of alcohol, caffeine, or nicotine; psychiatric, mood, or anxiety disorders; stress; myoclonus; and disorders in circadian rhythms, breathing, or sleep behavior.[1,2] Providers should consider the type and cause of insomnia when establishing treatment goals and forming a therapeutic plan. The primary goal is to improve daytime functioning. In some patients, educational and behavioral therapy may be sufficient to treat the underlying problem. (Table #1) In others, pharmacotherapy may be necessary. Benzodiazepines are currently the mainstays of pharmacotherapy for insomnia, however, use of zolpidem and antidepressants such as trazodone, amitriptyline, and doxepin is increasing.[3]

TABLE 1:

Behavioral Modifications[3]

1. Limit or stop caffeine, nicotine and alcohol
2. Go to bed and rise at relatively constant times.
3. Avoid exercising in the latter part of the day.
4. Avoid daytime naps.
5. Avoid heavy meals before bedtime. Do have a light snack.
6. Avoid "worrying" in bed. Try writing down worries to pick up in the morning.
7. Limit the time spent in bed.
8. Not all rules work for everyone. Experiment to find a combination that works.

Treatment Guidelines:

Sedative/Hypnotic Use in Sleep Disorders[1-12]

1. Use in combination with educational and behavioral interventions that focus on stimulus control (behaviors that disrupt sleep) and temporal control (stabilization of the sleep-wake cycle).
2. Individualize drug selection, i.e. selection of a pharmacologic agent should be based on each individual patient's chief sleep symptom (increased sleep latency, frequent nocturnal awakenings, decreased total sleep time), age, concomitant diseases (e.g. renal and hepatic impairment), abuse potential, lifestyle (social and work schedule), ability to adhere to the regimen, and anticipated duration of use.
3. Use the lowest effective dose of the appropriate agent. In most trials evaluating the usefulness of benzodiazepines for the treatment of sleep disorders, inclusion criteria resulted in patients with more severe, chronic insomnia who required high doses. Many patients may derive benefit from lower doses that offer the advantage of decreased adverse effects. When benzodiazepines are used in the elderly, the dosage should be decreased because equivalent effects can be achieved at half the dose normally administered to younger patients.
4. Use intermittent dosing (two to four times per week) to reduce the development of tolerance.
5. Prescribe only for short-term use, i.e. no greater than two to four weeks. At this time, reassess the patient's sleep disorder.
6. Educate the patient on the intended duration of therapy (i.e. the treatment plan), the potential side effects of the chosen agent, and what to expect.
7. Discontinue the agent gradually to avoid withdrawal symptoms. It is important to educate the patient on how to recognize this condition and the appropriate action to take should it occur. These symptoms range from mild dysphoria, abdominal and muscle cramps, vomiting, sweating, and tremor to convulsions. Withdrawal symptoms most often occur when benzodiazepines are discontinued abruptly in patients receiving excessive doses over long periods of time (10 to 16 weeks). Symptoms typically are mild during the first several days, then peak on the 5th to 9th day. Treatment options include re-administration of the benzodiazepine or administration of a substitute.
8. Following discontinuation, monitor the patient for rebound insomnia characterized by recurrence of insomnia to levels worse than before treatment began. Rebound insomnia usually follows abrupt withdrawal and occurs within the first 1 to 3 nights following discontinuation. This phenomena is less likely to occur with long-acting agents such as flurazepam and quazepam because the long half-lives of their active metabolites provide a gradual taper upon discontinuation and can be minimized by using the lowest effective dose and tapering the dose upon discontinuation.
9. Agents with shorter half-lives are generally preferred in order to minimize daytime sedation (particularly in the elderly.)[1]

If behavior modifications are not successful and it is decided to begin pharmacotherapy, choice of the best agent and appropriate dose are the next considerations. (See treatment guidelines.) Results from a recent cross-sectional analysis of "The Cardiovascular (CV) Health Study" (a community based, prospective, observational study of CV disease and stroke) indicates Medicare patients are frequently overdosed.[5,6] In this study, median doses of triazolam, temazepam, and flurazepam prescribed to Medicare patients aged 65 and older were 0.25 mg/d, 15 mg/d, and 30 mg/d respectively. The Oregon Pro DUR data is consistent with this report.

It is well-known that many factors related to aging can alter benzodiazepine safety and efficacy in this population. These factors include alterations in drug pharmacokinetic and pharmacodynamic parameters (reduced drug clearance, increased drug sensitivity, increased percentage of adipose tissue, changes in plasma protein binding), the presence of concomitant diseases, polypharmacy, and changes in diet and exercise that often occur with the aging process.[7]

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■ **INSOMNIA**, cont'd from Page 4

The consequences of overdosing, including prolonged sedation, dependence, withdrawal, and cognitive and psychomotor impairment, are often problematic in this population. In addition, overdosing of benzodiazepines in the elderly place them at risk for falls, hip fractures, and auto accidents.[1,5] This is especially evident with the long-acting agents such as flurazepam. To ensure the safety and efficacy of benzodiazepine hypnotics, please refer to the dosing guidelines in Table 2.

Finally, what is the appropriate length of treatment? A 1997 meta-analysis of 22 placebo-controlled, double-blind studies evaluated the use of benzodiazepines and zolpidem in 1,894 middle aged patients for efficacy in four areas (sleep-onset latency, total sleep time, number of awakenings, and sleep quality).[4] The authors concluded that the benzodiazepines as well as zolpidem were superior to placebo for the treatment of short-term (mediation duration=7 days, range=4 to 35 days) insomnia. Because of a relative deficiency of comparable longitudinal and controlled clinical trials with follow-up data, common outcomes, and uniform definitions of treatment response, the authors were unable to evaluate benzodiazepine or zolpidem use beyond 4 weeks (chronic insomnia). In fact, the authors conclude these agents can not be recommended for the routine treatment of chronic insomnia, without more tangible data. The National Institutes of Health (NIH) has also recognized the lack of data supporting the use of these agents in chronic insomnia. As a result, in 1984 the NIH Conference on Sleeping Pills and Insomnia developed recommendations advising against their use for longer than 4 weeks.[8] The RetroDUR program has sent approximately 50 letters to providers in the last year concerning the long-term use of benzodiazepines.

Extended length of therapy is of particular concern in the elderly population where benzodiazepine hypnotics and related agents have less safety and efficacy testing.[1,5,7] In 1998, patients over 60 years, received 49% of all benzodiazepine prescriptions.[6]

TABLE 2: Sedative/Hypnotic Dosing and Pharmacokinetics [7,10,12,13]

Drug	Recommended Dose (mg/d)		Duration of Action*	Time to Onset (min.)	Quantity	Cost to OMAP✣
	Adult	Geriatric				
Triazolam ❶	0.125-0.25mg	0.125mg	Short	15-30	#14	$6.80 - 7.40
Zolpidem	10mg	5mg	Short	30	#14	$22.15 - 27.25
Temazepam	15-30mg	7.5-15mg	Int.	45-60	#14	< $1.00
Estazolam	1-2mg	0.5mg	Int.	15-30	#14	$15.00 - 16.75
Lorazepam ❷	2mg	1mg	Int.	30-60	#14	$10.95 - 19.85
Diazepam ❷	10mg	5mg	Long	30	#14	< $1.00
Flurazepam ❸	15-30mg	15mg	Long	30-60	#14	< $1.00
Quazepam	7.5-15mg	7.5mg	Long	20-45	#14	$28.10 - 30.70

* The duration of action is an important determinant of adverse effects such as daytime sedation, impaired psychomotor performance, and rebound insomnia (e.g. flurazepam). This effect is magnified in the elderly.

✣ Cost does not include dispensing fees and reflects Aug. '98 pricing.

❶ Several reports suggest that triazolam may be associated with a greater potential to produce anterograde amnesia and psychomotor impairment than other benzodiazpines.

❷ Not FDA approved.

❸ Flurazepam is the only agent that does not increase REM latency

However, according to two reports, all safety and efficacy trials in adult and geriatric patients evaluated short-term interventions only, ranging from several days to several weeks.[1,7] In fact, studies evaluating these agents in the elderly are of 56 nights or less (including placebo nights) and consist of small sample sizes (72 subjects or less). Nevertheless, 30.8% of the elderly population were prescribed benzodiazepines for an average of 119 days according to a 1990 analysis of benzodiazepine prescribing in the elderly in Canada.[9]

Meanwhile, health care professionals must use the available data to assist them in treating insomnia and other related sleep disorders. The estimated prevalence of insomnia among US adults is currently 10%, and the estimated direct annual cost is $10.9 billion.[2,4] More recent estimates of the overall economic cost of insomnia (includes self-treatment, cost of healthcare providers and insurance companies, and cost to society) in the US range from $30 to $35 billion.[2] Prudent prescribing of drugs, in addition to non-pharmacologic therapy, can potentially result in increased therapeutic successes, a reduction in potential adverse outcomes, and ultimately healthcare dollars. Please refer to the general prescribing and dispensing guidelines.

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12. Facts and Comparisons

■ **MIGRAINE**, continued from page 1

Table 1:
Headache Response Characteristics

DRUG	Onset (min.)	% Response at 2 hours	Recurrence %
Sumatriptan 6mg (SC inj)	< 15	82	35-40
Sumatriptan 20mg (NS)	< 30	62	35-40
Sumatriptan 50mg (PO)	60	64	35-40
Zolmitriptan 2.5mg (PO)	30-60	65	22-37
Naratriptan 2.5mg (PO)	90	48	17-28
Rizatriptan 10mg (PO)	30	71	44
Dihydroergotamine 2mg (NS)	30	60	13-28

Adverse Effects – All of the "triptans" and DHE preparations have vasoconstrictive actions, therefore they are contraindicated in patients with ischemic heart disease (IHD), or cerebral or peripheral vascular disease. Deaths have occurred when IHD patients have received these products. Similarly, they are contraindicated in patients with uncontrolled hypertension or hemiplegic or basilar migraine. Each agent should not be used within 24 hours of any other triptan or ergot product. In patients at increased risk for cardiovascular disease, these drugs should be only be used with extreme caution. Please consult prescribing information for a complete list of contraindications, precautions, drug interactions and adverse effects. It should be emphasized that these drugs are very safe if careful attention is paid to patient selection.

In general, most adverse effects are mild to moderate in intensity and are short lived. The most common effects include unusual sensations including tingling, warmth, flushing, heaviness, dizziness, neck and throat tightness. Somnolence and nausea can occur and the later appears most common with the DHE nasal spray. The sumatriptan and DHE nasal sprays are associated with additional side effects related to nasal administration such as rhinitis and taste disturbance.

Zolmitriptan (Zomig®, *Zeneca*)

Zolmitriptan is available as 2.5 and 5 mg tablets. It is equally effective in migraine subtypes such as menstrual migraine, migraine on awakening, and migraine with or without aura. The recommended initial dose is 2.5mg, however doses of 1mg are also effective. In patients whose headache persists or reoccurs, an additional dose may be administered after two hours. Doses of zolmitriptan should not exceed 10mg per 24 hours. The adverse effect profile resembles sumatriptan.

In clinical trials, a few patients who were previously unresponsive to sumatriptan responded to zolmitriptan. It has been claimed that zolmitriptan's improved bioavailability and CNS penetration offer and advantage over oral sumatriptan. However, in a report of a controlled trial comparing zolmitriptan 5 mg and sumatriptan100 mg, headache response at 2 and 4 hours was similar (61% vs. 64%, and 82% vs. 86%, respectively) indicating the drugs have comparable effectiveness. For doses of 1.25mg or 2.5mg, zolmitriptan tablets may be broken and administered as half-tablet doses which results in considerable cost savings. This can also be done with 50 mg sumatriptan tablets for doses of 25mg.

Naratriptan (Amerge®, *Glaxo-Wellcome*)

Naratriptan is available as 1 and 2.5mg tablets. It is given as a single 1 or 2.5mg dose, with more patients responding to the 2.5mg dose. If significant relief has not been achieved, the dose may be repeated once in 4 hours. The maximum dose is 5mg in 24 hours. Naratriptan is metabolized by cytochrome P-450 isoenzymes to inactive compounds. Dosage adjustments are frequently required in patients with renal or hepatic dysfunction; naratriptan is contraindicated in patients with a creatinine clearance of less than 15 ml/min.

When compared to other "triptans", naratriptan has a slower onset of action and a lower response rate at 2 hours, but a comparable response at 4 hours. The primary advantage is that naratriptan has a low recurrence rate, which might be attributed to a longer elimination half-life compared to sumatriptan (6 hours vs. 2 hours). The agent is reported as producing a slight reduction in adverse effects, although this reduction was not significant in clinical trials.

Rizatriptan (Maxalt®, *Merck*)

Rizatriptan is available in 5 and 10mg caplets or orally dissolving tablets which have similar efficacy. The recommended initial dose is10mg, which may be repeated after 2 hours if headache recurs. Efficacy is comparable to oral sumatriptan at recommended doses. Doses above 10mg are associated with greater adverse effects. A therapeutic response can be detected in 30 minutes.

Dihydroergotamine Nasal Spray (Migranal®, *Novartis*)

The initial recommended dose is 0.5mg (1 spray) in each nostril, repeated in 15 minutes for a total of 2mg. Higher doses are not more effective. A disadvantage of this preparation is its complicated dosing apparatus; using the spray involves several steps including opening a glass ampule, loading the ampule into the sprayer, priming the sprayer, and then administering the drug to each nostril. Associated adverse effects include rhinitis, taste disturbances, nausea, nasal mucosa irritation, and dizziness.

Recurrence rates appear comparable to naratriptan and less than that seen with the other "triptans," possibly due to its long half-life (10 hours). DHE is less effective than the triptans in reducing vomiting and nausea associated with migraines, and antiemetics such as metoclopramide can be administered concurrently if needed.

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■ **MIGRAINE**, continued from Page 6

Sumatriptan Nasal Spray
(Imitrex® Nasal Spray, Glaxo-Wellcome)

Sumatriptan nasal spray is available in 5 and 20 mg single-use spray canisters. Doses of 5 to 20 mg are effective in aborting migraine, with 20mg having the highest response rate, but also a higher rate of some adverse effects. Doses above 20 milligrams do not provide additional therapeutic benefit. If the headache returns, the dose may be repeated after 2 hours, not to exceed a total daily dose of 40 milligrams. No adjustments are necessary for hepatic or renal failure. The single-use canisters offer an advantage over the DHE nasal product. The dose is applied as a single spray to one nostril for doses of 5mg or 20mg. A dose of 10mg can be given by using two 5mg canisters and applying 5 mg to each nostril. However the 10mg dose is not recommended because in clinical trials, there was no difference in response between 5mg and 10mg, and using two 5mg canisters doubles the cost of therapy.

Sumatriptan demonstrates rapid absorption from the nasal mucosa. Onset of relief can occur in less than 30 minutes and peak effect occurs about 1 to 2 hours post dose. Adverse effects are similar to conventional sumatriptan with the addition of local nasal symptoms like rhinitis, burning, and a bad taste.

TABLE 2:
Cost Comparison of Various Abortive Migraine Drugs

DRUG	DOSE	COST✦ $
Ibuprofen plus metoclopramide	600 mg/10 mg	<1
Naproxen sodium plus metoclopramide	550 mg/10 mg	<1
Zomig	½ x 5 mg tablet 1 x 2.5 mg tablet	7 13
Imitrex	½ x 50 mg tablet 1 x 50 mg tablet	7 14
Maxalt	10 mg	14
Amerge	2.5 mg	15
Migranal Nasal Spray	2 mg	15
Imitrex Nasal Spray	20 mg	18
Imitrex StatDose Inj.	6 mg	46

✦ Cost does not include ispensing fees and reflects Aug. '98 pricing.

Treatment Recommendations:

The International Headache Society (IHS) has developed guidelines to help clinicians manage migraine headache patients. For abortive therapy of mild to moderately severe migraine attacks, the IHS guidelines recommend an adequate trial of NSAIDs with or without the addition of an antiemetic, depending on the character of the attack. In one study of moderate to severe migraine headaches, metoclopramide plus a NSAID was as effective as oral sumatriptan, and well tolerated. Effective NSAIDs include ibuprofen 600 mg Q6 hr or naproxen sodium 550 mg X 1 then 275 mg Q 6 hr as needed. Metoclopramide 10 mg enhances absorption of NSAIDs by promoting gastric motility, plus it reduces nausea and vomiting. Combination products such as acetaminophen and dichoralphenazone (Midrin) and aspirin or acetaminophen with caffeine and butalbital (Fiorinal or Fioricet) are also prescribed for the treatment of migraine. However, routine use of these agents is discouraged due to a lack of benefit over single entity preparations coupled with their propensity to cause dependence and/or rebound headache.

Upon failure of NSAID therapy (characterized by lack of pain, nausea, or photophobia/phonophobia relief within 4 hours post drug administration or if the patient is intolerant of NSAIDs), IHS guidelines recommend a trial of oral or nasal "triptans" and reserving injectable preparations for very severe or resistant cases.

The newer oral agents offer few advantages over oral sumatriptan and are very similar. For patients willing to take half-tablet doses, zolmitriptan can offer substantial cost savings. A few patients that do not respond to oral sumatriptan may respond to zolmitriptan. For patients that frequently require repeat dosing for recurrent headaches, consider an agent with a low recurrence rate such as naratriptan. Nasal spray products provide a viable alternative for patients with severe nausea or vomiting. Sumatriptan nasal spray offers several advantages over DHE nasal spray, including greater ease of use, better relief of nausea, and lower cost, but DHE has a lower recurrence rate.

Patients should be continually monitored for response to these agents and for overuse. Although, several investigations revealed only 1 to 4% of patients as "overusers", these patients account for approximately 20% of total use. The safety and effectiveness of regular use of these agents is not known. Overuse of abortive therapy can be prevented by limiting the number of doses prescribed and refills, and carefully monitoring frequency of use. Migraine prophylaxis is indicated when more than 3 attacks occur per month. There are several medications that are effective for prophylaxis, including b-blockers (propranolol, atenolol, & metoprolol), verapamil, and tricyclic antidepressants (amitriptyline & nortriptyline). ■

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We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

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