OREGON DUR BOARD NEWSLETTER©

Vol. 3 No. 2 http://pharmacy.orst.edu/ **Spring 2001**

Chronic Insomnia: Misuse of Hypnotic Therapy in Oregon

*By: **Ann Hamer**, Pharm.D.*

Motivated by concerns of hypnotic misuse, OMAP conducted an internal review of hypnotic prescribing patterns. Specific areas of concern were chronic hypnotic use, excessive dosing in the elderly and duplicate therapy. A review of all patients filling two hypnotic prescriptions on the same day discovered that at least 19 patients received both Ambien (zolpidem) and Sonata (zaleplon) at the same time during the first 9 months of last year. It is interesting to note that despite the fact that insomnia guidelines recommend only short-term (7-10 days) hypnotic drug therapy, the average duration of sedative use in the year 2000 was 3 to 6 months.

Of 525 patients receiving zaleplon therapy, approximately 12% received higher than the recommended dose of 10 mg qhs (range: 2-60 mg). Out of 264 patients on triazolam therapy, approximately 14% received more than 0.25 mg qhs (range: 0.055-2.0 mg). Results showed 81 patients over the age of 64 (over 50% of this group) received excessive doses.

INTRODUCTION – Sleep is a basic requirement. Without the benefit of a good night's sleep, a person may experience daytime sedation, increased levels of anxiety, depression and medical illness, decreased productivity and an increased propensity for accidents. Up to one-third of primary care patients experience sleep difficulties. Of those patients, approximately 10% have chronic insomnia, or the subjective experience of an inadequate quantity or quality of sleep that has persisted for at least one month.[1,2] The following is a review of the appropriate diagnosis and treatment of chronic insomnia.

DIAGNOSIS – Idiopathic chronic insomnia is very rare. Insomnia, therefore, should be considered a symptom; a symptom of an underlying pathological condition. The identification and elimination of all possible causes should take precedence. Table 1 provides a list of common causes of insomnia in the primary care patient.

To best diagnose and treat insomnia, it is critical to perform a thorough clinical interview. This should include a review of medical conditions, a complete medication history, interviews with bed partners, and data from a sleep diary, including sleep latency, sleep duration, number of awakenings and subjective assessments of sleep quality and quantity.

TREATMENT–NONPHARMACOLOGIC THERAPY – The first step in the treatment of chronic insomnia should be the elimination of the causative factor(s) if possible. Underlying medical conditions should be treated appropriately. For example, an underlying depressive disorder should be treated with an antidepressant.

Nonpharmacologic therapy, consisting of both behavioral and cognitive changes, is a reasonable second step. Nonpharmacologic interventions for insomnia are primarily short-term cognitive-behavioral therapies aimed at alleviating the factors that are presumed to perpetuate insomnia. In other words, they attempt to modify poor sleeping habits, reduce autonomic and cognitive arousal, alter dysfunctional beliefs and attitudes about sleep, and educate patients about healthier sleep practices.[3] The results of 2 meta-analyses of behavioral treatments suggest that 70-80% of patients with primary insomnia experience improvements.[4]

Table 1. Common Causes of Insomnia

Drugs
- OTC medications (eg, pseudoephedrine)
- Nicotine
- Prescription drugs
  - methylphenidate, pemoline
  - theophylline
  - albuterol
  - quinidine
  - diuretics
  - dextroamphetamine
  - phenylephrine
  - SSRIs

Psychologic Causes
- depression
- anxiety
- conditioning
- mania or hypomania

Medical Conditions
- sleep apnea, restless leg syndrome
- pain
- thyrotoxicosis
- drug/alcohol intoxication or withdrawal
- dyspnea from any cause
- nocturnal myoclonus

Environmental Causes
- temperature
- noise
- eating, exercise, caffeine or alcohol use before bedtime
- jet lag
- shift work
- daytime napping

Sleep hygiene is a necessary component of all insomnia interventions, and may be sufficient as a stand-alone treatment. Other nonpharmacologic therapies include stimulus control, progressive muscle relaxation and sleep restriction. See Table 2 for a description of various nonpharmacologic interventions.

There are at least 15 studies available that have compared 2 or more of the following nonpharmacologic interventions: stimulus control, relaxation, sleep restriction and sleep hygiene education. Only 5 studies have found a statistically significant difference between response to these interventions; with stimulus control and sleep restriction being more effective than relaxation and sleep hygiene education.[3] Published studies show that while hypnotic drugs may produce faster sleep improvements, particularly in the first few days, behavioral methods such as relaxation and sleep hygiene education have comparable effect in the intermediate term and are clearly superior in long-term therapy. Even those patients on long-term combination therapy (hypnotic drugs plus behavior therapy) do not do as well as those with behavior therapy alone.[3]

There are at least 15 studies available that have compared 2 or more of the following nonpharmacologic interventions: stimulus control, relaxation, sleep restriction and sleep hygiene education. Only 5 studies have found a

– **CHRONIC INSOMNIA** - continued on page 2

INSIDE THIS ISSUE:

NOTICE:

This will be the final printed version of the Oregon DUR Board Newsletter. Future and past DUR Board Newsletters may be found online at http://pharmacy.orst.edu/ You may also subscribe to the DUR Board subscription list service at this internet location.

– **CHRONIC INSOMNIA** - continued from page 1

Table 2. Nonpharmacologic Therapies for Insomnia

THERAPY	DESCRIPTION
Sleep Hygiene	• Limit/stop the use of nicotine, alcohol and caffeine • Keep regular sleep and wake times, even on days off from work • Exercise regularly, but no later than late afternoon or early evening • Only use the bed for sleep or sex • Avoid daytime naps • Avoid poor sleep environments • Do not eat heavy meals before going to bed
Stimulus Control	< Patient uses a set of instructions designed to establish in the bedroom cues for sleep instead of wakefulness
Sleep Restriction	< Length of time spent in bed is limited to create partial sleep deprivation, resulting in deeper, more continuous sleep
Relaxation Training	< Biofeedback, autogenic training, progressive muscle relaxation and hypnosis
Cognitive Therapy	• Psychotherapy aimed at changing the patient's perception of the insomnia

statistically significant difference between response to these interventions; with stimulus control and sleep restriction being more effective than relaxation and sleep hygiene education.[3] Published studies show that while hypnotic drugs may produce faster sleep improvements, particularly in the first few days, behavioral methods such as relaxation and sleep hygiene education have comparable effect in the intermediate term and are clearly superior in long-term therapy. Even those patients on long-term combination therapy (hypnotic drugs plus behavior therapy) do not do as well as those with behavior therapy alone.[3]

To improve the outcome of nonpharmacologic therapy, patients should be thoroughly educated about each technique and appropriate expectations. Table 3 provides some useful online resources for patients.

Table 3. Patient Resources

Muscle Relaxation Techniques
< http://ourworld.compuserve.com/homepages/har/relax.htm
< http://www.mckinley.uiuc.edu/health-info/stress/rela-exe.html
Sleep Hygiene
< http://www.thesleepsite.com/hygiene.html

TREATMENT–PHARMACOLOGIC – Pharmacologic therapy is indicated when nonpharmacologic approaches are insufficient to relieve the insomnia. When used in combination with behavioral therapy, patients tend to respond well with long-term benefits.[3] In general, hypnotic drug therapy should be used intermittently as needed and for a limited duration (#3 weeks).

Barbiturates and Other Older Hypnotics – These agents have fallen out of favor due to their high propensity for adverse effects, tolerance, and dependence.

Antidepressants – While there are few data that focus on the use of antidepressants in primary insomnia, these agents have been used successfully to treat insomnia. At low doses, these agents have minimal side effects and are inexpensive. It is recommended that practitioners start with a low-dose tricyclic antidepressant (eg, amitriptyline) or trazodone. When prescribing tricyclic antidepressants (TCAs), it is important to consider their safety. In low doses (10-25 mg amitriptyline), these drugs are typically well tolerated. Elderly patients are more susceptible to anticholinergic side effects and should be prescribed lower starting doses of both TCAs and trazodone. Side effects become more prominent with higher doses such as those used in the treatment of depression. TCAs can be fatal in overdose. Caution should be used when prescribing TCAs with medication that could inhibit their metabolism (ie SSRIs). Priapism, a rare side effect of trazodone, can be of concern with male patients taking doses greater than 150mg. SSRIs are not recommended for use in patients with primary insomnia; they may induce or worsen pre-existing sleep disorders.

Benzodiazepines – Benzodiazepines have traditionally been recognized as the mainstay of therapy for the treatment of insomnia. Benzodiazepines, like all sedating medications, should not be used if there is any suspicion of obstructive sleep apnea. Prior to selecting a particular benzodiazepine, several factors need to be taken into consideration including: patient's age, liver function, pharmacokinetics of the drug, specific insomnia symptoms, and substance abuse history. Lorazepam, temazepam and oxazepam are considered the benzodiazepines of choice in the presence of hepatic dysfunction. These drugs undergo glucuronide conjugation and their half-lives are only slightly altered by hepatic disease. Elderly patients should not receive long-acting benzodiazepines such as diazepam, clonazepam or flurazepam. Due to reduced liver metabolism and drug accumulation, such agents have been linked to increased falls, hip fractures and motor vehicle accidents.[4] For further information on treating insomnia in the elderly, see the final section on treating insomnia in special populations.

Triazolam (Halcion) is a benzodiazepine with a short 6 to 7 hour duration and quick 15 to 30 minute onset of action. Its amnestic side effects have received a lot of bad press. Like any benzodiazepine, triazolam should be used cautiously. It should be given in small doses (0.125 mg to 0.25 mg) and for short periods of time (7 to 10 days). Interestingly, triazolam and zolpidem (a newer nonbenzodiazepine hypnotic) have been documented to cause similar impairment of memory and abuse potential.[5,6]

Benzodiazepines are associated with many adverse effects, particularly with the use of high doses long-term. These agents should be dosed intermittently, for a limited duration and at the lowest dose possible.[1,7] Tolerance and dependence may occur after only 1 to 2 weeks with short and intermediate-acting agents.[8] Benzodiazepines should be withdrawn gradually (eg, 25% per week) to avoid withdrawal reactions (including seizures) and rebound insomnia. Patients who have been on benzodiazepines long-term will require a slower, more individualized taper.

Nonbenzodiazepine Hypnotics – Two newer nonbenzodiazepines, zolpidem (Ambien) and zaleplon (Sonata), are thought to be selective for the BZ-1 receptor subtype. Both agents are indicated for the short-term treatment of insomnia. An advantage of these agents over some benzodiazepines is their rapid onset of action and short elimination half-life. Zaleplon, with an average onset of activity of 15 to 20 minutes, can be dosed during the middle of the night with little risk of daytime sedation. It should be recognized that the average onset of action for triazolam is 15 to 30 minutes as well. Drawbacks to the nonbenzodiazepine hypnotics include impaired memory and concentration, headache, GI upset, drug tolerance, cost and lack of efficacy in some patients.

According to the manufacturers of both zolpidem and zaleplon, duration of therapy should be limited to 7-10 days.[9,10] There are no published data available that support the use of either agent long-term. In fact, in two unpublished controlled trials, it was determined that the beneficial effects of zolpidem are only short term, with tolerance developing by the fifth week of use. Chronic standard zolpidem therapy (5-10 mg qhs) is considered to be no better than placebo.[9]

Only two 4-5 week zaleplon trials have been performed in chronic insomniacs. Results of these studies showed that while zaleplon significantly decreases time to sleep onset or sleep latency (10-20 minutes) compared to placebo, it does not have any effect on sleep duration or number of awakenings.[10] Other sleep laboratory studies performed in outpatient chronic insomniacs have had a maximum duration of 28 days. A summary of these findings demonstrated that zaleplon significantly reduced latency to persistent sleep compared to placebo during the first two nights of therapy only.[10] Zaleplon comparative efficacy trials have failed to clearly demonstrate an advantage over the short-acting benzodiazepine triazolam.[11]

Nonbenzodiazepines should only be used in patients with primary sleep latency disorders. All agents within this class have failed to demonstrate consistent improvements in sleep duration, number of awakenings, and overall sleep quality. There are no distinct advantages of these agents over conventional benzodiazepines (such as triazolam). Evidence does not support the long-term use of nonbenzodiazepine hypnotics.

Natural Products – There are many over-the-counter herbal products that are touted as sleep aids. Valerian (from the underground parts of Valeriana officinalis) causes both CNS depression and muscle relaxation. It is reported to decrease sleep latency and improve subjective sleep. There are few studies available that provide evidence for the hypnotic efficacy of valerian. In addition,

– **CHRONIC INSOMNIA** - continued on page 3

– **CHRONIC INSOMNIA** - continued from page 2

there are safety concerns associated with its use. Based on the1994 Dietary Supplement Health and Education Act (DSHEA), herbs, vitamins, minerals and amino acids can be marketed as dietary supplements. As such, herbal manufacturers are not required to provide safety, purity and efficacy data. As a result, the content and purity of herbal preparations may vary from batch to batch. Of specific concern with valerian, it is feared that valepotiates in high concentration may be cytotoxic[8] More data must be collected on this drug before its role in insomnia can be defined.

Table 4. Data From Two Controlled Long-Term Zolpidem Trials.[9]

SLEEP CHARACTERISTIC	WEEK ONE	WEEK TWO	WEEK THREE	WEEK FOUR	WEEK FIVE
Study #1: 10 mg qhs for 5 weeks *(arrow indicates when efficacy is greater than placebo)*					
Sleep Latency	→	→	→	→	→
Sleep Efficiency	→			→	
Number of Awakenings	no better than placebo during entire study duration				
Study #2: 10 mg qhs for 4 weeks *(arrow indicates when efficacy is greater than placebo)*					
Sleep Latency	→	→	→	→	→
Total Sleep Time	→				
Number of Awakenings	→				
Sleep Quality	→				

Melatonin, a neurohormone synthesized from tryptophan and secreted by the pineal gland, has recently gathered a lot of press as a sleep aid. Melatonin's role in regulating the sleep-wake cycle, particularly in jet-lag, is well documented. Low-dose melatonin as a hypnotic is considered to be variably effective. Data suggest that the efficacy of melatonin is affected by time of administration (best if 2 hours before bed), product bioavailability (not FDA regulated), and length of therapy. Melatonin appears to be more effective with repeated doses.[8] It should be stressed, however, that ongoing need for a sleep aid should be thoroughly evaluated to rule out underlying causes. Further safety and efficacy data are needed.

Recommendations for the Pharmacologic Treatment of Insomnia

- < Nonpharmacologic therapy is a critical addition to all treatment strategies.
- < Pharmacotherapy should not be considered the mainstay of treatment for chronic insomnia.
- < If pharmacotherapy is necessary, sedating antidepressants are reasonable first choices.
- < All sedative hypnotics should be given for a limited duration.
- < If a longer duration is necessary, as-needed intermittent therapy is as effective as chronic therapy.
- < Zolpidem and zaleplon are not recommended beyond 10 days of therapy.
- < Drug therapy should be withdrawn slowly to avoid rebound insomnia.

Table 5 provides a summary of the drug classes used as sedative/hypnotics.

TREATING INSOMNIA IN SPECIAL POPULATIONS

Psychiatric Illness

Insomnia and Depression – Sleep disturbances are a common part of depressive disorders, and as such, are included in all contemporary sets of diagnostic criteria for major depression. It is thought that insomnia in depression is caused by a dysfunction of the serotonin systems[12] , and that the stimulation of serotonin-2 receptors causes changes in sleep architecture seen with selective serotonin reuptake inhibitors (ie, fluoxetine, sertraline, citalopram, paroxetine and fluvoxamine) and serotonin-norepinephrine reuptake inhibitors (ie, venlafaxine).[13] Management of depression with these agents may necessitate the short-term use of coprescribed low-dose trazodone or other sedative. With continued use of SSRIs, symptoms of insomnia should improve, enabling the discontinuation of dual therapy. An alternative approach to the management of comorbid depression and insomnia is the use of antidepressants that *block* the serotonin-2 receptor, such as mirtazapine or nefazodone. Both of these agents are equally effective antidepressants compared to SSRIs and they alleviate insomnia and improve sleep architecture. Antidepressants with serotonin-2 blocking properties are good single treatment options for depressed patients with marked insomnia.[13]

Table 5. Pharmacologic Therapies for Insomnia

DRUG	ADVERSE EFFECTS	EFFECT ON SLEEP STRUCTURE[5]	COST FOR 10 DAY TREATMENT ($)*
BENZODIAZEPINES			
clonazepam *(Klonopin)*	rebound insomnia daytime sedation headache confusion hypotension hangover dependence withdrawal respiratory depression	**9**sleep latency[a] **8**total sleep time[b] **9**delta sleep[c] **9**REM sleep[d]	$6.80
temazepam *(Restoril)*			$7.00
triazolam *(Halcion)*			$5.90
NONBENZODIAZEPINE HYPNOTICS			
zolpidem *(Ambien)*	headache N/V confusion dizziness tolerance/withdrawal	**9**sleep latency **8**total sleep time **8**delta sleep **:** REM sleep	$22.40
zaleplon *(Sonata)*	headache somnolence dizziness tolerance/withdrawal	**9**sleep latency **8**total sleep time **8**delta sleep **9**REM sleep	$22.30
ANTIDEPRESSANTS			
amitriptyline *(Elavil)*	drowsiness CV effects seizures hypotension anticholinergic effects	**9**sleep latency **8**delta sleep **9**REM sleep	$0.90
imipramine *(Tofranil)*			$4.50
trazodone *(Desyrel)*	dry mouth dizziness drowsiness N/V hypotension	**9**sleep latency **8**total sleep time **:** delta sleep **:** REM sleep	$2.80
OVER-THE-COUNTER AGENTS			
diphenhydramine (Nytol, Sominex)	dyskinesias headache sedation dry mouth weight gain tolerance	**9**sleep latency **8**total sleep time **?**delta sleep **?**REM sleep	$1.70
doxylamine (Unisom)			$3.40

**Based on AWP from Red Book Update. January 2001; 20(1).*
a. Sleep latency = time to onset of sleep
b. Total sleep time = duration of sleep
c. Delta sleep = slow-wave, deep, restorative sleep
d. REM sleep = Rapid Eye Movement sleep

Regulation of the Sleep-Wake Cycle in Bipolar Affective Disorder – There is some evidence to suggest that the disruption of sleep in bipolar patients may precipitate a manic episode.[14,15] Disrupted sleep schedules may occur as a result of psychosocial stressors such as jet lag, school examinations or rotating work shifts. Sleep is typically considered a priority in the treatment of manic patients, thus necessitating the use of a short-term sedative/hypnotic. There are no data regarding the need, efficacy or adverse effects of chronic sedative administration in this patient population. It is therefore recommended that sedative/hypnotics be prescribed on an acute basis only.

Elderly – Sleep structure changes with age. The biphasic propensity for sleep seen in young adults becomes multiphasic in the elderly. Studies have shown that in the elderly, sleep latency increases and sleep efficiency decreases, as does time in deep sleep.[16]

Treatment of insomnia in the elderly adult should follow guidelines similar to those of younger adults. Good sleep hygiene and stimulus control education

– **CHRONIC INSOMNIA** - continued on page 4

– **CHRONIC INSOMNIA** - continued from page 3

is imperative. Daily exercise and exposure to daylight can help reinforce the circadian cycle. Select patients may require the use of a sleep-promoting medication. Over-the-counter medications (antihistamines) are rarely recommended due to their anticholinergic side effects. Low-dose antidepressants (such as trazodone) are an excellent first choice, particularly in patients with comorbid depression. Low-dose short-acting benzodiazepines are also a reasonable choice. Dosing of these agents is generally one-half the dose for younger adults. Caution should be used when prescribing medications that are affected by poor renal or hepatic function. Again, long-acting benzodiazepines should be avoided in the elderly.

CONCLUSION – Chronic insomnia is rarely a primary disorder. More commonly, it is a symptom of an underlying medical or psychiatric illness. A thorough evaluation of the patient is warranted prior to the diagnosis of chronic idiopathic insomnia. Nonpharmacologic therapy is considered first-line in all patients. Short-term sedative/hypnotics may be required in certain patients in whom the insomnia does not resolve. If these agents are used longer-term, they should be prescribed intermittently. Chronic use of sedative/hypnotics is strongly discouraged. Agent selection should be based on symptoms, side effects, efficacy studies and cost.

Article Reviewer: Jonathan M. Meyer, M.D., Adjunct Assistant Professor, OHSU Department of Psychiatry.

References

1. Rajput V, Bromley SM. Chronic insomnia: a practical review. *Am Fam Physician* 1999; 60:1431-1442.
2. National Heart, Lung, and Blood Institute Working Group On Insomnia. Insomnia: assessment and management in primary care. *Am Fam Physician* 1999; 59:3029-38.
3. Morin CM, et al. Nonpharmacologic treatment of chronic insomnia. *Sleep* 1999; 22: 1134-1156.
4. Doghramji K. Sleepless in America–Diagnosing and Treating Insomnia. Available at: http://www.medscape.com. Accessed April 11, 2001.
5. Mintzer MZ, Griffiths RR. Triazolam and zolpidem: effects on human memory and attentional processes. *Psychopharmacol* 1999; 144:8-19.
6. Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacol* 1999; 144:220-33.
7. Gluydts R, Peeters K, De Bouyalsky I, Lavoisy J. Comparison of continuous versus intermittent administration of zolpidem in chronic insomniacs: a double-blind, randomized pilot study. *J Int Med Res* 1998; 26:13-24.
8. Wagner J, Wagner ML, Hening WA. Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. *Ann Pharmacother* 1998; 32: 680-691.
9. Ambien package insert. Chicago, Illinois. Searle, December 1999.
10. Sonata package insert. Philadelphia, Pennsylvania. Wyeth-Ayerst, August 1999.
11. Drug Evaluation. *Zaleplon.* Micromedex 2000.
12. Thase ME. Treatment issues related to sleep and depression. *J Clin Psychiatry* 2000; 61 suppl 11:46-50.
13. Thase ME. Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* 1999; 60 suppl 17:28-31.
14. Leibenluft E, Suppes T. Treating bipolar illness: focus on treatment algorithms and management of the sleep-wake cycle. *Am J Psychiatry* 1999; 156:1976-1981.
15. Malkoff-Schwartz S, et al. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes. *Arch Gen Psychiatry* 1998; 55:702-707.
16. Meyer TJ. Evaluation and management of insomnia. *Hosp Pract* 1998; 33:75-78, 83-86.

Controlling The Rising Cost of Medications

By: ***Lori Syed****, Pharm.D. &* ***Dean Haxby****, Pharm.D.*

Health care costs have been increasing at an alarming rate. One of the primary factors driving this increase is spending for prescription drugs. While prescription drugs account for approximately 9% of total health care costs, they were responsible for 44% of the total increase in 1999. In 2000, expenditures for prescription drugs increased by 19%. A March 2000 study conducted by the University of Maryland projects that prescription drug costs may increase by as much as 18% a year over the next 5 years. This means that by 2004, prescription costs would be double that spent in 1999. As spending on prescription drugs makes up a larger portion of health care costs, fewer resources are available for other health care services, including provider reimbursement.[1]

The rising cost of pharmaceuticals can be attributed to several key factors. In 2000, an increase in the number of prescriptions written caused 42% of the rise, while a shift to higher cost drugs accounted for 36%. Other factors accounting for the remainder of the rise include increased prices of existing drugs and longer durations of therapy. It is clear that aggressive marketing to providers and consumers is reaping rewards for the pharmaceutical manufacturers. While some newer drugs offer advantages over older, existing agents, many do not. Yet new drugs are aggressively marketed, regardless of their merits.[2] Fortunately, there are a number of tactics clinicians can take to improve the cost effectiveness of their prescribing. The purpose of this article is to point out strategies that can help contain prescription drug costs, while maintaining quality of care.

Become Better Informed About Drug Prices – It is very difficult to make cost effective choices without knowing the relative cost of drugs. Become familiar with the costs of the drugs that you commonly prescribe. A recent study demonstrated that lack of provider knowledge of drug prices was a major contributor to higher cost prescribing. Sources of drug pricing information include pharmacists, managed care prescribing guides, the Medical Letter and the Red Book.

Frequently Review Patients' Drug Profiles and Avoid Polypharmacy – Be sure that each drug prescribed has an indication, and look for those indications which have resolved or changed. This is especially important following a hospital admission. Try to limit the number of medications prescribed. As the number of prescribed medications increases, the chance for adverse effects, drug interactions or non-adherence increases. When assessing the lack of effect of a drug, first assess compliance, then consider if an adequate dose has been tried. If it becomes necessary to change the regimen, consider discontinuing the product and changing to a different medication, rather than just adding another medication onto the regimen. Avoid treating side-effects with more drugs. It is important for physicians to evaluate for side-effects of the medications they prescribe, and for pharmacists to discuss effects and key monitoring parameters with patients. Finally, when changing or discontinuing medications, be certain that a patient clearly understands the change, and if necessary, understands to stop taking the previous medication.

Use Generics First if Possible – Many popular medications have already converted to generic status or will be doing so very soon. Prices for generic products are usually about 25% less than the brand during their first year on the market, and then may fall as low as 80% less thereafter.[3] Unfortunately, when a drug goes generic, there is little or no marketing of the product and use may decrease. Many providers have been lead to believe that generic products are inferior to brand-name products. It is clear that this is not the case and the FDA carefully regulates quality and ensures equivalence before a generic drug can be substituted for the equivalent brand-name product. Most important is to use products that are available generically in place of other drugs in a class that are brand-only but have similar clinical effects. Table 2 provides examples of commonly prescribed brand name drugs, for which similar generic drugs can be used at a much lower price.

Carefully Evaluate New Drugs – Using newer, more expensive agents in place of older drugs is one of the largest factors contributing to higher drug prices. While some newer drugs may offer improvements to existing therapies, many do not. It is important to critically evaluate new drugs and make sure there is adequate evidence to support claimed advantages. Uwe Reinhardt, an economist from Princeton, discussed a serious deficiency in medical literature regarding the efficacy of newer products when compared with the progenitor products.[4] Head-to-head comparative literature simply does not exist. Generally, we are using these newer agents because we believe them to be better, or because increased marketing suggests that they are better, but there is often very little evidence to support claims that are made or inferred. Frequently, drugs are released without much information about long-term use, or use outside of the carefully defined populations of clinical trials. Once released, problems can occur that may be serious enough to bring about a withdrawal from market. Recent examples of this phenomenon include Redux, Lotronex, Rezulin, Posicor, Seldane, Propulsid and Duract. Several excellent sources of information about new drugs include the Medical Letter, pharmacy and therapeutics committees and clinical pharmacists. The FDA website, www.fda.gov, posts transcripts of many advisory committee meetings that can provide extensive information about new drugs.

Avoid Unnecessary Use of Medications – This is particularly important with antibiotic use. Not only is unnecessary prescribing financially costly, but it is harmful in terms of limiting antibiotic effectiveness. Antibiotic-resistant

– **RISING COSTS** - continued on page 5

– **RISING COSTS** - continued from page 4

Table 1. Less expensive options for commonly prescribed drugs

Prescribed Drug	Cost ($)*	Alternative Drug	Cost ($)*	Cost Savings ($)
Prevacid 30 mg qd x 30 days	107	**Protonix 40 mg qd x 30 days**	81	**26**
Prilosec 40 mg qd x 30 days	157			**76**
Biaxin 500 mg bid x 10 days	71	**Zithromax 250 mg qd (Z-pak dosing)**	39	**32**
Levaquin 500 mg qd x 10 days	77	**Tequin 400 mg qd x 10 days**	67	**10**
Norco 10/325 1 tab qid x 30 days	92	**hydrocodone/APAP 10/500 1 tab qid x 30 days**	44	**48**
		hydrocodone/APAP 7.5/500 2 tabs qid x 30 days	43	**49**
OxyContin 40 mg bid x 30 days	223	**MS Contin 30 mg tid x 30 days**	151	**72**
Cozaar (losartan) 50 mg qd x 30 days	38	**Micardis (telmisartan) 40 mg qd x 30 days** **Micardis (telmisartan) 80 mg ½ tab qd x 30 days**	37 21	**1** **17**
Actos 15 mg qd x 30 days	80	**Metformin 500 mg bid**	47	**33**
Avandia 4 mg qd x 30 days	70			**23**

* Costs of brand name products are reported as AWP - 13% + $2.50.
This represents a common reimbursement equation. Costs of generic products are reported as MAC + $2.50, again a common reimbursement method for generics.

Streptococcus pneumoniae is becoming an ambulatory care epidemic and is directly related to the overuse of antibiotics. Recent guidelines in the Annals of Internal Medicine suggest that most adult acute respiratory tract infections need not be treated with antibiotics.[5] Studies indicate that the addition of antibiotics has relatively little effect on the duration and outcome of these types of infections. Additionally, mild to moderate cases of otitis media will often resolve on their own without the use of an antibiotic. There is no benefit to treating colds or the flu with antibiotics unless a secondary infection establishes itself. Many clinics have initiated a program in which physicians dispense or prescribe a "cold and flu" kit, containing acetaminophen for aches and fever, antihistamines and decongestants for nighttime and daytime symptom relief and written advice addressing expected symptom duration and non-pharmacologic methods for treating symptoms.

Dosing Strategies and Using Half-Tablets – Many drug products have a single price for different strengths, so the price is not proportional to the amount of active ingredient. Using half-tablets when appropriate can result in substantial savings. Cohen and Cohen reported in April 2000 that there was a potential savings in the U.S. of up to $1.45 billion annually, just from splitting the newer psychotropic agents.[6] There has been a lot of press regarding this issue lately, and while half-tab use should not be mandated, if the patient and the drug have been carefully selected, it can be a powerful method of cost-savings.

Selecting the Right Medications for Tablet Splitting – One of the most important aspects of this process is selection of the appropriate medication. It is critical to select medications for stable chronic conditions whose steady-state pharmacokinetics allow minor variations in total dose from day to day without affecting the response to the drug. Data suggest that a weight variance of 10-20% can occur in split tablets.[7,8] Medications that are enteric-coated should not be split, nor should many extended- or controlled-release products. Medications that routinely break or crumble should also not be selected for tablet-splitting. Some non-scored tablets and tablets with asymmetric shapes can be split, but these should be evaluated carefully before initiating tablet splitting.

Generally, patients should not split a month's supply of tablets all at one time, as this can increase the amount of drug lost in crumbling. It is best to cut one tablet at a time, and then use the other half-tablet for the next dose.

Patients Need to be Carefully Selected, Too – In order for a tablet-splitting program to be successful, the patients need to be carefully selected and educated regarding the process.[9] Patients with physical disabilities such as visual impairments should not be expected to split tablets. Likewise, patients with arthritis, Parkinson's disease or other conditions that cause tremors or loss of dexterity should not split tablets. Patients with cognitive impairment or memory deficiency should only split tablets if they have a daily caregiver who is educated in the process and can assist with the task. Patients and caregivers who are resistant to the idea of using half-tablets should not be made to do so, as it is more important to ensure compliance and to maintain the correct dosages.

Table 2. Generic options for commonly prescribed drugs

Prescribed Drug	Cost/ Year ($)	Alternative Drug	Cost/ Year ($)	Cost Savings/ Year ($)
Pepcid 20 mg bid	1236	**cimetidine 400 mg bid**	108	**1128**
Axid 150 mg bid	1320			**1212**
Pepcid 20 mg bid	1236	**ranitidine 150 mg bid**	276	**960**
Axid 150 mg bid	1320			**1219**
Valtrex 500 mg bid	2208	**acyclovir 400 mg bid**	504	**1704**
Famvir 250 mg bid	2328	**acyclovir 400 mg bid**	504	**1824**
Relafen 500 mg bid	876	**etodolac 400 mg bid**	276	**600**
Daypro 600 mg ii caps qd	1080	**naproxen 500 mg bid**	144	**936**
Mobic 7.5 mg bid	1272	**salsalate 1000 mg bid**	336	**936**
Toprol XL 50 mg qd	228	**atenolol 50 mg qd**	60	**168**
Covera HS 240 mg qhs	600	**verapamil (Calan SR) 240 mg qd**	384	**216**
Accupril 20 mg bid	720	**captopril 50 mg bid**	120	**50**

Patient Education – When patients have been selected for making use of half-tablets, it is important that they understand the process and the correct doses. Commercially available tablet-cutters are available for splitting tablets.

Table 3. Half-tablet usage for common drug dosing

Prescribed Drug	Cost/ Year ($)	Preferred Drug	Cost/ Year ($)	Cost Savings $/Year
Zestril (lisinopril) 20 mg qd	348	**Zestril 40 mg ½ tab qd**	264	**84**
Zestril 10 mg bid	636			**372**
Zoloft (sertraline) 50 mg qd	792	**Zoloft 100 mg ½ tab qd**	420	**341**
Celexa (citalopram) 20 mg qd	708	**Celexa 40 mg ½ tab qd**	384	**324**
Paxil (paroxetine) 20 mg qd	828	**Paxil 40 mg ½ tab qd**	456	**372**
Lipitor 20 mg bid	2076	**Lipitor 80 mg ½ tab qd**	576	**1500**
Micardis 20 mg qd	444	**Micardis 40 mg ½ tab qd**	252	**192**
Zomig 2.5 mg po prn (4 headaches treated with 2 doses per month)	1260	**Zomig 5 mg ½ tab po prn** (4 headaches treated with 2 doses per month)	732	**528**
Imitrex 50 mg po prn (4 headaches treated with 2 doses per month)	1368	**Imitrex 100 mg ½ tab po prn** (4 headaches treated with 2 doses per month)	696	**672**
Zocor 20 mg qd	1332	**Zocor 40 mg ½ tab**	684	**648**
Mavik (trandolapril) 2 mg qd	288	**Mavik 4 mg ½ tab qd**	156	**132**

CONCLUSIONS – The cost of health care continues to rise, and prescription drug costs remain a significant contributor to this increase. Fortunately, prescribers can help curb this increase by becoming better informed about drug prices. Clinicians can help contain prescription costs, while ensuring quality care by periodically reviewing patient's drug profiles, selecting generics when appropriate for care, avoiding the use of unnecessary medications and by carefully evaluating new drugs using evidence-based research before

– **RISING COSTS** - continued on page 6

– **RISING COSTS** - continued from page 5

including them in one's arsenal of commonly prescribed drugs. Finally, clinicians can help decrease drug costs by selecting once-daily drug regimens, or half-tablet doses when they are appropriate.

Article Reviewer: Norm Muilenburg, R.Ph., Drug Information Specialist, Kaiser Permanente, Portland, Oregon.

References

1. Mullins, Palumbo and Stuart. The impact of pipeline drugs on pharmaceutical spending. Presented at a joint BCBS/HIAA Symposium; April 13-14, 2000
2. Levin-Epstein, M. Broad-based coalition to study effectiveness of new pharmaceuticals. *Managed Care*. 2000;9:13-14.
3. USA Today, Thursday, April 19, 2001
4. Reinhardt, Uwe. How to lower the cost of drugs. Op-Ed, New York Times. January 3, 2001
5. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. *Ann Intern Med.* 2001;134:479-486.
6. Cohen CI, Cohen SI. Potential cost savings from pill splitting of newer psychotropic medications. *Psychiatr Serv.* 2000;51:527-529.
7. Gupta P, Gupta K. Broken tablets: does the sum of the parts equal the whole? *Am J Hosp Pharm.* 1988;45:1498.
8. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacother* 1998;18:193-7.
9. Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *Am J Health-Syst Pharm.* 1999; 56:2542-2545.

More on COX-2 Inhibitors: CLASS and VIGOR Studies Prompt a New Debate - GI Safety versus Cardiac Risk

*By: **Michele Koder**, Pharm.D.*

The cyclooxygenase-2 inhibitors or COX-2s, celecoxib (Celebrex, Pharmacia/Pfizer) and rofecoxib (Vioxx, Merck), continue to be a controversial topic. On February 7th and 8th, 2001, Pharmacia/Pfizer and Merck aimed to demonstrate improved gastrointestinal (GI) safety over traditional NSAIDs to the FDA's Arthritis Advisory Committee. Upon submission of the original new drug applications (NDAs) in 1999, there was evidence of comparable efficacy and reduced incidence of endoscopic ulcers with COX-2s relative to the comparator NSAIDs studied (ibuprofen, diclofenac, and naproxen). Yet, the clinical significance of endoscopic ulcers has long been a matter of debate. Since the original NDA databases did not differentiate COX-2s from the comparator NSAIDs in terms of GI symptoms or PUBs (gastroduodenal Perforations, symptomatic Ulcers, or Bleeds), the standard NSAID GI warning template was included in the labeling for both products. Subsequently, the manufacturers conducted postmarketing studies, the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), in an attempt to resolve this issue. Based on results of these studies, the manufacturers submitted supplemental NDAs in which they petitioned the FDA to remove the NSAID GI Warning Template from their product labels. The Arthritis Advisory Committee's recent task was to review the CLASS and VIGOR studies and provide recommendations to the FDA regarding these petitions.

CLASS and VIGOR Highlights – CLASS and VIGOR were large, double-blind, randomized, comparator-controlled, company-sponsored studies designed to compare the incidence of clinically meaningful GI safety outcomes (eg, PUBs) of COX-2s to nonselective NSAIDs.[1,2] A summary of each is available in Table 1.

CLASS represents 1441 and 1384 patient-years of exposure for celecoxib and NSAIDs respectively. Approximately 57% of patients completed 6 months of therapy. CLASS did not demonstrate a statistically significant advantage in terms of the primary endpoint (complicated PUBs) at any time for celecoxib compared to NSAIDs, although trends were evident in favor of celecoxib. Post-hoc analysis of upper gastrointestinal (UGI) complications in the non-aspirin cohort resulted in an annual incidence of UGI complications of 0.44 % (n = 5) in the celecoxib group versus 1.27 % (n = 14) in the NSAID group (RR = 0.35; p = 0.04). Aspirin use, which was permitted, increased the risk of UGI complications by over 4-fold in the celecoxib group (p = 0.01) but not in the NSAID group. No significant differences were evident with respect to global safety and cardiac events, although there was a trend toward increased angina episodes and myocardial infarctions in the celecoxib group.

In VIGOR, the mean drug exposure was 8 months (range 0.5-13). About 29% of patients in each group discontinued their medication prior to study termination. Treatment with rofecoxib did result in significant reductions in both primary and secondary endpoints (PUBs and complicated PUBs respectively). The relative risk reduction was maintained in all important subgroups (eg, patients with a prior history of PUB, increased age). The number-needed-to-treat (NNT) to prevent 1 PUB was 62 and to prevent 1 complicated PUB was 191. Aspirin use was not permitted in the study. Furthermore, despite low absolute event rates (rofecoxib 1.7 % and naproxen 0.7 %), significantly more patients in the rofecoxib group experienced confirmed, cardiovascular thrombotic events, particularly myocardial infarctions, compared to naproxen. The RR for naproxen was 0.42. In a post-hoc analysis of patients in whom aspirin cardioprotection was "indicated" based on cardiovascular disease (CVD) risk factors and national guidelines, the RR for naproxen was 0.20. The corresponding NNT to result in a cardiovascular event was 156 for the entire patient population and 15 for patients with an indication for aspirin. It is expected that this NNT would be lower in the subset of patients at high risk for CVD events. Patients receiving rofecoxib also experienced more hypertension and congestive-heart-failure adverse events.

In each study, there was no separation between the time-to-UGI event curves until after 30-90 days. Therefore, there does not appear to be an advantage of COX-2s when used short-term. CLASS, VIGOR, and postmarketing data[3] confirm the high risk of complicated ulcers in elderly patients (≥ 65 years) and in patients with a prior history of ulcer disease or using steroids. Finally, the absolute event rates of UGI events in both studies were consistent with the range reported for the NSAID class in the GI warning template.

In summary, the risk reduction in UGI events did not translate into an overall safety benefit of rofecoxib or celecoxib over the comparator NSAIDs studied. Evaluation of routine safety parameters (deaths, serious adverse events, dropouts) showed no significant difference.

Table 1: CLASS and VIGOR Summary

	CLASS	VIGOR
Number Enrolled	8059	8016
Patients	OA and RA 69% Female Mean age 60 ~40% $ 65; ~12% $75	RA 80% Female Mean age 58 ~ 25% $ 65; ~ 5% $ 75
Randomization (n)	celecoxib 400 mg bid* (3987) ibuprofen 800 mg tid (1985) diclofenac 75 mg bid (1996)	rofecoxib 50 mg bid* (4047) naproxen 500 mg bid (4029)
Mean Exposure (Months)	4.2	8
Aspirin Use	>20%	No
UGI Complications, Annualized % (n) **NNT for COX-2**	RR = 0.53 (NS) 1E Outcome NNT=442	RR = 0.4 (p= .005) 2E Outcome NNT=191
Symptomatic Ulcers + UGI Complications, Annualized % (n) **NNT for COX-2**	RR = 0.59 (p = 0.02) 2E Outcome NNT=209	RR = 0.5 (p < 0.001) 1E Outcome NNT=62
MI % (n)	0.5 (19); 0.3 (14)† RR = 0.9 (NS)	0.4 (20); 0.1 (4) RR = 0.2 (p-NR)
NNT for rofecoxib CV event; CV event in ASA-indicated patient		NNT=156 NNT=15
Withdrawals due to Adverse Events	18.4 (732) 20.6 (822) RR = 0.89; (p < .01)	16.4 16.1 RR = 1.02; (NS)

OA = osteoarthritis; RA= rheumatoid arthritis; UGI= upper gastrointestinal, NR=not reported, NS=nonsignificant

* Higher than maximum recommended dose. The maximum recommended dose is 200 mg bid and 25 mg bid for celecoxib and rofecoxib respectively.

†Combined NSAIDS (ibuprofen plus diclofenac)

– **COX2 INHIBITORS** - continued on page 7

– **COX2 INHIBITORS** - continued from page 6

Arthritis Advisory Committee, Discussion and Recommendations – Present at the meeting were 4 rheumatologists, 1 gastroenterologist, 2 endocrinologists, 2 biostatisticians, 1 guest expert, 4 members of the FDA, 1 cardiologist, 1 consumer representative and manufacturer representatives. Committee members heard presentations from both Pharmacia/Pfizer and Merck, as well as gastrointestinal, medical/safety, cardiorenal, statistical and postmarketing safety reviews by expert members or consultants of FDA Advisory Committees. In their comprehensive review of material presented, members unanimously voted to retain the NSAID GI Warning Template for both celecoxib and rofecoxib on the basis of similar absolute event rates despite a relative advantage over NSAIDs.[4,5] The panel concluded that neither study demonstrated a "clinically meaningful" overall safety advantage for COX-2s over NSAIDs or supported a superiority claim for either product. The committee acknowledged that there is a large continuum of adverse event rates within the nonselective NSAID class and that it is difficult to generalize data from both CLASS and VIGOR to the general population.

It is evident from both CLASS and VIGOR that concomitant aspirin complicates the benefit-risk ratio since aspirin appears to offset the GI safety advantage of COX-2s. The committee expressed concern over the fact that the age group most likely to receive COX-2s is also the age group with the highest cardiovascular mortality and which is most likely to be on low-dose aspirin for either primary or secondary prevention. The committee noted that it is difficult to make general conclusions regarding UGI and cardiovascular toxicity based on post-hoc analyses of aspirin and non-aspirin-using subgroups and non-prespecified endpoints. They recommended that additional studies be conducted to further evaluate the concomitant use of aspirin and COX-2s. Also recommended were nonspecific additions to the products' labeling warning of cardiovascular safety and concurrent aspirin use.

Pharmacia/Pfizer and Merck disputed the committee recommendations in further discussions with the FDA. Subsequent press releases issued from both manufacturers in mid-April stated that the FDA has issued letters that GI labeling changes have been deemed "approvable" contrary to the recommendation of the advisory committee.[6,7] "Approvable" letters typically indicate the FDA's willingness to approve an application with the caveat that certain criteria be met or additional information be submitted. The letters do not contain the revised labeling. Although not required, the FDA usually follows advisory committee recommendations. If confirmed, these decisions mark a rare divergence on the part of the FDA.

Table 2: NSAID / COX-2 Cost Comparison[8]

Drug	Usual Dose	Cost per Month ^	Cost per Year ^
Salsalate*	1500 mg BID	$ 30	$360
Ibuprofen*	600-800 mg TID	$ 7-10	$84-120
Naproxen*	500 mg BID	$ 10	$120
Diclofenac*	75 mg BID	$ 40	$ 480
Celecoxib	200 mg QD 100 mg BID 200 mg BID	$ 67 $ 79 $ 134	$ 804 $ 948 $ 1608
Rofecoxib	12.5 mg QD 25 mg QD 50 mg QD	$ 67 $ 67 $ 98	$ 804 $ 804 $ 1176

* Cost of generic product.
^ AWP-11% or HCFA MAC rounded to the nearest dollar

CONCLUSION – These trials underscore an important dilemma when assessing the overall benefit:risk ratio of the COX-2s versus nonselective NSAIDs. It is difficult to make large generalizations based on CLASS and VIGOR due to the relatively short duration of the studies, the limitation to a small sample of the NSAID class and the exclusion of patients on aspirin in VIGOR. In theory, as the risk for developing arthritides such as osteoarthritis and rheumatoid arthritis increase with age, so does the risk of CV disease. In patients predisposed to CVD, a GI safety advantage of COX-2s may be offset by a cardiovascular detriment; therefore, the decision to use COX-2s or nonselective NSAIDs is highly dependent on individual patient characteristics and risks.

Based on the results of CLASS and VIGOR, the patients most likely to benefit from COX-2s are patients with risk factors for PUBs (eg, age > 60 years, history of PUB or corticosteroid use) and who are not taking, or are not candidates for aspirin cardioprotection. For patients at high risk for PUBs who require an NSAID and aspirin for cardioprotection, a nonselective NSAID plus a cytoprotective agent (eg, ibuprofen plus misoprostol or a proton pump inhibitor) would be preferred. For patients with low GI risk, salsalate, which exhibits a degree of COX-2 selectivity, remains a less costly alternative. Patients who fail 2 or more nonselective NSAIDs are also potential candidates for COX-2s. Short-term use of COX-2s is not recommended due to a lack of benefit over nonselective NSAIDs.

The comparative costs of COX-2s and NSAIDs remain an important factor in clinical decision-making. The COX-2s ranked among the top selling drugs in 2000.[9] Celebrex ranked #6 on the list, earning over $2 million, while Vioxx, with over $1.5 million in sales, ranked #13. Table 2 provides a comparison of costs to OMAP.

References

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: A randomized controlled trial. *JAMA* 2000; 284: 1247-55.
2. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *NEJM* 2000; 343: 1520-8.
3. Weaver J. Safety Evaluator, Division of Drug Risk Evaluation I, HFD-430OPDRA. Postmarketing Safety Review. December 29, 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_09_gi2.pdf Accessed March 2001.
4. Arthritis Advisory Committee for the Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. NDA # 20-988/S009, Celebrex, (celecoxib, Searle). February 7, 2001. Available at: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_01.pdf, http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_02.pdf, and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_03.pdf. pp 1-235. Accessed March 2001.
5. Arthritis Advisory Committee for the Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. NDA #21-042/S007, Vioxx, (rofecoxib, Merck). February 8, 2001. Available at: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_01.pdf, http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_02.pdf, and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_03.pdf. pp 1-241. Accessed March 2001.
6. Approval of softer Vioxx warning label expected. Available at: http://www.pharmscope.com/news/index.cfm?ID=15681&action=story&curDate=04/14/2001&NewsCatID=3&row=4. Accessed 4/11/01.
7. Celebrex labeling changes approved. Available at: http://www.pharmscope.com/news/index.cfm?ID=15818&action=story&curDate=04/14/2001&NewsCatID=3&row=1. Accessed 4/13/01.
8. April 2001 Update, 2000 Drug Topics Red Book. Medical Economics Company, Inc. Montvale NJ.
9. Top 200 drugs by retail sales in 2000. *Drug Topics* 2001; 6: 18.

DUR Board Vacancies

The DUR Board is a federally mandated board of health care providers that review and comment on the Prospective and Retrospective Drug Use Review programs for fee-for-service Medicaid recipients, administered by the Office of Medical Assistance Programs (OMAP). Education efforts (including this newsletter) addressing inappropriate prescribing patterns are a responsibility of the Board. It is also responsible for reviewing OMAP drug use policies and making recommendations to the agency.

The Oregon DUR Board is recruiting for two physician positions and one pharmacist position for the twelve-member board, which meets quarterly. This is an opportunity to have a voice in Oregon Medicaid drug use policy. Qualified persons must have experience in prescribing or dispensing drugs to Medicaid recipients or expertise in drug use review or quality assurance. Please make this announcement known to others who may be interested.

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

OSU College of Pharmacy
Portland Campus at OHSU
840 SW Gaines, MC 212
Portland, OR 97201-3098
E-mail: ketchumk@ohsu.edu

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 any correspondence to:

Kathy L. Ketchum, R.Ph., MPA:HA
OSU College of Pharmacy, 840 SW Gaines, Mail Code: GH212, Portland, OR 97201-3098
E-mail: ketchumk@ohsu.edu; Phone: (503) 494-1589; Fax: (503) 494-8797

Address Changes: Oregon Medicaid providers and pharmacies can provide OMAP with change of address information by fax at: (503) 945-6873 or by calling: 1-800-422-5047.

Produced and Supported by the
Oregon State University
College of Pharmacy

OSU College of Pharmacy
840 SW Gaines Street, MC: GH212
Portland, OR 97201-3098

Nonprofit Org.
US Postage Paid
Portland, OR
Permit #11