



The DUR Discovery

Exploring ways to improve pharmacotherapy

Why Drug Utilization Review?

Principles and Rationale

by Chris Owens, PharmD

Enacted nearly 15 years ago, the Omnibus Budget Reconciliation Act of 1990 (OBRA '90) was a legislative decision with significant impact on the practice of pharmacy that is still felt today. Two important aspects of OBRA '90 include specific patient counseling requirements and a mandate that each state establish a Drug Utilization Review (DUR) program to evaluate the prescribing and dispensing practices of outpatient prescription medications for Medicaid recipients. The DUR program's continuing mission is to assure that prescriptions are appropriate, medically necessary, and unlikely to result in adverse outcomes.

A DUR program consists of two parts: a governing board to oversee activities and a contractor to carry them out. The current DUR board is comprised of three physicians, three pharmacists, and one nurse practitioner. The board is responsible for evaluating practitioner prescribing or dispensing behavior, determining appropriate educational or corrective interventions, and overseeing the activities of the DUR contractor. Information obtained by the contractor is reviewed by the board members on a quarterly basis. The board's primary emphasis is educational; it does not censure nor withhold payment from Medicaid providers. However, in cases of obvious abuse, fraud, or malpractice, the board is obligated to report such instances to the appropriate authorities.

The College of Pharmacy at Idaho State University has served as the state's DUR contractor since 1993. During this time, significant effort has been expended

towards the design, implementation, and management of a comprehensive program to improve patient care and reduce overall drug costs in the state of Idaho. The following are examples of DUR activities:

- Retrospective analysis of patient drug usage, physician prescribing, and pharmacy dispensing activities
- Identification of current drug-related issues in the Medicaid population
- Identification and review of critical patient profiles
- Research studies into drug-related trends and the application of those studies into cost-savings plans

As well as having responsibility for data collection and analysis, the DUR contractor staff prepares and distributes educational materials to Medicaid providers and pharmacies. A biannual

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newsletter, such as the one you are reading now, highlights important DUR topics and is also prepared and distributed by the DUR staff. Past educational leaflets and newsletters may be accessed in pdf format for future reference on the ISU College of Pharmacy's website at: <http://pharmacy.isu.edu/live/services/dur/index.htm>. Comments and suggestions for the DUR program are welcome and can be made by contacting the DUR staff at (208) 282-4794 or by email DUR@otc.isu.edu.

Soma Safety

by Chris Owens, PharmD

Centrally-acting skeletal muscle relaxants (SMRs) are agents commonly used in the treatment of spasticity and acute painful musculoskeletal conditions of local origin, such as low back pain. Traditionally, SMRs have been classified as a single group; however, the adverse effect profile and potential for abuse among these agents differ significantly (see Table 1). The precise mechanism by

Although introduced in the 1950s, carisoprodol continues to be widely prescribed. However, beginning in the late 1980s, concern regarding its abuse has been growing. Anecdotal descriptions of a “buzz” or euphoria have been documented, particularly when combined with opioids. In addition, documented cases of withdrawal symptoms, drug-seeking behavior, and fatalities related to

Table 1: Muscle Relaxants

Brand	Generic	Usual Dose	Brand Cost*	Generic Cost*	Comments
Lioresal®	Baclofen	10-20mg TID	\$21.32	\$12.99	GABA analog; not as effective as other SMRs for pain
Soma®	Carisoprodol	350mg TID	\$106.01	\$13.99	Sedation and abuse potential
Parafon Forte DSC®	Chlorzoxazone	500mg TID	\$47.67	\$11.99	Hepatotoxicity; urine discoloration (red or orange)
Flexeril®	Cyclobenzaprine	10mg TID	\$35.99	\$7.99	Related to TCAs; use with caution in cardiac patients
Dantrium®	Dantrolene	100mg TID	\$87.09	N/A	Hepatotoxicity; photosensitivity
Skelaxin®	Metaxalone	800mg TID	\$62.89	N/A	Least sedating; Do not use in hepatic dysfunction or patients with history of drug-induced anemia
Robaxin®	Methocarbamol	1000mg QID	\$22.99	\$7.99	May lower seizure threshold; some abuse potential reported
Norflex®	Orphenadrine	100mg BID	\$69.99	N/A	Related to diphenhydramine; anticholinergic
Zanaflex®	Tizanidine	4mg TID	\$43.99	\$27.99	Related to clonidine; anticholinergic

*Cost based on 30 tablets per www.drugstore.com (4/2004)

which SMRs exert their clinical effects are poorly understood, but are thought to be strongly associated with their sedative properties. The evidence for their efficacy is extremely limited; however, better outcomes have been associated with SMRs in combination with acetaminophen or NSAIDs.

The abuse of SMRs in general has been reviewed in the literature. Carisoprodol (Soma®) is of particular concern and although it is unclassified in Idaho at this time, it is a schedule IV controlled substance in several other states. Despite its unclassified status, Idaho pharmacies have been asked to include carisoprodol in their monthly reporting of controlled substances and use of this agent is currently being tracked by the Idaho Board of Pharmacy.

carisoprodol have also been reported. Following oral administration, carisoprodol is metabolized in the liver to meprobamate, which is also biologically active. Meprobamate alone is a sedative-hypnotic formerly available under the trade names Miltown® or Equanil® (It is now only available generically). In the 1960s, meprobamate had a street value and was sold as “Uncle Milties” or “Bams.” Pharmacologically, meprobamate is related to the barbiturates and is a schedule IV controlled substance.

According to Idaho Medicaid claims data, carisoprodol was the second most prescribed SMR in 2003 (after Flexeril®) with approximately 2,000 patients and 10,000 claims that year. In terms of cost, carisoprodol was

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Opioids For Non-Malignant Pain

by Nikki Murdock, PharmD and Chris Owens, PharmD

Chronic non-malignant pain (CNMP) is a common cause of disability and is estimated to affect one in five adult Americans. The American Pain Society has endorsed the use of opioids for refractory chronic non-cancer pain when used according to published guidelines. Long-acting oral opioids are especially useful due to an extended duration of action, dosing convenience, and a tolerable adverse effect profile for most patients.

The two long-acting oral opioids morphine sulfate and oxycodone are routinely used in clinical practice and dosing and equipotent dose conversion guidelines are readily available. Methadone, on the other hand, is less commonly used and possesses important properties that clinicians must be aware of, including a variable (often long) half-life and extensive bioavailability, which make accumulation a concern following multiple doses. Furthermore, interpatient variability is even greater with methadone compared with other opioids. Individualization of dosing according to patient response is essential. Table 1 summarizes some important differences between long-acting oral opioids.

Although clinicians should not be deterred from using methadone to treat CNMP, particular attention must be paid to its dynamic and kinetic intricacies. Experience from the Veteran's Affairs (VA) medical system on the initiation and titration schedule of methadone demonstrates the drug's effectiveness and safety when used appropriately. A summary of VA guidelines for using methadone in CNMP is included in table 2.

It is important to note that with any opioid there may be large interpatient variability in the equianalgesic conversion ratio and a single ratio may not be applicable to all patients. Opioid dosing must be individualized and titrated slowly to response. As a general rule, start low and go slow. If a patient develops marked sedation (which may be a precursor to respiratory depression),

hold or decrease subsequent doses and/or lengthen the dosing interval. Patients should be reassessed frequently (~ once weekly) for adverse effects (drowsiness, lethargy, constipation) and efficacy during titration periods and then once monthly after a stable daily dose has been reached.

It is important to explain to patients that initial doses of a long-acting agent may often be inadequate for pain relief; starting low will help to avoid serious adverse effects such as respiratory depression. Patients should be encouraged to keep a pain medication diary, especially during the initiation and titration phases to help in

Table 1: Equipotent Doses for Oral Long-Acting Opioids

Generic	Brand	Equi-analgesic		Cost**†
		Dose (mg)	Dosing interval	
Morphine Sulfate	MS Contin®	30-40	30mg Q 8-12 hrs	\$59.78
	Avinza®*	30-40	30mg Q 24 hrs	\$81.30
	Kadian®*	30-40	30 mg Q 12-24 hrs	\$67.78
Oxycodone	Oxycontin®	15-30	20mg Q 12 hrs	\$88.33
			40mg Q 12 hrs	\$156.72
Levorphanol	Levo-Dromoran®	4	2mg Q 8 hrs	\$64.34 (60 tabs)
Methadone	Dolophine®*	10-20	10mg Q 6-24 hrs	\$6.33
	Methadone*	10-20	10mg Q 6-24 hrs	\$4.23

*Idaho Medicaid Preferred Drugs

**Cost based on 30 tablets per Redbook 2004.

† Prices are not reflective of the acquisition costs for Idaho Medicaid.

Table adapted from MICROMEDEX® Narcotic Analgesic Comparative Review (cited 6/2004)

achieving an appropriate dose. Oftentimes patients may want to be maintained on shorter-acting opioids for "quick relief," however, better outcomes and improved analgesia are associated with stabilized long-acting therapy with minimal use of shorter-acting agents available only for breakthrough pain.

For further information on appropriate monitoring of methadone therapy, you can visit the VA's website (<http://www.vapbm.org/pbm/drugmonitoring.htm>).

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Table 2: VA Guidelines for Methadone

Dosing for Initiation of Methadone			
Dosing Strategy	Initial Methadone Dose	Increments	Comments
Slow Titration	2.5mg q 8 hrs	↑ by 2.5mg q 8 hrs every 5 to 7 days	As a general rule, start low and go slow
Rapid Titration	2.5mg q 6 to 8 hrs	↑ by 2.5mg q 6 to 8 hrs as often as every other day over ~4 days	As a general rule, start low and go slow

Dosing for Patients Previously Receiving Opioid Therapy			
Morphine-Equivalent Dose of Opioid (mg/day)	Calculated Methadone Dose (mg/day)	Initial Methadone Dose	Increment
<200	15mg	5mg q 8 hrs	↑ by 15mg every 5 to 7 days PRN
200-500	~7% of morphine equivalent	Calculated methadone dose given in divided doses q 8 hrs	↑ by 15mg every 5 to 7 days PRN
>500	~7% of morphine equivalent	1/3 of calculated methadone dose given in divided doses q 8 hrs (with 2/3 of previous opioid dose)	Add 1/3 of calculated methadone dose every 5 days. Decrease previous opioid by 1/3 every 5 days. Complete conversion period=15 days

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ranked third among the SMRs in 2003, with a total expenditure of \$280,709. Of note, the majority of carisoprodol users in 2003 were prescribed the agent for longer than two weeks of therapy and half of these patients also received concomitant opioids.

It is recommended that if SMRs are prescribed, physicians should keep in mind that published studies support the use of non-opioid analgesics in combination

with them. Short-term use (< 2 weeks) is recommended as studies have not demonstrated long-term efficacy, and tolerance may develop rapidly. The Idaho Medicaid Pharmacy and Therapeutics (P&T) Committee recently reviewed the SMRs and determined that insufficient evidence exists to establish one of these agents as superior; however, due to reports of abuse potential, carisoprodol use is discouraged. Other SMRs with similar efficacy are preferable. If you have concerns regarding a particular patient, you may contact the Idaho Board of Pharmacy to request records of any controlled substance or carisoprodol prescription filled in the state.

Idaho Board of Pharmacy Contact Information:
Phone: (208) 334-2356
FAX: (208) 334-3536
Internet: <http://www.accessidaho.org/bop/index.html>

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Cost Corner: NSAIDS

by Tracy Pettinger, PharmD and Chris Owens, PharmD

Several pain and inflammatory conditions require the chronic use of non-steroidal anti-inflammatory drug (NSAID) therapy. Though effective for symptomatic relief, gastrointestinal (GI) adverse effects often limit their use, especially in elderly patients or those with pre-existing GI conditions. Agents with COX-2 selective activity are a relatively new group of NSAIDs with an improved GI safety profile. In clinical trials, these drugs have been shown to have comparable analgesic and anti-inflammatory actions to traditional NSAIDs, but also afford significant GI protection. Two such trials include the **Vioxx Gastrointestinal Outcomes Research (VIGOR)** study and the **Celecoxib Long-term Arthritis Safety Study (CLASS)**. In the VIGOR study, there were 2.1 GI events per 100 patient-years in the rofecoxib group compared with 4.5 GI events per 100 patient-years in the naproxen group ($p < 0.001$). The CLASS demonstrated similar results, with a GI event or symptomatic ulcer rate of 2.08% in the celecoxib group compared with 3.54% in the diclofenac and ibuprofen groups, respectively ($p = 0.02$). There are three COX-2 inhibitors currently available—celecoxib (Celebrex®), rofecoxib (Vioxx®), and valdecoxib (Bextra®). Of note, several traditional NSAIDs also have significant COX-2 selectivity in *in vitro* human assay studies, although the clinical applicability of these studies is unknown (See Table 1). The COX-2 inhibitors are much more expensive than traditional NSAIDs (See Table 1) and Idaho Medicaid spent over \$1.26 million on COX-2 inhibitor therapy in 2003 alone.

Currently, COX-2 inhibitors are recommended for patients in whom short- or long-term NSAID therapy is necessary, but where the potential for GI adverse effects and complications is high. At-risk patient populations include the elderly, those on concurrent corticosteroid therapy, individuals with poor overall health status, and those with a history of GI complications (peptic ulcers and/or GI bleeding). Although the risk of GI adverse events is reduced with COX-2 inhibitors, they are not free of GI adverse effects entirely. While it has been

shown that the rate of GI adverse events due to NSAID therapy is cut in half with the use of COX-2 inhibitors, it is still double that of the general population who are not

Table 1: Monthly Cost (AWP) of NSAIDs and GI Protective Agents

Generic	Brand	Strength	Cost/Month AWP*	COX-2 Selectivity**
COX -2 Inhibitors				
Celecoxib	Celebrex®	200mg QD	\$86.39	9
Rofecoxib	Vioxx®	25mg QD	\$86.27	80
Valdecoxib	Bextra®	20mg QD	\$91.47	18
Non-Selective NSAIDs				
Diclofenac	Voltaren®	75mg BID	\$62.58	4
Etodolac	Lodine®	400mg BID	\$107.86	23
		400mg ER QD	\$49.47	
Ibuprofen	Motrin®	800mg TID	\$9.59	0.4
Indomethacin	Indocin®	25mg TID	\$33.39	0.2
		75 mg ER QD	\$57.90	
Ketorolac	Toradol®	10mg QID	\$81.28	0.0003
Meloxicam	Mobic®	7.5mg QD	\$77.10	11
Naproxen	Naprosyn®	500mg BID	\$77.92	0.3
GI Protective Agents				
Esomeprazole	Nexium®	40mg QD	\$132.63	n/a
Lansoprazole	Prevacid®	30mg QD	\$151.93	n/a
Omeprazole	Prilosec OTC®	20mg QD	\$19.99	n/a
		(28 tabs)		
Pantoprazole	Protonix®	40mg QD	\$105.38	n/a
Rabeprazole	Aciphex®	20mg QD	\$128.26	n/a
Misoprostol	Cytotec®	200mcg QID	\$143.90	n/a

* Cost based on 30 tablets/capsules per Redbook 2004

**Based on 80% inhibitory concentration ratios of COX-2 relative to COX-1 in human whole blood assays

taking NSAIDs. In addition, the use of low-dose aspirin (81mg) therapy was shown to diminish the beneficial GI effects of COX-2 inhibitors in the CLASS trial.

Besides COX-2 therapy for GI protection, the use of a traditional NSAID coupled with a proton pump inhibitor (PPI) or misoprostol has also been shown to be of benefit. Patients who are already on a PPI or misoprostol do not necessarily need a COX-2 inhibitor for further GI protection. In one pharmaco-economic study, the number of GI events with celecoxib therapy was 115 per 1000 patients compared to 119 and 220 per 1000 patients in

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those on a traditional NSAID plus a PPI or misoprostol, respectively. The combination of a PPI and a traditional NSAID may also provide a less expensive treatment option. Prilosec OTC[®], which requires no prior authorization and is covered by Idaho Medicaid, is much less expensive than the others in this class (See Table1).

In summary, COX-2 inhibitors should be reserved for patients who are most at-risk for GI complications. The use of a PPI and a traditional NSAID may actually be less expensive while also affording similar GI protection. While sample medications can be provided free of charge to the patient, especially when initiating anti-inflammatory therapy, it is important to consider that either Medicaid or the patients themselves may eventually assume the cost of these higher priced medications.

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