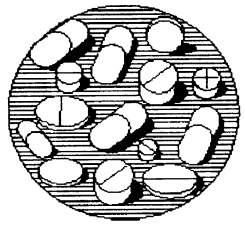
OREGON DUR BOARD NEWSLETTER



Vol. 1 No. 4 May 1999

COX-2 Inhibitors – The Next Generation of NSAIDs: A Review of Celecoxib (Celebrex®)

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Celecoxib (Celebrex®) is the first of a new generation of NSAIDs to become available in the United States. It is a selective COX-2 inhibitor and is approved for the treatment of osteoarthritis and rheumatoid arthritis. This article reviews celecoxib and its place in therapy.

PHARMACOLOGY Cyclooxygenase (COX) is an enzyme which mediates the production of prostaglandins (PG) involved in regulatory cell functions and inflammatory processes. Two isoforms of COX have been identified. COX-1 is found in most cells and tissues. It is a 'housekeeping enzyme' and is responsible for the production of PGs involved in homeostatic functions. Its effects can be seen in the gastrointestinal (GI) tract, kidneys, and platelets where it generates PGs responsible for GI cytoprotection, and renal and vascular homeostasis.[1,2,3] COX-1 also contributes to the production of inflammatory PGs and has been identified in the synovial fluid of rheumatoid arthritis (RA) patients.[3]

COX-2 is not generally expressed in the basal state but is rapidly induced in cells such as macrophages and neutrophils at sites of inflammation. It is responsible for the production of pro-inflammatory prostaglandins [1,2,3] and synovial tissues of RA patients contain increased levels of COX-2. [2]

Both COX-1 and COX-2 have been isolated in inflamed gastric mucosa. It is believed that COX-2 is induced in response to inflammation and its adaptive response may be to increase PG production in the gastric mucosa.[3] The effects of COX-2 inhibition on this mechanism are unknown.

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Inside this issue:

Recommendations for the Pharmacologic Management of Chronic Pain

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Chronic pain affects over 50 million Americans (20% of the US population) and results in over $70 billion annually in health-care costs and lost productivity.[1] This article will focus on the oral pharmacologic treatment of chronic pain. This area has a divergence of opinions and practice with much of the debate centered on opioid drugs.[2 3 4 5 6 7 8 9] However, considerable information and experience has been gained through the long-term use of opioids in cancer patients that can be adapted to other chronic pain conditions. Several guidelines are available for the treatment of cancer pain (e.g. WHO and ACHPR). [10 11]

Acute pain and chronic pain differ in many respects and are therefore managed differently. The goals of chronic pain therapy are to decrease pain and suffering and increase daily functioning and physical activity. Chronic pain is typically classified into four types: 1) pain persisting beyond the normal healing time for a disease or injury, 2) pain related to chronic degenerative disease or a persistent neurological condition, 3) pain that emerges or persists (even recurring for months to years) without an identifiable cause and 4) cancer pain.[10] Frequently, a chronic pain sufferer presents with a complex collection of signs and symptoms that may not have a direct connection to the initial injury and tissue damage that started the process (Table 1).

Table 1. Symptoms, signs and problems of chronic pain

Pain	Depression, anxiety
Inactivity	Anorexia
Altered family dynamics	Sleep disturbances
Increased health care visits	Frustration, anger
Frequent use of medication	Decreased libido
Financial stresses & concerns	Decreased self-esteem
Work issues	Diminished physical condition
Legal issues	
Diminished involvement in social activities	

Given the complexity of most chronic pain problems, successful treatment must proceed on several fronts. The chance for success is enhanced if multiple interventions are combined in a coordinated effort. For patients with a poor response to initial

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In theory, agents which are selective inhibitors of COX-2 might produce less toxicity than non-selective inhibitors. However, much remains to be learned regarding the contribution of COX-1 and COX-2 to inflammatory disease and NSAID safety.[3] One should not assume that all gastric, renal and hemostatic toxicity is principally the result of COX-1 inhibition and that COX-2 inhibitors will be devoid of these toxicities. Other mechanisms distinct from PG inhibition are also thought to be involved in the safety and efficacy of NSAIDs.[3]

Celecoxib is the first available NSAID designed to selectively inhibit COX-2. Other NSAIDs are non-selective or less selective for COX-2. Peak absorption of celecoxib occurs approximately three hours after an oral dose and although food delays time to peak plasma levels, total absorption is relatively unaffected.[4] Celecoxib is extensively metabolized in the liver via cytochrome P450 (CYP 2C9 with minor metabolism through CYP2D6). Its metabolites are inactive. The half life of celecoxib is approximately 11 hours which allows once or twice daily dosing.[4]

EFFICACY NSAIDS have only modest benefit in the treatment of osteoarthritis (OA) and are now considered as second-line to acetaminophen therapy. Celecoxib has comparable efficacy to ibuprofen, naproxen or diclofenac in the treatment of osteoarthritis. Celecoxib at doses of 100mg or 200 mg twice daily was statistically comparable in efficacy to naproxen 500mg twice daily in treatment of OA, although celecoxib 50mg twice daily was not better than placebo.[4] Response to celecoxib 200mg once daily versus 100mg twice daily was no different in patients with OA.[5,6]

NSAIDs play an adjunctive role in the treatment of rheumatoid arthritis (RA); they are not a substitute for aggressive treatment with disease modifying antirheumatic drugs. Celecoxib is comparable to ibuprofen, naproxen or diclofenac in the treatment of RA.[5,6]

Celecoxib has also been studied in pain models of acute post-surgical pain and osteoarthritis pain flare. In acute OA pain flare, celecoxib has a slow onset of pain relief of about 24 hours. Although celecoxib was shown to be more effective than placebo, onset of pain relief was quicker with ibuprofen and naproxen in acute post-surgical pain models. The FDA Advisory committee did not feel the data was strong enough to substantiate the use of celecoxib for relief of acute pain, thus celecoxib was not approved for this indication.[5]

ADVERSE EFFECTS Endoscopically proven ulcers occurred in 26% of OA and RA patients receiving naproxen 500 mg twice daily for 12 weeks, compared to 4% taking celecoxib or placebo for a comparable period of time.[5,6] Serial endoscopies over a 6 month period demonstrated significantly greater incidence of gastric and duodenal ulcers in ibuprofen (800 mg TID) and diclofenac (75 mg BID) groups in comparison to celecoxib 200 mg BID) at all time points.[4,5] However, one study showed no significant difference between celecoxib and diclofenac in terms of endoscopic ulcers.[4,5] Dyspepsia and other GI symptoms occur with celecoxib as with other NSAIDs.

It is not clear if endoscopic findings are a reliable predictor of major GI events. The prevalence of endoscopic lesions in patients on long-term NSAID treatment is about 15% to 25%.[7,8,9] However most patients never develop a clinically significant GI complication. The risk of hospitalization for serious GI adverse effects is approximately 1% in patients treated for 3-6 months and 2%-4% in patients treated for one year.[4,6,9]

The correlation between COX-2 selectivity and GI toxicity is not proven (Table 1). It is proposed that gastric mucosal safety is a multi-factorial problem which involves a variety of mechanisms in addition to PG production.[3] Any conclusion regarding GI safety profile for COX-2 inhibitors in the general population must await large endoscopic and outcomes studies which will evaluate the true risk of NSAID-induced GI events (i.e. ulceration, perforation, bleeding).

In terms of renal effects, current adverse effects data for celecoxib indicate that the incidence of renal adverse effects is similar to comparator NSAIDs. Peripheral edema and changes in sodium excretion occurred at similarly low rates with both celecoxib and naproxen, and more frequently than placebo.[5] Celecoxib does not cause significant inhibition of platelet activity.[5]

Table 1. GI Toxicity Index

NSAID	*GI toxicity index ✣*	*Ratio of concentrations needed to inhibit 50% of COX enzymes Cox-2/Cox-1 ✦*
Salsalate	*0.81 ± 0.51*	*Not available (NA)*
Ibuprofen	*1.13 ± 0.29*	*15*
Aspirin	*1.18 ± 0.18*	*166*
Sulindac	*1.68 ± 0.29*	*100*
Diclofenac	*1.81 ± 0.35*	*0.7*
Naproxen	*1.91 ± 0.21*	*0.6*
Piroxicam	*2.03 ± 0.24*	*250*
Indomethacin	*2.39 ± 0.34*	*60*
Celecoxib	*Unknown*	*0.00266 (1/375)*

✣ *Sum of GI symptoms/patient-year in 6,276 courses of treatment (Singh G. Recent considerations in NSAID gastropathy. Amer J Med 1998;105(1B):31S-38S)*

✦ *A value of 1 would indicate equal inhibition of the two forms of COX. >1 indicates predominant COX-1, <1 indicates predominant COX-2. (Taketo MM. COX-2 inhibitors in tumorigenesis (Part1). J Nat Cancer Institute 1998;90:1529-1536. ; Vane RF and Botting RM. Mechanism of action of anti-inflammatory drugs. Scand J Rheumatol 1996;25(suppl102):9-21)*

DRUG INTERACTIONS Caution is advised with drugs that inhibit CYP2C9 (e.g. fluconazole) or are metabolized by CYP2D6 (e.g. fluoxetine). Patients taking CYP2C9 inhibiting drugs should be initiated at the lowest dose of celecoxib. Co-administration of celecoxib and lithium may result in increased lithium concentrations. It is advised that lithium concentrations should be monitored when celecoxib is added to, or removed from therapy. Notably, celecoxib does not appear to affect prothrombin time when co-administered with warfarin, although caution is still advised. There is no known interaction between celecoxib and methotrexate.[4]

DOSAGE Celecoxib is indicated for relief of signs and symptoms of osteoarthritis and rheumatoid arthritis. The recommended dose for osteoarthritis is 100mg twice daily or 200mg once daily (which is less expensive). For rheumatoid arthritis 100mg to 200 mg twice daily is recommended. Geriatric patients of low weight (<50kg) and patients with hepatic insufficiency should be initiated with the lowest dose.[4]

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RECOMMENDATIONS Celecoxib has similar efficacy to ibuprofen, naproxen or diclofenac in the treatment of osteoarthritis or rheumatoid arthritis. Failure to respond to these NSAIDS is not an indication for celecoxib.

It is not clear whether there is a consistent relationship between endoscopic lesions and clinically relevant complications.[8] At this time, there is no published data to indicate that celecoxib would decrease the risk of clinically important gastrointestinal complications in the general population.

Prior to prescribing NSAIDs, patient risk factors (Table 2) and therapeutic alternatives should be considered. The simplest way to eliminate risk of NSAID induced gastropathy is to avoid use of NSAIDs, especially in high-risk patients.

Table 2. Risk factors for NSAID-induced gastropathy[7,8,9]

- Elderly
- Prior history of peptic ulcer
- High NSAID dose
- Concurrent use of anticoagulants, corticosteroids, ethanol, or tobacco

The American College of Rheumatology recommends non-pharmacologic modalities and acetaminophen in doses up to 4,000mg/day in patients with osteoarthritis requiring analgesia.[10] Patients with OA failing to respond to acetaminophen should try low-dose ibuprofen (<1600 mg/day) or nonacetylated salicylates (e.g. salsalate) and potentially topical analgesics (e.g. methylsalicylate or capsaicin cream).[10] Inadequate response to this second step may justify use of full-dose NSAIDs. [10]

Table 3. Cost comparison of NSAIDs

Drugs	Dose	OMAP Cost per month**
Piroxicam* (Feldene®)	20 mg QD	$2.32
Ibuprofen* (Motrin®)	600 mg TID	$3.35
Aspirin*	650 mg QID	$6.58✦
Sulindac* (Clinoril®)	150 mg BID	$9.82
Naproxen* (Naprosyn®)	500 mg BID	$10.21
Salsalate* (Disalcid®)	1500 mg BID	$27.91
Etodolac* (Lodine®)	400 mg BID	$32.61
Diclofenac* (Voltaren®)	75 mg BID	$51.63
Nabumetone (Relafen®)	500 mg BID	$60.36
Misoprostol/Diclofenac (Arthotec®)	200μg/75 mg BID	$69.67
Celecoxib (Celebrex®)	200 mg QD 100 mg BID 200 mg BID	$60.31 $71.27 $120.61

* Prices listed for generic
** 2/99 Red Book AWP - 11% or MAC
✦ Estimated price

If it is decided that an NSAID is required and will be used long-term, the patient's risk factors for development of NSAID-induced gastropathy should be considered. Patients who are at a low risk should be placed on the least toxic, least expensive, and lowest effective dose of an older NSAID such as ibuprofen or naproxen. When patients at higher risk for GI events (>2 risk factors) require NSAID treatment then use of a protective agent will help to prevent gastropathy. Prophylaxis for all patients taking NSAIDs is unnecessary[7] but it has been shown that selective use of preventative agents will reduce the cost per averted GI event.[11]

Since there is strong evidence to support the efficacy of misoprostol[7,10,11] and some evidence supporting omeprazole [7] for prevention of NSAID-induced gastropathy, one of these agents should be selected for use in patients with multiple risk factors. Misoprostol is also preferred in high risk patients following the healing phase of NSAID-induced ulcers to maintain ulcer remission if NSAIDs must be continued. H2 antagonists have little or no effect in the prevention of NSAID induced gastric ulceration.[7]

With the currently inconclusive evidence for selective COX-2 inhibitors, celecoxib should not be considered a substitute for cytoprotection.

Before celecoxib is widely used, it would be prudent to consider the experience with the use of meloxicam, a COX-2 inhibitor which has been available in Europe.[6] In clinical trials meloxicam appeared to be relatively safe in terms of gastrointestinal effects. However, within 21 months of the product launch in the UK, the Committee on Safety of Medicines (CSM) changed the guidelines for use of meloxicam in response to several reports of severe gastrointestinal effects. There were a total of 1,339 adverse events reported to the CSM, of which 41% were gastrointestinal and 18% of these were reports of perforations, ulcer or bleeding (99 cases and 5 deaths).[5]

There is potential for celecoxib to be used incorrectly if it is perceived to be safe. The FDA has required the product labeling for celecoxib to contain the same warnings regarding adverse events as other NSAIDS [5] Until post-marketing data is available celecoxib should not be assumed to be any safer than currently available NSAIDs in terms of major GI effects. ■

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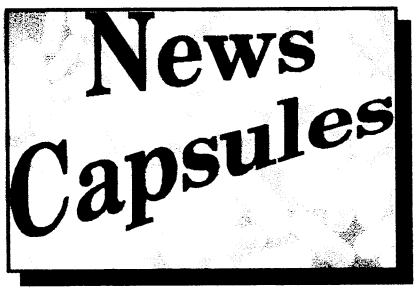

CAUTION RECOMMENDED WITH NEW PDE-III INHIBITOR.

Cilostazol (Pletal®), approved by the FDA in January 1999, is the first new compound approved for the treatment of intermittent claudication in 15 years. As there are few effective treatment options available for this condition and there is an increasing elderly population in the US, the potential market for this agent is large.

Cilostazol is a phosphodiesterase (PDE) III inhibitor. This is a class of drugs which includes agents such as milrinone and vesnarinone, positive inotropes which were associated with increased deaths in patients with class III-IV heart failure. Animal studies have shown that cilostazol acts as positive inotrope. For these reasons it is expected that cilostazol will have a PDE III class effect in patients with severe heart failure.

Clinical studies of cilostazol did not include patients with severe heart failure, although some patients had histories of myocardial infarction or diabetes. There were a total of 19 deaths during clinical trials, 12 patients on cilostazol and 7 on placebo. Five of the deaths could be described as sudden death (2 cilostazol and 3 placebo). These studies were not large enough to establish whether cilostazol has any adverse survival effects on patients without heart failure. The manufacturers have agreed to study the mortality effects of cilostazol in over 1,800 sicker patients in clinical trials of about a year duration.

Meanwhile, cilostazol has been approved for use by the FDA but it should never be used in any patients with cardiac failure of any severity. FDA approval of cilostazol was on the basis that patients, without heart failure, who are properly informed of the risks of treatment could decide whether to accept the incompletely characterized risk of cilostazol. We wish to re-emphasize this to prescribers to ensure that patients are made aware of these risks.

Other treatment options are available. It is already known that exercise programs and smoking cessation are effective in the treatment of intermittent claudication. A supervised exercise program, equivalent to walking a treadmill for 30 minutes three times a week is an alternative option which could be made available to patients.

Reference: Approval of Cilostazol http://www.fda.gov/cder/news/cilostazol/approval.htm

CAUTION WITH LEFLUNOMIDE DOSES

- Leflunomide (Arava®) is an immunosuppressant agent which was approved for use in the treatment of rheumatoid arthritis in November 1998.
- The maintenance dose of leflunomide is 10-20mg daily. This maintenance dose should not be exceeded due to an increased risk of side-effects.
- Leflunomide has a long half-life and the manufacturers recommend a loading dose schedule in order to reach steady-state rapidly. Without a loading dose it is estimated that it would take nearly two months to reach steady state concentrations.
- The loading dose of leflunomide is 100mg per day for three days. All patients should be switched to the maintenance dose, 10mg-20mg daily, after this three day period.

As with other immunosuppressants, leflunomide is a potentially harmful if used at excessive doses. It is critical that the loading dose period does not extend for longer than this three day period. For this reason the DUR Board has set the excessive dose ProDUR alert for this drug at **20mg daily**.

RETROSPECTIVE DUR TAKES PROVIDER REQUESTS

The drug use review (DUR) program is responsible for improving quality and coordination of health care to Medicaid recipients. The retrospective DUR program (RetroDUR) assists the State of Oregon in complying with federal regulations, detecting fraud and abuse, and identifying trends in medication use. The RetroDUR program also coordinates with a prospective DUR program.

Each month a council of Oregon physicians and pharmacists perform blind reviews of several hundred patient drug profiles using state-funded health care. These profiles are selected according to therapeutic classes chosen by the DUR Council or are patient profiles specifically requested by a provider. If potential problems are identified, letters of information are sent to providers requesting feedback.
These programs can assist providers by:

- Alerting you to patients who access multiple providers.
- Tracking suspected drug seekers.
- Identifying drug duplications, interactions, or contraindications with information you may not have been aware of.

Review requests can be made by calling Rose-Ellen Hope of First Health Services Corporation at 503-391-0184. There is no charge to the provider for this service.

The following recommendations are offered to Providers to improve chronic pain treatment:

1.) Patients that use opioid drugs chronically (often defined as daily use for more than 3 months) should get pain prescriptions from one provider and one pharmacy to insure good coordination of care. It may be prudent to initiate a pain management contract with the patient to meet the Oregon Intractable Pain Law and adhere to Federation of State Medical Boards (FSMB) recommendations.
2.) Chronic pain patients should be treated with scheduled doses of analgesic. "As needed" doses may also be required for acute exacerbations. Prescribing analgesics on an "as needed" basis only does not adequately control pain and may negatively influence the situation.
3.) Meperidine, propoxyphene, agonist-antagonist opioids and partial agonist opioids are not recommended for chronic use and should be limited to treatment of acute pain.
4.) Duplicate long-acting (e.g. Oxycontin® and Duragesic®) or duplicate short-acting (e.g. Percocet® and Vicodin®) compounds are inappropriate. However, a scheduled long-acting compound and an "as needed" short-acting compound is recommended by many pain experts.
5.) Regular pain assessment by the provider is recommended, especially in the early stages. This may be daily, weekly or monthly depending on the situation. Limit the supply of analgesic to correlate with the assessment period. 30-day supplies are appropriate for stable patients.
6.) Recognize or prophylactically treat for known side-effects (e.g. constipation or histamine release with opioids).
7.) Patients that repeatedly seek refills early may not be adequately controlled and therefore should be immediately reevaluated and potentially referred to a pain specialist (preferably a multi-disciplinary clinic) or alternatively to an addiction specialist.

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primary care treatment, referral to a multi-disciplinary pain clinic providing integrated care can serve to establish a pain management plan and provide patients with greater access to treatment options. Furthermore, a meta-analysis of the literature revealed significant, lasting changes in pain, mood, work and use of the health care system when patients were treated at multi-disciplinary pain centers as compared with patients not receiving treatment or those receiving single-discipline treatment. [12]

Critical issues to consider for chronic pain management with analgesics are:

- Patient assessment as to appropriateness of long-term analgesic use
- Establishment of the goals and parameters of therapy before initiating analgesics
- Evaluation and follow-up of pain relief
- Drug selection to maximize functioning, minimize adverse effects and maximize cost-effectiveness.

Effective pain relief can be accomplished by the anticipation and prevention of pain. If pain is persistent or recurs daily, it is important to use continuous (around-the-clock) dosing of the drug selected. Patients should be given "as needed" doses for anticipated increases in pain (i.e. traveling, procedures, bedtime), for breakthrough pain and when initiating therapy to determine the daily dosing requirements. Unless pain is totally out of control, maximum doses over a two week period should be tried before moving to a different drug.

NSAIDs Many treatment algorithms suggest using NSAIDs first for chronic pain not controlled by acetaminophen. Most of the literature evaluating their efficacy, dose response and adverse effects involves patients with either rheumatoid arthritis or osteoarthritis and the applicability of these data to other chronic pain patients has been questioned.[13] The exact correlation between the anti-inflammatory effect of NSAIDs and pain relief is not known, but the lack of an ongoing inflammatory process in many patients with chronic pain may explain the frequent failure of NSAIDs to provide analgesia in this subset of pain sufferers.

NSAID use is associated with an increased incidence of hospitalization and death from ulcer disease, alteration in platelet function and risk of renal impairment.[14 15 16] NSAIDs have an important, but limited role in chronic pain management. They are often effective for acute "flares" of chronic conditions and for patients with painful arthritides and certain types of headaches and fibromyalgia. It is important to caution patients regarding the potential adverse effects of NSAIDs and discourage patients from taking more than one NSAID (including aspirin) at a time.

Opioids Opioids have been used for centuries to treat pain, and they provide the mainstay of acute and chronic pain treatment today. If opioids are selected, setting realistic expectations for the patient is key factor for success. Side effects, adverse consequences and alternatives need to be discussed in detail. Many pain experts require the patient to sign an "opioid contract". The contract serves as a foundation for the mutual understanding between provider and patient of the implications of using opioids in the management of chronic nonmalignant pain. Additionally, in Oregon, the contract serves to meet the requirements of the Intractable Pain Law and is recommended in the guidelines produced by the Federation of State Medical Boards (FSMB) of the United States.

Opioids interact at specific receptors to mediate a host of effects including analgesia, sedation and antitussive actions. Opioid side effects including cognitive impairment, constipation, nausea, and vomiting are well known. Although these adverse effects are often manageable, they occur frequently and may limit the acceptance of opioids by patients and clinicians.

Continued exposure to high doses of opioids can cause tolerance (progressive decline in the effectiveness of drug, requiring higher doses for the same analgesic effect). Tolerance to morphine causes a partial tolerance to other drugs in the class and vice versa. Apparent tolerance needs evaluation because it may actually be disease progression. It is important to note that tolerance to serious adverse effects (sedation and respiratory depression) typically appears more quickly than to the analgesia, thus enhancing safety. When titrated appropriately, pure opioid use is not associated with a maximum effective dose or "ceiling".

Dose-related tolerance should not be confused with addiction which is mediated differently physiologically and has a large psychological component. A study has examined the incidence of induced opioid addiction in 12,000 patients and found that only four cases of new addiction were identified among patients with no previous history of drug abuse.[17] Furthermore, experience has shown that addicts can benefit from judicious use of opioids for pain treatment. Inadequate treatment of pain can induce a syndrome called "pseudoaddiction" which is manipulative behavior exhibited by patients merely to get good pain control.[18]

Opioid drugs are dosed to achieve a therapeutic effect that is balanced against the adverse effects experienced. The dose required depends on the severity of pain perceived as well as on the patient's prior exposure to opioids. For this reason, patients with a history of abuse of street narcotics (e.g. heroin) may require extremely high doses of opioid to treat simple acute pain. However, rapid dose escalation is most common when pain is not treated effectively, the disease process is worsening, there is an environmental life crisis influencing the situation or in drug addiction.

It is difficult to predict which opioid, at which dose, will work best for any given individual. There are some notable differences between opioids. Codeine is converted enzymatically in the body to morphine by an enzyme lacking in 3-10% of the population and is of lower potency.

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Codeine, propoxyphene and the more potent hydrocodone are primarily available in combination and therefore reach a maximum dose based on the combination ingredient (aspirin, acetaminophen or ibuprofen). Propoxyphene is of limited potency and its metabolite can accumulate over time and is associated with seizures. It is thus not recommended for long-term, continuous use. Meperidine is useful for severe acute pain, but should not be used for extended periods or in patients with renal insufficiency because of the risk of toxicity due to the build up of its metabolite (normeperidine).

Mixed opioid agonist-antagonists or partial agonists (e.g. butorphanol, pentazocine, nalbuphine or buprenorphine) can precipitate withdrawal symptoms in opioid dependent patients and have toxicity limitations. They are not first line agents for chronic pain. Additionally, the use of a mixed or partial agonist in combination with a pure opioid (e.g. Stadol-NS® , Vicodin®) is counterproductive as they compete for the same receptor and reverse the effect of the other.

Morphine is the gold standard for the treatment of severe, chronic pain not controlled by scheduled doses of acetaminophen, NSAIDs or opioid combinations. However, other drugs in the class (methadone, hydromorphone, oxycodone and fentanyl) are equally effective and may be better suited in individual situations.

Methadone, once reserved for opioid addiction treatment, is a low cost, effective alternative for the treatment of severe pain. The advantage of methadone is its high potency and long half-life which may allow twice or three times daily dosing. It has a potential to accumulate with repetitive dosing, particularly in elderly patients. Providers should use caution and watch for excessive sedation during the first week of therapy or after recent dose increases.

Tramadol is another alternative for chronic pain patients. It is a centrally acting analgesic that binds weakly to μ-opioid receptors (10-fold less than codeine) and also inhibits norepinephrine and serotonin reuptake.[19] It appears to be clinically effective for the management of some moderate to moderately severe pain, providing comparable efficacy to acetaminophen with codeine.[20] However, the potential for abuse of tramadol has recently been highlighted. It is also associated with seizures at doses above 400mg/day. The ceiling dose is less in patients with reduced hepatic or renal function, the elderly, thosepatients that are a seizure risk and when combined with drugs that interact at the CYP2D6 isoenzyme (e.g. TCAs and SSRIs). The usefulness of this drug is limited by these factors. Tables 2 and 3 compare equipotent or usual doses and cost of analgesics for chronic pain.

Table 2 - Opioid Analgesics for Severe Chronic Pain

Long Acting Opioid	Equipotent dose to MS 10mg IV*	Dosing Interval	OMAP Cost/Month**
Methadone (generic)	10 mg^	q8h	$12.60
Duragesic Patch®	25 mcg (based on 24hr equivalent)	q3d	$104.65
Oxycontin®	20 mg^	q12h	$119.70
MS Contin®	30 mg	q8-12h	$101.15 - 151.70
Ora Morph®	30 mg	q8-12h	$101.15 - 151.70
Short Acting Opioid			
Morphine liquid (generic)	30 mg	q3h	$92.55
Oxycodone tablet (generic)	15 mg^	q3h	$156.65
Oxycodone liquid (generic)	15 mg^	q3h	$216.60
Hydromorphone tablet (generic)	8 mg	q3h	$241.35
Morphine tablet (generic)	30 mg	q3h	$362.60
*No set dosing exists for opioids. These numbers are presented to illustrate the relative potencies and titration is always necessary. MS=Morphine sulfate			
**12/98 Red Book AWP - 11% or MAC			
^Doses are more conservative (½ the dose) than published literature and are based on clinical experience.			

A variety of medications that were not originally designed as analgesics are helpful for certain types of chronic pain (Table 4). They lack FDA approval for pain indications but are none-the-less very effective for certain conditions (e.g. neuropathic pain or headaches). Adjuvant medications often used in selected chronic pain states include antidepressants, antiarrhythmics, anticonvulsants and topical agents.[21,22,23,24,25]

Please turn to **Chronic Pain**, on page 7

Table 3 - Combination Analgesics for Mild to Moderate Pain

Drug	Equipotent dose to MS 10mg IV*	Dosing Interval	OMAP Cost/Month**	Maximum Safe Dose***
Acetaminophen 500mg / Hydrocodone 5mg (generic for Vicodin®)	7.5 mg	q4h	$11.78	8 tablets/day
Acetaminophen 325mg / Oxycodone 5mg (generic for Percocet®)	15 mg	q4h	$29.70	12 tablets/day
Acetaminophen 300mg / Codeine 30mg (generic for Tylenol #3®)	200 mg	q4h	$31.50	12 tablets/day
Acetaminophen 500mg / Hydrocodone 7.5mg (generic for Lortab®)	7.5 mg	q4h	$33.07	8 tablets/day
Aspirin 325mg / Codeine 30 mg (generic for Empirin #3®)	200 mg	q4h	$99.00^	22 tablets/day
Aspirin 325mg / Oxycodone 4.5mg (generic for Percodan®)	15 mg	q4h	$129.62	22 tablets/day
Ibuprofen 200mg / hydrocodone 7.5mg (Vicoprofen®)	7.5 mg	q4h	$143.06	16 tablets/day

* Based on the opioid component only; these numbers are presented to illustrate the relative potencies and titration is always necessary. MS = morphine sulfate.

** Reflects equipotent or maximum dose (whichever is lower); 12/98 Red Book AWP - 11% or MAC

*** Based on APAP, ASA or ibuprofen

^ Estimated.

Chronic Pain, continued from page 6

These medications typically take several days to weeks to achieve efficacy, may require dose titration and have limited use for patients with acute pain. They do not bind to opioid receptors and lack anti-inflammatory activity. Most adjuvant medications appear to work either as nerve membrane stabilizers (e.g. anticonvulsants, mexiletine) or affect levels of neurotransmitters involved in pain pathways (e.g. antidepressants).

Tricyclic antidepressants (TCAs) can improve disturbed sleep, which is often a problem in patients with chronic pain.[26] They have proven efficacy in treating neuropathic pain and in headache prophylaxis. Selective serotonin reuptake inhibitors (SSRIs) are inferior to TCAs in the treatment of neuropathic pain.

Carbamazepine has a long history of beneficial use in treating trigeminal neuralgia and it may be helpful for other sharp, shooting neuropathic pains. A newer anticonvulsant, gabapentin, holds promise for the treatment of neuropathic pain.[27 28 29] It offers several advantages including relatively quick onset, no known drug interactions, and no metabolism in the body. However it should not be used as a first line agent. A commonly prescribed adjuvant, barbiturates (e.g. in Fiorinal®) are known to aggravate the rebound headache phenomenon and should be avoided when treating chronic or recurring headaches

A particular note should be made of the benzodiazepines. Although they are frequently prescribed for chronic pain patients, they have little demonstrated efficacy in chronic pain management and should be used with caution in this population.[30 31] ◘

A summary of chronic pain treatment recommendations can be found on page 5.

Table 4 - Selected adjuvant medications for chronic pain management

Drug	Dose*	Comments	OMAP Cost/Month**
Tricyclic antidepresants[32 33]			
Amitriptyline	10-150mg qhs	most anticholinergic effects	$0.60 -2.03
Imipramine	10-150mg qhs	sig. anticholinergic effects	$1.18-5.61
Doxepin	10-150mg qhs	very sedating	$1.19-7.63
Desipramine	10-150mg qhs	fewer anticholinergic effects	$1.91-6.98
Nortriptyline	10-100mg qhs	fewer anticholinergic effects	$2.96-10.98
SSRIs [34 35]			
Fluoxetine	20-60mg qd	unproven efficacy in neuropathic pain	$66.79-200.40
Paroxetine	20-60mg qd	unproven efficacy	$59.50-178.45
Anticonvulsants			
Carbamazepine	100-400mg tid	hepatic induction & hematopoietic side effects, drug interactions	$13.20-52.82
Phenytoin	100-250mg bid	limited utility, drug interactions	$13.87-34.67
Gabapentin	100-800mg tid	titrate dose, acts quickly, no drug interactions known	$34.40-206.32
Antiarrhythmic [36]			
Mexiletine	150-250mg qid	titrate dose, proarrhythmic potential	$74.66-103.33
Topical			
Capsaicin cream	0.025%-0.25% bid-qid	burns initially; releases substance P, then depletes neuronal stores	Not Available

* All medications should be titrated to minimum effective dose.
** Cost determined by AWP-11% or MAC from 12/98 Red Book.

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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.
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Produced and Supported by the
OSU College of Pharmacy

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