PAIN NEWS

FOX CHASE CANCER CENTER

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IN THIS ISSUE:

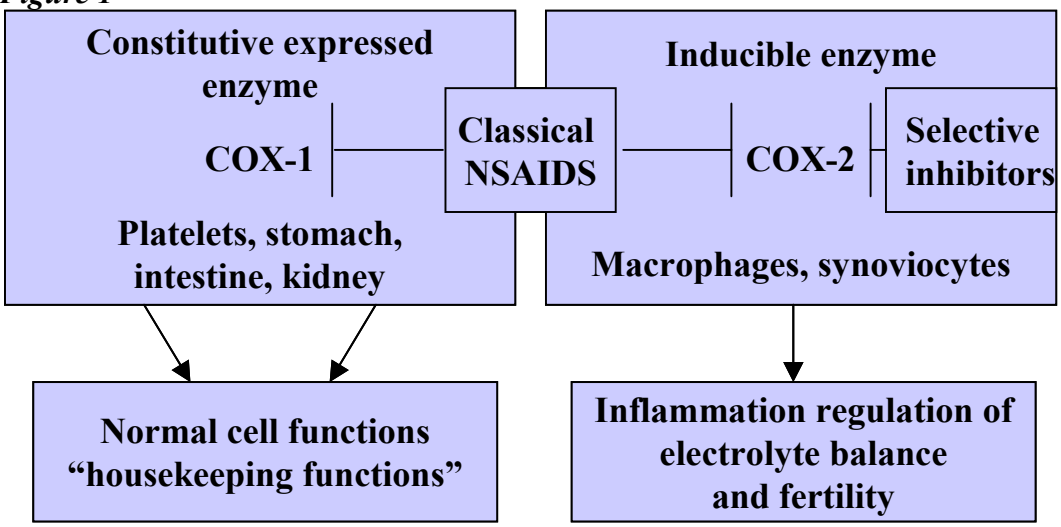
SELECTIVE COX-2 INHIBITORS

Rachel Clark-Vetri, Pharm.D.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed classes of drugs worldwide. More than 111 million prescriptions for NSAIDS are written annually (Lema MJ. Introduction: The role of coxibs in pain management. *Journal of Pain Symptoms Management* 2003; 25:S3-S5). In general, the NSAIDS are well tolerated, with dyspepsia being the most common adverse effect. There are a small percentage of patients that experience serious gastrointestinal events, such as bleeding, obstruction and perforation secondary to NSAID use. These events come with an estimated cost of $28,000 per event and contribute to more than 16,000 deaths per year in the U.S. (Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594-606).

The non-selective NSAIDS exert their anti-inflammatory and analgesic activity by the inhibition of the two isoforms of the cyclooxygenase enzyme, COX 1 and COX 2. COX-1 is generally considered the "housekeeping gene" and responsible for maintaining GI mucosal integrity and platelet aggregation. COX-2, known as the "inflammation gene," is involved in the inflammatory process, mitogenesis and bone formation. Both isoforms are known to have effects on maintaining normal renal function. The rationale of developing a new class of NSAIDS – the coxibs, that selectively inhibit only COX-2, was to maintain the efficacy of COX-2 inhibition while minimizing the side effects mediated by COX-1 inhibition. (Wolfe MM. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1999;340:1888-99).

Figure 1



Continued on 4

Opioid-Induced Nausea

Monica Domenick, RN, BSN, OCN
Ann Pellegrino MSN,CRNP,OCN

Nausea is a common side effect of narcotic analgesia. Nausea can occur with the initiation of pain medication, an increase in pain medication, or from sudden withdrawal of pain medication. The incidence of nausea in patients taking oral morphine ranges from 10-40% (McGuire, Yarbo & Ferrell, 1996). The nausea usually subsides in a couple of days; however, a small percentage of patients will continue to experience nausea.

Opioids can cause nausea by stimulating the chemoreceptor trigger zone. The patient will have nausea or vomiting shortly after taking the opioid. Antiemetics such as odansetron, prochlorperazine, dexamethasone and haloperidol can be used to control nausea. Some patients may experience vestibular sensitivity. When this occurs, patients will have nausea and/or vertigo with movement. In this patient population, scopolamine, dimenhydrinate and meclizine are good choices for control of nausea. Opioids increase gastric tone, which can cause bloating, early satiety, nausea and vomiting. Medications that increase gastric motility, such as metoclopramide, work well in this group of patients. Benzodiazepines (lorazepam) are not true antiemetics, but may be useful as an adjunct to antiemetic medications. The most common cause of nausea in these patients stems from opioid-induced constipation. It is important to treat constipation aggressively.

Management

- Assess and treat other causes of nausea and vomiting, such as elevated digoxin level, uremia, hypercalcemia, and bowel obstruction.
- Provide a prescription for an antiemetic.
- Consider antiemetics with different mechanisms of action.
- Prophylactic use of antiemetics is not recommended secondary to the sedating side effects.
- Try adding a co-analgesic, such as a NSAID or an antidepressant to lower opioid requirement.
- If pain control is achieved, try decreasing the dose of opioid by 25%.
- If nausea persists, try a different opioid or a different route of administration.
- Occasionally patients may require around-the-clock doses of antiemetics for persistent nausea.

Patient Education Points

- Nausea is a common side effect.
- Nausea will last usually 24-48 hours.
- Nausea can be controlled with medication.
- Take pain medications on a full stomach.
- Take an antiemetic one half hour prior to taking pain medication.

References

McGuire, D., Yarbo, C. & Ferrell, B., 2nd ed. *Cancer Pain Management*. Jones & Bartlett: 1996. ☻

EMEND® (Aprepitant Capsules)

Judith Mancuso, LGPN

EMEND®, the first in a new class of antiemetics, was approved by the FDA in March 2003. Aprepitant binds to the NK1 receptors in the central nervous system. Added to the $5HT_3$ receptor antagonists (odansetron, granisetron, dolasetron) and corticosteroids, EMEND significantly improved control of acute and delayed cisplatin-induced emesis.

Chronic, continuous use of EMEND can not be recommended because it has not been studied. The drug interaction profile may change during chronic continuous use. EMEND should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through the CYP3A4 pathway. Efficacy of oral contraceptives during treatment may be reduced because of the changes in CYP enzymes. Co-administration of EMEND with warfarin may result in a decreased INR for the same reason. Steroid doses are affected by inhibition of CYP3A4. Oral dexamethasone should be reduced by 50%, IV methyl prednisone should be reduced by 25% and oral methyl prednisone by 50%.

Aprepitant has been administered commonly with docetaxel, ifosfamide, vinblastine, vincristine, etoposide, vinorelbine, paclitaxel and imatinib mesylate. Despite the fact that these agents are metabolized by CYP3A4, the doses did not need to be adjusted.

Dosage and Administration

EMEND is given orally as part of a three-day regimen that includes a corticosteroid and a $5HT_3$ antagonist. Recommended dose of EMEND is 125 mg orally one hour prior to chemotherapy treatment (day 1) and 80 mg once daily in the morning on days 2 and 3. The following regimen is used in treatment:

EMEND *(cont'd from Page 2)*

EMEND can be taken with or without food. There is no dosage adjustment is necessary for the elderly, patients with renal insufficiency, or patients with mid to moderate hepatic insufficiency.

Table 1

	Day 1	Day 2	Day 3	Day 4
EMEND®	125 mg	80 mg	80 mg	None
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron	32 mg IV	None	None	None

Adverse Reactions/Side Effects

Most common side effects are:

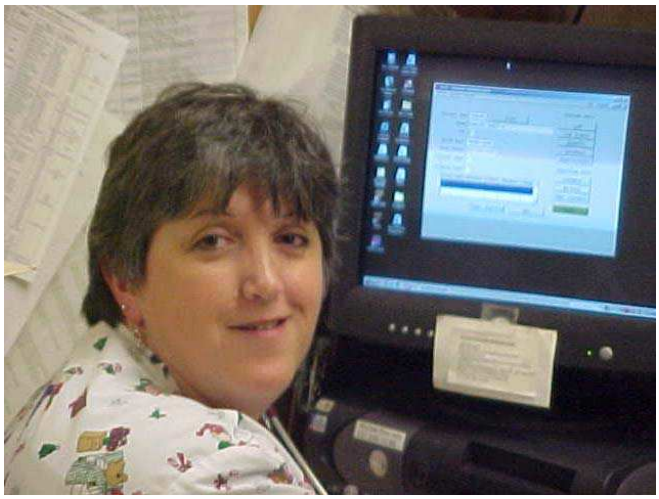
- Fatigue/Asthenia
- Diarrhea
- Hiccups
- Constipation

Reference

Merck Package Insert, March 2003.
NCCI Clinical Practice Guidelines. Antiemesis: V2.2003 ☻

CONGRATULATIONS!

To Kathy MacDonald on the acceptance of her abstract entitled, *"Pain Resource Nurses, More Than Just A Title: Advocates For Change,"* for a podium session at the 2004 Oncology Nursing Society Congress in Anaheim, California. Kathy works in Radiation Oncology at Fox Chase Cancer Center. ☻



ABHR

Monica Dominick RN, BSN, OCN

Ativan®, Benadryl®, Haldol® and Reglan®:

- Compounded/combination product
- Utilized for refractory nausea and vomiting
- Alternative dosage form:
  - Suppository, troche, or suspension
- Multiple sites of action:

Ativan® (lorazepam)
- Site of action: central nervous system (CNS)
- Potent anxiolytic

Benadryl® (diphenhydramine)
- Site of action: histamine receptor
- Useful in CNS and vestibular mechanisms of nausea

Haldol® (haloperidol)
- Site of action: dopamine receptors
- Useful in obstructive and visceral mechanisms of nausea

Reglan® (metoclopramide)
- Prokinetic agent, blocks $5HT_3$ receptors and possibly dopamine receptors
- Useful in gastric distension and gastric paresis

Advantages

- Single administration of multiple medications
- Easy for patient and caregiver
- Useful in dysphagia
- No need for IV access
- Utilized in "squashed stomach syndrome" – patients with ascites or bulky tumor
- Useful in multi-symptom challenge – nausea and anxiety

Disadvantages

- Combination may provide more agents than really needed.
- May cause unnecessary sedation, extra pyramidal symptoms.
- Need compounding pharmacy – not commercially available. ☻

SELECTIVE COX-2 INHIBITORS

(cont'd from Page 1)

There are currently three coxibs commercially available in the U.S. (Table 1) (*Physician Desk Reference* 2002; 56th edition Medical Economics Co., Inc., Montvale, NJ). Celebrex® is the most commonly prescribed of the coxibs and ranks as the twelfth most prescribed drug in the U.S in 2002. Vioxx® and Bextra®, that came to market later, also hold positions on the Top 200 drug selling list (Vaczek D. Top 200 drugs of 2002. *Pharmacy Times* 2003; April; 20-24). All three agents have equal analgesic efficacy to non-selective NSAIDS such as naproxen, sulindac and diclofenac in rheumatoid and osteoarthritis patients as well as for acute pain. The widely advertised advantage of these new generation NSAIDS is the reduced incidence of GI toxicity, specifically ulcer formation, bleeding, obstruction and perforation.

The two largest trials that addressed the safety profile of the coxibs are the CLASS (Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib versus nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study: A randomized controlled trial. *Journal of the American Medical Association* 2000;284:1247-55) and VIGOR (Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine* 2000;343:1520-28) trials. Both trials showed a reduction in endoscopic ulcers and symptomatic ulcers when compared to non-selective NSAIDS. Evidence of endoscopic ulcers, however, will not predict which patients will go on to have a serious GI event including bleeding, ulceration, obstruction and perforation. Only the VIGOR trial that tested Vioxx® was able to show a statistically significant reduction in complicated upper GI events after one year of use. The CLASS trial, comparing celecoxib to diclofenac and ibuprofen, was unable to show a statistical difference at six months in complicated upper GI events. In addition, the CLASS trial also revealed that the addition of an aspirin per day to a patient's regimen would negate any benefit that celecoxib has at preventing symptomatic ulcers.

There is a concern that these products may increase thrombosis by offsetting the natural homeostasis of prostaglandin and thromboxane production. The VIGOR trial found that patients taking rofecoxib had a significantly higher risk of having a myocardial infarction. It is noteworthy to say that this has been the only trial up to this date with these findings and a likely explanation could be found in examining the trial design. The VIGOR trial enrolled rheumatoid arthritis patients who are at a higher risk of thromboembolic events than the normal population. No aspirin use was allowed in the study and rofecoxib has no anti-platelet activity. The comparator, naproxen, however, does have activity against platelet aggregation (Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Archives of Internal Medicine* 2002;162:1111-15). This critical difference in the protective effect of naproxen and lack of protection from rofecoxib could account for the difference in myocardial infarction rates in the study results. Although this explanation could explain the findings, the theory that the coxibs may increase thrombosis cannot be completely discounted and still needs further study.

Other side effects that might be anticipated from the coxibs are renal dysfunction, edema and increase in blood pressure (DeMaria AN, Weir M. Coxibs-Beyond the GI tract: Renal and cardiovascular issues. *Journal of Pain and Symptom Management* 2003;25:S41-S49). Renal dysfunction is relatively uncommon with NSAIDS with an incidence of 1-5%. Patients with an increased risk of this side effect are those that have prostaglandin-dependent renal function such as patients with dehydration, underlying renal disease and congestive heart failure. The risk of renal dysfunction should be considered similar to that of older NSAIDS and appropriate monitoring is warranted. If renal dysfunction becomes evident, the coxibs should be discontinued.

Table 2

Drug Names (Manufacturer)	FDA Indications	Dosage
Celecoxib (Celebrex®-Pharmacia)	• Osteoarthritis • Rheumatoid arthritis • FAP • Acute Pain and dysmenorrhea	• 100 mg q12h • 100-200 mg q12h • 400 mg q12h • 200 mg q12h
Rofecoxib (Vioxx®-Merck)	• Osteoarthritis • Rheumatoid arthritis • Acute Pain and dysmenorrhea	• 12.5-25 mg once a day • 25 mg once a day • 50 mg once a day
Valdecoxib (Bextra® - Pharmacia)	• Osteoarthritis • Rheumatoid arthritis • Dysmenorrhea	• 10 mg once a day • 10 mg once a day • 20 mg once a day

The coxibs are also known to interact with blood pressure medicines and increase blood pressure and edema. Ace-inhibitors, angiotensin II antagonists, beta-blockers and diuretics are more likely to interact with coxibs than other antihypertensives. Patient initiated on coxibs should have their blood pressure checked periodically. A dose-adjustment in blood pressure medicines may be sufficient to overcome any increase in blood pressure or peripheral edema.

SELECTIVE COX-2 INHIBITORS

(cont'd from Page 4)

The coxibs are an effective addition to the list of NSAIDS. Their selectivity makes them less toxic to the gastrointestinal tract short-term, although the long-term benefit is still unclear. The lack of anti-platelet activity may also have an additional benefit of reduced bleeding risk in cancer patients that experience thrombocytopenia from treatment or disease. The major disadvantage of the coxibs is cost and since the cost-benefit of these products is unknown, the use of them should be based on individual needs.

Reference

Lema MJ. Introduction: the role of coxibs in pain management. Journal of Pain Symptom Management 2003;25:S3-S5.

Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594-606.

Wolfe MM. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1999;340:1888-99.

Physician Desk Reference 2002; 56th edition Medical Economics Co, Inc, Montvale, NJ.

Vaczek D. Top 200 drugs of 2002. *Pharmacy Times 2003*;April;20-24.

Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study: A randomized controlled trial. *Journal of the American Medical Association* 2000;284:1247-55.

Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine* 2000;343:1520-28.

Rhame E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Archives of Internal Medicine* 2002; 162:1111-15.

DeMaria AN, Weir M. Coxibs-Beyond the GI tract: Renal and cardiovascular issues. *Journal of Pain and Symptoms Management* 2003;25:S41-S49.

Answers to ***Word Find***: 1. Palladone 2. Octreotide

PRINCIPLES OF CHEMOTHERAPY EMESIS CONTROL

- Assess risk factors
- Prevent nausea and/or vomiting
- Use lowest effective dose of antiemetics
- Consider toxicity of antiemetic agents
- Assess risk factors
- Oral route as effective as IV

WORD FIND

1. What analgesic for chronic moderate to severe pain in cancer patients is presently awaiting FDA approval?

___ _A_ _L_ _L_ ___ _D_ ___ _N_ ___

2. What supplemental coanalgesic drug for cancer pain is given for bowel spasm?

___ _C_ _T_ ___ _E_ ___ _T_ _I_ _D_ _ _

Answers in page opposite column

Answers to **Matching Game**:
1L. 2D. 3K. 4M. 5J. 6B. 7C. 8E. 9G. 10A. 11F. 12H. 13I. 14N.

PALONOSETRON (ALOXI)

Ann Pellegrino, MSN, CRNP, OCN

Category

$5HT_3$ receptor antagonist with prolonged duration of action – half life 40 hours.

Indication

The prevention of acute nausea and vomiting associated with highly emetogenic chemotherapy.

Contraindications

Hypersensitivity

Precautions

In patients with prolonged cardiac conduction intervals. Hypokalemia, hypomagnesemia, cumulative high dose anthracycline therapy.

Metabolism

Renal excretion. Long half-life, 40 hours, allows coverage for delayed nausea.

Dosage and Administration

0.25 mg IV 30 minutes prior to chemotherapy. Infused over 30 seconds. Repeat dosing within 7 days is not recommended. No dose adjustments needed for renal or hepatic dysfunction.

Side Effects

Headaches, constipation, diarrhea, dizziness, fatigue, asthenia.

Prescribing information 2003 MGI Pharma, Inc. ☻

LETTER TO THE EDITOR

Great newsletter – I always learn something! I think the answer key for the matching game is incorrect on page 4 related to Aredia, Darvon. The answer key is ordered top to bottom, listing 14, followed by 4. It should be 4 Darvon (propoxyphene), followed by 14 Aredia (pamidronate). Do I get a prize for finding this? How about a free subscription to the PRN newsletter? Ha, ha!

Anne Jadwin, RN, MSN, AOCN, CNA

Ed. Response: You are correct. Please accept our apologies for the error. Thanks so much for catching it. It is great to have readers like you. A free subscription works for me! ☻

MALIGNANT BOWEL OBSTRUCTION

Pam Kedziera, RN, AOCN, MSN

- Occlusion of lumen or absence of normal propulsion
- Related to site of disease
- Splenic flexure tumors obstruct 49%
- Occurs in 5-50% of gynecologic tumors
- Symptoms include severe nausea, vomiting, and abdominal pain

Treatment

- Nasogastric tube – uncomfortable to patient
- IV fluids (limit to 1,000 mL/day) – increases secretions, may worsen ascites and third spacing
- Surgery – resection, decompression, venting gastrostomy
- Rx – analgesics anticholinergics, antiemetics
- Octreotide – slows irregular, ineffective peristalsis and inhibits secretion of gastric acid and VIP
- Stimulant laxatives are contraindicated
- Steroids – helpful as antiemetic
- Antispasmodics – hyoscine butylbromide

Reference

Caraccin – Economou, D. Bowel Management: Constipation, Diarrhea, Obstruction and Ascites.

Ferrell, B., and Coyle, N., eds. *Textbook of Palliative Nursing*. Oxford, University Press, 2001. ☻

LIDODERM PATCH

Bonnie Carolan-McNulty, RN, MSN

Lidoderm is a new way to provide local anesthesia for neuropathic pain. The lidocaine 5% is provided in patch form and is about the size of an adult hand. This patch is placed on unbroken skin, directly onto the area of pain. The patch can be cut to size and you can wear up to three patches at one time. The patches are worn for no more than 12 hours within a 24-hour period (for example, 12 hours with the patch on, then 12 hours with the patch off). Wearing patches longer could result in increased absorption of lidocaine, which could lead to serious side effects. Patches are never reused and are provided in a zipper-seal package, which will keep unused patches from drying out. A possible side effect is that the skin around the patch could develop redness, swelling, irritation or burning. If these should occur, remove the patches and do not reapply until irritation goes away.

Several pain management patients have tried the lidocaine patches and find that they have helped to allow them to be more active without side effects. ☻

METHADONE IN THE MANAGEMENT OF CHRONIC PAIN

Thomas Samuel, M.D.

Methadone is an opioid analgesic that has been used for over sixty years in both the treatment of chronic pain and in opiate addiction. In the recent past, methadone developed a sordid reputation because of its association with opioid abuse. The mere mention of methadone often conjures images of shady back alleys and unkempt heroin abusers, staggering in and out of smoky addiction clinics, with little hope of recovery. Despite this perception, methadone has been used for many years quite effectively in the management of chronic cancer-related pain. This short discussion will review some of these useful and clinically practical treatment indications, as well as discuss the pharmacologic characteristics of methadone, in the hopes of restoring its much maligned reputation.

Unlike its cousin, morphine, methadone acts via several processes to induce analgesia. The affinity of methadone to block the mu- and kappa-pain receptors is similar to morphine, however it has greater affinity than morphine to the delta-pain receptor, inducing increased analgesia. Also unlike morphine, methadone blocks the NMDA receptor within the central nervous system while inhibiting neuronal serotonin and norepinephrine re-uptake at the CNS receptor level. This peculiar action of methadone makes it an effective tool in treating somatic, visceral, and neuropathic pain. These combined actions of methadone to produce pain receptor blockade, NMDA blockade, and the up-regulation of CNS serotoninergic/noradrenergic pathways leads to synergistic pain relief via multiple mechanisms not employed by other opioids.

The pharmacology of methadone is somewhat complicated and yet for those familiar with its use, its biologic effects can be used advantageously in multiple clinical situations. Methadone has greater oral bioavailability than morphine (80% vs. 35%) and greater protein binding in tissues (high lipid solubility) allowing for an extended elimination phase (13-58 hours). Along with its rapid distribution phase (4 hours), these pharmacodynamics allow for the use of methadone as both a long and short acting analgesic. Methadone is extensively processed in the liver and primarily fecally eliminated, although a small portion of its metabolites is eliminated via the kidneys. Dose adjustments are only recommended for patients with advanced hepatic disease.

The clinical uses of methadone are multiple and varied. It can be administered orally (via tablet or liquid formulation) or parenterally (either intramuscularly, by continuous subcutaneous infusion, or intravenously). In opioid naive patients, a recommended starting dose of 5mg p.o. q6-8h for 3 days must be further adjusted to longer intervals of administration once peak plasma levels have been achieved. For patients who have been on other opioids, published data on conversions from morphine to methadone have described ratios of anywhere from 2.5:1 to 15:1. Any conversion from an opioid to methadone should be done carefully with frequent follow-up to avoid undue side effects like excess sedation. Often these conversions are best conducted by pain specialists with experience in dose adjustments and resources available for close monitoring, especially in patients with high opioid tolerances. Side effects of methadone are similar to those found in other opioid analgesics including generalized pruritus, sedation, constipation, urinary retention, and respiratory depression.

One might ask why use methadone when there are an array of other opioids available for use. Studies have shown that up to 80% of patients with cancer related pain may require a change in their opioid regimen due to unacceptable pain control or side effects. Switching opioids or opioid rotation is an effective method of improving pain control, reducing opioid toxicity, avoiding opioid tolerance, and allowing for improved methods of administration (e.g., transdermally vs. orally). Methadone is another opioid that can be used for rotation with the additional benefits of both long and short acting effects as well as greater versatility in dealing with multiple etiologies of pain. Research also indicates that methadone may cause less tolerance and constipation compared to other opioids.

In short, methadone is a drug whose utility far outweighs its reputation and should be considered more often in the treatment of chronic pain. Although its pharmacology is complex, when administered and managed by pain physicians in cooperation with other physicians, it can be an effective tool to reduce cancer related pain. It's time to take methadone out of the shadows of heroin addiction clinics and into the light of modern medical clinical settings. ☻

PRN MATCHING GAME

A. Pamidronate	1. ____Steroid given to treat acute spinal cord compression.
B. Clonidine	2. ____NSAID for relief of mild pain.
C. Toradol	3. ____Oral opioid for relief of moderate pain and as a cough suppressant.
D. Ibuprofen	4. ____Antidepressant medication used in treatment of neuropathic pain.
E. Zometa	5. ____Oral or parenteral opioid used in the treatment of moderate to severe pain.
F. Trilisate	6. ____This antihypertensive, coanalgesic drug is used for the treatment of neuropathic pain.
G. Hydromorphone	7. ____NSAID given parenterally for moderate pain. Can cause renal failure.
H. Duragesic	8. ____15-minute parenteral infusion Q3-4 weeks for bone pain.
I. OxyContin	9. ____Narcotic analgesic can increase respiratory depression upon interaction with nortriptyline. This narcotic is only available in a short-acting form.
J. Morphine	10. ____2-hour infusion give Q4 weeks for the relief of bone pain.
K. Codeine	11. ____NSAID may cause gastritis or bleeding but does not affect platelets.
L. Dexamethasone	12. ____Transdermal narcotic analgesic for the management of severe chronic pain.
M. Pamelor	13. ____Extended-release narcotic for relief of moderate to severe pain. Crushing and ingesting this medication can lead to toxic effect.
N. Neurontin	14. ____Anticonvulsant used to treat neuropathic pain.

Continued on page 3