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This addendum updates clinical advances in pain management since the publication of "Pain: Current Understanding of Assessment, Management, and Treatments" in December of 2001.

The original monograph was developed by the National Pharmaceutical Council (NPC) as part of a collaborative project with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and was reviewed for accuracy by an editorial advisory board of experts in pain management.

Special Update to:

Pain: Current Understanding of Assessment, Management, and Treatments

Pain is the most common reason individuals seek health care services and about 9 in 10 Americans regularly suffer from pain. As the population ages, the number of people who will need treatment for pain from back disorders, degenerative joint disease, rheumatologic conditions, visceral disease, and cancer is expected to rise tremendously.

To facilitate an effort toward improving pain management, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the National Pharmaceutical Council (NPC) created two monographs addressing the subject of pain.

The first monograph "Pain: Current Understanding of Assessment, Management, and Treatments" was published in December 2001 by NPC. This monograph focused on the importance of treating pain, its epidemiology, etiology, general diagnosis, and treatment. This monograph also provided an easy to use reference on current pharmaceuticals and other pain management treatments and techniques. The second monograph "Improving the Quality of Pain Management Through Measurement and Action" was published in March 2003 by JCAHO. This monograph provided an overview of existing guidelines, standards, and performance measurement approaches for organizations to assess current performance in pain management. This monograph also provided examples and case studies of innovative pain management initiatives. Both monographs are available at www.npcnow.org or www.jcaho.org.

Since the publication of both monographs, new products for pain management have been approved, there has been news about existing products used for pain management, and clinical treatment guidelines have been updated. This addendum was created to provide the most recent information about advances in pain management and to supplement the previous monographs.

Recent Clinical Changes and News

The selective cyclooxygenase (COX)-2 inhibitor rofecoxib (Vioxx) was voluntarily withdrawn from the U.S. market by Merck on September 30, 2004 because of safety concerns that led to early termination of a clinical trial involving patients taking the drug to prevent recurrent colon polyps.^{1,2} The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial showed an increased risk of cardiovascular events (including myocardial infarction and stroke) in patients receiving rofecoxib (Vioxx) compared with placebo,

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particularly for those patients who had been taking the drug for longer than 18 months.¹

Valdecoxib (Bextra) is the most recent selective COX-2 inhibitor introduced in the United States (in late 2001). Steven's-Johnson syndrome (a potentially fatal skin reaction) has been identified in postmarketing experience in patients receiving valdecoxib (Bextra) and a "black box" warning about this reaction has been added to the product labeling.³ Information about valdecoxib's (Bextra) contraindication after Coronary Artery Bypass Graft (CABG) has also been added to the product labeling.³ Valdecoxib is contraindicated for the treatment of post-operative pain immediately following CABG and should not be used in this setting. Preliminary data linking valdecoxib (Bextra) with myocardial infarction and stroke were presented at the American Heart Association Scientific Sessions in New Orleans in November 2004.⁴

Two FDA committees recently evaluated whether the cardiovascular events associated with rofecoxib (Vioxx) are a class effect and are associated with the other two selective COX-2 inhibitors in the class, celecoxib (Celebrex) and valdecoxib (Bextra). The FDA's Arthritis Drugs and the Drug Safety and Risk Management Advisory Committees met February 16-18, 2005 and determined that the increased cardiovascular risk seen with rofecoxib (Vioxx) is a class effect; however, variation in the risk among doses and drugs within the COX-2 class call for a case-by-case consideration of each drug. The following recommendations for each COX-2 were made:⁵

1. Rofecoxib (Vioxx) manufactured by Merck may be allowed to re-enter the market; the final committee vote was 17 to 15. Merck stated that it may consider reintroducing rofecoxib (Vioxx) in the United States.
2. Celecoxib (Celebrex) manufactured by Pfizer should remain on the market with suggested label warnings, which will include a "black box" warning about the increased risk of cardiovascular events. The final committee vote was 31 to 1 that the overall risk to benefit profile for celecoxib (Celebrex) supports continued marketing in the United States.
3. Valdecoxib (Bextra) also manufactured by Pfizer should also remain on the market. Pfizer should revise the product labeling to address the cardiovascular concerns. The final committee vote on valdecoxib (Bextra) was 17 to 13 with two abstentions.

Clinical Practice Guidelines

The following clinical practice guidelines were released or updated since publication of "Pain: Current Understanding of Assessment, Management, and Treatments" in December 2001.

American College of Rheumatology

1800 Century Place, Suite 250
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<http://www.rheumatology.org>

- *Guidelines for the Management of Rheumatoid Arthritis (2002 update)*
- *Recommendation for the Medical Management of Osteoarthritis of the Hip and Knee (2000 update)*

The American Geriatrics Society

The Empire State Building
350 Fifth Avenue, Suite 801
New York, NY 10118
(212) 308-1414

<http://www.americangeriatrics.org>

- *Guidelines on the Management of Persistent Pain in Older Persons (2002 revision)*
- *Exercise Prescription for Older Adults with Osteoarthritis Pain: Consensus Practice Recommendations (2001)*

American Pain Society

4700 West Lake Avenue
Glenview, IL 60025
(847) 375-4715

<http://www.ampainsoc.org>

- *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis (2002)*
- *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th edition (2003 revision)*
- *Guideline for the Management of Cancer Pain in Adults and Children (2003)*

Final Agency Rulings for COX-2's

Based on the subsequent recommendations of the FDA's Arthritis Drugs and the Drug Safety and Risk Management Advisory Committees, on April 7, 2005, the FDA asked Pfizer to remove Valdecoxib (Bextra) from the market and include a "black box" warning for Celecoxib (Celebrex) labeling.⁶ The FDA stated that the request is based on a lack of adequate data on the cardiovascular safety of long-term use of Valdecoxib (Bextra); reports of serious and potentially life-threatening skin reactions; and a lack of any demonstrated advantages for Valdecoxib (Bextra) compared with other NSAIDs.⁶ Pfizer has complied with the FDA's requests and is exploring options with the agency to return Bextra to the market at a later time.

FDA is still leaving open the possibility that Merck's Rofecoxib (Vioxx) could re-enter the market. The FDA has stated that they will carefully review any proposal from Merck for resumption of rofecoxib (Vioxx).

The FDA has also requested that manufacturers of all prescription NSAIDs revise their labeling to include a boxed warning on the increased risk of cardiovascular events and gastrointestinal bleeds.⁶

Recently Approved Products

Several new drug products used to manage pain have been approved since the monograph "Pain: Current Understanding of Assessment, Management, and Treatments" was published in December 2001.

Duloxetine (Cymbalta) manufactured by Eli Lilly is a new serotonin-norepinephrine reuptake inhibitor that is approved by FDA for the management of diabetic peripheral neuropathic pain (and major depression).

Pregabalin (Lyrica) manufactured by Pfizer treats neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin (Lyrica) is similar to gabapentin (Neurontin, which carries an FDA-approved indication for the management of postherpetic neuralgia in adults) in that both drugs are analogs of gamma-amino butyric acid. The two compounds appear to share similar mechanisms of action, binding to the calcium channels, modulating calcium influx, resulting in analgesic, anxiolytic, and anticonvulsant activity.^{7,8} However, pregabalin provides an effect equivalent to gabapentin at lower doses. Therefore, the dose-related adverse events associated with gabapentin (e.g., fatigue) may be less of a problem with pregabalin. How the safety and efficacy of the two drugs for managing postherpetic neuralgia compare remains to be determined in clinical trials. Favorable results have been reported with pregabalin in randomized, double-blind trials comparing the drug with placebo for treating postherpetic neuralgia or diabetic peripheral neuropathy.^{9,10}

Clinical Practice Guidelines (continued)

The following clinical practice guidelines were released or updated since publication of "Pain: Current Understanding of Assessment, Management, and Treatments" in December 2001.

Society of Nuclear Medicine

1850 Samuel Morse Drive
Reston, VA 20190
(703) 708-9000
<http://interactive.snm.org>

- Procedure Guideline for Palliative Treatment of Painful Bone Metastases (2003)

National Consensus Project for Quality Palliative Care

One Penn Center West
Suite 229
Pittsburgh, PA 15276-0100
(412) 787-1002
<http://www.nationalconsensusproject.org>

- Clinical Practice Guidelines for Quality Palliative Care (2004)

Four new products have been approved by FDA for the acute treatment of migraine with or without aura in adults. They are new selective 5-HT_{1B/1D} receptor agonists:

1. Almotriptan (Axert) manufactured by Ortho-McNeil Pharmaceutical
2. Eletriptan (Relpax) manufactured by Pfizer
3. Frovatriptan (Frova) manufactured by Elan Pharmaceuticals
4. Naratriptan (Amerge) manufactured by GlaxoSmithKline

Please consult the manufacturer's product labeling for specific information about dosage form, dosing, administration, warnings, contraindications, and adverse events for all of the recently approved products.

Products in Research and Development

Etoricoxib (Arcoxia) manufactured by Merck is a selective COX-2 inhibitor that has been evaluated for treating acute gouty arthritis pain,¹¹ osteoarthritis pain,¹² acute pain,¹³ chronic pain,¹⁴ and rheumatoid arthritis pain.¹⁵ It appears to cause less gastrointestinal (GI) toxicity than nonselective nonsteroidal anti-inflammatory drugs.¹⁶ Whether etoricoxib increases the risk of cardiovascular events remains to be evaluated.

Lumiracoxib (Prexige) is another new selective COX-2 inhibitor that is under investigation by Novartis for the treatment of various types of pain, including osteoarthritis pain,^{17,18} rheumatoid arthritis pain,¹⁹ and acute pain.²⁰ The GI safety profile of lumiracoxib was superior to that of ibuprofen and comparable to that of celecoxib in patients with rheumatoid arthritis.¹⁹ In an acute postoperative dental pain study, lumiracoxib was more effective than celecoxib.²⁰ The GI and cardiovascular safety of lumiracoxib was evaluated in a study of patients with osteoarthritis.¹⁷ The risk of cardiovascular events was no greater in patients treated with lumiracoxib than in patients treated with ibuprofen or naproxen, regardless of aspirin use.

A new dual-acting COX-2 inhibitor known as 406381 was found to have preclinical activity in models of inflammatory pain and neuropathic pain by GlaxoSmithKline.²¹ Phase II studies of patients with osteoarthritis or rheumatoid arthritis demonstrated greater efficacy from active treatment with this compound than from placebo. The compound was more effective than celecoxib in some study endpoints, with a similar adverse event profile.²¹

Ziconotide (Prialt, SNX-111), by Elan Pharmaceuticals, is the first selective neuronal N-type, voltage-sensitive calcium channel blocker to enter clinical drug development. There are several types of voltage-dependent calcium channels (e.g., L, N, P), and conventional calcium channel blockers (e.g., diltiazem, verapamil) act at L-type calcium channels. The therapeutic usefulness of N-type

Materials available from the NPC/JCAHO collaborative project:

“An Overview of Two Monographs on Pain Management”
(www.npcnow.org)

“Pain: Current Understanding of Assessment, Management, and Treatments”
(www.npcnow.org or www.jcaho.org)

“Improving the Quality of Pain Management Through Measurement and Action”
(www.npcnow.org or www.jcaho.org)

CE Credit for Pharmacists, available through the American Pharmaceutical Association
(www.pharmacist.com/education.cfm)

Lesson Expires: 12/15/07

CE Credit for Physicians, Psychiatrists and Psychologists, available through the American Pain Society
(<http://www.ampainsoc.org/ce/enduring.htm>)

Lesson Expires: 6/30/07

CE Credit for Physician Assistants, available through the American Academy of Physician Assistants
(<http://www.aapa.org/cme/hs-progs.html#pain>)

Lesson Expires: 12/01/06

CE Credit for Nurses and Nurse Practitioners, available through NP Central
(<http://www.npcentral.net/ce/pain/>)

Lesson Expires: 1/31/06

calcium channel blockers as analgesics has been hypothesized since N-type calcium channels modulate the release of glutamate, substance P, and other pro-nociceptive neurotransmitters in the central nervous system. Ziconotide has been used intrathecally with encouraging results in patients with chronic pain from cancer or AIDS that were refractory to opioid analgesics²² and in patients with acute postoperative pain.²³

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- ⁵ *Celebrex Should Stay on Market, FDA Panel Says, But Splits on Vioxx, Bextra*: FDC Reports, “The Pink Sheet”, An Elsevier Company; February 21, 2005. Vol. 67, No. 8, page 3.
- ⁶ *FDA’s COX-2 Safety Plan: Remove Bextra, Add Black Box To Celebrex*: FDC Reports, “The Pink Sheet” Daily, An Elsevier Company; April 7, 2005.
- ⁷ BioPortfolio. Anticonvulsants: Pfizer's pregabalin to top success of Neurontin? Available at: http://www.bioportfolio.com/news/datamonitor_38.htm. Accessed November 23, 2004.
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