Osteoarthritis Management in the Post-Rofecoxib Era: A Closer Look at Pharmacologic Options

Needs Assessment

In 2005 the Food and Drug Administration (FDA) requested the voluntary withdrawal of two selective nonsteroidal antiinflammatory drugs (NSAIDs), rofecoxib and valdecoxib, and changed the labeling of all remaining NSAIDs to reflect the new awareness of potential risks associated with this class of drugs. [FDA *Postmarket Drug Safety* 2010] Last year, the FDA changed the labeling of acetaminophen, adding warnings about the risks of adverse gastrointestinal (GI) and liver reactions. [FDA *Federal Register* 2009] One area of clinical research is actively focused on further clarifying these risks and evaluating the safety and tolerability of analgesics, including NSAIDs, commonly used to manage osteoarthritis (OA). ***Providers are challenged to stay abreast of current evidence-based findings that inform treatment choices for OA patients at risk of treatment-related complications.***

Gap Analysis

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
OA providers may lack **knowledge** of how the choice of NSAID or concomitant CV medications can alter CV homeostasis	*Recent survey; Literature review; Expert opinion*	Present recent evidence-based studies of CV homeostasis in OA patients managed with an NSAID	3 (Knowledge)
OA providers may lack **knowledge** of differences in efficacy and tolerability among GPA classes	*Literature review; Expert opinion*	Present recent evidence-based studies of GPA efficacy and tolerability in OA patients managed with an NSAID	3 (Knowledge)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
OA providers may lack **knowledge** of the relative efficacy and tolerability of analgesics; which may alter risk:benefit analyses	*Literature review; Expert opinion*	Present recent evidence-based studies of narcotic and non-narcotic analgesic efficacy and tolerability in OA patients	3 (Knowledge)
OA providers may lack **knowledge** of new theories on the pathophysiology of OA, which may alter risk:benefit analyses	*Literature review; Expert opinion*	Review current findings on OA pathophysiology, and how that might alter risk:benefit and pharmacoeconomic analyses	3 (Knowledge)

GPA = gastroprotective agent

Osteoarthritis (OA) is the most prevalent articular disease and the most common cause of chronic disability in older Americans. The current goals of OA treatment are management of joint pain and stiffness, and improvement in joint function and disability. [Harvey *Med Clin N Am* 2009] In recent evidence-based guidelines, there is general agreement that the best treatment plan for mild to moderate OA includes both non-pharmacologic and pharmacologic management. Effective non-pharmacologic approaches include exercise, body weight reduction, walking aids, knee braces, and patient education. [Zhang *Osteoarthritis Cartilage* 2008] When a combination of non-pharmacologic and pharmacologic treatment fails to provide adequate pain relief and improvement in physical function, surgical intervention such as with joint replacement is recommended. [Zhang *Osteoarthritis Cartilage* 2008]

Even in this post-rofecoxib era, pharmacologic management of OA is usually addressed with analgesics or nonsteroidal antiinflammatory drugs (NSAIDs).

According to a report from the Centers for Disease Control, the majority of OA patients are 65 years old or older, [CDC *MMWR* 2006] and the majority of the population over 65 years has OA. [Hunter *Med Clin N Am* 2009] Comorbid conditions and concomitant medications, common in this elderly patient population, can confound pharmacologic management of OA.

The safety and tolerability of oral analgesic and NSAID use in OA patients is an active, ongoing area of clinical research. For example, clinical studies are documenting differences in the cardiovascular (CV) safety of NSAIDs. It is well known that NSAID therapy leads to an imbalance in prostaglandins synthesized by COX-1 and COX-2 isoenzymes, compromising CV homeostasis. Perhaps less well known is the differences in relative potency of COX-1 and COX-2 inhibition that render some of the six classes of NSAIDs less of a threat to CV stability than the others. [Chan C *J Hypertens* 2009; Fendrick *Osteopath Med Prim Care* 2009; Laine *Sem Arthritis Rheum* 2008; Solomon *Circulation* 2008; MacDonald *J Hypertens* 2008; ARC *Arthritis Rheumatism* 2008; Antman *Circulation* 2007; Farkouh *Ann Rheum Dis* 2007; Cannon *Lancet* 2006; McGettigan *JAMA* 2006; Sowers *Arch Intern Med* 2005]

Similarly, medications to manage CV disease do not have uniform interactions with concomitant NSAID therapy. [MacDonald *J Hypertens* 2008] Individual NSAIDs can have a different impact on antiplatelet efficacy and tolerability of low-dose aspirin [Fendrick *Osteopath Med Prim Care* 2009; Farkouh *Ann Rheum Dis* 2007; Renda *Clin Pharmacol Ther* 2006], and some classes of antihypertensives are more effective than others when combined with an NSAID. [White *Am J Med* 2009] ***Providers need to be aware of how the choice of NSAID or concomitant CV medications can alter CV homeostasis.***

Another concern with chronic NSAID therapy is the potential for serious gastrointestinal (GI) reactions, especially in patients at risk. Gastroprotective agents (GPAs) are commonly employed to mitigate this risk, but co-therapy may pose a challenge to adherence. [Van Soest *Aliment Pharmacol Ther* 2007] Recent studies have revealed differences in the efficacy and tolerability among the classes of GPAs when combined with an NSAID. [Goldstein *ARC abs* 2009; Chan F *Lancet* 2007; Goldstein *Clin Gastroenterol Hepatol* 2007; Scheiman *Am J Gastroenterol* 2006] ***Providers need to be***

aware of differences in efficacy and tolerability between classes of GPAs.

Osteoarthritis treatment guidelines cite acetaminophen (up to 4 mg/d) as the drug of first choice for the symptomatic management of mild to moderate OA, not because it has superior efficacy but because past studies have shown that acetaminophen has a better tolerability profile than NSAIDs. [Harvey *Med Clin N Am* 2009] However, acetaminophen (>2 mg/d) can also lead to adverse GI [Rahme *Arthritis Rheum* 2002; García-Rodríguez *Epidemiology* 2001] and CV reactions, possibly by its effect on endothelial function. [Chan A *Circulation* 2006; Forman *Hypertension* 2005]

In 2009 the FDA changed acetaminophen labeling to reflect the potential for adverse GI events, or drug-induced acute liver failure when the daily dose is only slightly above the maximum limit (4 mg/d) or when given to patients who are moderate alcohol drinkers. [FDA *Federal Register* 2009] There is a recent trend to replace acetaminophen with opioids for the control of OA pain. [Harvey *Med Clin N Am* 2009] Opioids significantly reduce pain intensity, and provide small improvement in physical function. [Avouac *Osteoarthritis Cartilage* 2007] However, the benefits of opioid therapy, especially strong opioids (eg, oxymorphone, oxycodone, oxytrex, fentanyl, morphine sulfate), are limited by a high frequency of adverse events and discontinuation of therapy. [Zhang *Osteoarthritis Cartilage* 2008; Avouac *Osteoarthritis Cartilage* 2007; Solomon *ARC abs* 2009; Hale *Clin Ther* 2007] ***Providers need to be aware of recent findings that may alter risk:benefit analyses of non-narcotic and narcotic analgesics.*** [Woodcock *N Engl J Med* 2009]

Ideally, pharmacologic management of OA would also limit progression of joint damage. Many agents, in varying stages of development, are striving to become the first disease modifying osteoarthritic drug (DMOAD). [Kuritzky *Medscape CME Rheumatol* 2009] For this indication, major licensing authorities (FDA and European Medicines Agency) require the ability to both delay structural progression of OA, and improve symptomatic pain and physical function. [Hunter *Med Clin N Am* 2009]

Investigations into the pathophysiology of OA are beginning to yield interesting findings, some with potentially immediate clinical application. There is growing evidence that joint damage is not caused by cartilage

degeneration alone, but involves the entire OA joint. Studies have shown that structural damage leads to inflammation of the synovium, which sensitizes nocioceptive processing of pain signals from affected joints, and may play a role in disease progression. [Felson *Arthritis Res Ther* 2009; Bonnet *Rheumatol* 2005] A recent longitudinal, clinical study, employing MRI imaging, documented the correlation of OA pain with the presence of synovitis but not the degradation of cartilage, which is aneural and avascular. [Felson *Arthritis Res Ther* 2009; Hill *Ann Rheum Dis* 2007]

Perhaps for this reason, many potentially DMOAD drugs in development are directly or indirectly targeting the inflammatory processes in OA joint tissues. Some of the more promising new chemical entities include induced nitric oxide synthesis (iNOS) inhibitors; bradykinin receptor antagonists; an inhibitor of nerve growth factor, the monoclonal antibody, tanezumab; and inhibitors of tumor necrosis factor (TNF)-α. [Hunter *Med Clin N Am* 2009] Other DMOAD hopefuls are aimed at delaying structural progression of OA. By targeting molecules that regulate bone remodeling, compounds such as the NF-κB (RANK)/ RANK ligand (RANKL)/osteoprotegerin (OPG) system [Tat *Keio J Med* 2009] and calcitonin [Karsdal *Osteoarthritis Cartilage* 2008], these products may reduce the formation of subchondral bone lesions.

A great deal of controversy surrounds the use of slow acting compounds, or nutriceuticals in the management of OA. There are varying levels of clinical evidence that symptomatic relief is provided by a number of these agents (chondroitin sulfate, glucosamine sulfate, avocado/soybean unsaponifiables, diacereine, and hyaluronic acid) when compared to a placebo. [Bruyère *BMC Musculoskelt Disord*. 2008] More controversial is the claim that any of these agents slow the rate of disease progression. [Hunter *Med Clin N Am* 2009]

As our understanding of the pathophysiology of OA evolves, it is possible that the combined analgesic-antiinflammatory actions of NSAIDs may offer additional benefits over oral analgesics alone for OA patients. [Harvey *Med Clin N Am* 2009] ***Providers need to be informed of recent findings in the pathophysiology of OA and how it may alter the risk:benefit analyses of NSAIDs.*** [Woodcock *N Engl J Med* 2009]

Learning Objectives

- Discuss the optimal approach to the combined management of OA patients with CV disease.

- Recognize differences in the efficacy and tolerability among classes of gastroprotective agents used to mitigate GI adverse events in OA patients managed with an NSAID.
- Evaluate the benefits and tolerability of non-narcotic and narcotic analgesics used to manage OA pain.
- Evaluate current understanding of OA pathophysiology and how it might translate into clinical management for improved patient outcomes.

Intended Audience

- Primary care providers
- Rheumatologists
- Pharmacists
- Nurses

Proposed Agenda

Osteoarthritis Management in the Post-rofecoxib era: A Closer Look at Pharmacologic Options

I. Introduction

- Ideal OA treatment combines non-pharmacologic and pharmacologic management
- This program will concentrate on pharmacologic management with oral fast-acting agents (rather than slow-acting agents), and evaluations of the relative efficacy and potential risks of these systemic agents

II. CV homeostasis in OA patients managed with an NSAID

- Evidence-based findings on the relative impact of NSAID classes on CV homeostasis
  - Hypertension
  - Fatal, non-fatal cardiovascular events (MI, stroke)
- Evidence-based findings on the relative impact of concomitant CV medications
  - Antiplatelet prophylaxis (aspirin, thienopyridine agents)
  - Antihypertensive agents (calcium channel blockers, ACE inhibitors, ß-blockers)

III. Mitigation of GI events in OA patients managed with an NSAID

- Evidence-based findings on the relative efficacy and tolerability of classes of GPA agents (PPIs, misoprostol, H_2 receptor blockers)
- Compliance with co-therapy

IV. Analgesics (non-narcotic and narcotic) to control OA pain

- Relative efficacy
- Evidence-based findings on tolerability
  - CV effects (acetaminophen)
  - GI effects (acetaminophen, tramadol)
  - Liver toxicity (acetaminophen)
  - CNS effects (narcotic analgesics: CNS depression, decreased seizure threshold)
  - Pulmonary effects (acetaminophen: COPD, asthma)

V. Recent support for current understanding of OA pathophysiology

- Involvement of all OA joint tissues
- Role of synovitis in pain perception
- Impact of inflammation on disease progression

VI. Does the role of inflammation in OA alter our management choices?

- Potential changes in risk:benefit evaluations
- Potential changes in pharmacoeconomic evaluations

VII. Questions and answers

VIII. Concluding remarks

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All faculty members will be screened for possible conflicts of interest (COI) and the program will be executed in a manner that is consistent with OIG, FDA, ACCME, and ACPE standards and guidelines.

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