Therapeutic Approaches to Osteoarthritis
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Release Date: November 1, 2003
Expiration Date: November 1, 2006

Target Audience:
Physicians, pharmacists, nurse practitioners, physician assistants, and certified case managers.

Program Goal:
The speaker presents recommended diagnostic and treatment strategies for osteoarthritis that can be appropriately utilized in the primary care setting.

Program Overview:
This program utilizes a case study format to address osteoarthritis (OA), its incidence and risk factors. Diagnostic considerations and treatment strategies are also reviewed. A comprehensive evaluation of COX-2 inhibitor NSAIDS is included.

Statement of Need:
Osteoarthritis is the most common type of arthritis, affecting an estimated 21 million adults in the United States. Osteoarthritis primarily affects cartilage causing joint pain and stiffness. Disability results most often when the disease affects the spine and the weight-bearing joints (the knees and hips). Most people over age 60 have osteoarthritis to some degree, but its severity varies, and some people develop more severe symptoms than others.

Intended Outcome:
It is anticipated that physicians and other healthcare practitioners will develop an enhanced appreciation for the diagnostic and treatment considerations surrounding osteoarthritis.

Educational Objectives:
Upon completion of this activity, participants should be able to:

1. Identify incidence and risk factors for OA
2. Differentiate between RA and OA
3. Identify non-drug and herbal approaches to treatment
4. Review the risks and benefits of the different COX-2 inhibitor drugs

Principal Faculty:
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Boehringer Ingelheim

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- *Sound Card & Speakers
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THERAPEUTIC APPROACHES TO OSTEOARTHRITIS: AN ONLINE CME PROGRAM

This program will be addressing therapeutic approaches to osteoarthritis as presented by Dr. David Silver. Dr. Silver is the Clinical Chief of Rheumatology at Cedars-Sinai Medical Center in Los Angeles, California, and Assistant Clinical Professor of Medicine at U.C.L.A. School of Medicine.
INTRODUCTION

In the United States about 70-million people (one in four Americans) are affected by one form of arthritis or another. Over half of those have osteoarthritis, the most common form of arthritis. Osteoarthritis (OA) is one of the leading causes of morbidity and loss of work in America today. The estimated total economic burden is greater than $80-billion due to loss of work, medical care, long-term care, adaptive devices, and other supportive services. Unlike other diseases, at this time there are no disease-modifying agents available.
RISK FACTORS

There are numerous risk factors associated with the development of osteoarthritis. The most common risk factors are age and obesity. Aging adds to the wear and tear on joints, often leading to the development of osteoarthritis. Added weight increases the amount of force transmitted to joints which can lead to injury and eventually the development of osteoarthritis.

Previous trauma can have a long-term effect despite the best treatment possible at time of injury. The best example is the 22-year-old who tears the ACL and medial meniscus while skiing downhill. Twenty years later, despite the best surgical repair possible, this individual begins to develop symptoms of osteoarthritis.

Crystal deposition is a condition that most clinicians don’t consider. Evidence from numerous medical centers, including U.C.L.A. and University of Alabama, Birmingham have indicated that in patients who have osteoarthritis of the knee, 70% will have evidence of basic calcium or CPPD crystals upon an arthroscopy examination. Whether this sets up a breeding ground for inflammation, furthers the disease process, or is simply a product of cartilage degradation is not yet clear but it may represent a target for therapeutic intervention. In addition, many patients who have existing osteoarthritis can have inflammatory reactions as a result of these crystals and will often respond well to anti-inflammatories or corticosteroids.

Neuropathies can also lead to the development of osteoarthritis. The classic example is the person with diabetes who also has a Charcot joint (a joint that is unable to feel any pain or sense of position) leading to movements that cause injury and damage, and the development of an accelerated form of osteoarthritis. This is not only seen in diabetic neuropathies but other forms of sensory neuropathies as well. In addition, patients with motor neuropathies or muscle weakness are more prone towards joint injury, and the eventual development of osteoarthritis.

Women are much more likely to develop osteoarthritis than men. Almost three-quarters of all people with osteoarthritis are women. This is partially a result of genetic factors but in addition, women on average live six to seven years longer than men and have more opportunity to develop the disease. African-Americans are more prone than Caucasians to developing osteoarthritis.
GENETICS AND OSTEOARTHRITIS

- Familial tendency
- Early onset, inflammatory OA
- Recent article showing HLA association with development of osteoarthritis.


GENETICS AND OSTEOARTHRITIS

There is now a greater understanding of the important role genetics play in the development of osteoarthritis. Patients who present with a fairly advanced form of osteoarthritis at a relatively young age often report a strong family history of osteoarthritis, and have no obvious evidence of trauma or other risk factor to explain why they have this disease. Still other patients who have been very physically active, sustained numerous injuries, and remain very active in their 80’s may show no evidence of the disease or have very mild disease.

There appears to be an early onset, inflammatory type of osteoarthritis seen in patients as young as their thirties. There are genetic factors that play a role in the disease development. Recent studies have shown an association of human leukocyte antigen (HLA) with the development of osteoarthritis. What role HLA has is not yet clear but it may impact the type of collagen or other matrix laid down in the cartilage of patients who seem to have a predisposition for osteoarthritis.
OA AS AN INFLAMMATORY DISEASE

Although previously believed to be just a degenerative process, over the past several years OA has been shown to be an inflammatory disease. This is not to say it is an inflammatory-like rheumatoid arthritis with significant autoimmune processes leading to joint destruction, but inflammation plays an important and crucial role in the progress and development of osteoarthritis. Supporting evidence includes an increase in inflammatory cytokines such as IL-1, IL-6 and TNF-alpha; increased activity in an enzyme called nitric oxide synthase which has numerous functions in regulating inflammation and other cartilage functions; increased prevalence of crystals; and up-regulation of cycle oxygenase type 2.

Understanding of the role of inflammation in osteoarthritis may lead to other appropriate potential targets for disease modification. For example, it is not yet clear why anti-inflammatory drugs seem to provide more symptomatic relief than acetaminophen.
CARTILAGE IN OA

The former belief that an injury to a joint with cartilage slowly wearing away until it is no longer there is a great underestimation of the complexity of this disease. Osteoarthritis is a dynamic process. Studies using animal models with meniscus tears that progress to disease have shown that there is an attempt of the cartilage to actually repair itself. A new cartilage matrix is laid down albeit not of the same quality as that of the previous cartilage matrix. What does occur is the increased production of metalloproteinases, collagenases and other enzymes; eventually leading to degradation and ultimately the roughened, irritated surface seen later on in the disease.

Metalloproteinase inhibitors have been evaluated preliminarily in clinical trials to determine their influence in the loss of cartilage in osteoarthritis. Although preliminary studies were very promising, metalloproteinase inhibitors are not being extensively studied. As we learn more of the specific targets types of metalloproteinases and collagenases involved in cartilage degradation, they may prove to be targets for future disease modification.

Other structures are known to play a crucial role in the symptoms of osteoarthritis as well such as osteophyte formation and changes in the surrounding structures. These should not be neglected when evaluating a patient with osteoarthritis.
CASE PRESENTATION

A 67-year-old woman presents with an 18-month history of increasing left knee pain. She has noted difficulty walking, getting up from a chair, and the inability to get up from a squatting position. She notes occasional swelling and about 10 to 15 minutes of morning stiffness. Other complaints include pain at the base of the right thumb and slight hip pain. She does not recall any antecedent trauma to the joints, and no precipitating incident that led to the development of pain.
CASE PRESENTATION CONT

- Past Medical History: Mild hypertension well controlled, hyperlipidemia
- Meds: Atenolol, Atorvastatin
- NKDA
- Former high school soccer player, used to be physically active
- Retired last year as administrative assistant
- Married, 2 kids, FH of “rheumatism”

CASE PRESENTATION CONTINUED

Her past medical history is significant for well-controlled mild hypertension and hyperlipidemia. She takes Atenolol and Atorvastatin. She has no known drug allergies. She is a former high school soccer player and used to be very physically active although she has not been physically active for the last 10 to 20 years. She retired last year as an administrative assistant. She is married, has two grown children, and reports a family history of rheumatism.
CASE PRESENTATION CONT

• PE: 118/80, pulse = 64
• Height 5'5", 170lbs.
• Mild bony hypertrophy, crepitance with full ROM left knee. Heberden’s nodes, changes in 1st CMC (carpo-metacarpal) joints of thumbs bilaterally.
• Otherwise essentially normal PE

CASE PRESENTATION CONTINUED

On physical examination, she was noted to have a blood pressure of 118/80 and a pulse of 64. She is 5 foot 5 inches tall and weighs 170 pounds. Examination reveals mild bony hypertrophy around the knee with crepitus. Full range of motion is noted. She also has Heberden’s nodes and changes in the first CMC (carpo-metacarpal) joints of the thumbs bilaterally. Otherwise, her physical examination is essentially normal.
ARE X-RAYS HELPFUL IN MAKING THE DIAGNOSIS OF OA?

A. Yes
B. No

Given this information, consider what your next diagnostic recommendations might include.

Are x-rays going to be helping in making the diagnosis of osteoarthritis (OA)?

A. Yes
B. No
X-RAYS AND OA

• OA diagnosis made predominately on history and physical exam
• X-rays poorly correlate with disease severity
• May consider if trying to differentiate between OA and other forms of arthritis

Dieppe PA, Cusnaghan J, Shepstone L. Osteoarthritis Cartilage, 1997

X-RAYS AND OA

X-rays can be an important tool used to differentiate the type of arthritis. However, the diagnosis of osteoarthritis is not dependent upon x-ray findings. In fact, the diagnosis of osteoarthritis is predominantly based on history and physical examination. X-rays have been found to poorly correlate with a patient’s reporting of disease severity. Many patients with the worst looking x-rays will be very physically active, while other patients who have minimal if any changes in x-rays, may be walking with a cane.

X-rays can be used when questioning the diagnosis or to differentiate between other forms of arthritis, especially in a patient who has had a history of rheumatoid arthritis (RA) but now appears to have a clinical picture of osteoarthritis. The other role of x-ray in osteoarthritis is considering surgical intervention. If the patient has only minimal x-ray changes, referring them to an orthopedic surgeon for a total joint replacement may be inappropriate as opposed to the patient with significant joint destruction.
# HOW TO DIFFERENTIATE OA FROM RA BY EXAM AND HISTORY

<table>
<thead>
<tr>
<th>RA</th>
<th>OA</th>
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</thead>
<tbody>
<tr>
<td>Age onset 25–50 years</td>
<td>Age onset after 40 years</td>
</tr>
<tr>
<td>Acute or subacute onset</td>
<td>Slowly progressive onset</td>
</tr>
<tr>
<td>Joint involvement symmetric</td>
<td>Less symmetric joint involvement</td>
</tr>
<tr>
<td>Associated fatigue</td>
<td>No systemic symptoms</td>
</tr>
<tr>
<td>Involves large &amp; small joints</td>
<td>Rarely involves wrists, ankles, elbows</td>
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<tr>
<td>Rheumatoid nodules</td>
<td>Rheumatoid nodules absent</td>
</tr>
<tr>
<td>AM stiffness &gt;30 min</td>
<td>AM stiffness &lt;15 min</td>
</tr>
<tr>
<td>Hands: MCPs, PIPs, wrists</td>
<td>Hands: first CMC, DIP, PIP</td>
</tr>
<tr>
<td>Boggy, warm joint swelling</td>
<td>Firm, cool joint enlargement</td>
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## HOW TO DIFFERENTIATE OA FROM RA BY EXAM AND HISTORY

The question for many practitioners is how to differentiate osteoarthritis from rheumatoid arthritis based on examination and history. Patients will often claim to have the diagnosis of rheumatoid arthritis and still have many factors and a physical exam inconsistent with that diagnosis. Understanding the differences between the two diseases can aid in making a proper diagnosis and develop an appropriate treatment plan.

Rheumatoid arthritis is an autoimmune disease that involves the synovium as well as the surrounding structures. Patients with RA have a typical age of onset between 25 and 40 although there will be a second peak later in life in the sixth and seventh decades. The onset of RA tends to be more acute or subacute, with the typical patient saying reporting increasing symptoms of about four to six weeks. An occasional patient will notice sudden onset of inflammation of the joints over a few days. The joint involvement in rheumatoid arthritis tends to be symmetrical. There is an associated fatigue with the release of the inflammatory cytokines. RA involves the large and small joints, although typically it involves the joints of the hands and spares the distal interphalangeal (DIP) joints. Rheumatoid nodules are present in a significant amount of patients. They are characterized as rubbery-feeling substances on the extensor surfaces common in the elbows, wrists, and hands. A typical symptom of rheumatoid arthritis is morning stiffness lasting greater than 30 minutes. The most common joints involved include the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, wrists as well as the metatarsophalangeal (MTP) joints of the feet. The joints in rheumatoid arthritis feel boggy, warm and have a very typical appearance. Later on in the disease, the classic ulnar deviation, significant bunion deformities and other classic joint changes develop, which can help confirm the diagnosis.

Osteoarthritis, with the exception of very aggressive athletes with early injuries, is almost always seen in patients after the age of 40. It tends to be slowly progressive. OA is not necessarily symmetric and an asymmetric distribution is quite typical. Patients do not have systemic symptoms unless their pain is so severe that it impacts other daily functions. Osteoarthritis, unlike rheumatoid arthritis, rarely affects the wrists, ankles and elbows and very typically involves the DIP joints with the formation of Heberden’s nodes. Rheumatoid nodules are not seen in osteoarthritis. Morning stiffness is not a typical component although some patients who need to take a few minutes to “get going” in the morning. Common joints of involvement include the first carpo-metacarpal (CMC) joint, the joint at the base of the thumb and the DIP joint. The joints, unless there is a flare up of symptoms, are cool and more firm to touch without significant amounts of boggy synovitis.
WHAT SHOULD YOU DO NEXT?

A. Exercise and weight reduction program
B. Start Acetaminophen up to 4 g/D
C. Start Glucosamine/Chondroitin
D. Start NSAID
E. Start COX-2 inhibitor
EXERCISE AND OA

Most clinicians understand that exercise is an overall good thing in patients with osteoarthritis. The evidence to support this is quite substantial. Patients who are immobilized with OA begin to feel better once they start moving; joint stiffness diminishes, flexibility increases, and pain often diminishes.

It is important to remember in osteoarthritis that exercise is not changing the joint itself. Exercise does not promote re-growth of cartilage and does not change the underlying process. Changes in many of the surrounding structures are actually the cause of the pain in this disease. Pain is often related to muscle stiffness, lack of flexibility in tendons, ligaments and muscles, and osteophytes which may be pressing on nerve endings. Cartilage itself has no nerve endings. We know that exercise can have a marked positive impact on those structures. There are very specific studies which have indicated quadriceps strength better correlates with symptoms of osteoarthritis of the knee than an x-ray. One could almost draw an inverse corollary between quadriceps strength and the patient’s symptoms of osteoarthritis of the knee; the stronger the quadriceps muscles, the less pain the patient will experience. Studies have also shown that patients who embark on a six to twelve-week quadriceps strengthening program can on average notice a 30 to 50% reduction in osteoarthritis symptoms of the knee. Although exercise has been studied less in other joints, it would seem that more flexible, more limber muscles, joints, and tendons would all lead to improved symptoms and reduce pain.

There is a recent study reported in the Annals of Internal Medicine (2003) that indicates patients with significant mal-alignment of the knee should be carefully monitored while engaging in a quadriceps strengthening program. Dr. Sharma at Northwestern and her colleagues have stated that patients with a greater than 5% mal-alignment of the knee and strong quadriceps may actually be prone towards more aggressive or more rapid symptoms and changes in the joint.

Motivating patients to mobilize is crucial. Understanding that joint alignment may play a key role is important for physical therapists to incorporate that into any rehabilitation program. Patients who present for an initial evaluation for osteoarthritis have difficulty understanding that by increasing activity they can actually reduce symptoms. Unfortunately, most patients present with the notion that exercise is causing problems. Understanding the right kind of exercise, guidance with the physical therapist, and instructions that can be easily taught in an office will go a long way towards helping patients with osteoarthritis.
WEIGHT, DIET AND OA

Maintaining an appropriate body weight is also crucial. Overweight patients with osteoarthritis can get into a cycle of inactivity: “I can’t exercise because of my pain, therefore I gain weight and because I gained weight, I can’t exercise again because my pain is increased.” Breaking that cycle is crucial to reducing symptoms of osteoarthritis. Even small reductions in weight in massively obese people have a profound impact in reducing symptoms.

A patient who is 100 pounds overweight does not necessarily need to lose the whole 100 pounds to make a significant impact. A 20 pound weight loss will produce a marked reduction in symptoms, most commonly in the lower extremities.

A healthy diet may have a positive impact as well. Studies have shown that patients who consume high-normal levels of vitamin C, D, and E have a lower risk of osteoarthritis than the average population. This was demonstrated in the large Framingham study outside of Boston by Dr. Felson and his colleagues. Encouraging patients to take a multivitamin may do no harm, and supports better nutrition.
CASE STUDY CONTINUED

The patient was then started on acetaminophen for two weeks with no relief. The dose was increased up to four grams per day with no significant change in symptoms. She was started on glucosamine and chondroitin at appropriate doses but noticed little benefit over two months. Not surprisingly, the patient did not consistently exercise as was recommended and lost only four pounds over the three-month period.
GLUCOSAMINE/CHONDROITIN

The use of glucosamine and chondroitin came into the mainstream public back in 1997 after the release of the book *The Arthritis Cure: The Medical Miracle That Can Halt, Reverse, and May Even Cure Osteoarthritis* by Jason Theodosakis, Brenda Adderly, Barry Fox and Terry J Dubrow.

There is a good body of evidence to support that glucosamine and chondroitin in combination help relieve the pain and symptoms of osteoarthritis, and there is a possibility that it may preserve cartilage. Three European studies, the largest with an enrollment of 370 patients in Belgium, demonstrated that patients who took glucosamine and chondroitin over two years had significant pain relief and seemed to have joint space preservation when compared to placebo.

It is important to understand some of the nuances of this study. The patients who took placebo over the two years on average lost 0.4 mm of cartilage when compared to no loss in the treatment group. Whether 0.4 mm of cartilage is functionally significant is not clear. In addition, there were some questions raised about the x-ray methodology used in this study, which may have impact on the measurements made. However, both non-randomized trials and the double-blind, placebo-controlled trials support the benefit of glucosamine and chondroitin.

The N.I.H. has embarked on a large multi-center trial looking at 1,800 patients in a five-arm, double blind, randomized study. The five arms include glucosamine alone, chondroitin alone, combination therapy, a COX-2 inhibitor and placebo studying pain and joint preservation. The large study sample size as well as the separation of the glucosamine and chondroitin groups will hopefully answer the questions: Are glucosamine and chondroitin effective pain relievers and do they preserve joint space.

The recommended dose for glucosamine is 1,500 mg per day unless the patient is very slight, and chondroitin 1,200 per day. It has been observed that many patients do not see relief of symptoms for two to four months. Patients who take the drug should be instructed that they will need to take it for at least 12 to 16 weeks.

There is a caution that glucosamine and chondroitin should be avoided by persons with diabetes; or at the very least, there should be careful monitoring of individuals who have elevated glucose levels since the drugs are known to raise blood sugar. Otherwise, these medications seem to be well tolerated and there are no other known untoward side effects.
CASE STUDY CONTINUED:

Back to the case study, this patient was started on Ibuprofen 600mg tid. She noted dyspepsia in 3 days and was switched to Diclofenac. She continued to report dyspepsia while on medication.
DYSPEPSIA IN NSAID USERS

- Prevalence ~ 15% - 60% (x2 of nonusers)
- No relationship to ulcers or clinical events
- Most common reason for NSAID discontinuation

Laine, L. *Semin Arthritis Rheum*, 2002

**DYSPEPSIA IN NSAID USERS**

An important factor to consider when patients with osteoarthritis are treated with non-steroidal anti-inflammatory drugs is that dyspepsia is the most common reason patients discontinue the medicine. Although dyspepsia has no relation to ulcers or other clinical events, it is the most common reason that patients stop taking NSAIDS. The prevalence of dyspepsia in NSAID users runs 15 to 60%, or at least double the normal population. This is an important factor in deciding the therapy chosen for OA patients or for potentially switching the patient to one of the newer COX-1 sparing agents.
WHAT WOULD YOU DO NEXT?

A. Try a different NSAID
B. Corticosteroid injection into the knee
C. Topical NSAID
D. Add a PPI
E. Try a COX-2 inhibitor
TREATMENT

• Joint injection
  – Corticosteroids
  – Hyaluronic Acid
• Arthroscopy
• Joint replacement

Karlsson J, Sjogren LS, Lohmander LS. *Rheumatology (Oxford)*, 2002

TREATMENT OF OA

Corticosteroid injections have been used for many years in treating symptoms not only of osteoarthritis of the knee but numerous other rheumatologic conditions. The fact that corticosteroids are effective in some patients goes to further confirm the inflammatory nature of this disease. The mechanism of action of corticosteroids is reduction of inflammation. There are some patients who can get several months of relief when given corticosteroids injection. The question always raised deals with how many corticosteroids injections can be safely given within a specified period of time. Unfortunately, little if any research has been done on this subject. Practitioners have raised the concern that infrequent injection of corticosteroids might actually accelerate the process of osteoarthritis since it is believed that oral corticosteroids may enhance the process. However, there is little if any research to support or confirm this hypothesis. In fact, many rheumatologists will claim that two to three injections per year of corticosteroid can be safely given without any significant harm to the joint.

If patients do get significant relief and if symptoms are isolated to one or two joints predominantly, corticosteroid injections in those patients can be of great benefit. The other injection that has been used more frequently used recently is uronic acid. The trade name is more commonly known as Synvisc® or Hyalgan®. These are only approved for osteoarthritis of the knee, and have been shown in randomized clinical trials to reduce symptoms of osteoarthritis of the knee greater than placebo injections. The injections are a thick gelatinous substance, about 2 cc per injection, and given in a series of weekly shots three to five weeks in a row. Most patients tolerate the injections fairly well, although rarely there will be an acute inflammatory response to the injection which can be easily treated by a further injection of corticosteroids. Pseudoseptic knee can occur after the injection. The knee appears warm, swollen and almost like that of a septic joint although there is no infection present. Fortunately, this complication is very rare.

Patients who respond initially to the injections often will respond to subsequent injections. Injections are now covered by most major health plans. Unfortunately, it is only available and approved for osteoarthritis of the knee, although ongoing research is evaluating other joints. For patients who benefit from uronic acid injection treatment, it can be repeated every six months. Patients often will have better relief with subsequent injections.

Arthroscopy is a tool in osteoarthritis that is being used less and less. A recent study in the *New England Journal of Medicine* (2002) by Moseley et al indicated that arthroscopy of the knee in patients with osteoarthritis provided no benefit in terms of symptom relief or disease progression. There may be specific circumstances in which arthroscopy would have a role; for example, in patients with a very large osteophyte, which is symptomatic, or a particular flap of cartilage that needs repairing. The benefit of arthroscopy in terms of flushing the joint, removing the inflammatory mediators and CPPD crystals has not borne out based on these studies. It is now believed that the role of arthroscopy in osteoarthritis is limited.

Despite all interventions, many patients require joint replacement. In appropriate patient candidates, joint replacement can provide marked symptom relief with improved function in a very rapid fashion. The quality of hip, knee, and shoulder replacements has greatly improved. Unfortunately surgical remedies for osteoarthritis of the hands and other joints have not been as successful. For a patient who is healthy enough to tolerate surgery and has very isolated symptoms in one joint, joint replacement may be appropriate if other modalities don’t work.
NSAIDS POSE SIGNIFICANT RISK

The mainstay of therapy for osteoarthritis has been the use of non-steroidal anti-inflammatory drugs (NSAID). Non-steroidal anti-inflammatory drugs have the advantage of pain relief and may also work on joint inflammation. Many practitioners have been reluctant to use NSAIDs because of the risk for gastrointestinal bleeds.

The problem of gastrointestinal bleeds should not be underestimated. An article in the *New England Journal* discussing selected causes of death in the U.S. population in 1997 (Wolfe et al, 1999) revealed that in 1997 an equivalent number of people in the United States died as a result of NSAID-induced bleeds as died from HIV. During the same time period, news about the HIV epidemic dominated media coverage. This was justifiable, but during that same timeframe there was little if any coverage on NSAID-induced GI bleeds. From a cost perspective, approximately 20 to 35% of all the money spent on arthritis care in the U.S. was spent on treating the complications of NSAID therapy. This left many clinicians reluctant to treat osteoarthritis with NSAIDs despite the fact that it is a most effective and consistent weapon in the treatment of osteoarthritis. Patients were advised to take acetaminophen, and only if their symptoms got worse to change to a full prescription-strength NSAID. There are now alternatives available that may help limit the exposure to significant GI events.
ACETAMINOPHEN AND OA

The first line of therapy in OA has always been acetaminophen. Acetaminophen was the first choice in the American College of Rheumatology Guidelines in the 1990’s for the treatment of osteoarthritis. It was found in studies in the early 1990’s that acetaminophen given at 4 grams per day provided equivalent pain relief to non-steroidal anti-inflammatory drugs given at full prescription strength. Although this seems counter to what many physicians experience in clinical practice, acetaminophen has safety advantages over traditional non-steroidal anti-inflammatory drugs.

Studies in the late-90’s have consistently shown that acetaminophen does not appear to be as effective in most osteoarthritis sufferers. This is not to say that acetaminophen should not be a first choice of therapy, given its advantages. Acetaminophen is inexpensive, effective in many patients, and very safe.

But there is an emerging body of evidence that acetaminophen, when given at greater than 2 grams per day, may be associated with an increased risk of GI bleeds. This appears to be based on the fact that acetaminophen at higher doses may have some slight COX-1 inhibiting effects not previously recognized. Evidence at this time is non-conclusive that acetaminophen has the same GI risk as a traditional NSAID, and further studies are in progress. Patients taking acetaminophen must also be careful about not consuming too much alcohol as this may further increase the complications of the drug.
PROS & CONS OF PPIS

The addition of proton pump inhibitors to traditional NSAID’s have been shown to reduce the risk of GI events. The advantage of proton pump inhibitors is that they alleviate dyspeptic symptoms. If a patient who is already on a PPI for dyspepsia begins treatment with a traditional NSAID, a PPI will protect them from the dyspepsia side effects and may also reduce the effects of possible GI bleed. It is known that PPI’s are effective in treating and healing active ulcer disease, preventing GI ulcers (as demonstrated in studies), and probably prevent bleeding from already existing ulcers.
SELECTIVE COX-2 INHIBITORS

- Celecoxib: available in 100 mg and 200 mg capsules
- Rofecoxib: available in 12.5 mg, 25 mg, and 50 mg tablets and in liquid form
- Meloxicam: available in 7.5 mg and 15 mg tablets
- Valdecoxib: available in 10 mg and 20 mg tablets
- All can be dosed without regard to food intake

SELECTIVE COX-2 INHIBITORS

The advent of the selective COX-2 inhibitors has changed osteoarthritis treatment. Presently there are four drugs throughout the world that may be considered selective COX-2 inhibitors: celecoxib, rofecoxib, meloxicam, and valdecoxib. Although meloxicam is not listed as a COX-2 inhibitor in the United States, it is listed as a COX-2 inhibitor in most other countries of the world. A real plus about the newer drugs is that they tend to be once a day and can all be dosed without regard to food intake.

The advantages of the newer agents in theory, is they are GI safer. Theoretically COX-2 inhibitors inhibit the COX-2 enzyme more selectively than the COX-1 enzyme. The COX-1 enzyme is responsible for producing prostaglandins that protect the lining of the stomach, platelet function and many other housekeeping functions. This is in contrast to COX-2, which is stimulated with pain and inflammation and is responsible for some of the symptoms we see with osteoarthritis.
Attempts have been made to classify and determine the most COX-2 selective agents. Sir John Vein, who won the Nobel Prize in the 1970’s for the discovery of prostaglandins and cyclo-oxygenase, developed an assay called the human whole blood assay. He explored every available COX-2 and regular NSAID available on the market at that time to determine the COX-2 versus COX-1 selectivity. He and Professor Warner explored the “therapeutic inhibition of COX-2,” (so called 80% inhibition) because it is known that at approximately 80% inhibition of COX-2, full therapeutic effect of both traditional NSAID’s and COX-2 inhibitors is realized.

Traditional NSAID’s do not appear to have any increased selectivity for COX-2 over COX-1, yet many of the newer agents such as celecoxib, meloxicam and rofecoxib appear to be more selective. Valdecoxib, which was not available at the time of this study, has a selectivity profile very similar to that of rofecoxib.

COX-2 inhibitors are prescribed not because of improved efficacy but because of safety advantages. Although there is the opinion among patients that these newer drugs are more effective, clinical research does not suggest any increased efficacy over traditional NSAID’s when given at full prescription strength dose. Because these drugs similarly affect the COX-2 enzyme, it would be expected that they would all have a similar global effect on pain and inflammation.

This is not to say that there may not be individual drugs that work better in an individual patient. Every clinician has experienced this phenomenon. With numerous new agents now available, it is important to remind patients they should not necessarily expect better pain relief from a COX-2 inhibitor than they would have from their traditional NSAID’s.
ULCER COMPLICATION AND SYMPTOMATIC ULCER RATE IN NON-ASA USERS

With less concern for GI side effects, the tendency is to freely give the new COX agents and tell patients to take them on a regular basis. Although this leads to better pain relief, they are not more effective drugs. It should be emphasized that they are given because of the GI safety issues. Some evidence these drugs are truly GI safer than traditional NSAID’s follows.
CELECOXIB CLASS RESULTS:

The first large study done was called the CLASS Trial. This study enrolled 8,000 patients and looked at celecoxib versus ibuprofen and diclofenac in patients predominately with OA who were allowed to take aspirin for cardiovascular prophylaxis. This was a one-year, double blinded, randomized study.

The six-month intra-analysis showed a significant reduction in GI events in patients taking celecoxib at 400 mg twice a day versus the traditional NSAID’s. There are numerous reasons why this study did not show the differences expected. The one-year data in the CLASS study indicated no statistically significant differences between the three agents.
SUCCESS TRIAL

A newer study, the Success Trial, came out of Europe approximately two years ago. It studied 13,000 patients taking celecoxib versus traditional NSAID’s.

In this three-month study, a statistically significant reduction in GI events was seen in patients taking celecoxib versus patients taking traditional NSAID’s. This reassures that celecoxib does appear to reduce the risk of GI bleeds in patients versus traditional NSAID’s.
ROFECOXIB HAD A SIGNIFICANTLY LOWER PUB RATE THAN NSAIDS

The Vigor study was rofecoxib’s double blind, randomized trial, with 8,000 patients enrolled. This was a study looking at patients with rheumatoid arthritis with a comparator drug of naproxen. Patients were not allowed to take aspirin for cardiovascular prophylaxis in this study. Patients were followed for one year.

In this study, rofecoxib was shown to reduce the risk of GI bleeds when compared to the traditional NSAID (naproxen) by approximately 55%. There was only about a 20% drop out rate in this study. The results demonstrated that rofecoxib when compared to naproxen did reduce the risk of GI events, confirming the COX-2 theory.
CLINICALLY SERIOUS GI EVENTS

The data on meloxicam in reducing GI events is predominantly derived from pooled data. The main pooled study looked at 27,000 patients from two large, double blind, randomized trials done in Europe: the MELISSA and SELECT Trials. The comparator drugs in these studies were naproxen, diclofenac and piroxicam.

The results found looking at these 27,000 patients was a greater than 50% reduction in significant GI events when comparing meloxicam at the higher dose of 15 mg, versus the three traditional NSAID’s. Study findings reinforce that meloxicam appears to have a superior GI safety profile to traditional NSAID’s; this is less evident with valdecoxib.
VALDECOXIB AND GI EVENTS

- Selectivity profile similar to Rofecoxib
- Endoscopy data shows less ulcers
- No data from randomized or pooled trials to look a significant GI bleeds

Although there is clinical suspicion that valdecoxib will significantly reduce GI bleeds, the data is not presently available in the literature. There is significant data on endoscopies showing a reduction in GI ulcers, and selectivity data that would suggest this reduction, but to date no large trials have been conducted to confirm this since oral valdecoxib was released before the injectable formulation. Injectable valdecoxib should become available within the next 12 months.

Hopefully when injectable valdecoxib becomes available, this will offer a new option for patients who have significant osteoarthritis but are unable to take oral drugs. This injectable form of valdecoxib, recently approved by the F.D.A., should provide a new alternative for patients who are unable to take narcotics and oral NSAID’s.
MELOXICAM: INCREASED PRESCRIPTION IN GI RISK PATIENTS

There is a concern for the high-risk patient, and a need to justify the use of these more expensive drugs. There are a few specific trials looking at high-risk populations. A large trial studied meloxicam in Europe in about 4,300 patients who were considered high risk (Degner, Sigmund & Zeidler, 2000). In this study, patients who were taking meloxicam had a significantly higher risk from a previous history of GI bleed, peptic ulcer or other GI diagnoses. Despite that history, there was an almost 50% reduction in GI events and an almost 80% reduction in GI bleeds. The study implies that the use of meloxicam in this high-risk population does reduce the risk of GI events.

<table>
<thead>
<tr>
<th>GI risk factors</th>
<th>Meloxicam</th>
<th>other NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Recent use of acid-suppressing drugs (%)</td>
<td>10-12 (OR 2.2-2.8)</td>
<td>3-6</td>
</tr>
<tr>
<td>History of peptic ulcer (%)</td>
<td>6</td>
<td>3-4</td>
</tr>
<tr>
<td>GI diagnoses (%)</td>
<td>38 (OR 1.9-2.4)</td>
<td>20-24</td>
</tr>
<tr>
<td>(2) History of PUB (%)</td>
<td>12**</td>
<td>7</td>
</tr>
<tr>
<td>GI-events (%)</td>
<td>1.8</td>
<td>3.2*</td>
</tr>
<tr>
<td>GI-bleeding (%)</td>
<td>0.08</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

*p<0.01
** p<0.001

CELECOXIB AND HIGH RISK PATIENTS

A randomized study conducted in Hong Kong in December 2002 studied patients with recent GI bleeds who were selected to take celecoxib versus diclofenac and a PPI. The study showed no statistically significant difference between the two groups. Since the study enrollment was slightly over 100 patients per group, it appears it was not powered to detect any difference between the two groups.

It is known that the use of PPI plus an NSAID does reduce the risk of GI bleeds. To determine a difference between these two regimens, one would need a much larger sample size to draw any conclusions. Therefore, little if any new information was provided by this study.

It is also known that the addition of a proton pump inhibitor can reduce significant GI events. Although the H2 blockers do reduce the symptoms of dyspepsia, they do not appear to significantly reduce the risk of GI bleeds with the exception of some small studies looking at very high doses. For patients with dyspepsia, the use of a PPI plus a traditional NSAID may be another choice.
### IMPROVE TRIAL TREATMENT SUCCESS BY NSAID

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Usual Care</th>
<th>Meloxicam</th>
<th>Meloxicam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Success</td>
<td>(N)</td>
</tr>
<tr>
<td>ROFECOXIB</td>
<td>151</td>
<td>81</td>
<td>53.6%</td>
</tr>
<tr>
<td>CELECOXIB</td>
<td>79</td>
<td>49</td>
<td>62.0%</td>
</tr>
<tr>
<td>NAPROXEN</td>
<td>71</td>
<td>29</td>
<td>40.8%</td>
</tr>
<tr>
<td>DICLOFENAC</td>
<td>66</td>
<td>28</td>
<td>42.4%</td>
</tr>
<tr>
<td>PIROXICAM</td>
<td>58</td>
<td>21</td>
<td>36.2%</td>
</tr>
<tr>
<td>NABUMETONE</td>
<td>46</td>
<td>13</td>
<td>28.3%</td>
</tr>
<tr>
<td>ETODOLAC</td>
<td>38</td>
<td>17</td>
<td>44.7%</td>
</tr>
<tr>
<td>SULINDAC</td>
<td>35</td>
<td>8</td>
<td>22.9%</td>
</tr>
<tr>
<td>OXAPROZIN</td>
<td>34</td>
<td>16</td>
<td>47.1%</td>
</tr>
<tr>
<td>IBUPROFEN</td>
<td>18</td>
<td>7</td>
<td>38.9%</td>
</tr>
<tr>
<td>ARTHROTEC</td>
<td>13</td>
<td>5</td>
<td>38.5%</td>
</tr>
</tbody>
</table>


**IMPROVE TRIAL TREATMENT SUCCESS BY NSAID**

The purpose of the IMPROVE trial was an attempt to mimic real clinical practice. It differed from other clinical trial guidelines requiring patients to spend two hours with the study nurse, receive substantial patient education, fill out 20 pages of questionnaires and follow up on a very regular basis.

In this trial, the requirements for enrollment were simply that the patient’s doctor felt that the patient needed to be on a regular NSAID or COX-2 for treatment of their osteoarthritis symptoms. Unless the patient was intolerant of NSAID’s or COX-2’s, there were considered eligible to enroll in the trial. The end points of the trial were: did the drug work for a full six months and did the patient not discontinue because of lack of efficacy or because of a side effect.

Half the patients were randomized to get meloxicam and half the patients were given whatever other NSAID the patient’s physician felt was appropriate. It included celecoxib, rofecoxib, diclofenac, and naproxen. Participating patients were not required to come in for every two or four-week visits although they were contacted by phone once a month to track progress.
IMPROVE TRIAL SUCCESSES

In this trial, 67% of the patients on meloxicam were found to have success versus 45% of the patients in the usual care arm. When broken down by individual drug, celecoxib came in at 62%, rofecoxib at 54% and all the traditional NSAID’s fell below the 50% line. Although the study was not designed or powered statistically to compare individual NSAID’s, the percent of patients treated with meloxicam had greater success than any of the individual usual care NSAID’s.
NSAID/COX-2 AND DYSPEPSIA

- Dyspepsia most common reason for NSAID discontinuation, not GI bleed
- Approximately one-third less dyspepsia on COX-2 versus NSAID’s
- PPI lower rate of NSAID induced dyspepsia

Interestingly, results from this IMPROVE trial seem to indicate that patients on the newer medications experienced less dyspepsia, which is consistent with the clinical trial results. There were no statistically significant differences between the three newer drugs, but there appeared to be a difference between these three newer drugs and the older medications. Valdecoxib was not available when this study was conducted.

This study demonstrates that if a patient has failed more than one traditional NSAID because of dyspepsia, changing to one of these newer COX-2 inhibitors should be considered. Patients who take these newer drugs have an approximately one-third lower rate of dyspepsia than patients taking traditional NSAID’s. What’s important to remember is that dyspepsia, not GI ulcers, are the most common reason patients discontinue these medications.
CASE STUDY CONTINUED

Returning to the case presentation, the patient’s physician started the patient on a COX-2 selective inhibitor. The patient noted less dyspepsia and good pain relief. However, the patient’s insurance company withdrew approval for the medication. The patient’s pain responded for a few months to corticosteroid injections.
CARDIOVASCULAR ADVERSE EVENTS: ALL PATIENTS AND NON-ASA USERS

Another issue raised with these newer NSAID agents is cardiovascular safety. The GI safety advantages are important but should not outweigh other factors. The cardiovascular safety issues were raised in a study two years ago reported in *The Journal of the American Medical Association* from the Cleveland Clinic (2000), which implied an association between COX-2 inhibitors and myocardial events. However, methodological flaws in this study allows substantial doubt regarding the significance of any cardiovascular issues with the COX-2 inhibitors. When one looks at the CLASS study, that large 8,000-patient trial done on celecoxib versus ibuprofen and diclofenac, there was nothing to indicate either in the aspirin or non-aspirin users any increased risk of myocardial events or CVA’s when compared to traditional NSAID’s. In fact, if one looks at all this pooled data on this subject, there is nothing again to indicate any concerns.
ACUTE MYOCARDIAL INFARCTION (PER 1000 PERSON-YEARS)

Looking at meloxicam in a pooled analysis of over 40,000 patients up to doses at 22.5 mg, there was nothing to indicate any concern about myocardial infarction when compared to traditional NSAID’s.
CARDIOVASCULAR EVENTS: ROFECOXIB

Concern, however, has been raised with rofecoxib in terms of the VIGOR study, which did show an increased risk of myocardial infarctions when compared to patients taking naproxen. Participants were given a 50 mg dose of rofecoxib daily for up to one year, which is not a dose used in clinical practice.

A number of explanations have been potentially raised for these concerning findings regarding cardiovascular safety. First, naproxen might actually be a cardio-protective drug, although most studies have indicated naproxen or any other traditional NSAID is an adequate drug for cardiac protection. Unlike aspirin, standard NSAID’s reversibly bind to platelets and therefore do not inhibit platelet function enough to have a significant impact on formation of clot in the coronary arteries.

More recently, a theory has been raised that it could be related to the selectivity of rofecoxib, as it does appear to be more selective at least in vitro than celecoxib or meloxicam. If this were the case, one would expect to see the same problems with valdecoxib as well as other highly selective COX-2 inhibitors. Unfortunately there is not a large enough data set on valdecoxib yet to confirm or deny these findings, although pooling of the smaller studies does not seem to indicate any increased risk at this time.

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Rofecoxib (n=4047)</th>
<th>Naproxen (n=4029)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed CV events</td>
<td>45 (1.7)</td>
<td>19 (0.7)</td>
<td>0.42 (0.25, 0.72)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>28 (1.0)</td>
<td>10 (0.4)</td>
<td>0.36 (0.17, 0.74)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>11 (0.4)</td>
<td>8 (0.3)</td>
<td>0.73 (0.29, 1.80)</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>6 (0.2)</td>
<td>1 (0.04)</td>
<td>0.17 (0.00, 1.37)</td>
</tr>
</tbody>
</table>

Bombardier C, Laine L, Reicin A et al. NEJM, 2000
NEWER DATA ON CARDIOVASCULAR SAFETY

A further study looking cardiovascular safety was published by Ray et al in *The Lancet* in 2002. Using the Tennessee Medicaid database, they studied the risk of myocardial events in patients taking rofecoxib as well as all of the COX-2’s and selective NSAID’s. Study results indicated that patients taking rofecoxib at greater than 25 mg did have an increased relative risk of myocardial events when compared to traditional NSAID’s. However at 25 mg or less, there appeared to be no increased risk. Although patients may notice increased efficacy when increasing the dose of rofecoxib from 25 to 50 mg, it is important to emphasize to them to maintain their dose on a regular basis at the 25 mg or less level.

In addition, there are other large observational trials done by people such as Petrona et al, which have confirmed that there appears to be no cardio-protective effects of naproxen or any other traditional NSAID.
INCIDENCE OF HYPERTENSION BY DOSAGE

There does however appear to be an increased risk of hypertension with rofecoxib when compared to other standard NSAID’s or even COX-2 inhibitors. Risk for both hypertension and edema appears to be dose dependent. The problem with hypertension can be present in all NSAID’s and COX-2 inhibitor; this problem is non-dosed dependent, but it does not appear to be the same as what is seen with rofecoxib. We have seen a slight increase in hypertension with celecoxib as well as that seen with meloxicam; however, the changes do not appear to be significant and are not significantly different than placebo.

It is important to remember this small risk of hypertension and edema when making choices on which agent to choose for patients with OA. These patients will need to be monitored, and you may need to stop the drugs if hypertension or edema appear following any traditional NSAID or COX-2 inhibitor. There is evidence from the literature that approximately 1-3% of patients who take a traditional NSAID or COX-2 may develop elevated blood pressure or peripheral edema which may or may not be present if you switch to a different agent (REF). In addition, patients taking ACE inhibitors need to be particularly cautious and watch for rises in blood pressure.
CONCLUSION

In conclusion, it is important to understand that osteoarthritis is something that healthcare practitioners deal with every day. Unlike 10 to 20 years ago, we now have things we can do to help our patients. As we begin to gain a greater understanding about the pathophysiology of this disease, and appreciated what is going on in the cartilage on a molecular basis, we will begin to devise disease-modifying drugs that can either retard or reverse symptoms. However, we are currently limited to the tools that we have. However, we can have a major positive impact in our patients’ lives by getting them to exercise, eat healthy, and incorporate medication strategies that can allow them to function with less pain and lead more active and fulfilling lives.
Thank you for your participation in this presentation.

This concludes our program. Thank you for participating in Therapeutic Approaches to Osteoarthritis.