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NSAIDs—Use of Over-the-Counter Nonsteroidal Anti-Inflammatory Drugs and Analgesics

Over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) are used to control pain and inflammation in a variety of musculoskeletal conditions, including arthritis, low back pain and sports injuries. The main objective of this protocol is to review NSAIDs that are commonly used in clinical management of musculoskeletal conditions. Dosage, side effects, contraindications, and interactions with other medications are presented, as well as a strategy for decision-making. Although not an NSAID, the analgesic acetaminophen is also discussed. Because treatment with NSAIDs may mask or confuse the benefit of other therapies, it may be prudent to delay use of NSAIDs in some cases until the effectiveness of alternative therapy is determined.

BACKGROUND

Reducing Pain and Inflammation

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed in the pharmacological management of pain and inflammation. These drugs work by inhibiting enzymes called cyclooxygenase 1 and 2 (COX 1-2). The COX 1-2 enzymes are responsible for the production of prostaglandins, hormone-like substances involved in inflammation and pain (Prisk 2003). NSAIDs have been routinely used for the initial onset, continued relief, and re-injury or exacerbations of musculoskeletal pain. As such, they should be recognized as potentially effective therapeutic adjuncts whose characteristics should be well understood by all clinicians. *(See Table I. Characteristics of Nonsteroidal Anti-Inflammatory Drugs.*)

At the same time, clinicians must be aware of the dangers and limitations of this powerful class of drugs, particularly in patients suffering from chronic pain (PDR 2004 [a, b, d], Donjon 1999).

Limitations of Evidence

Scientific evidence from drug trials may not apply to everyone taking a particular drug. For example, minority groups, children, the elderly, and persons at increased risk of adverse events are often deliberately excluded from trials. Furthermore, therapeutic benefits of drugs and adverse reactions are not measured using comparable scales. Finally, drugs tend to be used for a wider range of indications than those for which they are originally tested. Comprehensive databases linking prescriptions to hospital data and other health records are needed in order to assess the relative benefits and harms of drug use in a wide variety of patients (Simons 1999).

NSAIDs and ANALGESICS

There are three commonly used classes of NSAIDs and analgesics available over the counter: aspirin, propionic acid derivatives, and acetaminophen.

1. Aspirin

Aspirin is the prototype of NSAIDs and is effective in relieving pain, fever and inflammation. Aspirin also reduces the blood's ability to clot by affecting platelets. This can significantly reduce risk of heart attack and some types of stroke but may increase risk of gastrointestinal bleeding and other complications (Dalen 1992, Donjon 1999, Edwards *et al*. 2004, Eidelman 2003, PDR [a, b] 2004).

2. Propionic Acid Derivatives

Over-the-counter (OTC) formulations are available for three propionic acid derivative NSAIDs: ibuprofen, ketoprofen and naproxen sodium. These drugs have many of the same analgesic and anti-inflammatory qualities of aspirin, but present a lower risk of gastrointestinal bleeding; however, NSAIDs are not recommended for long-term management of rheumatic conditions (Lanza 1998, PDR [a] 2004, Strom *et al*. 1997).

WARNING: There is also clinical evidence that simultaneous use of aspirin and ibuprofen may attenuate the antiplatelet effect of aspirin, making it less useful for cardioprotection (Patel 2004).

Propionic acid derivative drugs cannot be substituted for aspirin to provide cardiac protection.

3. Acetaminophen (Tylenol®)

Acetaminophen is not an NSAID since it has no anti-inflammatory or blood thinning effects. It is effective for mild to moderate pain. Unlike NSAIDs, acetaminophen does not irritate the gastrointestinal tract and is considered the safest analgesic drug for geriatric patients (ACR 2000, Cryer BL 2002, 2003). However, overdose of acetaminophen can cause severe liver toxicity.

OTHER THERAPIES

1. Herbal Therapy

Currently there is increased interest in evidence-based complementary and alternative medicine for pain management in rheumatic disease and other musculoskeletal disorders (Gagnier 2004, van Tulder [a] 2004, Yokoyama *et al*. 2004). Some of these therapies may also be appropriate for initial management of conditions such as osteoarthritis (Blumenthal 2002, Little 2002).

The clinician and patient should weigh the evidence of likely effectiveness, potential side effects, and the cost of botanicals compared with more traditional analgesics and NSAIDs. Clinical evidence supporting the efficacy of herbal anti-inflammatory therapies is increasing (Ernst 2000).

A 2006 Cochrane review reported on three oral herbal medications tested in ten randomized controlled trials that included 1567 adults with non-specific acute or chronic low-back pain. (Gagnier 2006)

- Devil's Claw,(*Harpagophytum Procumbens*) in a standardized daily dose of 50 mg or 100 mg harpagoside, seemed to reduce pain more than placebo; a standardized daily dose of 60 mg reduced pain about the same as a daily dose of 12.5 mg of Vioxx.
- Willow Bark (*Salix Alba),* in a standardized daily dose of 120 mg and 240 mg of salicin reduced pain more than placebo; a standardized daily dose of 240 mg reduced pain about the same as a daily dose of 12.5 mg of Vioxx.
- Cayenne *(Capsicum frutescens)* was tested in plaster form and reduced pain more than placebo and about the same as the homeopathic gel Spiroflor SLR. Adverse effects were reported, but appeared to be primarily confined to mild, transient gastrointestinal complaints.

Herbal formulations commonly used in the clinics for NSAID effect contain a combination of Indian Frankincense (Boswellia serrata), Tumeric (Curcuma longa), White Willow (Salix alba), Wild Yam (Dioscorea villosa), and Black Cohosh (Actaea racemosa).

2. Nutritional Supplementation

Proteolytic enzymes (like bromelain) may be substituted for NSAIDs (with fewer side effects) for some types of acute trauma (Pizzorno 1999), but the effects will not be as rapid as over the counter medications.

There is also evidence that micronutrients like glucosamine sulfate, although slower acting, may aid in joint repair and relieve arthritic symptoms (Matheson 2003, McAlindo *et al*. 2000, Reginster *et al*. 2001, Towheed TE 2003). No investigations have been done on potential applications such as prevention of joint disease or broader treatment of musculoskeletal trauma. *See UWS protocol "Glucosamine & Chondroitin Sulfate."*

For more information on proteolytic enzymes and micronutrients, see UWS protocol "Diet, Nutritional Supplements and Botanicals for Musculoskeletal Conditions."

3. Prescription NSAIDs

This protocol is restricted to discussion and recommendation of over-the-counter NSAIDs. However, patients may be referred for prescription drug therapy when appropriate.

Many low-dose NSAIDs are available over the counter, but higher potency forms require a prescription. Co-management with a practitioner having access to prescription NSAIDs may be necessary for some patients, especially those with chronic osteoarthritis.

COX-2 Inhibitors

At therapeutic doses these *prescription* drugs reduce inflammation by selectively inhibiting the enzyme COX-2. COX-1 is not affected and is available to protect the intestinal mucosa, reducing gastrointestinal side effects. Although more expensive than NSAIDs, COX-2 inhibitors have fewer gastrointestinal side effects than traditional NSAIDs (Bardell 2002, FitzGerald 2001, 2004, Husni 2002, 2004, Schnitzer 2002, Silverstein 2000).

Emerging information is creating debate about whether the benefits of non-steroidal anti-inflammatory COX-2 inhibitors ("coxibs") outweigh their cardiovascular risks. Vioxx® and Bextra® have been removed from the market. The only remaining COX-2–specific drug, Celebrex, is required to have a boxed warning, the highest-level FDA warning, on the label.

Topical NSAID patches and gels

Since the early 1980s (Linn 2004) topical prescription of NSAID patches and gels have been used in Europe. In the US they have been used since 2007 (Altman 2009) (diclofenic). Multiple reviews have evaluated their clinical effectiveness for both acute and chronic musculoskeletal pain (Linn 2004, Altman 2009, Stanos 2007, Rainsford 2008, Moore 1998, Mason 2004).

They demonstrate that topical NSAIDs are significantly more effective than placebo for short term pain relief (2 weeks) and are probably comparable to oral NSAIDs. For the treatment of chronic pain from osteoarthritis, the results are mixed. Some trials have shown only short term pain relief (2 weeks) while others have shown longer lasting effects (12 weeks) (Stanos 2007).

Topical application appears to reduce the risk of serious systemic side effects (GI and renal) that can occur with oral NSAIDs. Pharmacokinetic studies (Rainsford 2008, Stanos 2007) have shown that plasma concentrations with topical NSAIDs are very low (less than 10%) compared to oral doses of the same agent.

A 1998 meta-analysis (Moore 1998) pooled results from 86 randomized, placebo-controlled trials of topical NSAIDs for a mix of painful conditions various painful diagnoses. Reports of adverse events for the 10,160 patients treated were mild and infrequent. These included local skin irritation in 3.6% and less than 0.5% reporting any systemic side effects.

A more recent (2004), meta-analysis (Mason 2004) of 26 double-blind, placebo-controlled trials found a similar, low rate of side effects. The rate of side effects for placebo and for topical NSAIDs was the same.

Clinical Warning: When treating a patient with a patch, do not apply a hot pack to the area.

RECOMMENDING NSAIDs/Analgesics

Checklist of Seven Steps

- ✓ **Step 1:** Decide whether home care should include an analgesic or anti-inflammatory drug.
- ✓ **Step 2:** Consider whether there is an effective botanical or nutritional supplement that may be used initially.
- ✓ **Step 3:** Decide if the use of an NSAID or analgesic is appropriate for the patient's specific condition.
- ✓ **Step 4:** Decide if an NSAID or analgesic is appropriate for the individual patient.
  - * Contraindications
  - * High-risk patients demanding caution
  - * Patients on other medications
- ✓ **Step 5:** Choose the appropriate treatment parameters based on the patient and the treatment goals.
- ✓ **Step 6:** Inform the patient of risks.
- ✓ **Step 7:** Monitor patient response.

STEP 1: Decide whether home care should include an analgesic or anti-inflammatory.

All treatments for inflammation, arthritis, and other musculoskeletal conditions should begin with a comprehensive assessment of the patient's pain and function (Mitka 2002, Turk 2002).

Many conditions do not have a major inflammatory component, and pain can be managed through a number of physical means. For example, many tendon injuries (tendinopathy) are, in fact, degenerative and not inflammatory conditions (Marsolais 2003).

Patient education and multidisciplinary rehabilitation are useful approaches to the management of common musculoskeletal disorders. Exercise, physiotherapy, cryotherapy, thermotherapy, ultrasound, and massage may be used (Brosseau [a, b, c, d] *et al*. 2004, Casimiro *et al*. 2004, Dagfinrud 2004, Karjalainen 2004, Kelley 2004, Keysor 2003, Manek 2001, Nadler *et al*. 2002, 2004, Pfleger 2003, Riemsma 2004, Simon 2002, Van den Ende 2004).

In some cases, the practitioner may wish to consider additional methods of controlling pain or inflammation.

STEP 2: Consider whether there is an effective botanical or nutritional supplement that may be used initially.

Decide if there are effective nutritional therapies or supplements that can be used in the initial management of the condition. (Refer to Pp. 2-3 of this protocol.)

STEP 3: Decide if the use of an NSAID or analgesic is appropriate for the patient's specific condition.

NSAIDs, analgesics, or both, may be necessary in managing osteoarthritis and other musculoskeletal conditions when the patient's pain is poorly controlled by other conservative measures. *The clinician's judgment and the apparent needs of the patient should help determine whether medications are indicated at all.* Potential side effects should be balanced against therapeutic benefit.

NSAIDs are more effective than placebo for acute injuries (maximum length of treatment 1 week), with an NNT of 3.9. In the case of chronic injuries where the maximum length of treatment was 2 weeks, the NNT was 3.1 (Ziltener 2010).

If a patient has an injured extremity with visible swelling, an over-the-counter NSAID may be used in addition to common physical therapy modalities, such as cold and ultrasound.

Some musculoskeletal conditions may be more responsive to NSAIDs than others. *It should be kept in mind, however, that long-term drug use increases the probability of adverse reactions* (Laufer 2004, Manek 2001). The effect of NAIDS on acute knee and ankle sprains have been the conditions most studied in humans.

Decision making will be based, in part, on the nature of the injury as well as weighing short term benefits against longer term outcomes. One study demonstrated that ibuprofen

reduced pain and swelling and improved range of motion and load bearing capacity faster than a placebo during the first week of care. (Ziltener 2010). Other studies, however, have shown that 6 months after treatment with the NSAID piroxicam (20mg/day for 7 days), range of motion was poorer, there was a greater occurrence of joint laxity and a higher re-injury rate (25%) compared to controls. (Ziltener 2010).

Specific Conditions

SUMMARY

- Tendon injuries
- Ankle sprains
- Tennis elbow
- Knee and hip conditions
- Acute LBP
- Acute LBP with sciatica
- Chronic LBP
- Osteoarthritis
- Fractures
- Delayed onset muscle soreness
- Dysmenorrhea
- Rheumatoid arthritis

1. Tendon injuries (in general)

A meta-analysis of 37 RCTs (17 placebo-controlled) demonstrated short-term pain relief (7 to 10 days), particularly for shoulder conditions. The analgesic effectiveness of NSAIDs, however, appears to be less for tendon injuries at the elbow, patellar, and Achilles. In particular, short-term treatment (up to 14 days) with celecoxib or naproxen (compared to a placebo) appears to be potentially effective for true shoulder bursitis and De Quervain's tenosynovitis, reducing pain intensity at rest while being well tolerated. (Ziltener 2010)

In the long term, there is no evidence that NSAIDs are effective and the risk of side effects rises. It is controversial whether or not the analgesic effect of NSAIDs permits athletes to increase the stress on their tendons prematurely, thereby compromising the long-term care. While there is some evidence that early graded activity in athletes with Achilles tendinopathy is at least as safe and beneficial as activity restriction, (Silbernagel 2007) there is little evidence to support or refute whether analgesics or NSAIDs are powerful enough to have a deleterious masking effect on this process. Authors speculate on both sides of this issue (Ziltener 2010, Magra 2006, Reider 2009).

2. Ankle sprains

Treatment with NSAIDs may result in a significant decrease in pain, time loss from activities, and perhaps total cost of treatment. **NOTE:** Early return to activity after NSAID therapy may result in an increase in short-term swelling and instability (positive drawer sign) lasting up to two weeks (Petrella [a, b] 2001).

3. Tennis elbow

Tennis elbow (lateral epicondylalgia) is an overuse syndrome that is challenging to treat. Reviews of RCTs conclude that in the early phase of disease, use of NSAIDs and avoidance of provoking activities is likely to be beneficial (Green [a, b] *et al*. 2004). Topical NSAIDs are significantly more effective than placebo in reducing tennis elbow pain in the short term (Asendelft 2003, Green [b] *et al*. 2004, Mellor 2003, Vicenzino 2003).

Although NSAIDs are better than placebo for controlling pain, there may be little functional improvement. Treatment with NSAIDs may be only marginally more effective than rest and immobilization. The efficacy of NSAIDs for long-term treatment is not supported by current evidence. However, manipulative therapy, acupuncture, orthotic devices, and taping have recently been shown to provide substantial initial pain relief (Brosseau [a, b, c, d] *et al*. 2004, Green [a] *et al*. 2004, Haar 2003, Struijs *et al*. 2004). Topical nitric oxide has also been shown to relieve symptoms in chronic extensor tendinosis at the elbow (Kreder 2004).

4. Knee and hip conditions

NSAIDs have been proven to be effective in reducing inflammation and are recommended for management of mild to moderate pain from knee sprains. Initial treatment of most acute knee ligament injuries includes rest, ice, compression and elevation (RICE) combined with a one- to two-week course of NSAIDs. In a medical setting, patients suffering from overuse knee injuries are advised to use NSAIDs, with the exception of aspirin, in order to control pain and inflammation during the acute phase (Brosseau [a] *et al*. 2004, Grainger 2004, Hochberg *et al*. 1995, Towheed [a, b] 2004, Watson 2004). There is evidence that diclofenac is effective for sprains, strains and contusions in general (Labell *et al*. 1997,

Mahler *et al*. 2003). On the other hand, current analysis does not support long-term use of NSAIDs for osteoarthritis of the knees (Bjordal 2004). The American College of Rheumatology (ACR) lists acetaminophen (Tylenol) as the initial drug of choice for geriatric patients with osteoarthritis of both the hip and knee because of its low toxicity (ACR 2000).

Exercise and ultrasound have also been shown to be effective in reducing knee pain due to osteoarthritis (Fransen 2004, Welch 2004). Transcutaneous electrical nerve stimulation for knee osteoarthritis has also been effective in some cases (Osiri 2004).

5. Acute low-back pain *without sciatica*

A 2009 Cochrane review of 65 trials provides strong evidence that NSAIDs are more effective than placebo in patients with uncomplicated acute low-back pain (Roelofs 2008). The effect size, however, was small. There does not seem to be a specific type of NSAID that is clearly more effective than others (Griffin 2002).

Acetaminophen (Tylenol) has been shown to be an effective analgesic for the treatment of moderate and acute pain and has fewer side effects compared to NSAIDs. In Chou's 2009 review, NSAIDs were judged to have a moderately beneficial effect based on good quality evidence. Nevertheless, acetaminophen is recommended as a basic first-line analgesic in acute pain (Deyo 2001, Koes 1997, 2001, Chou 2009).

6. Acute low-back pain with sciatica

The precise etiology of acute low-back pain with sciatica (nerve root symptoms) is often difficult to determine, although musculoligamentous processes are usually suspected (Deyo 2001). Treatment should be conservative, emphasizing time, reassurance, manual therapy, physical therapy, and education (Dagfinrud 2004, Haas *et al*. 2004). Management may also include limited bed rest and exercise. However, prolonged bed rest has potentially harmful effects (Hagen 2000, 2002). While NSAIDs may be effective for short-term symptomatic relief in patients with uncomplicated low-back pain, they are often ineffective in patients with low-back pain with sciatica, particularly if there are nerve root symptoms (Koes 1997, 2001). A 2007 systematic review of systematic reviews for the American College of Physicians and the Pain Society resulted in no recommendations relative to NSAIDs or acetaminophen in the treatment of LBP with sciatica because of what was judged to be insufficient data. (Chou 2007). A 2008 Cochrane review likewise concluded that favorable effects of NSAIDs could not be demonstrated in this important subgroup of patients. (Cochrane 2008)

7. Chronic low-back pain

Compared to acute low back pain, the role and effectiveness of NSAIDs and other drugs is less clear. The reported strength of evidence and magnitude of treatment effect varies somewhat from review to review. Van Tulder suggested that there is only moderate evidence supporting the effectiveness of NSAIDs for management of chronic low-back pain (van Tulder [b] 2004). Chou's 2007 review reported that there was good evidence that NSAIDs were moderately beneficial. The evidence from the 65 trials included in the 2008 Cochrane review suggested the effect size was small for short-term symptomatic relief in patients with chronic low back pain without *sciatica*. Acetaminophen had fair evidence of a small therapeutic effect (Chou 2007) but was generally safer. The American College of Rheumatology (ACR), also recommends beginning with analgesics (e.g., acetaminophen, Tylenol). Them, if the patient does not respond to Tylenol, consider switching to NSAIDs, such as ibuprofen or ketoprofen (ACR 2000).

Overuse of analgesic drugs has been shown to be most common in persons with chronic headache and much less common in those with chronic neck and back pain (Atlas 2001, Deyo 2001, Griffin 2002, Koes 1997, Zwart *et al*. 2004). Nevertheless, NSAID overuse is still a potential problem with chronic low-back pain (Deyo 2001).

The physician and patient should proceed with caution in the treatment of chronic low-back pain. One strategy is to eliminate anti-inflammatories or analgesics, or use them on a limited basis during the rehabilitation program. Back schools have been shown to be an effective supplement or alternative to NSAID treatment for chronic back pain (van Tulder 1997, Heymans 2004). Other alternatives are

botanical medicine, percutaneous electrical nerve stimulation, and ultrasound (Gagnier 2004, Little 2004, PDR [c] 2004, Yokoyama *et al*. 2004).

8. Osteoarthritis

Osteoarthritis is the most common form of arthritis and the major cause of disability in elderly people (Felson 1988). It represents a major disease burden for patients, health services and society (Peat 2001). Zhang (2004) found that NSAIDs were better than acetaminophen for pain relief (ES = 0.20, 95% CI 0.10 to 0.30 compared to (ES = 0.21, 95% confidence interval (CI) 0.02 to 0.41). Clinical response rate was also higher with NSAIDs than with acetaminophen (RR = 1.24, 95% CI 1.08 to 1.41), and the number of patients who preferred NSAIDs was more than twice the number of those preferring acetaminophen l (RR = 2.46, 95% CI 1.51 to 4.12). However, NSAIDs were associated with more frequent gastrointestinal discomfort than acetaminophen (RR = 1.35, 95% CI 1.05 to 1.75). Consequently, there is some question whether NSAIDs should still be considered the first drug of choice as opposed to acetaminophen or other means of pain control. (Phillips 2010)

Randomized controlled trials of topical NSAIDs demonstrated that NSAIDs were superior to placebo in relieving the pain due to osteoarthritis, but only in the first two weeks of treatment. After two weeks, there was no evidence of efficacy superior to placebo. *No trial data supports the long-term use of topical NSAIDs in osteoarthritis* (Lin 2004).

9. Fractures

The harmful effects of NSAIDs vary, depending on the substance used and how long it is being taken. A delay in bone consolidation has been reported. Because of these effects on bone formation, some authors recommend to avoid NSAIDs at least during the first weeks after a fracture. In cases of stress fractures, they should not be used for the same reasons. (Ziltener 2010)

10. Delayed onset muscle soreness

NSAIDs are ineffective after the symptoms of DOMS have set in. Prophylactic use of NSAIDs to prevent DOMS has had mixed results (Baldwin 2003, Cannavino *et al*. 2003, Cheung 2003, Gulick *et al*.1996). One recent study suggests that NSAIDs may actually impede muscle recovery (Prisk 2003). Supplementation of 1 gram of Vitamin C three times a day, for three days prior to exercise and continued through the initial exercise period may help to decrease DOMS (Kaminski 1992, Timmer *et al*. 2003).

11. Pain associated with dysmenorrheal

Women who suffer from dysmenorrhea have an overproduction of uterine prostaglandins. This contributes to painful cramps. NSAIDs have been found to reduce pain by inhibiting prostaglandin synthesis and are effective in adult and adolescent dysmenorrhea. NSAIDs are not as effective in managing pain associated with endometriosis (Majoribanks 2004).

12. Rheumatoid arthritis

Non-opioid analgesics should be used in place of NSAIDs when possible for managing pain in early rheumatoid arthritis. Acetaminophen is the analgesic of choice, especially in the presence of pregnancy, peptic ulcer disease, or signify-cant cardiac, renal, and other comorbidities. Adequate pain control may require regular dosing. In established RA, both conventional NSAIDs and COX-2 inhibitors are more effective than simple analgesics in relieving the signs and symptoms of active disease.19,33 However, this advantage must be balanced against the potential side effects. Combining acetamino-phen with an NSAID may enable a reduction in the dose of the NSAID and may be particularly useful while waiting for a definitive diagnosis of RA to be made. In addition, practitioners should consider omega-3 supplementation as an adjunct for management of pain and stiffness which also may enable a reduction of NSAID doses. (Clinical guideline for the diagnosis and management of early rheumatoid arthritis. The Royal Australian College of General Practitioners, August 2009)

For quick summary, see table on next page.

Quick Summary: NSAID Recommendations (modified from Ziltener 2010)

Type of Injury	NSAID Impact	Comments
Bone: fracture	Contraindicated	Probable harmful effects on bone formation especially in the first weeks
Bone: stress fracture	Contraindicated	Probable harmful effects on bone formation especially in the first weeks
Ligament: acute sprain (e.g., appropriate for mild to moderate knee sprain)	Possibly and potentially useful in the short-term	Reduces pain and swelling Faster return to athletic activities Long-term residual laxity (???) Short-term use (<5 days)
Low back pain, acute with sciatica	May not be useful	No proven efficacy. Often ineffective if there are nerve root symptoms.
Low back pain, acute without sciatica	Possibly and potentially useful	Strong evidence NSAIDs are more effective than placebo for acute LBP (small effect size). Acetaminophen recommended as a basic first choice.
Low back pain, chronic	Potential limited usefulness	There is only moderate evidence supporting the effectiveness of NSAIDs for management of chronic low-back pain. Acetaminophen may be better first choice because of side effects
Muscle: acute muscle tear	Probably not useful and perhaps not indicated	Inhibits protein synthesis and inflammatory reaction
Muscle: contusion	Potentially useful	In case of deep contusion or history of myositis ossificans
Osteoarthritis	Possibly and potentially useful.	Consider acetaminophen as first choice. RCTs suggest topical NSAIDs are superior to placebo, but only in the first two weeks of treatment.
Rheumatoid arthritis	Possibly and potentially useful	Start with analgesic; combining acetaminophen with an NSAID may reduce NSAID dose.
Tendon: overuse tendinopathy	Probably not useful	Short term analgesic effect only (perhaps more so in shoulder conditions than elbow, patellar or Achilles tendinopathy; no benefit for healing
Tendon: true acute tenosynovitis/bursitis (e.g., DeQuevain's)	Possibly and potentially useful	Reduces acute inflammations Helps recovery

STEP 4: Decide if an NSAID or analgesic is appropriate for the individual patient.

1. NSAID Contraindications

Caution: Patients in the following categories should avoid all use of NSAIDs unless otherwise specified.

- Allergy to aspirin, iodides, or other NSAIDs. It is important for the pharmacist or health professional to ask about sensitivity to these medicines when taking the patient's drug history. A patient who is allergic to aspirin may also be allergic to NSAIDs (PDR [a, b] 2004).
- Pre-existing renal disease
- Active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract. If a patient is at a particularly high risk for ulcers and yet may benefit from the therapeutic effect of NSAIDs, consider referral for combination therapy of NSAIDs and prophylactic treatment for ulcers.
- Pregnancy
- Use of warfarin, Coumadin® or other anti-coagulation medications
- Children and teenagers should never be given aspirin for treatment of the symptoms of viral infections because of the possibility of Reye's Syndrome, a potentially fatal inflammation of the brain.
- The effects of ketoprofen (Orudis®) have not been adequately studied in younger children. It should not be used in the treatment of children under the age of 16 years.
- Children under the age of 12 years should not take naproxen sodium (Aleve®).
- Children under the age of two years should not take ibuprofen (Advil®, Motrin®, Nuprin®) (Berde 2002, PDR [a, c] 2004).

2. High-Risk Patients for NSAIDs

Caution: An increased potential for adverse side effects exists for patients with the following conditions, status or habits.

- History of abdominal pain or gastroesophageal reflux disease (GERD) (GI bleeding, 7-fold increase in risk)
- Diabetes (renal failure)
- Hypertension (exacerbation)
- Liver disease (hepatitis)
- Congestive heart failure (exacerbation)
- Lupus (renal failure)
- Asthma (bronchoconstriction)
- Renal artery stenosis (renal failure)
- Age greater than 75 years (GI bleeding, renal failure)
- History of peptic ulcer disease (GI bleeding)
- Alcohol use (GI symptoms, liver disease)
- Corticosteroid therapy (GI symptoms)
- Smoking (GI symptoms)

The 2009 Geriatrics Society Guidelines (Ickowicz 2009) strongly recommends that acetaminophen should be the "initial and ongoing" drug treatment for persistent musculoskeletal pain. On the other hand, nonselective NSAIDs and COX-2 selective inhibitors should be considered "with extreme caution" for patients in whom "other (safer) therapies have failed."

An excellent source of management information is ARAMIS PMR (Arthritis, Rheumatism and Aging Medical Information System, Post-Marketing Surveillance) program developed by Stanford University. ARAMIS rates NSAID toxicity and is based on analysis of thousands of rheumatoid arthritis cases from all over North America. Their questionnaire, called the Stanford Calculator of Risk for Events (SCORE), is a simple and accurate predictor of the risk that a given patient will suffer a bleed during NSAID therapy (http://aramis.stanford.edu). (*See Table II. Assessment Tool to Determine Risk of NSAID-Induced GI Toxicity*.)

Acetaminophen

High risk patients include those with the following conditions:

- Liver disease.
- Chronic alcohol use
- Hypersensitivity to drug (including possible cross reaction with allergy to aspirin).
- Renal impairment 9epscially fro long term use)
- G6PD deficiency
- PKU (phenylalanine-containing forms)

3. Patients on other medications

Clinicians should be aware of common drug interactions associated with NSAID use (PDR [a, b] 2004). (*See Table X. OTC Drug Interactions and Contraindications*; *Table XI. Drugs that Interact with OTC NSAIDs and Aspirin*.)

Patients must be very careful when taking acetaminophen. Acetaminophen is found in many other OTC preparations. In 2003, the FDA issued an alert to the public regarding the importance of knowing the components of "hidden" acetaminophen and NSAIDs in OTC and prescription preparations, highlighting the possibility of liver damage and other adverse reactions associated with excessive doses. The alert also cautioned medical practitioners who commonly used combination analgesics to have an explicit limit on the total daily dose of acetaminophen in order to avoid unintended liver toxicity (FDA 2003). The same warning should apply to overuse of NSAIDs in OTC products. (*See Table VI. Non-Prescription Products Containing Acetaminophen*; *Table VII. Non-Prescription Products Containing NSAIDs*.)

Herbal supplements and herbs should also be used with caution.

Warning: Bromelains are pineapple enzymes that inhibit pro-inflammatory prostaglandins and are often used in the treatment of arthritis and other inflammatory conditions. Bromelain, however, must be used with caution in patients with peptic ulcer or a history of bleeding hemostatic disorders, those who are taking anticoagulant medication, aspirin or NSAIDs, (Krinski *et al*. 2002) as well as those with known allergies to pineapple.

STEP 5: Choose the appropriate treatment parameters based on the patient and the treatment goals.

1) Choose appropriate NSAID or analgesic
2) Choose dosage
3) Choose time- or pain-based schedule
4) Choose length of course

1. Choose appropriate NSAID or analgesic

Except for specific arthritic conditions (e.g., gout), there are no clear clinical guidelines to assist in selecting one particular agent over another in terms of efficacy. In the case of low back pain, the various products appear to be equally effective. NSAIDs are reported to be either slightly more effective than analgesics (Philips 2010) or equally effective. (Roelofs 2008) *But because of safety considerations as well as cost, it is recommended that therapy begin with a low dose of acetaminophen (Tylenol) followed by ibuprofen and other NSAIDs as needed to enhance analgesia and allow a decreased NSAID dose*. This approach is now considered first-line pharmacologic therapy (Towheed [a, b] 2004).

Serious adverse upper GI events n the elderly are dose dependent. Therefore, if nonselective NSAIDs are used in combination with Tylenol, they should be started in low, analgesic doses and increased to full anti-inflammatory doses only if lower doses do not provide adequate symptomatic relief. In the patient who is at increased risk for a serious upper GI adverse event, gastro-protective agents should be used, even if NSAIDs are given at low dosage (Hochberg [a, b] 1995, Lanza 1998).

Combination therapy: analgesic + NSAID

Acetaminophen (paracetamol) and an NSAID may also be combined for acute pain management. A systematic review of RCTs assessed prescription level acetaminophen /NSAID combinations compared to either class of drug alone for managing acute postoperative pain. The study was funded by the manufacturer of an acetaminophen /ibuprofen combination tablet. Twenty RCTs involving 1852 patients compared acetaminophen-NSAID combinations with acetaminophen alone. The combination was more effective than acetaminophen alone for at least one of three measures (pain score, need for supplemental analgesia, globally assessed pain relief) in 16 studies (80%). The mean reduction in pain intensity was 35%: the mean reduction in need for supplemental analgesics was 39%.

Fourteen studies involving 1129 patients compared the efficacy of an analgesic combination to that of an NSAID alone. Nine studies (64%) demonstrated that the combination was more effective. The mean reduction in pain intensity was 38%, and the mean reduction in need for analgesic supple-

mentation was 31%. The incidence of side effects did not differ significantly between combination therapy and either single-drug therapy. (Ong 2010)

Clinical Warning: Combinations of NSAIDs (*not* in combination with acetaminophen) often increase risk of adverse reactions. Single-agent therapy is advocated for initial treatment. **Using multiple NSAIDs doubles the risk for GI bleeding.** NSAIDs should always be taken with food and a full glass of water (8 oz.). They may also be taken with antacids (PDR [a, b] 2004). Furthermore, there is evidence that the use of aspirin and ibuprofen compared to aspirin alone may attenuate the antiplatelet effect of aspirin and increase the risk of myocardial infarction (Patel 2004).

Rapid acting

Because ibuprofen and ketoprofen have a more rapid onset than naproxen sodium, they may be more effective in treating acute pain. With chronic pain, any of the NSAIDs can be used. Naproxen has the longest half-life (14 hours) while ibuprofen or ketoprofen have a half-life of 2 hours. For this reason naproxen is given twice daily, while ibuprofen or ketoprofen is usually administered from two to four times a day. (PDR [a] 2004, Donjon 1999, Towheed [a, b] 2004)

Topical application

Topical application of NSAIDs is an alternative strategy for reducing gastrointestinal adverse reactions, maximizing local delivery, and minimizing systemic toxicity. Although NSAIDs have been used topically for decades, there is currently no trial data to support long-term use in the treatment of osteoarthritis (Lin *et al*. 2004).

2. Choose dosage

Summary of dosage recommendations

- Recommend dosage based on desired effect (analgesic or anti-inflammatory).
- Do not exceed daily maximum dose. (*See Table IV*.)
- Adjust dose based on size and age of the patient. Doses should generally be lower in pediatric and geriatric patients than for younger adults. (*See Table V*.)
- Begin with a smaller dose and increase only if necessary – the higher the dose of the NSAID, the greater the chance for adverse effects.

The OTC dosage recommendations for NSAIDs that appear on the packaging are generally one-half the standard prescription dosage. (*See Table III. Abbreviations Commonly Used in Prescribing*.) These recommendations for OTC NSAIDs provide drug levels generally effective for pain control, but *insufficient* for optimal management of inflammation (McFarlane *et al*. 1998, Patino *et al*. 2003). This lower-dose standard for OTC NSAIDs minimizes the chance of adverse side effects (Donjon 1999, PDR [a] 2004).

When appropriate, the clinician may recommend doses that differ from the standard. (*See Table IV. Dosage Information for OTC NSAIDs*.

A number of factors may influence dose recommendations. These include the patient's size and age. Pediatric and geriatric patients are more sensitive to a variety of drugs and are more likely to experience drug interactions and side effects. (Berde 2002, 2004, Donjon 1999, Nicolaus 2004, PDR [a, c] 2004). (*See Table V. Dosage Information for OTC NSAID Use in Children*.) Pre-existing medical conditions may also influence dosage. For example, patients with benign prostatic hypertrophy (BPH), diabetes, or renal insufficiency are at higher risk of nephrotoxicity and require lowered dosages of certain drugs. (*See NSAID Side Effects on Pages 12-14*.)

3. Choose time- or pain-based schedule.

Patients consuming daily analgesics for pain should be placed on a *time contingent* and not a *pain contingent* medication schedule. This is a well-accepted strategy for reducing the behavioral reinforcement of pain medication over time. In addition, time-contingent medicating eliminates the problem of needing higher doses and more time to reduce pain levels, and prevents the cycle of under-medication and pain alternating with overmedication and drug toxicity (Dieppe *et al*. 2004).

4. Choose length of course

For control of inflammation, a 10- to 14-day trial at a higher dosage than on the label is suggested to judge the clinical benefit of any single agent. The analgesic effect of NSAID

therapy may not fully take effect until inflammation has subsided.

Once the initial anti-inflammatory effect has been obtained, dosage can be adjusted as needed. In the event of a recurrence of symptoms, clinical judgment on a case-by-case basis will determine the continued need for NSAIDs and the proper type and dose.

STEP 6: Inform the patient of risks.

Whether the practitioner is recommending OTC NSAIDs or the patient has already self-prescribed them, a Procedures Alternatives Risks Questions (PARQ) conference must be held at UWS clinics. A Patient Adverse Reaction Questionnaire may also be administered. A copy of the clinic's educational sheet on side-effects will also be given to the patient.

The following FDA cautions must be part of the WSCC PARQ conference when recommending NSAIDs.

- GI toxicity is a potentially serious adverse effect. (*See Table II. Assessment Tool to Determine Risk of NSAID-Induced GI Toxicity.*)
- GI toxicity must be identified as potentially life-threatening.
- List symptoms of GI toxicity
- In the event of serious side effects, the patient should stop taking the medication and contact the clinician. Rare cases in which there are severe side effects, go to an emergency room or urgent care center. **Severe side effects include rectal bleeding, hematemesis (including vomitus appearing as "coffee grounds"), abdominal pain, dizziness, syncope and tachycardia.**
- Renal toxicity should be identified as a potential side effect.
- Smoking and/or alcohol consumption will increase the risk of side effects.

Analgesics

For acetaminophen precautions, see Page 14.

NSAID Side Effects

1. **Gastrointestinal**
2. **Renal**
3. **Pulmonary**
4. **Impediment of healing time**
5. **Female infertility**
6. **Drug Interactions**
7. **Cardiovascular**
8. **Hearing loss**

1. Gastrointestinal Side Effects

The most common serious adverse effects of NSAID use involve the gastrointestinal tract. (*See Table VIII. OTC NSAIDs: Gastrointestinal Side Effects.*) The risk of developing chronic ulcers for patients on NSAID therapy is three-to-six times higher than that of the general population, and for patients over the age of 60 years the risk is even higher. It is estimated that 10 to 20% of patients experience dyspepsia during NSAID treatment. Other common gastrointestinal side effects include: nausea and vomiting, indigestion, epigastric burning, fluid retention, constipation, diarrhea, flatulence, stomatitis, anorexia, and rectal bleeding. Gastrointestinal complications from NSAID use result in 50,000 to 100,000 hospitalizations and 16,000 deaths annually (Guttman 197, Singh 1997, Chan 2004, Cryer 2002, Hawkey 2003, James 2003, Langman 2003, PDR [a] 2004, Price 2003, Sung *et al.* 2000, Whittle 2003).

One month of regular NSAID dosing carries a much higher relative risk (RR) of GI bleeding. The RR is 4.0 for such traditional NSAIDs as diclofenac and naproxen, 3.0 for diclofenac taken with misoprostol, 1.9 for rofecoxib and 1.0 for celecoxib. As a result it has been recommended to limit the length of administration, take NSAIDs with meals, and/or to take a proton pump inhibitor. (Ziltener 2010)

Previous research from TARGET demonstrated that lumiracoxib was associated with reduced rates of gastrointestinal ulcer complications and anemia compared with ibuprofen and naproxen. However, the rates of ulcer complications were similar with these 3 medications among patients receiving aspirin.

Side effects increase if the recommended dosage is exceeded. NSAIDs have a ceiling effect, limiting how much pain can be controlled. Beyond this limit, there are no additional benefits from increasing dosage. (*See Table IX. Comparison of Toxic Effects of OTC NSAIDs and Aspirin.*)

Smoking and/or alcohol use, when combined with NSAIDS, have been shown to substantially increase the risk of gastrointestinal side effects as well as contributing to anemia, fatigue, shortness of breath, and/or rapid pulse.

WARNING: Because of their anti-clotting action, NSAIDs should never be used by a patient who is taking blood thinners, such as Coumadin or warfarin (PDR [a] 2004)**.**

2. Renal Side Effects

As a group, NSAID users face a four-fold risk of developing acute renal failure. This risk is greatest during the first month of use, sometimes occurring within days of beginning therapy (Gambaro 2003, Perneger *et al*. 1994). In addition, the risk of renal failure is cumulative. That is, the risk increases steadily over the entire period that the drug is used.

Patients with renal adverse effects due to NSAIDs may present with increased blood pressure, edema, aggravation of congestive heart failure, and reduced renal function (i.e., increased blood urea nitrogen (BUN) and creatine levels). Less commonly, NSAIDs can cause acute renal failure, papillary necrosis, hyperkalemia, proteinuria, and other renal syndromes (Mastalerz 2004).

NOTE: Patients with pre-existing kidney disease should never take NSAIDs.

3. Pulmonary Side Effects

Pulmonary effects that may result from NSAID use include bronchoconstriction (a concern in asthma), an increase in mucus, and edema. NSAIDs may also reduce pulmonary blood flow (PDR [a] 2004, Mastalerz 2004).

4. Impediment of Healing Time

NSAIDs are commonly prescribed for musculoskeletal injuries because these conditions are believed to be inflammatory. However, because inflammation is a necessary part of the healing process, decreasing it may be counterproductive (Stovitz 2004).

Recent studies have shown that NSAIDs have a paradoxical effect on healing. Early signs of improvement are followed by impairment of healing later. Because of these profound side effects, NSAIDs should not automatically be the first choice for treating musculoskeletal injuries (PDR [a] 2004).

Both NSAIDs and COX-2 inhibitors have a similar capacity to delay ulcer and bone healing and fail to improve tendon regeneration (Gerstenfeld 2004, Harder 2003, Marsolai 2003). There is also concern that many NSAIDs (e.g., Naprosyn, Aleve, Advil, Motrin) inhibit glycosaminoglycan synthesis and may actually contribute to the deterioration of the joint (Dingle 1996). (*See Table IX. Comparison of Toxic Effects of OTC NSAIDs and Aspirin.*)

5. Female Infertility

Regular use of NSAIDS has been linked to reversible infertility in previously normally ovulating females. Three clinical trials have determined that inhibition of COX-2 may lead to Luteinized Unruptured Follicle (LUF) Syndrome. Physicians prescribing NSAIDs to young women should be aware of this side effect (Marjoribanks 2004).

6. Drug Interactions

Clinicians should be aware of drug interactions associated with NSAID use. (*See Table X. OTC Drug Interactions and Contraindications*; *Table XI. Drugs that Interact with OTC NSAIDs and Aspirin.*)

7. Cardiovascular

Possible adverse effects of standard prescription NSAIDs on the cardiovascular system continue to be under scrutiny. Relatively high RR values have been found for certain non-selective NSAIDs, such as diclofenac and indomethacin, which have respective RR values of 1.40 and 1.30. (Ziltener 2010)

Popular brands, such as Advil, Aleve, Motrin and generic ibuprofen, will have label changes alerting consumers of possible cardiovascular risks associated with long-term use. Practitioners are advised to keep current with these changes and other pending recommendations.

In addition, a 2007 study demonstrated that ibuprofen increases the risk for cardiovascular events compared with lumiracoxib among patients with an elevated cardiovascular risk who are receiving aspirin. Ibuprofen was also associated with an increased risk of incident congestive heart failure among high-risk patients. (Hudson 2007)

8. Hearing loss

Regular use of aspirin, NSAIDs, or acetaminophen increases the risk of hearing loss in men, and the impact is larger on younger individuals. In a prospective long term study of 26,917 men, multivariate-adjusted hazard ratios of self reported hearing loss in regular users (2+ times/week) compared with men who used the specified analgesic <2 times/week were 1.12 (95% confidence interval [CI], 1.04-1.20) for aspirin, 1.21 (95% CI, 1.11-1.33) for NSAIDs, and 1.22 (95% CI, 1.07-1.39) for acetaminophen. For NSAIDs and acetaminophen, the risk increased with longer duration of regular use. The magnitude of the association was substantially higher in younger men. For men younger than age 50 years, the hazard ratio for hearing loss was 1.33 for regular aspirin use, 1.61 for NSAIDs, and 1.99 for acetaminophen. (Curhan 2010)

Acetaminophen side effects

Liver damage from overuse of acetaminophen now exceeds viral hepatitis as the most common cause of hepatitis in the USA. The daily recommended limit for acetaminophen has been reduced to 3,250 milligrams per day, and the FDA has asked for stronger labels warning of liver side effects. It is not uncommon for some patients to take 7 to 8 grams/day.

Toxicity

The minimum toxic dose of acetaminophen for a single ingestion is 7.5-10 g. Higher doses yet (12 g) have high potential for hepatotoxicity. Adults who ingest more than 350 mg/kg of body weight develop severe hepatotoxicity if they are not appropriately treated. In children, the minimum single toxic dose of acetaminophen is 150 mg/kg. Children who have acutely ingested 250 mg/kg or more of acetaminophen pose significant concern for acetaminophen-induced hepatotoxicity. Suspicion of acetaminophen toxicity should prompt an immediate referral to an emergency room.

STEP 7: Monitor patient response

Patients taking NSAIDs should be monitored periodically for side effects, effectiveness, and dosage appropriateness.

Individual Variation

Efficacy of specific NSAIDs should be assessed on a patient-to-patient basis.

One of the most striking findings in all careful evaluations of NSAIDs is the wide range of responses among the subjects studied. Four- to five-fold differences are observed in plasma half-life and other pharmacokinetic measurements in patients who have been given the same weight-adjusted dose (Golan *et al.* 2005).

Inadequate Response

If pain is intolerable, the practitioner should again consider alternative pain strategies, such as referral to an acupuncturist, pain clinic, or for consideration of a stronger analgesic prescription. Often a mild narcotic like acetaminophen with codeine every 6 hours can be effective on a limited basis (10-14 days). *Referral for opioid analgesics should be done with extreme caution in patients with a history of drug addiction.*

Chronic pain patients are more problematic. The American Pain Society guidelines recommend that strong narcotics such as morphine or Demerol be avoided. http://www.ampainsoc.org/advocacy/opioids.htm

The Oregon DHS Public Health Office of Disease Prevention and Epidemiology has published a review newsletter (Oregon 2007) detailing significant adverse events associated with opioid prescriptions along with risk screening strategies and tools.

Substance abuse, serious systemic side effects (cardiac arrest) and death by suicide are all risks associated with prescription opioid use.

Table I. Characteristics of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

have ceiling effect (not effective for severe pain)
are analgesic at lower doses (prompt response) and anti-inflammatory at higher doses (delayed response)
are non-addicting (have no abuse potential)
do not cause respiratory depression
increase risk for drug interaction because of high protein binding
block platelet aggregation (irreversible with acetylsalicylic acid, reversible with other NSAIDs)

Table II. Assessment Tool to Determine Risk of NSAID-Induced GI Toxicity

Patient's Name _____ DOB _____ Chart # _____
Physician's Name _____ Intern's Name _____

Risk factors for NSAID-induced upper GI bleed include:

- Age > 65 years
- History of PUD or UGI bleeding
- Concomitant oral glucocorticoids
- Concomitant anticoagulants
- Smoking
- Alcohol consumption

Ask the patient the following six questions and assign points for each answer.
POINTS

1. How old are you? _____

Age	< 20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	81-85	>85
Points	0	1	3	4	5	6	8	9	10	12	13	14	16	17	18

2. On the following scale, how do you rate your current health status?

Health Status	Very Well	Well	Fair	Poor	Very Poor
Points	0	1	2	3	4

_____

3. Has a physician ever told you that you have rheumatoid arthritis (not osteoarthritis)?

Yes – 8 points No – 0 points _____

4. If you are taking prednisone or other corticosteroids, for how many months have you taken them in the past year?

Months	0	1-3	4-6	7-10	11-12
Points	0	1	3	4	5

_____

5. Have you ever been hospitalized for a stomach or intestinal problem such as bleeding or an ulcer?

Yes – 8 points No – 0 points _____

6. Have you ever had gastrointestinal side effects (heartburn, stomach pain, nausea, vomiting) while taking NSAID pain-relievers?

Yes – 2 points No – 0 points _____

TOTAL POINTS _____

Evaluation of patient's risk for an NSAID-induced bleed

Level 1 (0-10 points) – No risk. May use NSAID.
Level 2 (11-15 points) – Moderate risk. May use NSAID.
Level 3 (16-20 points) – Significant risk. May use standard NSAIDs for < 30 days.
Level 4 (>20 points) – Substantial risk. Do not use standard NSAIDs.

This tool was modified from one developed by Gurkirpal Singh, MD, director of the Arthritis Rheumatism and Aging Medical Information System, Post-Marketing Surveillance (ARAMIS PMR) at Stanford University. ARAMIS is a project of the National Institute of Health. More information about this tool may be found at the Stanford University Web site, http://www.stanford.edu/.

Table III. Abbreviations Commonly Used in Prescribing

Abbreviation	Meaning
q	every…
qd	every day, daily
bid	twice daily
tid	three times daily
qid	four times daily
cc	ml (milliliters)
tsp	teaspoon
h	hour

Table IV. Dosage Information for OTC NSAIDs

NSAID	Brand Name	Therapeutic Dose – Healthy Adults	Maximum Dose	Dose Available
Ketoprofen	Actron®	Analgesia: 12.5 mg - 25 mg qid Inflammation: 75 mg tid or 50 mg qid	300 mg qd	12.5 mg
Ketoprofen	Orudis KT®	Analgesia: 12.5 mg -25 mg qid Inflammation: 75 mg tid or 50 mg qid	300 mg qd	12.5 mg
Ibuprofen	Advil®	Analgesia : 200-400 mg q4-6h Inflammation: 400, 600, 800 mg tid-qid	3200 mg qd	200 mg
Ibuprofen	Motrin®	Analgesia: 200-400 mg q4-6h Inflammation: 400, 600, 800 mg tid-qid	3200 mg qd	200 mg
Ibuprofen	Nuprin®	Analgesia: 200-400 mg q4-6h Inflammation: 400, 600, 800 mg tid-qid	3200 mg qd	200 mg
Naproxen Sodium	Aleve®	Analgesia/Inflammation: 550 mg bid Acute gout: 750 mg, then 250 mg tid until relief.	1500 mg qd	220 mg

NOTE: Pediatric and geriatric patients are often more sensitive to medication and are given lower doses. A pre-existing medical condition may also be a factor. For example, patients with benign prostatic hypertrophy (BPH), diabetes, or renal insufficiency require lowered doses to avoid nephrotoxicity.

Table V. Dosage Information for OTC NSAIDs Use in Children

NSAID	Weight (lbs)	Age (yrs)	Dose
			tsp
Ibuprofen: Children's Motrin® or Advil® (Oral Suspension)	24-35	2-3	1
Each teaspoon (5ml) – 100 mg Ibuprofen	36-47	4-5	1 ½
	48-59	6-8	2
	60-71	9-10	2 ½
	72-95	10-11	3
			dropperful
Ibuprofen: Motrin® Drops	24-35	2-3	2
Each dropperful (12.5 ml) = 50 mg Ibuprofen			
			caplets
Ibuprofen: Jr. Strength Motrin® Caplets †	48-59	6-8	2
Each caplet contains 100mg Ibuprofen	60-71	9-10	2 ½
	72-95	11	3
† Not for use in children under the age of 6 years.			

NOTES:

Ibuprofen-containing products in the form of Nuprin®/Motrin® IB, Advil® Tablets, Advil® Cold & Sinus, and Vick's DayQuil® Sinus are not appropriate for children under the age of 12 years.

Naproxen Sodium is not to be used in children younger than 12 years of age. Follow adult guidelines for children older than 12 years of age.

Ketoprofen is not to be used in children younger than 16 years of age. Follow adult guidelines for children older than 16 years of age.

Table VI. Non-Prescription Products Containing Acetaminophen

Brand Name	Product containing acetaminophen
Actifed®	Cold & Allergy; Sinus
Alka-Seltzer®	All Products
Anacin®	Aspirin-Free Formula
Benadryl®	Allergy Sinus Headache; Severe Allergy & Sinus Headache
Comtrex®	All Products
Contac®	Severe Cold & Flu Maximum Strength Caplets; Non-Drowsy Caplets; Day & Night Cold & Flu
Coricidin®	D Cold; Flu & Sinus Tablets; HBP Cold & Flu Tablets
Dimetapp®	Non-Drowsy Flu Syrup
Dristan®	Cold Multi-Symptom Formula
Drixoral®	Allergy Sinus; Cold & Flu
Excedrin®	All Products
Feverall®	Suppositories
Goody's® Powders	All Products
Midol®	Maximum Strength Menstrual Formula; Maximum Strength PMS Formula
NyQuil® / DayQuil®	Cold/Flu Relief Liquid and LiquiCaps
Pamprin®	All Products
Percogesic®	All Products
Robitussin®	Cold, Multi-Symptom Cold & Flu; Multi-Symptom Honey Flu Liquid; Nighttime Honey Flu Liquid
Singlet®	Tablets
Sinutab® Sinus	Sinus Allergy Medication Maximum Strength Formula
Sudafed®	Cold & Cough Liquid Caps; Cold & Sinus Liquid Caps; Severe Cold Caplets and Tablets; Sinus Caplets and Tablets
Tavist®	Sinus Non-Drowsy Coated Caplets
TheraFlu®	All Regular and Maximum Strength Caplets and Hot Liquid
Triaminic®	Cold, Cough & Fever Liquid; Cough & Sore Throat Liquid; Cough & Sore Throat Softchews
Tylenol®	Allergy Sinus Formula; Severe Allergy; Arthritis Pain Extended Relief; Cold Formula; Cold & Flu; Extra Strength Pain Reliever; Flu Formula; Maximum Strength Sore Throat Adult Liquid; PM Pain Reliever/Sleep Aid; Regular Strength; Sinus; Women's Tylenol
Vanquish®	Caplets
Vicks®	44 M Cough; Cold & Flu Relief Liquid and LiquiCaps

Table VII. Non-Prescription Products Containing NSAIDs*

Brand Name	Product containing NSAIDs
Advil®	Cold and Sinus Caplets and Tablets; Ibuprofen Tablets, Caplets, and Gel Caplets; Flu and Body Ache Caplets; Migraine Liquigels
Aleve®	Tablets, Caplets, and Gelcaps; Cold and Sinus Caplets
Alka-Seltzer®	Original, Extra Strength, Cherry, and Lemon/Lime Effervescent Antacid and Pain Reliever; Alka-Seltzer PM
Anacin®	Regular Strength, Extra Strength Tablets
Bayer®	Genuine Aspirin Tablets & Caplets, Extra Strength Plus Aspirin Caplets, Extra Strength PM Aspirin Plus Sleep Aid, Extra Strength Arthritis Pain Regimen Formula, Extra Strength Aspirin Caplets & Tablets, Vanquish Caplets
BC®	Arthritis Strength Powder, Allergy Sinus Cold Powder, BC Powder, Sinus Cold Powder
Bufferin®	All Products
Dristan®	Sinus Pain Formula
Ecotrin®	Enteric Coated Aspirin Regular Strength, Maximum Strength
Excedrin®	Extra Strength Migraine Caplets, Geltabs, Tablets; Migraine Tablets
Goody's®	Body Pain Formula Powder; Extra Strength Headache Powder; Extra Strength Pain Relief Tablets
Halfprin®	Tablets
Midol®	Maximum Strength Cramp Formula Tablets
Motrin®	IB Caplets, Tablets, and Gelcaps; IB Pain Reliever/Fever Reducer Tablets, Caplets, and Gelcaps; Migraine Pain Caplets; Sinus/Headache Caplets
Orudis®	KT Tablets

*Non-Steroidal Anti-Inflammatory Drugs. List does not include low-strength adult aspirin therapy products.

Table VIII. OTC NSAIDs: Gastrointestinal Side Effects[†]

Increased risk of developing chronic ulcers
Nausea
Abdominal and epigastric pain
Dyspepsia (indigestion)
Constipation
Diarrhea
Flatulence
Stomatitis
Vomiting
Anorexia
Rectal bleeding

[†] Smoking and alcohol use have been shown to increase the risk of gastrointestinal side effects.

Table IX. Comparison of Toxic Effects of OTC NSAIDs and Aspirin

Drug Name	Gastrointestinal Irritation	Peptic Ulcer	CNS Effects	Tinnitus	Hepatitis	Renal Effects
ASA (aspirin)	XXXX	XX	X	XXX	XX	X
Ibuprofen	XX	X	X	X	XX	XX
Ketoprofen	XX	X	X	X	XX	XX
Naproxen	XX	XX	XX	XX	XX	XX

X = Low Risk
XX = Average Risk
XXX = Above Average Risk
XXXX = High Risk

Table X. OTC Drug Interactions and Contraindications

OTC Drug	Interactive Drug	Type of Interaction
Aspirin (salicylates)	Antacids	lowers aspirin serum levels
	Anticoagulants (heparin, warfarin)	increases risk of bleeding
	Caronic anhydrase inhibitors (acetatozolamide, dichlorphenamide)	increases salicylate toxicity
	Cytotoxics (methotrexate)	reduces methotrexate excretion
	NSAIDs and corticosteroids	increases stomach irritation
	Sulphonylureas	increases effect
	Uricosurics (probenecid, sulphinyrazone)	reduces uricosuric effects
Ibuprofen	Diuretics	reduces diuretic effect
Acetaminophen (Tylenol®)	Alcohol	increases liver damage in heavy drinkers
	NSAIDs and corticosteroids	increases stomach irritation

Contraindicated Use of NSAIDs	Moderate Interaction
Pediatric or adolescent patients with viral illness or fever, aspirin may cause Reye's syndrome	Corticosteroids
Lactation: metabolic acidosis	Platelet aggregation inhibitors: Lepirudin (addictive side effects)
Pregnancy: especially in 3rd trimester or near term, may cause excess bleeding	Valproic acid
Live influenza virus vaccine, Reye's syndrome	Ticlopidine
Anticoagulants: Warfarin, Heparin, Mifepristone, may cause excess bleeding	Carbonic anhydrase inhibitors
Ketorolac, Methotrexate: simultaneous use of NSAIDs slows excretion	Oral antidiabetics
	Uricosurics
	Geriatric: more susceptible, may need to reduce dose

Table XI. Drugs that Interact with OTC NSAIDs and Aspirin*

Compiled by Patricia Canfield, DO, WSCC Clinics

DRUG NAME	BRAND NAME	Interactions with			
		Aspirin	Naxopren	Ibuprofen	Orudis
I. Ace Inhibitors – may potentiate renal states/loss of hypotensive effect.					
Captopril	Capoten, Capozide		✓	✓	
Enalapril Maleate	Vaseretic, Vasotec		✓	✓	
Fosinopril Sodium	Monopril		✓	✓	
Lisinopril	Prinivil, Prinzide, Zestoretic, Zestril		✓	✓	
Moexipril Hydrochloride	Univasc		✓	✓	
Pindolol	Visken		✓	✓	
Propranolol Hydrochloride	Inderal, Inderide		✓	✓	
Quinapril Hydrochloride	Accupril		✓	✓	
Ramipril	Altace		✓	✓	
Sotalol Hydrochloride	Betapace		✓	✓	
Timolol Hemihydrate	Betimol		✓	✓	
Timolol Maleate	Biocadren, Timclide, Timoptic		✓	✓	
Trandolapril	Mavik		✓	✓	
NOTE: Ace Inhibitors are used to treat cardiovascular problems.					
II. Antacids containing Aluminum, Calcium or Magnesium – may potentiate renal disease states					
Aluminum Carbonate	Basajel		✓		
Aluminum Hydroxide	AlternaGel, Ascriptin, Gaviscon, Gelusil, Maalox, Mylanta, TempoSoft Antacid		✓		
Aluminum Hydroxide Gel	Alterna Gel, Aludrox, Amphojel, Ascriptin, Gaviscon, Mylanta, Niphrox		✓		
Magnesium Hydrochloride	Aludrox, Ascriptin, Di-Gel, Gelusil, Maalox, Mylanta, Milk of Magnesia, Rolaids, TempoSoft Antacid		✓		
Magnesium Oxide	Beelith, Bufferin, Caltrate, Cana Arthritis, Mag-Ox, Uro-Mag		✓		
Sucralfate	Carafate		✓		
III. Anti-Coagulants – potential for prolonging prothrombin time					
Heparin	Hep-Lock	✓	✓	✓	✓
Warfarin	Coumadin	✓	✓	✓	✓

DRUG NAME	BRAND NAME	Interactions with			
		Aspirin	Naxopren	Ibuprofen	Orudis
IV. Beta Blockers – decrease anti-hypertensive effect					
Acebutolol Hydrochloride	Sectrol		✓		
Atenolol	Tenoretic, Tenormin		✓		
Benazepril	Lotensin, Lotrel		✓		
Betaxolol Hydrochloride	Betoptic Ophthalmic Solution, Kerlone		✓		
Bisoprolol Fumerate	Zebeta, Ziac		✓		
Carteolol Hydrochloride	Cartrol, Ocupress		✓		
NOTE: Beta Blockers are used to treat cardiovascular problems.					
V. Histamine H2 Receptor Antagonists – may potentiate renal states					
Cimetidine	Tagamet		✓		
Famotidine	Pepcid		✓		
Nizatidine	Axid		✓		
Ranitidine	Zantac		✓		
NOTE: Histamine H2 Receptor Antagonists are used to treat gastrointestinal problems.					
VI. Hydantoin Anti-Convulsants – potential for anti-convulsant toxicity					
Ethotoin	Peganone		✓		
Fosphenytoin	Cerebyrx		✓		
Mephenytoin	Mesantoin		✓		
Phenytoin	Dilantin		✓		
VII. Lithium – potential for lithium toxicity					
Lithium	n/a		✓	✓	✓
NOTE: Lithium is used to treat Bipolar disorders.					
VIII. Metformin Hydrochloride – may potentiate renal states					
Metformin Hydrochloride	Glucophage	✓			
NOTE: Metformin Hydrochloride is used to treat diabetes.					
IX. Methotrexate Sodium – potential for methotrexate toxicity					
Methotrexate Sodium	n/a		✓		✓
NOTE: Methotrexate Sodium is used to treat rheumatoid arthritis, psoriasis, and neoplastic diseases.					

DRUG NAME	BRAND NAME	Interactions with			
		Aspirin	Naxopren	Ibuprofen	Orudis
X. Other NSAIDs					
Including ASA					
	Advil	✓	✓	✓	✓
	Aleve	✓	✓	✓	✓
	Anaprox	✓	✓	✓	✓
	Ansaid	✓	✓	✓	✓
	Clinoril	✓	✓	✓	✓
	Dolobid	✓	✓	✓	✓
	Feldene	✓	✓	✓	✓
	Indocin	✓	✓	✓	✓
	Lodine	✓	✓	✓	✓
	Motrin	✓	✓	✓	✓
	Nalfon	✓	✓	✓	✓
	Naprosyn	✓	✓	✓	✓
	Nuprin	✓	✓	✓	✓
	Orudis	✓	✓	✓	✓
	Oruvail	✓	✓	✓	✓
	Ponstel	✓	✓	✓	✓
	Relafen	✓	✓	✓	✓
	Tolectin	✓	✓	✓	✓
	Toradol	✓	✓	✓	✓
	Voltaren	✓	✓	✓	✓
Including other Salicylates					
	Asacol	✓	✓	✓	✓
	Mono-Gesic	✓	✓	✓	✓
	Pentasa	✓	✓	✓	✓
	ROWASA	✓	✓	✓	✓
	Salflex	✓	✓	✓	✓
	Trilisate	✓	✓	✓	✓

DRUG NAME	BRAND NAME	Interactions with			
		Aspirin	Naxopren	Ibuprofen	Orudis
XI. DIURECTICS					
Thiazide Diuretics – decrease urinary excretion of potassium and chloride/decrease hypotensive and/or diuretic effect					
Chlorthiazide	Aldoclor, Diupres, Diuril			✓	✓
Clorhiazide Sodium	Diuril Sodium			✓	✓
Hydrochlorthiazide	Aldactazide, Aldoril, Apresazide, Capozide, Diazide, Esidrix, Esimil, Hydrodiuril, Hydropres, Hyzaar, Inderide, Lopressor, Lotensin, Moduretic, Oretic, Prinizide, Ser-Ap-Es, Timolide, Vaseretic, Zestoretic, Ziac			✓	✓
Hydroflumethiazide	Diucardin			✓	✓
Methytdothiazide	Endaron			✓	✓
Polythiazide	Minizide			✓	✓
Non-Thiazide Diuretics – decrease urinary excretion of potassium and chloride					
Amiloride Hydrochloride	Midamor, Moduretic				✓
Bumetamide	Bumex				✓
Chlorthalidone	Combipres, Tenoretic, Thalitone				✓
Ethacrynic Acid	Elecrin				✓
Metolazone	Mylerox, Zaroxolyn				✓
Spironolactone	Aldactazide, Aldactone				✓
Torsemide	Demadex				✓
Triamterene	Dyazide, Dyrenium				✓
Furosemide – may inhibit kidney function when administered with aspirin and other NSAIDs					
Furosemide	Lasix		✓	✓	
XII. Probenecid – extends half-life of ASA/NSAID and antagonizes uricosuric action					
Probenecid		✓	✓		✓
NOTE: Probenecid is used to treat gout and as an adjuvant therapy with antibiotics to prolong the plasma levels.					

DRUG NAME	BRAND NAME	Interactions with			
		Aspirin	Naxopren	Ibuprofen	Orudis
XIII. Benaspril Hydrochloride – interferes with blood pressure control					
Benazepril Hydrochloride	Lotensin, Lotrel			✓	
NOTE: Benazepril Hydrochloride is used to treat hypertension.					
XIV. Sulfonamides – potential sulfonamide toxicity					
Sulfamethizole	Urobiotic – used to treat infectious processes		✓		
Sulfamethoxazole	Bactrim, Gantanol, Septra – used to treat infections		✓		
Sulfasalazine	Azulfidine – used to treat ulcerative colitis		✓		
Sulfinpyrazone	Anturance – used to treat gout * See Section XVII.		✓		
Sulfisoxazole	Gantrisin - used to treat gout and infections		✓		
XV. Sulfonylureas – potential for sulfonylurea toxicity					
Chlorpropamide	Diabinese	✓	✓		
Glimepiride	Amuryl	✓	✓		
Glipizide	Glucotrol	✓	✓		
Glyburide	DiaBeta, Glynase, PresTabs, Micronase	✓	✓		
NOTE: Sulfonylureas are used to treat diabetes mellitus.					
XVI. ETOH					
ETOH		✓	✓	✓	✓
XVII. Gout Preparations – prolong clotting time					
Allopurinol	Zyloprim	✓			
Sulfinpyrazone	Anturane – antagonizes uricosuric action *See Section XIV	✓			
Sulfisoxazole	Gantrisin *See Section XIV.		✓		
XVIII. Corticosteroids – at high doses, increases incidence of GI tract bleeding					
Corticosteroids		✓	✓	✓	✓

*Protocol on over-the-counter analgesics, including aspirin, is in development.

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UNIVERSITY of WESTERN STATES
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SUMMARY SHEET: OTC NSAIDS and Analgesics

(Revised 6/29/10)

Checklist of Seven Steps

- ✓ **STEP 1:** Decide whether home care should include an analgesic or anti-inflammatory drug.
- ✓ **STEP 2:** Consider whether there is an effective botanical or nutritional supplement that may be used initially. *(See below.)*
- ✓ **STEP 3:** Decide if the use of an NSAID (or acetaminophen) is appropriate for the patient's specific condition. *(See below.)*
- ✓ **STEP 4:** Decide if an NSAID (or acetaminophen) is appropriate for the individual patient.
- ✓ **STEP 5:** Choose the appropriate treatment parameters based on the patient and the treatment goals.
- ✓ **STEP 6:** Inform the patient of risks. *(See below.)*
- ✓ **STEP 7:** Monitor patient response.

STEP 2: Botanical options include Devil's Claw, (*Harpagophytum Procumbens*) in a standardized daily dose of 50 mg or 100 mg harpagoside and Willow Bark (*Salix Alba),* in a standardized daily dose of 120 mg and 240 mg of salicin (a standardized daily dose of 240 mg reduced pain about the same as a daily dose of 12.5 mg of Vioxx).See protocol, p. 2 for other options.

STEP 3: NSAID Recommendations

Type of Injury	NSAID Impact	Comments
Bone: fracture	Contraindicated	Probable harmful effects on bone formation especially in the first weeks.
Bone: stress fracture	Contraindicated	Probable harmful effects on bone formation especially in the first weeks.
Ligament: acute sprain (e.g., appropriate for mild to moderate knee sprain)	Possibly and potentially useful in the short-term	Reduces pain and swelling Faster return to athletic activities May cause long-term residual laxity Short-term use (<5 days)
Low back pain, acute with sciatica	May not be useful	No proven efficacy. Often ineffective if there are nerve root symptoms.
Low back pain, acute without sciatica	Possibly and potentially useful	Strong evidence NSAIDs are more effective than placebo for acute LBP (small effect size). Acetaminophen recommended as a basic first choice.
Low back pain, chronic	Potential limited usefulness	There is only moderate evidence supporting the effectiveness of NSAIDs for management of chronic low-back pain. Acetaminophen may be better first choice because of side effects.
Muscle: acute muscle tear	Probably not useful and perhaps not indicated	Inhibits protein synthesis and inflammatory reaction.
Muscle: contusion	Potentially useful	In case of deep contusion or history of myositis ossificans
Osteoarthritis	Possibly and potentially useful.	Consider acetaminophen as first choice. RCTs suggest topical NSAIDs are superior to placebo, but only in the first two weeks of treatment.
Rheumatoid arthritis	Possibly and potentially useful	Start with analgesic; combining acetaminophen with an NSAID may reduce NSAID dose.
Tendon: overuse tendinopathy	Probably not useful	Short term analgesic effect only (perhaps more so in shoulder conditions than elbow, patellar or Achilles tendinopathy; no benefit for healing
Tendon: true acute tenosynovitis/bursitis (e.g., DeQuevain's)	Possibly and potentially useful	Reduces acute inflammations Helps recovery

Choosing an OTC

- NSAIDs have equal or slightly greater effectiveness than non-opioid analgesics in reducing pain, but with more common serious potential side effects. **An analgesic such as acetaminophen (e.g., Tylenol) is generally suggested as the drug of first choice unless it is contraindicated.**
- Acetaminophen and an NSAIDs may also be combined for acute pain management.
- **Clinical Warning:** Combinations of NSAIDs (*not* in combination with acetaminophen) often increase risk of adverse reactions. **Using multiple NSAIDs doubles the risk for GI bleeding.**

STEP 4: NSAID contraindications

Patients in the following categories should avoid all use of NSAIDs unless otherwise specified.

- **Allergy to aspirin, iodides, or other NSAIDs.** A patient who is allergic to aspirin may also be allergic to NSAIDs.
- **Pre-existing renal disease**
- **Active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract.** If a patient is at a particularly high risk for ulcers and yet may benefit from the therapeutic effect of NSAIDs, consider referral for combination therapy of NSAIDs and prophylactic treatment for ulcers.
- **Pregnancy**
- **Use of warfarin, Coumadin® or other anti-coagulation medications.** Because of their anti-clotting action, NSAIDs should never be used by a patient who is taking blood thinners, such as Coumadin or warfarin. Simultaneous use of aspirin and ibuprofen may attenuate the antiplatelet effect of aspirin, making it less useful for cardioprotection.

NSAID high risk patients *(See Table II to calculate risks for an individual patient.)*

- History of abdominal pain or gastroesophageal reflux disease
- (GERD) (GI bleeding, 7-fold increase in risk)
- Diabetes (renal failure)
- Hypertension (exacerbation)
- Liver disease (hepatitis)
- Congestive heart failure (exacerbation)
- Lupus (renal failure)
- Asthma (bronchoconstriction)
- Renal artery stenosis (renal failure)
- Age greater than 75 years (GI bleeding, renal failure)
- History of peptic ulcer disease (GI bleeding)
- Alcohol use (GI symptoms, liver disease)
- Corticosteroid therapy (GI symptoms)
- Smoking (GI symptoms)

Acetaminophen high risk patients

- Liver disease
- Chronic alcohol use
- Hypersensitivity to drug (including possible cross reaction with allergy to aspirin)
- Renal impairment 9epscially fro long term use)
- G6PD deficiency
- PKU (phenylalanine-containing forms)

STEP 5: Summary of drug & dosage recommendations

- Recommend NSAID dosage based on desired effect (analgesic or anti-inflammatory).
- Do not exceed daily maximum dose. (*See Table IV.*)
- Adjust dose based on size and age of the patient. Lower doses for pediatric and geriatric patients. (*See Table V.*)
- Begin with a smaller dose and increase only if necessary – the higher the dose of the NSAID, the greater the chance for adverse effects.
- **Warning:** The daily recommended limit for acetaminophen has been reduced to 3,250 milligrams per day. Beware of hidden amounts of acetaminophen and NSAIDs in other OTCs. (See tables VI and VII).

STEP 6: Clinic Policy

All patients on OTC NSAIDs, whether recommended by our clinics or not, are to be given a patient information sheet and a PARQ. The following FDA cautions must be part of the PARQ conference when recommending NSAIDs:

- GI toxicity is a potentially serious adverse effect. (*See Table II. Assessment Tool to Determine Risk of NSAID-Induced GI Toxicity.*)
- GI toxicity must be identified as potentially life-threatening.
- List symptoms of GI toxicity
- In the event of serious side effects, the patient should stop taking the medication and contact the clinician. Rare cases in which there are severe side effects, go to an emergency room or urgent care center. **Severe side effects include rectal bleeding, hematemesis (including vomitus appearing as "coffee grounds"), abdominal pain, dizziness, syncope and tachycardia.**
- Renal toxicity should be identified as a potential side effect.
- Smoking and/or alcohol consumption will increase the risk of side effects.

NSAID Side Effects

1. Gastrointestinal
2. Renal
3. Pulmonary
4. Impediment of healing time
5. Female infertility
6. Drug Interactions
7. Cardiovascular
8. Hearing loss