OPTUM®

Non-Steroidal Anti-Inflammatory Drugs (NSAID): The Risks and Benefits

Non-steroidal anti-inflammatory drugs (NSAIDs) are in a class of medications that provide broad therapeutic applications as an analgesic (pain reliever), antipyretic (lowers fever) and anti-inflammatory (reduces swelling) medication.[1] NSAIDs are comprised of a number of common over-the-counter (OTC) and prescription medications, such as aspirin, ibuprofen, naproxen, diclofenac, meloxicam and celecoxib to name a few. It's estimated that more than 70 million prescriptions and more than 30 billion doses of NSAIDS are consumed annually in the United States.[2] NSAIDs are some of the most commonly used medications in workers' compensation as well. They are the second most prescribed therapeutic class in our book of business, representing 13.4 percent of all prescriptions. They rank third in total spend at 10.7 percent; the most commonly prescribed NSAID being ibuprofen, representing 3.7 percent of prescriptions, followed by Celebrex® and Mobic® at 2.3 percent and 2.2 percent respectively.[3]

Herein, we discuss how NSAIDs work, the clinical uses, potential therapy concerns[4] and provide guidance on the best-practice clinical approach to NSAID use in workers' compensation.

It's estimated that more than **70 million prescriptions** and more than **30 billion doses** of NSAIDS are consumed annually in the United States.[2]

Method of action

NSAIDs primarily work by blocking an enzyme known as cyclooxygenase (COX) from performing its regular function.[5] There are two types of COX enzymes, COX-1 and COX-2. When COX-1 is activated, it promotes the regulation of a number of vital organ functions, such as kidney blood flow and gastric mucosa (stomach lining) protection.[1,5] In addition, COX-1 activity regulates platelet aggregation (causes blood clotting). Blocking COX-1 with NSAIDs produces both desirable and undesirable effects; although it helps prevent platelet aggregation (beneficial in the case of aspirin therapy to prevent heart attack), chronic use of NSAIDs frequently results in gastric ulcers due to reduced protection of the stomach lining.[1,5,6]

1.Rao, P. & Knaus, E.E. (2008 September 20) *Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): Cyclooxgenase (COX) inhibition and beyond.* J Pharm Pharm Sci; 11(2): 81s-110s.

2. Green, G.A. (2001). *Understanding NSAIDs: From aspirin to COX-2.* Clin Cornerstone; 3(5): 50-60.

3. Helios. (2015). *2015 workers' compensation drug trends report.*

4. Bronstein, A.C, Spyker, D.A., Cantilena Jr., L.R., Rumack, B.H. & Dart, R.C. (2012 December). *2011 annual report of the American Associate of Poison Control Centers' national poison data system (NPDS): 29th annual report.* Clin Toxicol; 50(10): 911-1164.

5. Knights, K.M., Arduino, M.A. & John, M.O. (2010). *Defining the COX inhibitor selectivity of NSAIDs: Implications for understanding toxicity.* Retrieved from: http://www.medscape.com/viewarticle/733075

6. McQuay, H.J. & Moore, A. (2006). *NSAIDs and coxibs: Clinical use.* In: McMahon, S.B. & Koltzenburg, M (eds) Wall and Melzack's Textbook of Pain, 5th ed., chapter 30 Elsevier, London.

COX-2 enzymes are induced during periods of inflammation brought on by injury or infection.[7,8] COX-2 activity, unlike COX-1 activity, primarily regulates inflammation, pain and fever.[7,8] COX-2 activity also prevents platelet aggregation (blood clotting), promotes vasodilation (blood vessel opening) and has been recently noted to affect salt and water retention.[7,8] Blockage of COX-2 provides the favorable effect of reducing inflammation, pain, fever and the rate of gastric ulcer events. Unfortunately, it also has the unfavorable effect of increasing the risk of myocardial infection (heart attack) and stroke – possibly by causing blood vessel narrowing, changes in water and salt balance and increased blood clotting.[7,8]

There are several NSAIDs available, both over-the-counter and prescription, due to the varying degrees in which each medication acts on COX-1 and COX-2. Older generation NSAIDs, such as aspirin and ibuprofen, almost exclusively inhibit COX-1, while never classes of NSAIDs predominately inhibit COX-2.

Figure 1 provides a sampling of the variation in several NSAIDs and their selectiveness for COX-2 enzymes along with associated risks.[9]

Figure 1: Safety comparison of some of the most commonly used NSAIDs*

NSAID	COX-2 Selectivity†	Gastrointestinal Risk	Cardiovascular Risk§	Clinical Use
aspirin	Low	Moderate	Low	Prevention of cardiovascular events, mild pain and inflammation
ibuprofen	Moderate	Low	Moderate to High	Rheumatoid arthritis, osteoarthritis, fever, mild to moderate pain, dysmenorrhea, headache, migraine, myalgia
diclofenac	High	Moderate	High	Rheumatoid arthritis, osteoarthritis, fever, mild to moderate pain, dysmenorrhea, migraine
indomethacin	Low	Moderate to High	Moderate	Rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, mild, moderate or severe pain
naproxen	Low	Moderate to High	Low	Gouty arthritis, mild to moderate pain, tendonitis, fever, rheumatoid disorders, osteoarthritis, dysmenorrhea, migraine prevention
meloxicam	High	Low	Moderate	Rheumatoid arthritis, osteoarthritis
celecoxib	High	Low	Moderate to High	Osteoarthritis, anklosing spondylitis, rheumatoid arthritis, acute pain, dysmenorrhea

* Only generic names provided. List not all inclusive; keep in mind NSAIDs carry varying risks of rare liver toxicity and renal injury.

† Selectivity is based on in vitro assay studies and should be interpreted with caution as different assay methods give different results. Moreover, no assay method can predict what will happen when the drug is given to patients. Clinical studies are the best way to determine the effects of NSAIDs in patients.

§ For patients with CV disease or risk factors for ischemic heart disease, the American Heart Association recommends for the following agents for pain (in order listed): acetaminophen, aspirin, tramadol, opioids (short-term), nonacetylated salicylates (e.g., diflunisal), NSAIDs with low COX-2 selectivity, NSAIDs with some COX-2 selectivity and COX-2 selective agents.

7. Ibid
8. Ibid
9. PL Detail-Document. (2015 September). *Managing NSAID risks.* Pharmacist's Letter/Prescriber's Letter.

Clinical uses

NSAIDs are frequently the first-line option for the treatment of conditions causing pain and inflammation. These medications are viewed favorably by prescribers when dealing with these conditions, as they provide an optimal treatment profile: efficacious, low cost, low risk (when dosed appropriately) and low abuse potential. Additionally, many are available for over-the-counter use, making them highly accessible.

There are also a variety of medications that contain NSAIDs in combination with other ingredients, including those used for the treatment of cough or cold symptoms, sleeplessness and pain relief. Many of these combination products are available OTC, as well as by prescription. For instance, Advil® PM contains ibuprofen and phenhydramine, and can be taken at bedtime to treat minor aches and pains that may be preventing someone from falling asleep. Another example is a prescription product Vicoprofen®. Vicoprofen contains iburprofen and hydrocodone, typically used for the short-term treatment of acute pain.

Clinical disadvantages and controversy

Despite the benefits of NSAIDs, there are a number of associated risks and adverse events with the use of these medications. One of the most common and poorly scrutinized risks is the unknowing concurrent use of multiple NSAIDs. Many patients are unaware that their medications, especially over-the-counter medications, contain or are NSAIDs and this places them at risk for over utilization and side effects. Moreover, there are multiple drug-drug interactions that can lead to potentially serious events.[10] For instance, because NSAIDs inhibit platelet aggregation and prolong bleeding time, additive effects may be observed in patients receiving platelet inhibitors (i.e., aspirin), anticoagulants (i.e., warfarin) or thrombolytic agents (i.e., alteplase). Therefore, it is imperative that patients make their prescribers and pharmacists aware of all the OTC and prescription medications they are taking in order to reduce these and other drug-drug interactions.

The risk of excessive or inappropriate dosing is of particular concern in NSAIDs that predominately block COX-2 (i.e., celecoxib, diclofenac and meloxicam) due to the propensity to increase the risk of heart attack, stroke and death, as noted in several studies.[11,12,13,14] One study published in 2013 evaluated the elevated cardiovascular risk of NSAIDs and concluded that diclofenac had an equivalent risk to rofecoxib (Vioxx – a drug no longer on the market) for cardiovascular-related adverse events.[13] Of the ten NSAIDs evaluated in the study, naproxen had the lowest risk of cardiovascular events, with ibuprofen and celecoxib showing elevated risk at high doses, and meloxicam and indomethacin demonstrating moderately elevated risk. Furthermore, a 2012 study by

10. Lexi-Comp, Inc. (2012). Lexi-Comp [database on the internet]. Retrieved from: http://online.lexi.com

11. Trelle, S. Reichenbach, S., Wandel, S., Hildebrand, P., Tschannen, B., Villiger, P.M., Egger, M. & Juni, P. (2011 January 11). *Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis.* BMJ; 342: c7086.

12. Kearney, P.M., Baigent, C., Godwin, J., Halls, H., Emberson, J.R. & Patrono, C. (2006 June 3). *Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials.* BMJ; 332(7553): 1302-8.

13. McGettigan, P. & Henry, D. (2013 February). *Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: An examination of sales and essential medicines lists in low-, middle-, and high-income countries.* PLoS Med; 10(2): e1001388.

the American Heart Association concluded that the use of NSAIDs (excluding aspirin) in the five years following a heart attack persistently led to an increased risk of death and/or recurrent heart attack by roughly 1.5 times.[14]

During a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee in February 2014, it was recommended that prescription labels for NSAIDs be evised to alert the public to the serious side effects that can occur in as early as the first few weeks of using NSAIDs. In July 2015, the Food and Drug Administration (FDA), after performing a comprehensive review of new safety information of NSAIDs, including observational studies, clinical trials and other scientific publications, strengthened an existing label warning that NSAIDs increase the change of heart attack or stroke. These risks may increase the longer NSAIDs are taken and when taken at higher doses. Ongoing trials, such as the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) continue to evaluate the safety of NSAIDs among patients with high cardiovascular risk.

NSAIDs also increase the risk of GI ulceration and bleeding, particularly with COX-1 dominating inhibitors (i.e., aspirin, ketoprofen and indomethacin). Long-term use of NSAIDs may lead to GI ulcers due to inhibitors of prostaglandins that protect the stomach wall.[15,16] Patients who require chronic NSAID therapy are often provided with proton pump inhibitors (i.e., omeprazole) to reduce gastric acid formulation to help lower the risk of GI ulceration and bleeding.[16,17,18] The American Geriatrics Society (AGS) Practical Guidelines recommend avoiding NSAIDs in older persons with persistent pain except in patients who have failed other therapies and have a favorable benefit versus risks assessment.[19] NSAID use increases the risk of GI bleeding and peptic ulcer disease in high age groups, including those ≥ 75 years old or taking oral or parenteral corticosteroids, anticoagulants or antiplatelet agents. As with younger patients, use of a proton pump inhibitor (PPI) or misoprostol reduces, but does not eliminate this risk. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately one percent of older patients treated for 3-6 months and in about 2-4 percent of older patients treated for one year; these trends continue with longer duration of use. Therefore, extreme caution, ongoing therapy evaluation and concurrent PPI or misoprostol use are advised if NSAIDs must be prescribed in older adults. (Figure 1 provides a summary of the GI and cardiovascular risks for the most commonly used NSAIDs.)

Kidney damage or even kidney failure is also of clinical concern with NSAID use because prostaglandins are partly responsible for the regulation of blood flow through the kidney.[20,21] Patients who are taking diuretics and/or ace inhibitors (i.e., patients with congestive heart failure and/or hypertension) are advised to avoid use of NSAIDs due to this potential for kidney toxicity.[21]

14. Olsen, A.M., Fosbol, E.L., Lindhardsen, J., Folke, F., Charlot, M., Selmer, C., Bjerring-Olesen, J., Lamberts, M., Ruwald, M.H., Kober, L., Hansen, P.R., Torp-Pedersen, C. & Gislason, G.H. (2012 October 16). *Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infraction: A nationwide cohort study.* Circulation; 126(16): 1955-63.

15. Ibid

16. Ibid

17. Ibid

18. Laine, L. (2002 April). Gastrointestinal safety of coxibs and outcomes studies: What's the verdict? J Pain Symptom Manage; 23(4 Suppl): S5-10; discussion: S11-4.

19. American Geriatrics Society (AGS) Panel on Pharmacological Management of Persistent Pain in Older Persons. (2009). Pharmacological management of persistent pain in older persons. J Am Geriatr Soc; 57: 1331-46.

20. Ibid

21. Ibid

The use of NSAIDs should also be avoided in pregnancy, as they have been associated with premature birth and miscarriage.[22,23]

Further complicating the picture is the lack of appropriate alternatives to NSAIDs for inflammation and pain relief. Opioid analgesics have demonstrated high abuse potential and are often more problematic to dose than NSAIDs.[24,25] Studies have also shown that opioid users are at a higher risk for bone fractures compared to those taking NSAIDs in older adult populations.[24,25] The same studies also found a possible correlation between opioid users and elevated risks of heart attack. It should be noted that NSAIDs have already been proven in multiple studies to cause cardiovascular problems, especially with selective COX-2 inhibitors.

Best practice clinical approach

The treatment of pain and inflammation requires a multi-focal, holistic view of the patient by the healthcare team. Each patient must be approached in a manner that mitigates the risks, while weighing the benefits of NSAIDs or alternative therapies. Non-pharmacological interventions, such as those for the treatment of musculoskeletal aches and pains, are generally preferred (i.e., weight loss and exercise). When pharmacological intervention is required, patients should be assessed for multiple parameters, including:

- Comorbidities – GI, cardiovascular and renal risk factors
- Concurrent use of multiple NSAIDs
- Potential drug-drug interactions
- Pregnancy
- Demographics (i.e., age, sex, etc.)

Selection of an appropriate treatment is determined on a case-by-case basis, and in some instances, NSAIDs may not be suitable or even contraindicated. When NSAIDs are indicated, the general accepted rule of thumb for dosing is to start at the lowest effective dose and use for the shortest period of time.[26]

In the last two years, the FDA approved two new lower dose formulations of diclofenac (Zorvolex®) and indomethacin (Tivorbex®). While both of these agents are indicated to treat mild to moderate acute pain, Zorvolex has an added indication to treat osteoarthritis pain. These formulations were approved at dosages that are 20% lower in strength than currently available products, and were developed to address the FDA's public health advisory recommending that NSAIDs be used at the lowest effective dose for the shortest period of time. According to the manufacturer, these drugs are formulated as submicron particles that increase surface area, leading to faster dissolution and absorption. It is important to note however, these agents still carry the same black box warnings as other NSAIDs. While these lower-dose formulations are now available, they cost much more with a relatively similar risk profile when compared

22. Ostensen, M.E. & Skomsvoll, J.F. (2004 March). *Anti-inflammatory pharmacotherapy during pregnancy.* Expert Opin Pharmacother; 5(3): 571-80.

23. Nakhai-Pour, H.R., Broy, P., Sheehy, O. & Berard, A. (2011 October 18). *Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion.* CMAJ; 183(15): 1713-2.

24. Solomon, D.H., Rassen, J.A., Glynn, R.J., Garneau, K., Levin, R., Lee, J. & Schneeweiss, S. (2010). *The comparative safety of opioids for nonmalignant pain in older adults.* Arch Intern Med; 170: 1979-86.

25. Solomon, D.H., Rassen, J.A., Glynn, R.J., Lee, J., Levin, R. & Schneeweiss, S. (2010 December 13). *The comparative safety of analgesics in older adults with arthritis.* Arch Intern Med; 170(22): 1968-76.

26. Official Disability Guidelines (ODG). (2013). *The evidence based guideline company.* 18th ed. Pain Chapter, Work Loss Data Institute.

to OTC medications, such as ibuprofen (Advil®) and naproxen (Aleve®), which are available at lower strengths compared to their prescription counterparts.

At Optum®, NSAIDs are allowed on some of our Medication Plans and formularies where medical guidelines, evidence-based medicine and our training and experience would indicate the use of NSAIDs is appropriate for the injury.

The following case studies highlight two claims; one wherein an NSAID medication is safe, appropriate medication therapy and another when an alternative would be better suited for the injured worker.

Case Study 1: Patient case where NSAID is preferred

Dan is a 47-year-old male who sustained a lower back injury in December 2012 following a forklift accident. He received physical therapy and was able to return to work at a reduced capacity; however, he continued to report lower back pain and radicular symptoms in his left lower extremity. Dan was not a candidate for surgery and was diagnosed with chronic low back pain and radiculitis.

Dan also has unrelated diabetes and depression. His medications for his comorbid conditions including metformin 500mg twice daily and sertraline 100mg daily. His diabetes and depression are well controlled. The medications for his workers' compensation claim include oxycodone 5mg up to four times daily as needed for pain and Lyrica 150mg three times daily.

After a comprehensive review of the medical records by a pharmacist, it was discovered that his pain is well controlled most of the time with his current drug therapy, and he is trying to increase his exercise daily after work. His pain scores average 7 out of 10 with medications, although recently he has noticed some increased pain at night after excercising. He mentions he is only taking oxycodone two to three times daily. Urine drug screens have been consistent with his medications, with no evidence of illicit drug use. His pain management physician has a medication agreement on file and documents that Dan is compliant with medications and reports no adverse side effects.

At his last office visit, Dan was wondering if he could take iburprofen over-the-counter as needed after excercise to help relieve his pain. Given that he has no history of cardiovascular or gastrointestinal issues, his pain management physician agrees that taking ibuprofen over-the-counter as needed is appropriate, and advises him of the potential risks with higher doses and long-term use.

Case Study 2: Patient case where opioid is preferred over an NSAID

Bob is a 67-year-old male who sustained a neck injury in March 2000 while lifting heavy machinery. Subsequent to the injury and cervical spine surgery, he has been diagnosed with cervical radiculitis, myofascial pain, chronic pain syndrome, postlaminectomy syndrome cervical region and depression. Bob als has unrelated atrial fibrillation, hypertension, chest pain with exertion and obsessive compuslive disorder. It is not known what medications he is taking for his comorbid conditions. His medications for his workers' compensation claim include:

- hydrocodone/acetaminophen 10mg-325mg four times daily as needed for pain
- celecoxib 400mg daily at bedtime
- gabapentin 600mg three times daily
- duloxetine 60mg once daily

After a comprehensive review of the medical records by a pharmacist, it was discovered that Bob has been complaining of increased gastric distress and heart palpitations since the addition of celecoxib 400mg in January 2015. In addition, it was determined that celecoxib was being prescribed by his psychiatrist, rather than his pain management physician. The risk for adverse effects from celecoxib may increase with elevated dosage and/or duration of use, and in older adults witih cardiovascular disease or risk factors for cardiovascular disease (i.e., high blood pressure). Bob is taking a higher dose of celecoxib (400mg) and has a documented cardiovascular condition. As suc, celecoxib is not recommended for use in this patient and should be discontinued. Onging intermittent use of an opioid (hydrocodone-actaminophen) for pain in this case is preferred, however, the physician and other healthcare providers must continue to monitor the patient for risks and complications.

Despite the risks, NSAIDs are a valuable tool for treating minor aches and pains associated with a workplace injury, but it is important to understand these risks and evaluate the appropriateness of therapy.

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About Optum for Workers' Compensation

The workers' comp division of Optum collaborates with our clients to deliver value beyond transactional savings while helping ensure injured workers receive safe and effective clinical care. Our innovative and comprehensive medical cost management programs include pharmacy, ancillary and managed care services from first report of injury to settlement.