Therapeutic Class Overview
Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

INTRODUCTION

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large class of medications with analgesic, anti-inflammatory, and anti-pyretic properties used for a wide variety of conditions including pain, rheumatoid arthritis (RA), osteoarthritis (OA), primary dysmenorrhea, ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), acute migraine, and acute gout *(Conaghan 2012).*
  - RA is an autoimmune inflammatory arthritis that is treated with conventional, biologic, or targeted small molecule disease-modifying antirheumatic drugs (DMARDs) such as Trexall (methotrexate), tumor necrosis factor (TNF) inhibitors, non-TNF biologics, or Janus kinase inhibitors. Analgesics, including NSAIDs, have a limited role in most patients with active disease, but may be considered as a temporary adjunctive option. *(Moreland et al 2020, Singh et al 2015).*
  - OA is the most common form of arthritis, and is a degenerative inflammatory disease that can be pharmacologically treated with oral or topical NSAIDs, intraarticular (IA) glucocorticoid injections, acetaminophen, duloxetine, topical capsaicin, and tramadol *(Kolasinski et al 2020).*
  - Primary dysmenorrhea is menstrual pain in the absence of other pelvic pathology, and represents one of the most common causes of pelvic pain. It can be treated with oral NSAIDs, hormonal contraceptives, complementary and alternative therapies, and exercise *(ACOG 2018, Osayande et al 2013).*
  - AS is a chronic inflammatory arthritis characterized by sacro-iliac joint involvement that can be treated with NSAIDs, TNF inhibitors, sulfasalazine, methotrexate, tofacitinib, secukinumab, ixekizumab, locally administered glucocorticoids, physical therapy, or surgery *(Ward et al 2016, Ward et al 2019).*
  - JIA is a chronic idiopathic inflammatory disorder that affects pediatric patients. JIA encompasses multiple forms of arthritis in childhood, including what was previously described as juvenile rheumatoid arthritis before being supplanted by the newer term. Treatment for JIA includes conventional or biologic DMARDs, intravenous immunoglobulin, calcineurin inhibitors, IA glucocorticoids, and NSAIDs *(Grom 2018, Ringold et al 2013, Ringold et al 2019).*
  - Migraine is a disorder associated with severe headaches worsened by activity, light, and/or sounds, and can be treated with oral analgesics including NSAIDs and opioids, ergot derivative medications, triptans, antiemetics, and antiepileptics *(Marmura et al 2015, Oskoui et al 2019).*
  - Gout is the most common cause of inflammatory arthritis in adults, and typically presents acutely as synovitis due to tissue deposition of monosodium urate crystals. Acute gout can be treated with Colcrys (colchicine), systemic corticosteroids, and/or NSAIDs *(Khanna et al 2012, Qaseem et al 2017).*
- Some NSAIDs including ibuprofen and naproxen are available at lower strengths as over-the-counter (OTC) formulations, which do not require a prescription. The same compounds are also available in higher strengths as a prescription-only product. Other NSAIDs are available only by prescription regardless of strength.
- Both prescription-strength and OTC NSAIDs are widely utilized, accounting for over 111 million prescriptions annually and 60% of the OTC analgesic market in the United States (U.S.). The use of NSAIDs has been increasing over time and utilization is highest in individuals over 60 years of age *(Conaghan 2012, Davis et al 2017).*
- The therapeutic effects of NSAIDs are primarily attributed to inhibition of cyclooxygenase (COX) enzymes, which participate in the formation of mediators associated with inflammation and pain. Most NSAIDs block both related isoforms of the COX enzyme: COX-1 and COX-2 *(Solomon 2017).*
  - COX-1 regulates normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. Inhibition of COX-1 is theorized to contribute to some adverse events associated with NSAID use *(Solomon 2017).*
  - COX-2 is usually undetectable in most tissues, but its expression is increased during states of inflammation. For patients with a high risk for GI events, a selective COX-2 inhibitor may be preferred over a nonselective NSAID. Gastroprotective agents are also available to reduce the risk of NSAID-associated GI events. These agents include an exogenous prostaglandin (misoprostol), histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs) *(Solomon 2017).*

- In 2005, the Food and Drug Administration (FDA) began requiring all prescription NSAIDs to carry a boxed warning highlighting the potential for increased risk of cardiovascular (CV) events such as myocardial infarction (MI) and stroke, as well as gastrointestinal (GI) bleeding. OTC NSAIDs were also required to have labeling providing more specific information about these risks *(FDA Drug Safety Communication).*
  - In 2015, following an advisory committee review of additional evidence, the FDA required revisions to existing warnings for both prescription and OTC NSAIDs to strengthen messaging regarding potential risks of use. Statements were included regarding the risk potentially increasing with duration of use *(FDA Drug Safety Communication).*
- Most NSAIDs on the market have been generic for some time. In fact, many of the originator brand products have been discontinued, leaving only generic versions on the market. The newer patented NSAIDs Cambia (diclofenac potassium), Durlaza (aspirin ER), Qmiiz ODT (meloxicam), Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) are new formulations of previously approved molecular entities manufactured at a new strength, dosage form, and/or delivery system.
- This review includes an evaluation of orally administered, single-agent, prescription NSAIDs. Products that are available OTC are included if they are also available in a prescription-only strength or formulation.
- Medispan class: Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anaprox DS (naproxen sodium)	✔
Cambia (diclofenac potassium)	-
Celebrex (celecoxib)	✔
Daypro (oxaprozin)	✔
diclofenac	✔
diclofenac potassium	✔
diclofenac sodium DR	✔
diclofenac sodium ER	✔
diflunisal	✔
Durlaza (aspirin ER)	-
EC-Naprosyn (naproxen DR)	✔
etodolac	✔
etodolac ER	✔
Feldene (piroxicam)	✔
flurbiprofen	✔
ibuprofen	✔
Indocin (indomethacin)	✔ *
indomethacin ER	✔
ketoprofen	✔
ketoprofen ER	✔ †
ketorolac	✔
Lodine (etodolac)	✔
Meclofen (meclofenamate)	✔ †
Mefenam (mefenamic acid)	✔
Mobic (meloxicam)	✔
nabumetone	✔
Nalfon (fenoprofen)	✔
Naprelan (naproxen sodium SR)	✔
Naprosyn (naproxen)	✔
Qmiiz ODT (meloxicam)	-

Drug	Generic Availability
Relafen DS (nabumetone)	-
sulindac	✔
Tivorbex (indomethacin)	-
tolmetin	✔
Vivlodex (meloxicam)	-
Zipsor (diclofenac potassium)	-
Zorvolex (diclofenac)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)
*Only capsule formulation is available generically; the oral suspension and rectal suppository are branded products only.
†Available as a single-source generic product.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Anaprox DS (naproxen sodium)	✔	✔	✔	✔	✔	• Polyarticular juvenile idiopathic arthritis • Tendonitis or bursitis • Acute gout
Cambia (diclofenac potassium)						• Acute treatment of migraine
Celebrex (diclofenac potassium)	✔	✔	✔	✔	✔	• Juvenile RA
Daypro (oxaprozin)		✔	✔			• Juvenile RA
diclofenac or diclofenac potassium	✔	✔	✔	✔		
diclofenac sodium DR		✔	✔		✔	
diclofenac sodium ER		✔	✔			
diflunisal	✔	✔	✔			
Durlaza (aspirin ER)						• Reduce risk of death and MI in patients with chronic coronary artery disease • Reduce risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA
EC-Naprosyn (naproxen DR)		✔	✔		✔	• Polyarticular juvenile idiopathic arthritis
etodolac	✔ †	✔	✔			
etodolac ER		✔	✔			• Juvenile RA
Feldene (piroxicam)		✔	✔			
flurbiprofen		✔	✔			
ibuprofen	✔	✔	✔	✔		• Reduction of fever* • Juvenile RA*

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Indocin (indomethacin)		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
indomethacin ER		✔	✔		✔	• Acute painful shoulder
ketoprofen	✔	✔	✔	✔		
ketoprofen ER		✔	✔			
ketorolac						• Moderately severe acute pain‡
Meclofen (meclofenamate)	✔	✔	✔	✔	✔	• Reduction of fever • Juvenile RA • Acute painful shoulder • Acute gouty arthritis • Idiopathic heavy menstrual blood loss
Mefenam (mefenamic acid)	✔ §			✔		
Mobic (meloxicam)		✔	✔			• Juvenile RA
nabumetone		✔	✔			
Nalfon (fenoprofen)	✔	✔	✔			
Naprelan (naproxen sodium SR)	✔	✔	✔	✔	✔	• Tendonitis or bursitis • Acute gout
Naprosyn (naproxen)	✔	✔	✔	✔	✔	• Polyarticular juvenile idiopathic arthritis • Tendonitis or bursitis • Acute gout
Qmiiz ODT (meloxicam)		✔	✔			• Juvenile RA
Relafen DS (nabumetone)		✔	✔			
sulindac		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
Tivorbex (indomethacin)	✔ †					
tolmetin		✔	✔			• Juvenile RA
Vivlodex (meloxicam)			✔			
Zipsor (diclofenac potassium)	✔ †					
Zorvolex (diclofenac)	✔ †		✔			

*Indications for prescription oral suspension only†Acute pain only
‡Acute pain only, treatment limited to 5 days of total therapy
§Acute pain only, when therapy will not exceed 7 days
(*Prescribing information: Anaprox DS, EC-Naprosyn, Naprosyn 2019, Cambia 2019, Celebrex 2019, Daypro 2019, diclofenac potassium 2017, diclofenac sodium DR 2017, diclofenac sodium ER 2017, diflunisal 2016, Durlaza 2015, etodolac 2016, etodolac ER 2016, Feldene 2019, flurbiprofen 2017, ibuprofen 2019, ibuprofen suspension 2019, Indocin 2019, indomethacin ER 2019, ketoprofen 2018, ketoprofen ER 2019, ketorolac 2015, meclofenamate 2019, mefenamic*

acid 2020, Mobic 2018, nabumetone 2016, Nalfon capsule 2016, Nalfon tablet 2018, Naprelan 2019, Naprosyn 2019, Qmiiz ODT 2019, Relafen DS 2019, sulindac 2019, Tivorbex 2020, tolmetin capsule 2015, tolmetin tablet 2015, Vivlodex 2019, Zipsor 2019, Zorvolex 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Generally, the NSAID class has well-established efficacy as analgesic and anti-inflammatory medications. In addition to placebo-controlled pivotal trials for individual agents, several systematic reviews and meta-analyses have shown that NSAIDs compare favorably to placebo for pain reduction for various conditions. Most have also concluded that there is insufficient evidence that any one NSAID is more effective than any other *(Derry et al 2012, Enthoven et al 2016, Kroon et al 2015, Marjoribanks et al 2015, Wang et al 2016).*
  - A Cochrane review of NSAIDs for treatment of chronic low back pain evaluated 13 trials (N = 1354), and concluded that there is evidence that NSAIDs are more effective than placebo at reducing pain and disability. No difference in efficacy was seen between individual NSAIDs *(Enthoven et al 2016).*
  - A systematic review (N = 68 trials) of NSAID use in various types of chronic pain including OA, RA, soft-tissue pain, back pain, and AS found that there are no significant differences in pain relief between nonselective NSAIDs, partially selective NSAIDs (defined in the trial as meloxicam, nabumetone, and etodolac), and celecoxib. Comparisons between nonselective NSAIDs also found no clear differences in efficacy *(Peterson et al 2010).*
  - In a comparative effectiveness review, the Agency for Healthcare Research and Quality (AHRQ) assessed the efficacy of selective and non-selective NSAIDs, aspirin, acetaminophen, OTC supplements (chondroitin and glucosamine), and topical NSAIDs and rubefacients for treatment of OA. The review found that good evidence exists that nonselective NSAIDs do not differ significantly in efficacy for pain relief as compared to each other or to COX-2 selective NSAIDs *(Chou et al 2011).*
  - A Cochrane review including 80 trials (N = 5820) concluded that NSAIDs are a very effective treatment for primary dysmenorrhea. Insufficient evidence was found to determine if any individual NSAID is more effective than another NSAID, including comparisons between COX-2 selective and nonselective NSAIDs *(Marjoribanks et al 2015).*
  - A network meta-analysis of 26 trials (N = 3410) for treatment of pain due to AS found that there were no significant differences in efficacy between NSAIDs. Etoricoxib (an NSAID not available in the U.S.) was found to be superior to celecoxib, ketoprofen, and tenoxicam (also not available in the U.S.). No other significant differences between NSAIDs were found. All 20 evaluated NSAIDs reduced pain as compared to placebo *(Wang et al 2016).*
  - A systematic review of 39 studies (N = 4356) evaluating the use of NSAIDs for axial spondyloarthritis determined that there is high to moderate quality evidence that NSAIDs are efficacious for treatment of axial spondyloarthritis. NSAIDs were more beneficial than placebo and there was no difference in efficacy between the various evaluated NSAIDs, including COX-2 selective agents *(Kroon et al 2015).*
  - A Cochrane review of NSAIDs for treatment of acute gout including 23 trials (N = 2200) determined that while data is insufficient to draw firm conclusions, they do not conflict with guideline recommendations for the use of NSAIDs as first-line treatment. Additionally, moderate-quality evidence was found to support the claim that COX-2 selective NSAIDs and nonselective NSAIDs are probably equally beneficial *(van Durme et al 2014).*
- Comparative reviews have also been conducted evaluating the efficacy of oral NSAIDs as compared to topical NSAIDs and other non-NSAID agents for the treatment of various types of pain.
  - A Cochrane review of 34 studies (N = 7688) evaluated oral NSAIDs and topical diclofenac for treatment of OA pain. The review found that while both were significantly more effective than placebo, there appeared to be no difference in efficacy between the two treatment modalities for knee or hand OA *(Derry et al 2012).*
  - A network meta-analysis of 137 studies (N = 33,243) comparing acetaminophen, oral NSAIDs, and IA injections of corticosteroids or hyaluronic acid concluded that IA treatments were clinically superior to oral NSAIDs after 3 months of treatment. Oral NSAIDs were in turn clinically superior to acetaminophen for treatment of OA pain after the same duration of treatment *(Bannuru et al 2015).*
  - For treatment of OA, AHRQ has stated that topical and oral NSAIDs were found to have similar efficacy, although topical NSAIDS were associated with a lower risk of GI complications and a higher risk of dermatologic adverse events *(Chou et al 2011).*

- A network meta-analysis found that select NSAIDs (celecoxib, diclofenac, naproxen, and piroxicam) and opioids are similarly effective in reduction of pain for the treatment of knee OA *(Smith et al 2016).*
- A network meta-analysis comparing ibuprofen, diclofenac potassium, aspirin, and multiple triptans (including a combination of naproxen and sumatriptan) for treatment of migraine found that ibuprofen and aspirin were inferior to eletriptan and rizatriptan with respect to pain relief, but that diclofenac potassium was more effective than any other intervention for pain relief at 2 hours. However, diclofenac did have the largest rate of migraine recurrence requiring rescue therapy. Addition of naproxen to sumatriptan significantly reduced the rate of migraine recurrence as compared to sumatriptan alone. Overall tolerability was similar between the NSAIDs, which as a class was superior to that of the triptans *(Xu et al 2016).*
- A Cochrane review concluded that for primary dysmenorrhea, the NSAID class appears to be more effective than acetaminophen. However, this analysis was based on only 3 trials that compared NSAIDs with acetaminophen, and the quality of evidence was low *(Marjoribanks et al 2015).*
- A meta-analysis of 3 studies (N = 584) comparing oral prednisolone to oral NSAIDs for treatment of acute gout found similar efficacy between the agents *(Yu et al 2018)*.
- The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial evaluated the CV safety of celecoxib 100 to 200 mg twice daily compared with ibuprofen 600 to 800 mg 3 times daily and naproxen 375 to 500 mg twice daily. The randomized, multicenter, DB, noninferiority trial included 24,081 patients with increased CV risk who required NSAID therapy for OA or RA. The primary outcome measure was a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcome measures included GI and renal safety (*Nissen et al 2016*).
  - Celecoxib was noninferior to ibuprofen and naproxen with regards to CV safety. In the intent-to-treat population, a primary outcome event occurred in 2.3% of the celecoxib group, 2.5% of the naproxen group, and 2.7% of the ibuprofen group (hazard ratio [HR], 0.93 vs naproxen; HR, 0.85 vs ibuprofen; $p < 0.001$ for noninferiority to both).
  - Celecoxib was associated with a lower incidence of GI AEs compared to naproxen ($p = 0.01$) and ibuprofen ($p = 0.002$).
  - Celecoxib was also associated with a significantly lower incidence of renal AEs compared with ibuprofen ($p = 0.004$). Statistical significance was not reached when compared with naproxen ($p = 0.19$).

- Studies were conducted evaluating the efficacy of Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) as compared to placebo. All 3 products were found to be superior to placebo for the treatment of pain in individual randomized controlled trials. Studies were not conducted comparing efficacy or safety of these products vs existing higher-dose generic formulations of indomethacin, meloxicam, or diclofenac. Systemic exposure of Tivorbex, Vivlodex, and Zorvolex has not been shown to be equivalent to other formulations of oral indomethacin, meloxicam, and diclofenac, respectively.
- Qmiiz ODT (meloxicam) is an orally disintegrating tablet (ODT) that was approved based on a single-dose pharmacokinetic study that established equivalence between the 15 mg ODT tablet and meloxicam (Mobic) 15 mg tablet (*Radicioni et al 2013*).
- Several large systematic reviews and meta-analyses have analyzed the risk of adverse events with use of NSAIDs, including comparisons between the nonselective NSAIDs and between nonselective and COX-2 selective NSAIDs.
  - A large meta-analysis of 280 trials (N = 124,513) evaluating the CV and GI risk of various NSAIDs concluded that the vascular risk of high-dose diclofenac (150 mg daily or greater) and possibly ibuprofen are comparable to that of COX-2 selective NSAIDs. By contrast, high-dose naproxen (100 mg daily or greater) is associated with less vascular risk than other NSAIDs. All NSAIDs increased risk of upper GI complications by a factor of 2 to 4, although the lowest incidence was seen with COX-2 selective NSAIDs. None of the evaluated NSAIDs were found to increase risk of stroke *(Coxib and traditional NSAID Trialists' [CNT] Collaboration 2013).*
  - A Bayesian meta-analysis of MI risk with NSAID use in a cohort of 446,763 individuals found that all NSAIDs, including naproxen and celecoxib, were associated with an increased risk of acute MI. Risk was greatest with use of higher doses as well as during the first month of NSAID use. Risk did not appear to increase beyond the first 30 days of use *(Bally et al 2017).*
  - A comparative effectiveness review found that there were important safety differences among different NSAIDs with selective NSAIDs (ie, celecoxib) associated with a lower risk for GI complications and a higher risk for CV complications compared to non-selective NSAIDs. Additionally, meloxicam was associated with a lower risk of ulcer complications compared to other non-selective NSAIDs *(Chou et al 2011).*

CLINICAL GUIDELINES

- **RA:** The American College of Rheumatology (ACR) guideline does not address the role of analgesics in management of RA. Treatment of RA is guided by a treat to target approach using DMARD therapy. Analgesics, including NSAIDs, have a limited role in most patients with active disease, but may be considered as a temporary adjunctive option (*Moreland et al 2020, Singh et al 2015*).
- **OA:** The ACR strongly recommends the use of oral NSAIDs as a class for the treatment of hand, hip, and knee OA. However, topical NSAIDs should be considered prior to use of oral NSAIDs for OA of the knee (strongly recommended) or hand (conditionally recommended); topical administration of NSAIDs for hip OA is unlikely to be of benefit. The guidance notes the relative differences between NSAIDs were not considered, but clinicians should consider that certain NSAIDs may have a more favorable adverse effect profile. Additional strongly or conditionally pharmacologic recommendations include IA glucocorticoid injections, acetaminophen, duloxetine, topical capsaicin, and tramadol *(Kolasinski et al 2020).*
  - Doses of oral NSAIDs should be as low as possible and continued for as short of time as possible.
- **Primary dysmenorrhea:** Based upon a Cochrane review of 73 randomized controlled trials, the American Academy of Family Physicians recommends oral NSAIDs as first-line treatment for primary dysmenorrhea. Specifically, guidelines support the use of celecoxib, ibuprofen, mefenamic acid, and naproxen. Choice of NSAID should be based on individual patient characteristics as no NSAID has been shown to be more effective than any other. Treatment initiation is recommended 1 to 2 days before expected onset of menses, with treatment duration of 2 to 3 days *(Osayande et al 2014).* Additionally, the American College of Obstetricians and Gynecologists also recommends that NSAIDs should be a first line treatment for management of primary dysmenorrhea in adolescents *(ACOG 2018).*
- **AS:** A joint guideline by the ACR, Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network strongly recommends treatment of active AS with oral NSAIDs. Additionally, a conditional recommendation was provided for continuous treatment with NSAIDs over on-demand treatment. As no formal comparative effectiveness studies of NSAIDs were available, the guideline recommended against designating any particular NSAID as the preferred treatment option. Instead, choice of NSAID should be determined by each patient's history, risk factors, and comorbidities *(Ward et al 2016, Ward et al 2019).*
- **JIA:** ACR recommendations for JIA include initiation of NSAID monotherapy in patients without prior treatment for a maximum of 1 month. The guideline specifically states that continuation of NSAID monotherapy for longer than 2 months in patients with continued disease activity is inappropriate. Both recommendations were based on expert opinion *(Ringold et al 2013).* Updated recommendations for certain populations with JIA are available and recommendations for NSAIDs are specific to each population *(Ringold et al 2019)*:
  - Updated recommendations for patients with JIA and polyarthritis include a conditional recommendation for adjunct therapy with NSAIDs, largely for symptom management, particularly during initiation or escalation of therapy with DMARDs or biologics. Initial therapy with a DMARD is strongly recommended over NSAID monotherapy.
  - For those with active sacroiliitis, treatment with a NSAID is strongly recommended for initial therapy, with addition of a TNF inhibitor for those with active disease despite NSAID treatment. Patients with active enthesitis should also be offered NSAID therapy initially, with TNF inhibitors, methotrexate, and sulfasalazine as add-on options for those without an adequate response.
- **Acute migraine:** The American Headache Society guidelines for acute treatment of migraine include various degrees of recommendations for use of oral NSAIDs depending on the specific agent. Aspirin, diclofenac, ibuprofen, and naproxen are recommended as having established efficacy. Additional NSAIDs including flurbiprofen and ketoprofen are recommended as probably effective, while celecoxib was deemed to have conflicting or inadequate evidence to support or refute use (*Marmura et al 2015).* For children and adolescents with migraine, ibuprofen (oral solution, 7.5 to 10 mg/kg), acetaminophen, and triptans (primarily adolescents) have supportive evidence for use in acute migraine to relieve pain *(Oskoui et al 2019).*
- **Gout:** Oral NSAIDs are recommended both by the ACR and the American College of Physicians as an appropriate treatment option for acute gout, though the ACP guidance recommends corticosteroids over NSAIDs in patients without contraindications due to their more favorable adverse effect profile. Neither guideline found clinically important differences between NSAIDs and did not recommend any specific NSAID over the others *(Khanna et al 2012, Qaseem et al 2017).*
  - The ACR also supports use of low-dose NSAID therapy as an appropriate first-line method of prophylaxis for acute gout attacks.
  - No consensus was reached on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

SAFETY SUMMARY

- **Boxed warnings:**
  - All oral NSAID products with the exception of Durlaza (aspirin ER) share the 2 boxed warnings below for CV and GI risk:
    - Serious CV thrombotic events: NSAIDs cause an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. NSAIDs are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
    - Serious GI bleeding, ulcerations and perforation: NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
  - Ketorolac carries additional boxed warnings for the following:
    - Renal risk: Ketorolac is contraindicated in patients with advanced renal function impairment and in patients at risk for renal failure due to volume depletion.
    - Risk of bleeding: Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and in those at high risk of bleeding. Ketorolac is contraindicated as a prophylactic analgesic before any major surgery.
    - Risk during labor and delivery: The use of ketorolac tromethamine in labor and delivery is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions.
    - Concomitant use with NSAIDs: Ketorolac is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related side effects.
    - Special populations: Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine.
- **Contraindications:**
  - Most oral NSAID products share a contraindication for use in the setting of CABG surgery, as well as in patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Additional contraindications specific to individual compounds are listed below.
  - Celebrex (celecoxib)
    - History of allergic-type reactions to sulfonamides
  - Fenoprofen (Profeno only):
    - History of significantly impaired renal function
  - Meloxicam (Qmiiz ODT only):
    - Patients with phenylketonuria
  - Ketorolac:
    - Active or history of peptic ulcer disease; recent or history of GI bleeding or perforation
    - Prophylactic analgesic before any major surgery
    - Advanced renal impairment or patients at risk for renal failure because of volume depletion
    - Labor and delivery
    - Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding
    - Patients currently receiving aspirin or NSAIDs
    - Concomitant use with probenecid or pentoxifylline.
- **Warnings and precautions:**
  - Most oral NSAID products share similar warnings and precautions for:
    - Increased risk of CV thrombotic events
    - New onset or worsening of hypertension
    - Increased risk of hospitalization due to heart failure and increased edema
    - Risk of GI effects including ulceration, bleeding, and perforation
    - Risk of renal injury and toxicity
    - Potential for skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
    - Risk of premature closure of the ductus arteriosus when used in late pregnancy
    - Borderline elevations of one or more liver tests

- Potential for anemia
- Risk of severe bronchospasm in patients with preexisting aspirin-sensitive asthma
- Risk of Reye's syndrome

○ Ketorolac:

- The total combined duration of use of ketorolac tromethamine tablets and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in pediatric patients.

- **Adverse events:**
  - Adverse events were similar among products and commonly included GI complaints (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, gastric/duodenal GI ulcers, and vomiting), abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Anaprox DS (naproxen sodium)	Tablets	Oral	Twice daily
Cambia (diclofenac potassium)	Powder for oral solution	Oral	Once as needed
Celebrex (celecoxib)	Capsules	Oral	Once to twice daily
Daypro (oxaprozin)	Tablets	Oral	Once daily
diclofenac	Capsules	Oral	Two to four times daily
diclofenac potassium	Tablets	Oral	Two to four times daily
diclofenac sodium DR	Tablets	Oral	Two to four times daily
diclofenac sodium ER	Tablets	Oral	Once daily
diflunisal	Tablets	Oral	Two to three times daily
Durlaza (aspirin ER)	Capsules	Oral	Once daily
EC-Naprosyn (naproxen DR)	Tablets	Oral	Twice daily
etodolac	Capsules	Oral	Two to four times daily
etodolac ER	Tablets	Oral	Once daily
Feldene (piroxicam)	Capsules	Oral	Once daily
flurbiprofen	Tablets	Oral	Two to four times daily
ibuprofen	Capsules, Suspension, Tablets, Chewable tablets	Oral	Three to six times daily
Indocin (indomethacin)	Capsules, Suspension	Oral	Two to four times daily
indomethacin ER	Capsules	Oral	Once to twice daily
ketoprofen	Capsules	Oral	Three to four times daily
ketoprofen ER	Capsules	Oral	Once daily
ketorolac	Tablets	Oral	Four to six times daily
Lodine (etodolac)	Tablets	Oral	Two to four times daily
Meclofen (meclofenamate)	Capsules	Oral	Three to four times daily
Mefenam (mefenamic acid)	Capsules	Oral	Four times daily
Mobic (meloxicam)	Tablets	Oral	Once daily
nabumetone	Tablets	Oral	Once to twice daily
Nalfon (fenoprofen)	Capsules, Tablets	Oral	Three to four times daily
Naprelan (naproxen sodium SR)	Tablets	Oral	Once daily
Naprosyn (naproxen)	Suspension, Tablets	Oral	Twice daily
Qmiiz ODT (meloxicam)	Orally disintegrating tablets	Oral	Once daily

Drug	Available Formulations	Route	Usual Recommended Frequency
Relafen DS (nabumetone)	Tablets	Oral	Once to twice daily
sulindac	Tablets	Oral	Twice daily
Tivorbex (indomethacin)	Capsules	Oral	Two to three times daily
tolmetin	Capsules, Tablets	Oral	Three times daily
Vivlodex (meloxicam)	Capsules	Oral	Once daily
Zipsor (diclofenac potassium)	Capsules	Oral	Four times daily
Zorvolex (diclofenac)	Capsules	Oral	Three times daily

See the current prescribing information for full details

CONCLUSION

- Oral NSAIDs are efficacious for the treatment of pain, RA, OA, primary dysmenorrhea, AS, acute migraine, and acute gout. Multiple systematic reviews and meta-analyses have shown that NSAIDs are superior to placebo for these indications. Furthermore, practice guidelines for most of these conditions recommend NSAIDs as a first-line treatment option.
- The totality of currently available evidence on relative efficacy between the available NSAIDs suggests that in general, there does not appear to be a significant difference in efficacy among the NSAIDs. Clinical practice guidelines for the aforementioned conditions support this finding and either recommend the use of NSAIDs as a class or recommend a list of NSAIDs for potential use without specifying a preference between listed agents.
- All NSAIDs carry some degree of risk for adverse events including CV thrombotic events and GI bleeding, ulceration, and perforation. Available evidence for the relative risk of these adverse events amongst NSAIDs is conflicting and inconclusive at this time. All reviewed NSAIDs with the exception of Durlaza (aspirin ER) carry the same boxed warnings for CV and GI risk. Contraindications, warnings/precautions, and adverse effects are similar among products.
- Differences between oral NSAIDs include FDA-labeled indications, available dosage formulations and strengths, and dosing frequency.

REFERENCES

- ACOG Committee Opinion No. 760: Dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol*. 2018;132(6):e249-e258. doi: 10.1097/AOG.0000000000002978.
- Anaprox DS, EC-Naprosyn, Naprosyn [package insert], South San Francisco, CA: Genentech USA, Inc.; July 2019.
- Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ.* 2017;357:j1909.
- Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med.* 2015;162:46-54.
- Cambia [package insert], Lake Forest, IL: Assertio Therapeutics; September 2019.
- Celebrex [package insert]. Pfizer: New York, NY; May 2019.
- Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int.* 2012; 32(6):1491-1502.
- Chou R, McDonagh MS, Nakamoto E, et al. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. *AHRQ Comparative Effectiveness Reviews.* 2011. Available at: https://www.ncbi.nlm.nih.gov/books/NBK65646/ Accessed January 27, 2020.
- Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382:769-79.
- Davis JS, Lee HY, Kim J, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart.* 2017;4(1):e000550.
- Daypro [package insert], New York, NY: Pfizer Inc.; May 2019.
- Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2012;9:CD007400.
- Diclofenac potassium [package insert], Morgantown, WV: Mylan Pharmaceuticals, Inc.; August 2017.
- Diclofenac sodium delayed release [package insert], Elizabeth, NJ: Actavis Pharma, Inc.; October 2017.
- Diclofenac sodium extended release [package insert], Morgantown, WV: Mylan Pharmaceuticals, Inc.; October 2016.
- Diflunisal [package insert], Pennington, NJ: Zydus Pharmaceuticals Inc.; May 2016.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 27, 2020.
- Durlaza [package insert], North Haven, CT: New Haven Pharmaceuticals, Inc.; September 2015.
- Enthoven WT, Roelofs PD, Deyo RA, et al. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev.* 2016;10;2:CD012087

- Etodolac extended release [package insert], Hawthorne, NY: Taro Pharmaceuticals U.S.A., Inc.; April 2016.
- Etodolac [package insert], Baudette, MN: ANI Pharmaceuticals Inc.; November 2016.
- FDA Drug Safety Communication. Food and Drug Administration Web site. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm429364.htm. Accessed January 27, 2020.
- FDA Drug Safety Communication. Food and Drug Administration Web site. https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm?source=govdelivery. Accessed January 27, 2020.
- Feldene [package insert], New York, NY: Pfizer Inc.; May 2019.
- Flurbiprofen [package insert], North Wales, PA: Teva Pharmaceuticals U.S.A., Inc.; June 2017.
- Grom AA. Juvenile idiopathic arthritis: epidemiology and immunopathogenesis. UpToDate Web site. www.uptodate.com. Updated March 12, 2018. Accessed January 27, 2020.
- Ibuprofen [package insert], Bridgewater, NJ: Amneal Pharmaceuticals LLC; March 2019.
- Ibuprofen suspension [package insert], Parsippany, NJ: Actavis Pharma, Inc; March 2019.
- Indocin [package insert], Wayne, PA: Egalet Corporation; April 2019.
- Indomethacin extended release [package insert], Bridgewater NJ: Amneal Pharmaceuticals LLC; September 2019.
- Ketoprofen [package insert], East Brunswick, NJ: Heritage Pharmaceuticals Inc; May 2018.
- Ketoprofen extended release [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; June 2019.
- Ketorolac tromethamine tablet [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; July 2015.
- Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447-61.
- Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2020 Jan 6. doi: 10.1002/acr.24131. [Epub ahead of print]
- Kroon FP, van der Burg LR, Ramiro S, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). *Cochrane Database Syst Rev*. 2015;7:CD010952.
- Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2015;7:CD001751.
- Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3-20.
- Meclofenamate sodium [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; September 2019.
- Mefenamic acid [package insert], Basking Ridge, NJ: Micro Labs USA Inc.; January 2020.
- Mobic [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2018.
- Moreland LW, Cannella A. General principles of management of rheumatoid arthritis in adults. UpToDate Web site. www.uptodate.com. Updated January 21, 2020. Accessed January 27, 2020.
- Nabumetone [package insert], Princeton, NJ: Sandoz Inc.; September 2016.
- Nalfon capsule [package insert], Ridgeland, MS: Xspire Pharma; April 2016.
- Nalfon tablet [package insert], Ridgeland, MS: Xspire Pharma; September 2018.
- Naprelan [package insert], Morristown, NJ: Almatica Pharma Inc.; July 2019.
- Naprosyn suspension [package insert], Athens, GA: Athena Bioscience; July 2019.
- Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med*. 2016 Dec 29;375(26):2519-29.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 27, 2020.
- Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. *Am Fam Physician*. 2014;89(5):341-6.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019;93(11):487-499. doi: 10.1212/WNL.0000000000008095.
- Peterson K, McDonagh M, Thakurta S, et al. Drug Class Review: Nonsteroidal Antiinflammatory Drugs (NSAIDs): Final Update 4 Report [Internet]. Portland (OR): Oregon Health & Science University; 2010. Drug Class Reviews.
- Qmiiz ODT [package insert], Lake Forest IL: TerSera Therapeutics LLC; July 2019.
- Radicioni M, Connolly S, Stroppolo F, et al. Bioequivalence study of a novel orodispersible tablet of meloxicam in a porous matrix after single-dose administration in healthy volunteers. *Int J Clin Pharmacol Ther*. 2013;51(3):234-243. doi: 10.5414/CP201781.
- Relafen DS [package insert], Hazlet NJ: Carwin Pharmaceutical Associates, LLC; September 2019.
- Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):717-734. doi: 10.1002/acr.23870.
- Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013;65(10):2499-512.
- Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016;68(1):1-26.
- Smith SR, Deshpande BR, Collins JE, et al. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthr. Cartil.* 2016;24(6)962-72.
- Solomon DH. NSAIDs: pharmacology and mechanism of action. UpToDate Web site. www.uptodate.com. Updated August 19, 2019. Accessed January 27, 2020.
- Sulindac [package insert], Parsippany, NJ: Actavis Pharma, Inc.; July 2019.
- Tivorbex [package insert], Madisonville, LA: Basiem, LLC; January 2020.

- Tolmetin capsule [package insert], Cranbury, NJ: Morgantown, WV: Mylan Pharmaceuticals, Inc.; July 2015.
- Tolmetin tablet [package insert], Cranbury, NJ: Morgantown, WV: Mylan Pharmaceuticals, Inc.; July 2015.
- van Durme CM, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RB. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;9:CD010120.
- Vivlodex [package insert], Wayne, PA: Egalet US Inc, April 2019.
- Wang R, Dasgupta A, Ward MM. Comparative efficacy of non-steroidal anti-inflammatory drugs in ankylosing spondylitis: a Bayesian network meta-analysis of clinical trials. *Ann Rheum Dis*. 2016:75(6)1152-60.
- Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2016; 68(2);282-98.
- Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613. doi: 10.1002/art.41042.
- Xu H, Han W, Wang, et al. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. *J Headache Pain.* 2016;17(1):113.
- Yu J, Lu H, Zhou J, et al. Oral prednisolone versus non-steroidal anti-inflammatory drugs in the treatment of acute gout: a meta-analysis of randomized controlled trials. *Inflammopharmacology*. 2018;26(3):717-723. doi: 10.1007/s10787-018-0442-8.
- Zipsor [package insert], Newark, CA: Depomed, Inc.; May 2019.
- Zorvolex [package insert], Philadelphia, PA: Iroko Pharmaceuticals, LLC; May 2016.

Publication Date: March 9, 2020