Therapeutic Class Overview
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Therapeutic Class Overview/Summary:
This review encompasses the single-entity oral and injectable nonsteroidal anti-inflammatory drugs (NSAIDs).[1-37] NSAIDs are among the most commonly prescribed drugs worldwide to treat common pain and inflammatory conditions.[38] Some of the conditions NSAIDS have been Food and Drug Administration (FDA)-approved to treat include acute pain and inflammation, osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), painful shoulder (bursitis and/or tendonitis), acute gouty arthritis, and postoperative pain. Additionally several agents are indicated for the treatment of primary dysmenorrhea, clinically significant patent ductus arterioles, or fever reduction. Each year, approximately 60 million NSAID prescriptions are written, with the number of prescriptions for older patients approximately 3.6-fold higher than that for younger patients. NSAIDs have been prescribed for decades and a number are available generically and/or over-the-counter.[38] Salicylates, over-the-counter formulations of ibuprofen and naproxen, any topical and ophthalmic preparations of NSAIDs or combination products will not be included in this review. A list of medications reviewed is summarized in Table 1 and includes various salt formulations for the NSAIDs.

The primary mechanism of action of all NSAIDs is through the inhibition of cyclooxygenase (COX), resulting in impaired transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes.[39] The COX enzyme can be subdivided into related isoforms, including COX-1 and COX-2; however, important differences in the regulation and expression of these two enzymes in various tissues exist which are relevant to the mechanism of action of NSAIDs and their associated adverse effect profile. Specifically, the COX-2 enzyme is typically undetectable in most tissue except during states of inflammation; therefore, the anti-inflammatory properties of NSAIDs are associated with the inhibition of COX-2.[39] In contrast, COX-1 is expressed variably in most tissues and regulates normal cell processes including gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. The inhibition of COX-1 by NSAIDs is thought to be associated with the well-established gastrointestinal adverse reaction profile of these agents, which includes dyspepsia, peptic ulcer disease and bleeding.[40]

All NSAID-containing agents are associated with a Black Box Warning regarding the increased risk of serious gastrointestinal adverse reactions including bleeding, ulceration and perforation of the stomach and intestines, which can be fatal.[1-37] Additionally, ketorolac tromethamine, a potent NSAID, is also contraindicated in renal impairment, patients at risk of bleeding (i.e., before surgery), and during labor, delivery, breast-feeding and coadministration with other NSAIDs.[15-17] Due to these risks, ketorolac should only be administered for acute pain (≤5 days).[15-17]

NSAIDs have traditionally been grouped by their chemical characteristics. Currently available products have been derived from acetic acid, anthranilic acid, enolic acid, or propionic acid. However, with the development of products selective to COX-2, classification has begun to shift towards selectivity, rather than chemical structure.[41] There is only one selective COX-2 inhibitor currently available, celecoxib (Celebrex®). In addition, recent evidence suggests that some of the older NSAIDs such as diclofenac and meloxicam show some selectivity towards the COX-2 enzyme.[41] Due to the variability in NSAID half-life ($t_{1/2}$), a classification system has also been developed to group NSAIDs by half-life. Some NSAIDs such as ibuprofen and diclofenac are eliminated rapidly ($t_{1/2}$ of one to four hours), while other agents have a much greater half-life. Agents with $t_{1/2}$ greater than 10 hours include: celecoxib, naproxen, meloxicam, nabumetone, oxaprozin and piroxicam. Piroxicam has an estimated $t_{1/2}$ of 50 hours.[41-43] Agents with longer half-lives are generally given once per day.

Table 1. Current Medications Available in the Therapeutic Class[1-34]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Acetic Acid Derivatives			
Diclofenac (Zorvolex®)	Mild to Moderate Pain, Osteoarthritis	Capsule: 18 mg 35 mg	-
Diclofenac potassium (Cataflam®*, Zipsor®)	Acute Pain, Mild to Moderate Pain, Primary Dysmenorrhea, Osteoarthritis, Rheumatoid Arthritis	Capsule, liquid filled (Zipsor®): 25 mg Tablet, sugar coated (Cataflam®): 50 mg	a
Diclofenac sodium* (Dyloject®, Voltaren XR®*)	Acute Pain, Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis	Tablet, DR: 25 mg 50 mg 75 mg Tablet, film coated ER (Voltaren XR®): 100 mg Solution, injection (Dyloject®) 37.5 mg/mL	a
Etodolac*	Acute Pain, Osteoarthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis (age six and older)	Capsule: 200 mg 300 mg Tablet, ER: 400 mg 500 mg 600 mg Tablet, film coated: 400 mg 500 mg	a
Indomethacin* (Indocin®, Tivorbex®)	Acute Pain, Acute Gouty Arthritis, Acute Shoulder Pain, Ankylosing Spondylitis, Rheumatoid Arthritis, Osteoarthritis	Capsule: 20 mg (Tivorbex®) 25 mg 40 mg (Tivorbex®) 50 mg Capsule, ER: 75 mg Suppository: 50 mg (Indocin®) Suspension, oral: 25 mg/5 mL (Indocin®)	a
Indomethacin sodium	Closure of Patent Ductus Arteriosus (Neonatal patients)	Solution, lyophilized powder for injection: 1 mg/vial	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ketorolac tromethamine* (Sprix®)	Moderate to severe acute pain:	Nasal Spray, metered: 15.75 mg/spray Solution, injection (vial): 15 mg/mL 30 mg/mL 60 mg/2 mL 300 mg/10 mL Tablet, film coated: 10 mg	a
Nabumetone*	Osteoarthritis, Rheumatoid Arthritis	Tablet: 500 mg 750 mg	a
Sulindac*	Acute Gouty Arthritis, Acute Shoulder Pain, Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis	Tablet: 150 mg 200 mg	a
Tolmetin sodium*	Osteoarthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis (age 2 or older)	Capsule: 400 mg Tablet: 200 mg 600 mg	a
Anthranilic Acid (Fenamate) Derivatives			
Meclofenamate sodium	Fever Reduction, Mild to moderate pain, Primary dysmenorrhea, Rheumatoid arthritis, osteoarthritis	Capsule: 50 mg 100 mg	-
Mefenamic acid (Ponstel®*)	Mild to moderate pain, Primary dysmenorrhea	Capsule: 250 mg	a
Enolic Acid Derivatives			
Meloxicam (Mobic®*, Vivlodex®)	Osteoarthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis (age 2 and older)	Capsule (Vivlodex®): 5 mg 10 mg Suspension, oral (Mobic®): 7.5 mg/5 mL Tablet (Mobic®): 7.5 mg 15 mg	a
Piroxicam (Feldene®*)	Osteoarthritis, Rheumatoid Arthritis	Capsule: 10 mg 20 mg	a
Propionic Acid Derivatives			
Fenoprofen calcium* (Nalfon®*)	Mild to Moderate Pain, Osteoarthritis, Rheumatoid Arthritis	Capsule: 200 mg 400 mg Tablet, film coated:	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		600 mg	
Flurbiprofen*	Osteoarthritis, Rheumatoid Arthritis	Tablet: 50 mg 100 mg	a
Ibuprofen* (Caldolor®)	Fever Reduction, Mild to Moderate Pain, Moderate to Severe Pain, Osteoarthritis, Rheumatoid Arthritis, Primary Dysmenorrhea:	Injection (Caldolor®): 400 mg/mL 800 mg/mL Tablet, film coated: 400 mg 600 mg 800 mg	a
Ibuprofen Lysine (Neoprofen®)	Closure of Patent Ductus Arteriosus (Neonatal patients)	Solution, injection: 10 mg/mL	-
Ketoprofen*	Acute Pain, Primary Dysmenorrhea, Osteoarthritis, Rheumatoid Arthritis	Capsule: 50 mg 75 mg	a
Naproxen (EC-Naprosyn®*, Naprosyn®*)	Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis, Acute Gouty Arthritis, Juvenile rheumatoid arthritis (5 years of age and older)	DR Tablet (EC-Naprosyn®): 375 mg Suspension, oral: 125 mg/5 mL Tablet (Naprosyn®): 250 mg 375 mg 500 mg	a
Naproxen sodium (Anaprox®*, Anaprox DS®*, Naprelan®*)	Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis, Acute Gouty Arthritis, Acute Pain, Acute Shoulder Pain, Primary Dysmenorrhea	Tablet: 275 mg (Anaprox®) 550 mg (Anaprox DS®) ER tablet: 375 mg 500 mg 750 mg	a
Oxaprozin (Daypro®*)	Osteoarthritis, Rheumatoid arthritis, Juvenile Rheumatoid Arthritis (6 years of age and older)	Tablet: 600 mg	a
Selective COX-2 Inhibitors			
Celecoxib (Celebrex®*)	Acute Pain, Primary Dysmenorrhea, Juvenile Rheumatoid Arthritis (2 years of age and older)	Capsule: 50 mg 100 mg 200 mg 400 mg	a

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated NSAIDs to be more efficacious compared to placebo in the treatment of pain and inflammatory conditions. Although there are many head to head trials comparing various NSAIDs, there is no single agent that has been continuously found to be more efficacious or safe than the others.[44-75]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[76-82]
  - Although the efficacy of NSAIDs appears to be similar at equipotent doses, there is a wide variability of response between individual patients, which is believed to be associated with non-prostaglandin-mediated NSAID-induced mechanisms of action.
  - It is suggested that if a patient fails an NSAID of one class, an NSAID from a different class may be effective and is a reasonable option.[38]
- Other Key Facts:
  - There are many generic and over-the-counter (OTC) NSAIDs available.
  - In recent years, newer formulations of NSAIDs have been developed. Recently approved products include: enteric-coated tablets, liquid filled capsules, nasal spray, suppositories, oral suspensions, and injections.
  - Several NSAIDs have recently been formulated using the SoluMatrix Fine Particle Technology™.[83]
    - SoluMatrix™ is a patented dry milling technology, which grinds the drug particles into a superfine powder and protects those submicron particles from subsequent agglomeration (clumping together into big particles).
    - SoluMatrix Fine Particle Technology™ produces NSAIDs as submicron particles that are approximately 20 times smaller than their original size.
    - The reduction in particle size provides an increased surface area, leading to faster dissolution.
    - It may also allow the NSAID to be given at a lower dose than a standard-formulation.
    - Products currently approved that utilize the SoluMatrix™ technology include Zorvolex® (diclofenac capsules), Tivorbex® (indomethacin capsules), and Vivlodex® (meloxicam capsules).[83]

References

1. Zorvolex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2014 Aug.
2. Zipsor® [package insert]. Newark (CA); Depomed, Inc.; 2015 Aug.
3. Cataflam® [package insert]. East Hanover (NJ); Novartis Pharmaceuticals Corp.; 2011 Feb.
4. Diclofenac sodium delayed release tablets, diclofenac sodium tablets [package insert]. Columbus (OH); Boehringer Ingelheim Roxane Laboratories; Aug 2006.
5. Dyloject® [package insert]. Lake Forest (IL); Hospira, Inc.; 2014 Dec.
6. Voltaren XR® [package insert]. East Hanover (NJ); Novartis Pharmaceuticals Corp.; 2011 Feb.
7. Etodolac capsule, etodolac film coated tablet [package insert]. Hawthorne (NY); Taro Pharmaceuticals U.S.A., Inc.; 2015 Dec.
8. Etodolac extended release tablet [package insert]. Hawthorne (NY); Taro Pharmaceuticals U.S.A., Inc.; 2015 Aug.
9. Tivorbex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2014 Feb.
10. Indomethacin capsule [package insert]. Piscataway (NJ); Camber Pharmaceuticals, Inc.; 2011 Oct.
11. Indomethacin extended release capsule [package insert]. Piscataway (NJ); Camber Pharmaceuticals, Inc.; 2011 Oct.
12. Indocin® (indomethacin suspension) [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2010 Jan.
13. Indocin® (indomethacin suppository) [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2015 Jul.
14. Indomethacin lyophilized powder for solution injection [package insert]. Lake Zurich (IL); Fresenius Kabi USA, LLC; 2013 Nov.
15. Ketorolac tromethamine film coated tablet [package insert]. Morgantown (WV; Mylan Pharmaceuticals Inc.; 2015 Jul.
16. Ketorolac tromethamine injection solution [package insert]. Schaumburg (IL)SAGENT Pharmaceuticals; 2015 Jul.
17. Sprix® [package insert]. Wayne (PA); Egalet US Inc.; 2015 Jun.
18. Nabumetone tablet [package insert]. Princeton (NJ); Sandoz Inc.; 2015 Jul.
19. Sulindac tablet [package insert]. Laurelton (NY); Epic Pharma, LLC; 2015 Jul.
20. Tolmetin sodium capsule, tolmetin sodium tablet [package insert]. Cranbury (NJ); Sun Pharmaceutical Industries, Inc.; 2015 Feb.
21. Meclofenamate sodium capsule [package insert]. Morgantown (WV); Mylan Pharmaceuticals Inc.; 2015 Jul.
22. Ponstel® [package insert]. Florham Park (NJ); Shionogi Inc.; May 2013.
23. Vivlodex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2015 Oct.
24. Mobic® (meloxicam suspension), Mobic® (meloxicam tablet) [package insert]. Ridgefield (CT). Boehringer Ingelheim Pharmaceuticals, Inc.; 2012 Mar.
25. Feldene® [package insert]. New York (NY); Pfizer Inc.; 2015 Feb.
26. Nalfon® [package insert]. Ridgeland (MS); Xspire Pharma; 2012 Sept.
27. Fenoprofen calcium film coated tablet [package insert]. Morgantown (WV); Mylan Pharmaceuticals Inc.; 2015 Jul.
28. Flurbiprofen tablet [package insert]. Detroit (MI); Caraco Pharmaceutical Laboratories, LTC.; 2007 Aug.
29. Ibuprofen film coated tablet [package insert]. Princeton (NJ); Dr. Reddy's Laboratories, Inc.; 2007 Mar.
30. Caldolor® [package insert]. Nashville (TN); Cumberland Pharmaceuticals Inc.; 2015 Nov.
31. Neoprofen® [package insert]. Lebanon (NJ); Recordati Rare Diseases Inc.; 2013 Dec.
32. Ketoprofen capsule [package insert]. North Wales (PA); TEVA Pharmaceuticals USA, Inc.; 2015 Jul.

33. Naprosyn® (naproxen tablet), EC-Naprosyn® (naproxen delayed release tablet), Naprosyn® (napoxen suspension), Anaprox® (naproxen sodium tablet), Anaprox DS® (naproxen sodium tablet) [package insert]. South San Francisco (CA); Genentech USA, Inc.; 2013 Mar.
34. Naproxen suspension [package insert]. Greenville (SC); Palmetto Pharmaceuticals; 2013 May.
35. Naprelan® [package insert]. San Diego (CA); Victory Pharma, Inc.; 2009 Aug.
36. Daypro® [package insert]. New York (NY); G.D. Searle LLC Division of Pfizer Inc.; 2012 Dec.
37. Celebrex® [package insert]. New York (NY); G.D. Searle LLC Division of Pfizer Inc.; 2012 Dec.
38. Solomon DH. NSAIDs: Therapeutic use and variability of response in adults. In: Romain PL, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
39. Solomon DH. NSAIDs: mechanism of action. In: Romain PL (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2015 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
40. Feldman M. NSAIDs (including aspirin): pathogenesis of gastroduodenal toxicity. In: Grover S (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
41. Grosser T, Smyth E, FitzGerald GA. Chapter 34: Anti-inflammatory, Antipyretic, and Analgesic Agents; Pharmacotherapy of Gout. In: Brunton LL, Chabner BA, Knollmann BC (Eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011 [cited 2016 Jan 12]. Available from: http://accesspharmacy.mhmedical.com/.
42. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016 [cited 2016 Jan 12]. Available from: URL: http://www.clinicalpharmacology.com.
43. Micromedex® 2.0, (electronic version). Greenwood Village, CO: Truven Health Analytics; 2016 [citied 2016 Jan 12]. Available from: http://www.micromedexsolutions.com/.
44. Riff DS, Duckor S, Gottlieb I, Diamond E, Soulier S, Raymond G, et al. Diclofenac potassium liquid-filled soft gelatin capsules in the management of patients with postbunionectomy pain: a Phase III, multicenter, randomized, double-blind, placebo-controlled study conducted over 5 days. Clin Ther. 2009 Oct;31(10):2072-85. doi: 10.1016/j.clinthera.2009.09.011.
45. Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. Pain Med. 2009 Sep;10(6):1106-14. doi: 10.1111/j.1526-4637.2009.00647.x. Epub 2009 Jul 6.
46. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. Curr Med Res Opin. 2010 Aug;26(8):1915-23. doi: 10.1185/03007995.2010.495564.
47. Gan TJ, Daniels SE, Singla N, Hamilton DA, Carr DB. A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: a multicenter, double-blind, randomized, multiple-dose study. Anesth Analg. 2012 Nov;115(5):1212-20. doi: 10.1213/ANE.0b013e3182691bf9. Epub 2012 Aug 10.
48. Daniels S, Melson T, Hamilton DA, Lang E, Carr DB. Analgesic efficacy and safety of a novel injectable formulation of diclofenac compared with intravenous ketorolac and placebo after orthopedic surgery: a multicenter, randomized, double-blinded, multiple-dose trial. Clin J Pain. 2013 Aug;29(8):655-63. doi: 10.1097/AJP.0b013e318270f957.
49. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol. 2009 Mar;26(3):235-45. doi: 10.1055/s-0028-1103515. Epub 2008 Dec 9.
50. Kroll PB, Meadows L, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. Pain Pract. 2011 Jan-Feb;11(1):23-32. doi: 10.1111/j.1533-2500.2010.00402.x.
51. Southworth S1, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. Clin Ther. 2009 Sep;31(9):1922-35. doi: 10.1016/j.clinthera.2009.08.026.
52. Gibofsky A, Silberstein S, Argoff C, Daniels S, Jensen S, Young CL. Lower-dose diclofenac submicron particle capsules provide early and sustained acute patient pain relief in a phase 3 study. Postgrad Med. 2013 Sep;125(5):130-8. doi: 10.3810/pgm.2013.09.2693.
53. Gibofsky A, Hochberg MC, Jaros MJ, Young CL. Efficacy and safety of low-dose submicron diclofenac for the treatment of osteoarthritis pain: a 12 week, phase 3 study. Curr Med Res Opin. 2014 Sep;30(9):1883-93. doi: 10.1185/03007995.2014.946123. Epub 2014 Aug 6.
54. Altman R1, Daniels S, Young CL. Indomethacin submicron particle capsules provide effective pain relief in patients with acute pain: a phase 3 study. Phys Sportsmed. 2013 Nov;41(4):7-15. doi: 10.3810/psm.2013.11.2031.
55. ClinicalTrials.gov [internet]. Bethesda (MD): 2000- [cited 2015 Jun 5]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01543685?term=tivorbex&rank=24.
56. Altman R, Hochberg M, Gibofsky A, Jaros M, Young C. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin. 2015 Dec;31(12):2331-43. doi: 10.1185/03007995.2015.1112772.
57. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162(1):46.
58. Watson MC, Brookes ST, Kirwan JR, Faulkner A. Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee. Cochrane Database Syst Rev. 2000.
59. Towheed T, Shea B, Wells G, Hochberg M. Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. Cochrane Database Syst Rev. 2000.
60. 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.
61. Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev 2010; CD001751.
62. Owen PR. Prostaglandin synthetase inhibitors in the treatment of primary dysmenorrhea. Outcome trials reviewed. Am J Obstet Gynecol 1984; 148:96.
63. Zhang, WY, Li Wan, Po A. Efficacy of minor analgesics in primary dysmenorrhea: a systematic review. Br J Obstet Gynaecol 1998; 105;780.

64. Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception 2010; 81:185.
65. Budoff PW. Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA 1979; 241:2713.
66. Milsom I, Minic M, Dawood MY, et al. Comparison of the efficacy and safety of nonprescription doses of naproxen and naproxen sodium with ibuprofen, acetaminophen, and placebo in the treatment of primary dysmenorrhea: a pooled analysis of five studies. Clin Ther 2002; 24:1384.
67. Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout--a systematic review. Rheumatology (Oxford) 2006; 45:1422.
68. Schumacher HR Jr, Boice JA, Daikh DI, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002; 324:1488.
69. Rubin BR, Burton R, Navarra S, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis Rheum 2004; 50:598.
70. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Curr Med Res Opin 1991; 12:423.
71. Lomen PL, Turner LF, Lamborn KR, et al. Flurbiprofen in the treatment of acute gout. A comparison with indomethacin. Am J Med 1986; 80:134.
72. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. J Rheumatol 1988; 15:1422.
73. van Durme CM, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev 2014; 9:CD010120.
74. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol 2012; 39:1859.
75. Roelofs PD, Deyo RA, Koes BW, et al. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev 2008; CD000396.
76. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.
77. American Academy of Orthopedic Surgeons: Treatment of osteoarthritis of the knee. Rosemont (IL): 2013 [Guideline on the internet] [cited 2015 Feb 2]. Available from: http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf.
78. National Institute for Health and Clinical Excellence (NICE). Osteoarthritis: Care and management in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); Feb 2014 [cited 2015 Feb 2]. Available from: http://www.nice.org.uk/guidance/CG177.
79. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6.
80. National Institute for Health and Clinical Excellence (NICE). Rheumatoid Arthritis: The management of rheumatoid arthritis in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); Feb 2009 [cited 2015 Feb 2]. Available from: http://www.nice.org.uk/guidance/CG79.
81. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011 Jun;70(6):896-904.
82. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: adult cancer pain. Fort Washington (PA): 2014.version 1 [cited 2014 Apr 11]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
83. iCentra. iCentra: Making Drugs Better [webpage on the Internet]. King of Prussia (PA): SoluMatrix™; 2013 [cited 2016 Jan 12]. Available from: http://www.iceutica.com/solumatrix.

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Overview/Summary

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The primary mechanism of action of all NSAIDs is through the inhibition of cyclooxygenase (COX), resulting in impaired transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes.[39] The COX enzyme can be subdivided into related isoforms, including COX-1 and COX-2; however, important differences in the regulation and expression of these two enzymes in various tissues exist which are relevant to the mechanism of action of NSAIDs and their associated adverse effect profile. Specifically, the COX-2 enzyme is typically undetectable in most tissue except during states of inflammation; therefore, the anti-inflammatory properties of NSAIDs are associated with the inhibition of COX-2.[39] In contrast, COX-1 is expressed variably in most tissues and regulates normal cell processes including gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. The inhibition of COX-1 by NSAIDs is thought to be associated with the well-established gastrointestinal adverse reaction profile of these agents, which includes dyspepsia, peptic ulcer disease and bleeding.[40]

All NSAID-containing agents are associated with a Black Box Warning regarding the increased risk of serious gastrointestinal adverse reactions including bleeding, ulceration and perforation of the stomach and intestines, which can be fatal.[1-37] Additionally, ketorolac tromethamine, a potent NSAID, is also contraindicated in renal impairment, patients at risk of bleeding (i.e., before surgery), and during labor, delivery, breast-feeding and coadministration with other NSAIDs.[15-17] Due to these risks, ketorolac should only be administered for acute pain (≤5 days).[15-17]

NSAIDs have traditionally been grouped by their chemical characteristics. Currently available products have been derived from acetic acid, anthranilic acid, enolic acid, or propionic acid. However, with the development of products selective to COX-2, classification has begun to shift towards selectivity, rather than chemical structure.[41] There is only one selective COX-2 inhibitor currently available, celecoxib (Celebrex®). In addition, recent evidence suggests that some of the older NSAIDs such as diclofenac and meloxicam show some selectivity towards the COX-2 enzyme.[41] Due to the variability in NSAID half-life ($t_{1/2}$), a classification system has also been developed to group NSAIDs by half-life. Some NSAIDs such as ibuprofen and diclofenac are eliminated rapidly ($t_{1/2}$ of one to four hours), while other agents have a much greater half-life. Agents with $t_{1/2}$ greater than 10 hours include: celecoxib, naproxen, meloxicam, nabumetone, oxaprozin and piroxicam. Piroxicam has an estimated $t_{1/2}$ of 50 hours.[41-43] Agents with longer half-lives are generally given once per day.

Clinical trials have demonstrated NSAIDs to be more efficacious compared to placebo in the treatment of pain and inflammatory conditions. Although there are many head to head trials comparing various NSAIDs, there is no single agent that has been continuously found to be more efficacious or safe than the

others.[44-75] Although the efficacy of NSAIDs appears to be similar at equipotent doses, there is a wide variability of response between individual patients, which is believed to be associated with non-prostaglandin-mediated NSAID-induced mechanisms of action. Thus, it is suggested that if a patient fails an NSAID of one class, an NSAID from a different class may be effective and is a reasonable option.[38] A summary of current clinical guidelines and NSAIDs place in therapy for specific disease states are listed in Table 10.[76-82]

In recent years, newer formulations of NSAIDs have been developed. Recently approved products include enteric-coated tablets, liquid filled capsules, nasal spray, suppositories, oral suspensions, and injections. Additionally, several NSAIDs have recently been formulated using the SoluMatrix Fine Particle Technology™.[83] SoluMatrix™ is a patented dry milling technology, which grinds the drug particles into a superfine powder and protects those submicron particles from subsequent agglomeration (clumping together into big particles). SoluMatrix Fine Particle Technology™ produces NSAIDs as submicron particles that are approximately 20 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution. It may also allow the NSAID to be given at a lower dose than a standard-formulation. Products currently approved that utilize the SoluMatrix™ technology include Zorvolex® (diclofenac capsules), Tivorbex® (indomethacin capsules), and Vivlodex® (meloxicam capsules).[83]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Acetic Acid Derivatives		
Diclofenac (Zorvolex®)	NSAID	-
Diclofenac potassium (Cataflam®*, Zipsor®)	NSAID	a
Diclofenac sodium* (Dyloject®, Voltaren XR®*)	NSAID	a
Etodolac*	NSAID	a
Indomethacin* (Indocin®, Tivorbex®)	NSAID	a
Indomethacin sodium	NSAID	-
Ketorolac tromethamine* (Sprix®)	NSAID	a
Nabumetone*	NSAID	a
Sulindac*	NSAID	a
Tolmetin sodium*	NSAID	a
Anthranilic Acid (Fenamate) Derivatives		
Meclofenamate sodium	NSAID	-
Mefenamic acid (Ponstel®*)	NSAID	a
Enolic Acid Derivatives		
Meloxicam (Mobic®*, Vivlodex®)	NSAID	a
Piroxicam (Feldene®*)	NSAID	a
Propionic Acid Derivatives		
Fenoprofen calcium* (Nalfon®*)	NSAID	a
Flurbiprofen*	NSAID	a
Ibuprofen* (Caldolor®)	NSAID	a
Ibuprofen Lysine (Neoprofen®)	NSAID	-
Ketoprofen*	NSAID	a
Naproxen (EC-Naprosyn®*, Naprosyn®*)	NSAID	a
Naproxen sodium (Anaprox®*, Anaprox DS®*, Naprelan®*)	NSAID	a
Oxaprozin (Daypro®*)	NSAID	a
Selective COX-2 Inhibitors		
Celecoxib (Celebrex®*)	NSAID	a

COX-2=cyclooxygenase-2, NSAID=nonsteroidal anti-inflammatory drug
*Generic available in at least one dosage form or strength

Indications

Table 2. Food and Drug Administration Approved Indications[1-37]

FDA-Approved Indications	Diclofenac	Diclofenac Potassium	Diclofenac Sodium	Etodolac	Indomethacin	Indomethacin Sodiuim	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin Sodium	Meclofenamate Sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calcium	Flurbiprofen	Ibuprofen	Ibuprofen lysine	Ketoprofen	Naproxen	Naproxen Sodium	Oxaprozin	Celecoxib
Pain, Acute *		a ¶	a #	a	a ††		a ‖					a §							a	a ##	a ¶¶		a
Pain, Mild to Moderate *	a	a									a						a				a		
Pain, Moderate to Severe *,†															a		a ‖‖						
Signs and Symptoms Associated with Osteoarthritis	a	a	a	a	a			a	a	a	a		a	a	a	a	a §§		a	a	a	a	a
Signs and Symptoms Associated with Rheumatoid Arthritis		a	a	a	a			a	a	a	a		a ‡‡	a	a	a	a §§		a	a	a	a	a
Signs and Symptoms Associated with Juvenile Rheumatoid Arthritis				a **						a	a		a ‡‡							a	a ¶¶	a	a
Signs and Symptoms Associated with Ankylosing Spondylitis			a		a				a		a									a	a		a
Treatment of Primary Dysmenorrhea		a	a								a	a					a §§		a	a ##	a		a
Treatment of Acute Gouty Arthritis					a				a		a									a ##	a		
Treatment of Painful Shoulder‡					a				a		a									a ##	a		
Closure of Clinically Significant Patent Ductus Arteriosus in Preterm Infants						a												a					
Fever Reduction											a						a ‖‖						

*Recommendation to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.
†In combination with opioid analgesics.
‡Including subacromial bursitis/supraspinatus tendinitis.
§When therapy will not exceed one week (7 days).
‖Short-term therapy (≤5 days).
¶ Diclofenac potassium tablets.
#Dyloject® (diclofenac Na IV solution)
**Etodolac 24-hour ER tablet
††Indomethacin capsule
‡‡Meloxicam tablet, oral suspension
§§Ibuprofen tablets
‖‖Ibuprofen IV solution
¶¶Tablets
##Suspension

Pharmacokinetics

Table 3. Pharmacokinetics[1-37,42,43]

Generic Name	Bioavailability (%)	Protein Binding (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Acetic Acid Derivatives					
Diclofenac	50	99	65	4'-hydroxy-diclofenac	2
Diclofenac Potassium	50 to 55	99	65		1 to 2
Diclofenac Sodium	50 (oral) n/a (IV)	>99	65		~ 2 (oral) 2.29 (IV)
Etodolac	≥80	>99	72	None	6.4 (tab) 7.3 ± 4 (cap)
Indomethacin	~100 (oral) 80 to 90 (supp)	~99	~60	None	7.2 (IR cap) 4.5 (Indocin®) 7.6 (Tivorbex®)
Indomethacin Sodium	n/a (IV)	~99	Not Reported	None	4.5 12 to 21 (neonates)
Ketorolac tromethamine	100 (oral, IV, IM) 60 (nasal)	99	92	None	5.3
Nabumetone	Not Reported	99	75 to 80	6MNA	~24
Sulindac	~90	Highly Bound	50	Sulfides	7.8
Tolmetin Sodium	Not reported	Not reported	Yes‡	None	5
Anthranilic Acid (Fenamate) Derivatives					
Meclofenamate Sodium	100	>99%	70	3-Hydroxy-methyl	1.3 to 2
Mefenamic acid	Not reported	>90	52	None	2
Enolic Acid Derivatives					
Meloxicam	89	99.4	Not reported	None	15 to 20
Piroxicam	Not reported	99	Not reported	None	50
Propionic Acid Derivatives					
Fenoprofen Calcium	Not reported	99	Not reported	None	3
Flurbiprofen	96	>99	70	None	4.7 to 5.7
Ibuprofen	Not reported	99	45 to 79	None	1.8 to 4
Ibuprofen lysine	Not reported	95	80 (changed) 10 to 15 (unchanged)	None	26 to 43 (infants)
Ketoprofen	~90	>99	80	None	2.1 ± 1.2
Naproxen	95	>99	95	None	12 to 17
Naproxen Sodium	95	>99	95	None	Not Reported
Oxaprozin	95	99	65 (5 unchanged)	None	41.4
Selective COX-2 Inhibitors					
Celecoxib	Not reported	Not reported	Not reported	Not reported	11

Abbreviations: 6MNA=6-methoxy-2-naphthylacetic acid, COX-2=cyclooxygenase-2,

Clinical Trials

There have been a vast number of clinical trials conducted evaluating the efficacy and safety of the nonsteroidal anti-inflammatory drugs (NSAIDs). However the majority of literature supporting the use of these agents was either published decades ago or are lacking in statistical significance and detail. As such, older evidence will be summarized utilizing systematic reviews and meta-analyses. Selected trials are summarized in Table 4. Generally speaking there is limited evidence to suggest that one NSAID is safer or more effective than another for any given indication.

The efficacy of diclofenac potassium liquid-filled soft gelatin capsules (Zipsor®) was demonstrated in two double-blind, placebo-controlled trials, in patients with postoperative pain following bunionectomy with osteotomy. The study reported that by the end of the 48-hour inpatient period, pain intensity scores were approximately 1.3 in the diclofenac group, and 3.1 in the placebo group (P<0.001).[2,44] The results in the second study were noted to be similar to the first in the FDA-approved package insert; however, the study has not been pubplished and there is no additioanl information available.[2]

The efficacy of ketorolac tromethamine nasal spray on acute pain was evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical trials.[17,45,46] Both trials eavluated ketorolatc tromethamine every eight hours compared to placebo in postoperative acute pain in patienst who were undergoing elective abodominal and/or orthopedic surgery. The efficacy of ketorolac tromethamine nasal spray was demonstrated by a statistically significant greater reduction in the single-dose summed pain intensity difference score at six hours compared to placebo (83.3 ± 10.6 comapred to 37.2 ± 12.9, P=0.007) in the first trial.[45] In the second trial, the least square mean six hour summed pain intensity difference scores were also significantly higher in the ketorolac tromethamine group compared to placebo (117.4 versus 89.9, P=0.032; difference, 27.6; 95% CI, 2.5 to 52.7).[46] The incidence of adverse events was similar between the ketorolac tromethamine and placebo groups in both the trials.[45,46]

The effect of diclofenac sodium injection (Dyloject®) in the short-term treatment of acute pain was evaluated in two double-blind, placebo and active-controlled, multiple-dose clinical trials in patients with postoperative pain. In both trials, intravenous morphine was permitted as rescue medication for pain management.[5,47,48] Efficacy was demonstrated by a reduction in pain intensity as measured by the sum of the pain intensity differences over 0 to 48 hours in patients receiving diclofenac sodium as compared to placebo (P=0.032 and P<0.0001 for 18.75 and 37.5 mg, respectivly).There was no differnece between either dose of diclofenac sodium injection and active-control ketorolac tromethamine 30 mg.[47] Similar resutls were seen in the second study, with a reduction in pain intensity as measured by the sum of the pain intensity differences over 0 to 48 hours in patients receiving diclofenac sodium injection as compared to placebo (P<0.0001). The second study did note improved sum of pain intesnity difference scorese, faster onset of analgesia and significantly lower opioid requirement than the active-control ketorolac tromethamine (P<0.008).[48]

The saftey and efficacy of ibuprofen intravenous injection (Neoprofen®) for the closure of clinically significant pattent ductus arterious (PDA) was established in a double-blind, multicenter clinical study premature infants of birth weight between 500 and 1000 grams, less than 30 weeks post-conceptional age. The ibuprofen group had a significantly lower proportion of infants who died, dropped out, or required rescue (21/68; 30.9%) as compared with the placebo group (36/68; 52.9%; P=0.005). Excluding those who died before study day 14, a significantly lower proportion of infants needed rescue in the ibuprofen group compared with the placebo group (25.0% compared with 48.5%, P=0.003).[31,49]

The efficacy of ibuprofen injection (Caldolor®) for the treatment of acute pain was evaluated in two multi-center, randomized, double-blind, placebo-controlled studies.[30,50,51] The first study evaluated women who underwent elective hysterectomy while the second study evaluated patients who underwent elective abdominal or orthopedic surgery. The primary efficacy endpoint of both studies was the difference in median morphine use during the first 24 hours following surgery. The first study showed a 19% reduction in morphine requirement in the ibuprofen 800 mg injection group compared to placebo (P<0.001) and a

22% reduction in the second study (P=0.03). The second study also noted no significant difference in ibuprofen 400 mg injection and placebo (no P value reported).[30,50,51]

The efficacy of diclofenac submicron capsules (Zorvolex®) in the treatment of acute pain and osteoarthritis pain was demonstrated in two multi-center, randomized, double-blind trials.[1,52,53] The acute pain trail was both placebo and active controlled. Diclofenac submicron capsules 18 mg and 35 mg taken three times daily was compared to celecoxib (200 mg twice daily) and placebo in patients with pain following bunionectomy. There was a statically significant difference in sum of pain intesnity difference in the first 48 hours post surgery when diclofenac submicron 35 mg capsules, diclofenac submicron 18 mg capsules, and celecoxib 200 mg was compared to placebo (P< 0.001, P=0.010, and P=0.011, respectively).[52] In the osteoarthritis trial, diclofenac submicron capsules 35 mg twice daily and three times daily were compared to placebo. The primary endpoint was the mean change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score at week 12. Submicron diclofenac 35 mg TID significantly improved WOMAC pain subscale scores from baseline at week 12 compared to placebo (-44.1 versus -32.5; P=0.0024). Submicron diclofenac 35 mg BID provided numerical improvement in pain at week 12 that did not reach statistical significance compared with placebo (-39.0 compared with -32.5; P=0.0795).[53]

The FDA approval of indomethacin submicron capsules (Tivorbex®) was based upon the results of a phase III, double-blind, multi-center, placebo-controlled trial. The trial was conducted in 462 subjects aged 18 to 68 years following bunionectomy surgery. Patients were randomized to indomethacin 40 mg three times daily, indomethacin 40 mg twice daily, indomethacin 20 mg three times daily, celecoxib 400 mg loading dose followed by 200 mg twice daily or placebo in a 1:1:1:1:1 fashion. The primary efficacy endpoint was the overall summed pain intensity difference (SPID) measured on a Visual Analog Scale over 48 hours. All indomethacin groups showed a statistically significant reduction in SPID over 48 hours compared to placebo (P≤0.046). Celecoxib did not show a statistically significant reduction in SPID over 48 hours compared to placebo (P=0.103).[9,54,55]

The efficacy of meloxicam submicron capsules (Vivlodex®) in the management of osteoarthritis pain was demonstrated in a randomized, double-blind, multicenter, parallel-arm, placebo-controlled study comparing meloxicam submicron 5 mg or 10 mg taken once daily and placebo in patients with pain due to osteoarthritis of the knee or hip. The primary efficacy endpoint was the change from baseline to Week 12 in the WOMAC Pain Subscale Score. There was a statistically significant reduction in mean WOMAC scores for both meloxicam submicron groups compared with placebo (P=0.0005 and P=0.0059 for 5 mg and 10 mg respectively).[23,56]

A recent meta-analysis was conducted evaluating the relative efficacy of available treatments of knee OA. The analysis included clinical trials of adults and compared two or more of the following: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo. The analysis concluded that all active treatments, with the exception of acetaminophen, showed clinically significant improvements in pain. However, intra-articular treatments were superior to NSAIDs.[57] Two other systematic reviews evaluated differeces in NSAIDs compared to one another and conclude that there is insufficient data to suggest that any of the available NSAIDs are more effective than any other for OA of the knee or hip.[58,59]

A systematic review was conducted that evaluated the use of NSAIDs for the treatment of ankylosing spondylitis. Available evidence from clinical trials suggests that both nonselective and COX-2 selective NSAIDs have similar efficacy and that various NSAIDs are equally effective. Additionally, there is limited data to suggest that continuous NSAID use may reduce radiographic progression, but requires confirmation.[60]

Another recent systematic review of 73 randomized trials evaluated the use of NSAIDs to treat primary dysmenorrhea. The study concluded that NSAIDs were significantly more effective than placebo (odds ration [OR], 4.50; 95% CI, 3.85 to 5.27) or paracetamol (OR, 1.90; 95% CI, 1.05 to 3.44). However, data

is unclear if a particular NSAID is more effective or safe than the others.[61] Several studies have shown no difference in safety or efficacy, while others suggest that the anthranilic acid derivatives (e.g., mefenamic acid), may be slightly more effective than propionic acid derivatives (e.g., ibuprofen, naproxen).[62-66] There have been no randomized trials have compared the efficacy of NSAIDs versus hormonal contraception for treatment of primary dysmenorrhea.

The use of NSAIDs in the acute treatment of gouty arthritis was evaluated in a number of clinical trials and systematic reviews. Available data suggest NSAIDs are at least as effective and safe as other agents used for the treatment of gout with little or no differences between NSAIDs.[67-73] A randomized, double-blind, active-control study evaluated the safety and effectiveness of the selective COX-2 inhibitor celecoxib. The study concluded that high-dose celecoxib is significantly more effective than low-dose celecoxib and is comparable in efficacy to the nonselective NSAID indomethacin.[74] There are currently no randomized trials that compare NSAIDs with colchicine.

A 2008 systematic review of 65 randomized trials of NSAID use for low back pain included a meta-analysis of 11 trials for acute low back pain. Global symptomatic improvement after one week of NSAID therapy in patients with low back pain was modestly greater compared to those treated with placebo (relative risk, RR; 1.19; 95% CI, 1.07 to 1.35). The review also concluded that NSAIDs had similar efficacy compared with acetaminophen and mores side effects compared with either placebo or acetaminophen.[75]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Pain				
Riff et al[44] Diclofenac potassium liquid-filled soft gelatin capsule (DPSGC; Zipsor®) 25 mg Q6H vs placebo All other pain medication was discontinued at least four hours before the first dose of study drug. Patients could request rescue medication after the first study drug was taken.	DB, MC, PC, PG, RCT Patients ≥18 years of age scheduled to undergo primary unilateral first-metatarsal bunionectomy with distal osteotomy and internal fixation and had an NPRS score ≥4 on the day after surgery	N=201 4 days	Primary: Mean NPRS score over 48-hour in-patient period (first two days) Secondary: NPRS score at predefined times, SPID48, time-weighted sum of pain relief scores over the first eight hours, mean dosing interval, the proportion of patients requiring rescue medication, and the onset of perceptible and meaningful pain relief	Primary: There was a statistically significant reduction in pain intensity (mean NPRS score) over the inpatient 48-hour period in the DPSGC 25 mg compared with those receiving placebo (2.5 compared with 5.6; P<0.001). NPRS scores were significantly lower in the DPSGC 25 mg arm compared with the placebo arm at the time of administration of the second dose (P<0.001) and throughout the inpatient 48-hour multiple-dose period (P<0.001). Secondary: Patients receiving DPSGC 25 mg had significantly lower NPRS scores (i.e., less pain) compared with those receiving placebo as early as one hour after dosing (4.8 compared with 6.0; P<0.05) and continuing from two hours (4.9 compared with 6.6; P<0.01) through the remainder of the initial 8-hour single-dose period (P≤0.01). The number of patients requiring rescue medication on each day of the inpatient 48-hour period was significantly lower in the DPSGC 25 mg group compared with the placebo group (P<0.001). The overall mean dosing interval during the inpatient 48-hour multiple-dose period was significantly longer in the DPSGC 25 mg group compared with the placebo group (331.5 compared with 263.9 minutes; P < 0.001). Mean dosing intervals on days one through three were significantly longer for those treated with DPSGC compared with those receiving placebo (P<0.001). There was no significant difference in the median time to the onset of perceptible pain relief when DPSGC was compared to placebo (26.0 and 22.2 minutes). Meaningful pain relief, defined as ≥30% reduction in pain intensity, occurred significantly faster in the DPSGC group compared with the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo group (70.2 compared with 106.3 minutes; P=0.008) and in a greater proportion of patients (56.9% compared with 35.4%; P=0.003). Patients receiving placebo took the second dose of study medication significantly earlier than did those receiving DPSGC 25 mg (80.0 compared with 156.5 minutes; P<0.001). The proportions of patients in the DPSGC 25 mg and placebo groups who reported ≥30% reduction in pain during the initial single-dose period were 60.8% and 40.4%, respectively (P=0.004). Patients receiving DPSGC 25 mg reached this level of pain relief significantly faster than those receiving placebo (60.0 compared with 150.0 minutes; P=0.038) and maintained it significantly longer (median duration of ≥30% pain reduction, 222.5 compared with 102.5 minutes; P=0.002).
Brown et al[45] Ketorolac intranasal spray 30 mg Q8H vs placebo All patients had access to morphine sulfate PCA.	DB, MC, PC, RCT Patients ≥18 years of age undergoing major surgery and expected to remain in the hospital for at least 48 hours and up to 5 days	N=300 5 days	Primary: SPID6 score during the single-dose phase Secondary: Onset, peak effect, quality of analgesia, and duration of analgesia in the first six hours after single-dose phase, global evaluation of pain control, mean total morphine use, and quality of analgesia ratings	Primary: The mean ± standard error visual analog scale pain intensity rating at baseline was 54.0 ± 0.9 for the ketorolac group and 53.6 ± 1.1 for the placebo group. The mean ± SE SPID6 score for the ketorolac group was significantly higher compared with the placebo group (83.3 ± 10.6 vs 37.2 ± 12.9, P=0.007). Secondary: At all time points between 0.5 and 5 hours, significantly more ketorolac-treated subjects reported better quality of analgesia (P<0.05). At 6 hours, the difference approached significance and continued to favor the ketorolac group (P=0.068). The duration of analgesia was significantly longer in the ketorolac group as represented by the time to restarting PCA or requesting rescue medication (median time 3.0 hours in the ketorolac group compared with 1.3 hours in the placebo group, P<0.04). A significantly (P<0.05) greater proportion of patients in the ketorolac group reported meaningful pain relief compared with placebo within 1 hour (84% vs 70%) and at 1.5 hours (84% vs 72%). The difference at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				two hours approached statistical significance, indicating a trend that was still in favor of the ketorolac group (84% vs 73%, P=0.058). Morphine use was significantly lower in the ketorolac group compared with placebo group for all time intervals (P<0.001). The quality of analgesia rating for patients in the multi-dose regimen was significantly higher at eight hours in the ketorolac group compared with the placebo group (2.9 ± 0.06 vs 2.6 ± 0.1, P=0.011). The majority of patients in both groups reported the quality of analgesia as being very good or excellent through 48 hours after the first dose of study drug.
Singla et al[46] (abstract only) Ketorolac intranasal spray 30 mg Q8H vs placebo All patients had access to morphine sulfate PCA.	DB, MC, PC, RCT Patients ≥18 years of age who are undergoing abdominal surgery.	N= 321 5 days	Primary: Mean six-hour summed pain intensity difference scores, pain intensity difference, morphine use over 48 hours, day one global pain control scores, quality of analgesia, adverse events Secondary: Not reported	Primary: Least square mean six-hour summed pain intensity difference scores were significantly greater in the ketorolac group compared to placebo (117.4 compared with 89.9, P=0.032; difference 27.6, 95% CI, 2.5 to 52.7). Pain intensity difference indicated significantly better pain relief in the ketorolac group at 20 min after the first dose (P=0.01). Morphine use over 48 hours decreased 26% in the ketorolac group compared to placebo (P=0.004). Day one global pain control scores were significantly higher in the ketorolac group compared to placebo (P=0.009). Quality of analgesia was rated significantly higher (P=0.009) in the ketorolac group by 20 min after first dose. Adverse event and serious adverse event incidences were similar in both groups. Rhinalgia and nasal irritation, generally mild and transient in nature, occurred more frequently in the ketorolac group.
Gan et al[47]	AC, DB, MC, PC, PG, RCT	N=331	Primary: SPID over the	Primary: Mean SPID over the first 48 hours was significantly greater for both

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diclofenac sodium (Dyloject®) 18.75 mg IV bolus Q6H vs diclofenac sodium (Dyloject®) 37.5 mg IV bolus Q6H vs ketorolac tromethamine 30 mg IV bolus Q6H vs placebo Rescue medication (IV morphine) was available up to once every three hours.	Patients 18 to 65 years of age who were scheduled for abdominal or pelvic surgery within two weeks with moderate-to-severe postoperative pain	5 days	first 48 hours. Secondary: SPID over other periods, total pain relief, proportion of patients with clinically meaningful reduction in pain intensity, PID at each assessment, time from study drug administration to use of rescue mediation, frequency and amount of rescue medication used, patient-reported global evaluation of the study drug	doses of diclofenac sodium injection comparted to placebo (18.75 mg, P=0.032; 37.5 mg, P=0.0001). The same effect was seen between ketorolac and placebo (P<0.0001). There were no statistically significant differences in efficacy among the three active treatment groups. Secondary: SPID over first 24-hours was significantly greater than placebo for both diclofenac doses (18.75 mg, P=0.015; 37.5 mg, P<0.0001) and ketorolac (P<0.0001). For the 0- to 72-hour period, 18.75 mg diclofenac did not lead to a significantly greater SPID than placebo (P=0.08), but 37.5 mg diclofenac (P=0.0010) and ketorolac (P=0.0018) did significantly improve SPID. Mean PID was consistently greater with the active treatments than with placebo over the first 45 hours, with the exception of the 6-hour and 30-hour assessments. During the first 6-hour dosing period, the proportion of patients that had a ≥30% reduction in pain intensity was 55.3% (N=42) of patients receiving placebo, 76.8% (N=63) of patients receiving ketorolac, 64.3% (N=54) of patients receiving 18.75 mg diclofenac, and 69.8% (N=60) of patients receiving 37.5 mg diclofenac (no P values reported). The mean time to ≥30% pain intensity reduction among subjects reporting this decline within 6 hours after first study drug dose was rapid across all treatment groups (27 to 33 minutes for the modified ITT population). Median times to ≥30% pain intensity reduction did not differ among any of the active treatment groups and placebo (all P>0.05). Total pain relief was significantly greater with active treatment than with placebo over the 0- to 24- and 0- to 48-hour time intervals (P=0.0002 and P=0.0008, respectively). Use of both 18.75 mg and 37.5 mg diclofenac resulted in significantly greater mean total pain relief than placebo (18.75 mg: 0- to 24-hour interval [P=0.037], 0- to 48-hour interval [P=0.038]; 37.5 mg: 0- to 24- and 0- to 48-hour intervals [P=0.0018]), as did use of 30 mg ketorolac (P<0.0001 for the 0- to 24-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				hour interval and P=0.0001 for the 0- to 48-hour interval). There were no significant differences among active treatments. Median time to rescue morphine administration in the ITT population was 2:07 (hours:minutes) (95% CI, 1:15 to 2:40) for placebo but was significantly longer with 18.75 mg diclofenac (3:14; 95% CI, 2:10 to 5:05; P=0.014 vs placebo) and ketorolac (4:15; 95% CI: 3:05, not estimable; P=0.0007 compared with placebo). Time to rescue morphine administration did not meet statistical significance versus placebo with 37.5 mg diclofenac. (2:24; 95% CI, 1:50 to 4:23; P=0.0574). Active treatment decreased the frequency of rescue morphine administration, and for all time intervals studied, patients receiving active treatments required significantly less morphine compared with the placebo group (all P<0.0001). All active treatments led to a significant reduction in morphine dosage over the 0- to 48- and 0- to 72-hour intervals, as well (all P<0.0001). Patient global evaluations was significantly different in favor of each of the active treatment groups compared to placebo (P<0.001) at both 24 and 48 hours, with no significant differences among active treatment groups.
Daniels et al[48] (abstract only) diclofenac sodium (Dyloject®) 18.75, 37.5, or 50 mg injection vs ketorolac tromethamine 15 or 30 mg injection vs	AC, DB, MC, PC, PG, RCT Patients 18 to 85 years of age who were scheduled for orthopedic surgery with moderate-to-severe postoperative pain	N=227 5 days	Primary: SPID, onset of analgesia, opioid requirement, analgesic efficacy, adverse events Secondary: Not reported	Primary: Mean SPID scores were significantly different with diclofenac sodium injection and ketorolac than with placebo (P<0.0001), across all risk cohorts (P<0.05). Diclofenac was associated with better SPID scores, faster onset of analgesia, and significantly lower opioid requirement (P<0.008) than ketorolac. In patients more than or equal to 65 years, diclofenac was associated with significantly better analgesic efficacy (P=0.05), and lower opioid requirement versus ketorolac (no P value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Rescue medication (IV morphine) was available up to once every three hours.				The incidence of treatment-related adverse events was similar across groups.
Kroll et al[50] Ibuprofen IV (Caldolor®) 800 mg Q6H vs placebo IV morphine was available if needed.	DB, MC, PC, RCT Female patients 18 to 70 years of age scheduled for elective abdominal hysterectomy (benign or malignant) and were expected to require postoperative hospitalization or IV morphine analgesia lasting at least 24 hours.	N=319 5 days	Primary: Morphine requirement during the first 24 hours following surgery Secondary: Reduction in pain intensity, time to first subsequent narcotic analgesia for breakthrough pain, incidence of opioid-related side effects, resumption of ambulation, resumption of liquid intake and solid diet, and length of hospital stay	Primary: Patients who received IV-ibuprofen required significantly less morphine in the first 24 hours following surgery, compared with patients who received placebo (median mg of morphine used: IV-ibuprofen, 43.5 mg; placebo, 54.0 mg morphine), representing a 19% reduction in median morphine use for those receiving IV-ibuprofen (P<0.001). Secondary: Compared with patients receiving placebo, those receiving IV-ibuprofen reported statistically significantly lower pain assessment scores, both at rest and with movement, for all three time segments (during the first 24 hours, 6 to 24 hours, and 12 to 24 hours), as determined by the AUC for patient self-reported scores (P≤0.001). In addition to the morphine sparing-effect, patients receiving 800 mg IV-ibuprofen experienced a significant reduction in pain as measured by the VAS at rest AUC for the first 24 hours (21%, P=0.011), from 6 through 24 hours (27%, P<0.001), and from 12 through 24 hours (37%, P<0.001) and pain with movement for the first 24 hours (14%, P=0.010), from 6 through 24 hours (20%, P=0.001), and from 12 through 24 hours (24%, P<0.001) after surgery. The time to ambulation was significantly shorter in the IV-ibuprofen group than in the placebo group (23.4 hours vs. 25.3 hours, P=0.009). The incidence of treatment failure was numerically lower in the group of patients receiving IV-ibuprofen compared to those in the placebo group (4% vs. 7%); this difference, however, was not statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.250). Statistically significant differences were not observed in the other secondary efficacy variables.
Southworth et al[51] Ibuprofen IV (Caldolor®) 400 mg Q6H vs ibuprofen IV (Caldolor®) 800 mg Q6H vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age scheduled for elective, single-site orthopedic or abdominal surgery and were expected to require postoperative hospitalization or IV morphine analgesia lasting at least 24 hours.	N=406 5 days	Primary: Morphine requirement during the first 24 hours following surgery Secondary: Mean changes in pain intensity at rest and with movement, rate of treatment failure, time to resumption of gastrointestinal motility, mean number of nocturnal awakenings due to pain, the prevalences of opioid-related adverse events, time to resumption of ambulation, time to resumption of liquid intake and solid diet, and hospital length of stay	Primary: In the ITT population, median morphine use was significantly reduced during the first 24 hours of administration of study drug in patients who received ibuprofen 800 mg by 22% compared to placebo (P=0.030). There was no significant difference in morphine use between the ibuprofen 400 mg group and placebo group. Secondary: In the ITT population, the use of ibuprofen 800 mg IV was associated with significant reductions in pain at rest across all three time periods (P=0.001, P<0.001, and P<0.001 for 1 to 24, 6 to 24, and 12 to 24 hours, respectively) compared with placebo. Ibuprofen 400 mg IV was associated with significant reductions in pain at rest during the periods of 6 to 24 hours (P=0.013) and 12 to 24 hours (P=0.005) compared with placebo. The use of ibuprofen 800 mg IV was associated with significant reductions in pain with movement across all three time periods compared with placebo (P=0.002, P<0.001, and P<0.001 for 1 to 24, 6 to 24, and 12 to 24 hours, respectively). The use of ibuprofen 400 mg IV was also associated with significant reductions in pain with movement across all three time periods compared with placebo (P=0.021, P=0.004, and P=0.003, respectively). The rates of treatment failure were not statistically significant between study groups. No significant differences between study groups were noted with respect to time to gastrointestinal motility, mean number of nocturnal awakenings due to pain, time to resumption of ambulation, resumption of liquid intake and solid diet, or hospital length of stay.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gibofsky et al[52] (abstract only) Diclofenac submicron capsules (Zorvolex®) 35 mg TID vs diclofenac submicron capsules (Zorvolex®) 18 mg TID vs celecoxib 200 mg BID vs placebo	AC, DB, MC, PC, PG, RCT Patients 18 to 65 years of age with moderate-to-severe pain following bunionectomy with a pain intensity rating of ≥40 mm on a 100-mm VAS	N=428 48 hours	Primary: SPID48 Secondary: PID at scheduled assessments, adverse events	Primary: There was a statically significant difference in SPID48 when diclofenac submicron 35 mg, diclofenac submicron 18 mg, and celecoxib 200 mg was compared to placebo (P< 0.001, P=0.010, and P=0.011, respectively). Secondary: Diclofenac submicron particle capsules 35 mg (4.52) provided some pain control (higher mean PID) at 30 minutes following administration, in contrast to celecoxib 200 mg BID (0.80), diclofenac submicron particle capsules 18 mg (0.31), and placebo (0.12). Better pain control (PID) was noted across all active treatment groups at five hours compared with placebo (P≤0.03), and pain relief was sustained throughout the treatment period. The most frequent non-procedure-related adverse events were nausea, headache, dizziness, and vomiting.
Altman et al[54] (abstract only) Indomethacin submicron capsules (Tivrobex®) 40 mg TID vs indomethacin submicron capsules (Tivorbex®) 40 mg BID vs	AC, DB, MC, PC, RCT Patients 18 to 68 years of age who underwent bunionectomy with a pain intensity rating of ≥40 mm.	N=373 48 hours	Primary: PID over 48 hours Secondary: PID at other times, tolerability	Primary: Summed pain intensity differences were 509.6 ± 91.9, 328.0 ± 92.9, and 380.5 ± 92.9 for the indomethacin submicron capsule groups, respectively and 67.8 ± 91.4 for the placebo group. Indomethacin submicron capsules 40 mg TID, 40 mg BID, and 20 mg TID reduced pain intensity from 0 to 48 hours compared to placebo (P≤0.046 for all 3 groups). There was some evidence of patient analgesia for celecoxib (279.4 ± 91.9; P=0.103). Secondary: Some evidence of pain control was observed in patients as early as two hours following administration of indomethacin submicron particle capsules and was sustained throughout the treatment period. Indomethacin submicron particle capsules were generally well tolerated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
indomethacin submicron capsules (Tivorbex®) 20 mg TID vs celecoxib 200 mg BID vs placebo				by patients.
Patent Ductus Arteriosus				
Aranda et al[49] Ibuprofen IV (Neoprofen®) vs placebo	DB, MC, PC, PG, RCT Premature newborns ≤ 30 weeks' gestation, birth weight 500 to 1000 grams, <72 hours postnatal age, nonsymptomatic PDA with evidence of ductal shunting documented by echocardiogram	N=136 5 days	Primary: Proportion of patients with the presence of a symptomatic PDA requiring rescue with indomethacin or surgery, patients that died or dropped out before study day 14. Secondary: Safety	Primary: Based upon the intent-to-treat analysis of the primary endpoint, the ibuprofen group had a significantly lower proportion of infants who died, dropped out, or required rescue (21/68; 30.9%) as compared with the placebo group (36/68; 52.9%; P=0.005) for symptomatic PDA on or before study day 14. This significant difference was even more pronounced when adjusted for covariates (P=0.0014), including birth weight, gestational age, gender, maximum weight loss, use of oscillatory ventilation, and site. Excluding those who died before study day 14, a significantly lower proportion of infants needed rescue in the ibuprofen group compared with the placebo group (25.0% compared with 48.5%, P=0.003). With respect to rescue after study day 14, 5 (7.4%) ibuprofen infants and 4 (5.9%) placebo patients were rescued. The mean ages were 19 and 18 days in the ibuprofen and placebo groups, respectively. Of these patients, three ibuprofen patients and one placebo patient subsequently underwent surgery, and one patient in each group died due to NEC. Placebo treatment was the only factor statistically associated with an increased rescue outcome (P=0.001) with neither gestational age nor birth weight was related to the rates of rescue

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.187, P=0.817). Secondary: With respect to complications and adverse events, there were no differences in the proportion of babies who developed IVH, NEC, BPD, PPHN, or ROP between groups. None of the ibuprofen-treated infants had PVL, whereas four newborns in the placebo group had PVL diagnosed by head ultrasound at 36 weeks or prior to discharge (P=0.059).
Osteoarthritis Pain				
Gibosfsky et al[53] (abstract only) Diclofenac submicron capsules (Zorvolex®) 35 mg TID vs diclofenac submicron capsules (Zorvolex®) 35 mg BID vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with hip or knee OA, were chronic NSAID and/or APAP users with WOMAC scores ≥40 mm and OA flare following discontinuation of NSAID or APAP	N=305 12 weeks	Primary: Mean change from baseline in WOMAC pain subscale score at week 12 Secondary: Average total WOMAC score over 12 weeks, adverse events	Primary: Submicron diclofenac 35 mg TID significantly improved WOMAC pain subscale scores from baseline at week 12 compared to placebo (-44.1 versus -32.5; P=0.0024). Submicron diclofenac 35 mg BID provided numerical improvement in pain at week 12 that did not reach statistical significance compared with placebo (-39.0 compared with -32.5; P=0.0795). Secondary: Submicron diclofenac 35 mg TID (-35.9; P=0.0002) and submicron diclofenac 35 mg BID (-30.3; P=0.0363) improved the average total WOMAC score in treated patients over 12 weeks compared with placebo (-23.2). The most frequent adverse events in the submicron diclofenac-treated groups were diarrhea, headache, nausea, and constipation.
Altman et al[56] (abstract only) Meloxicam submicron capsules (Vivlodex®) 5 mg QD	DB, MC, PC, RCT Patients ≥40 years of age with hip or knee OA, were chronic	N=402 12 weeks	Primary: Mean change from baseline in WOMAC pain subscale score at week 12	Primary: The mean (standard error) WOMAC pain subscale score from baseline at week 12 for meloxicam submicron 5 mg and 10 mg once daily was -36.52 (2.49) and -34.41 (2.68) while mean WOMAC score for placebo was -25.68 (2.64). There was a statistically significant reduction in mean WOMAC scores for both meloxicam submicron groups compared with placebo (P=0.0005 and P=0.0059 for 5 mg and 10 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs meloxicam submicron capsules (Vivlodex®) 10 mg QD vs placebo	NSAID and/or APAP users with WOMAC scores ≥40 mm and OA flare following discontinuation of NSAID or APAP		Secondary: Not reported	respectively). Patients treated with meloxicam submicron capsules 5 mg or 10 mg reported significantly greater improvements in total WOMAC score and in WOMAC stiffness and function subscale scores at 12 weeks compared with placebo (no P value reported). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IV=intravenous, Q6H=every six hours, Q8H=every eight hours, QD=once daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intention-to-treat, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SE=standard error
Other abbreviations: APAP=acetaminophen, DPSGC=Diclofenac potassium liquid-filled soft gelatin capsule, NPRS=numeric pain rating scale, NSAID=non-steroidal anti-inflammatory drug, OA=osteoarthritis, PCA=patient controlled analgesia, PDA=patent ductus arteriosus, PID=pain intensity difference, SPID=summarized pain intensity difference, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1-37,43]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Acetic Acid Derivatives					
Diclofenac	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Caution advised.	Caution advised.	C* (D after 30 weeks of gestation)	Unknown
Diclofenac potassium	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Caution advised.	Caution advised.	C* (D after 30 weeks of gestation)*	Unknown
Diclofenac sodium	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Caution advised.	Caution advised.	C* (D after 30 weeks of gestation)	Unknown
Etodolac	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. FDA approved for children 6 years of age and older for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in children have not been established for other diagnoses.	Caution advised.	No dosage adjustment generally required; clearance could be reduced in patients with severe hepatic failure.	C*	Unknown
Indomethacin	Doses higher than 150 to 200 mg/day have been associated with increased adverse effects in the elderly without a corresponding increase in clinical benefits. Safety and efficacy in children ≤17 years of	Caution is advised. Treatment not recommended in patients with advanced renal disease.†	Caution advised.	C (D after 30 weeks of gestation)	Yes (% not reported)

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	age has not been established (Tivorbex®). Safety and efficacy in children ≤14 years of age has not been established (Indocin®).				
Indomethacin sodium	Safety and efficacy in elderly patients have not been established. FDA approved for premature infants.	Caution is advised. Contraindicated in patients with significant renal impairment.†			
Ketorolac tromethamine	Dosage adjustment required. Safety and efficacy in children ≤17 years of age has not been established.	Contraindicated in advanced renal dysfunction. †	Caution advised. Should be discontinued if liver function tests are abnormal after therapy initiation.	C*	Yes (% not reported)
Nabumetone	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Renal dose adjustment required.	Caution advised.	C*	Unknown
Sulindac	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Renal dose adjustment required.	Hepatic dose adjustment required.	C*	Unknown
Tolmetin sodium	Caution advised when used in the elderly. FDA approved for children 2 years of age and older for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in children have not been established for other diagnoses.	Renal dose adjustment required.	Caution advised.	C*	Yes (% not reported)
Anthranilic Acid Derivatives					

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Meclofenamate sodium	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. FDA approved for children 14years of age and older.	Renal dose adjustment required.	Caution advised.	C*	Yes (% not reported)
Mefenamic acid	Caution advised when used in the elderly. FDA approved for children 14years of age and older.	Caution advised.	Hepatic dose adjustment required.	C*	Yes (% not reported)
Enolic Acid Derivatives					
Meloxicam	Caution advised when used in the elderly. FDA approved for the treatment of juvenile rheumatoid arthritis in children 2 years of age and older (oral suspension [Mobic®]). Safety and efficacy in children have not been established for other diagnoses.	Caution advised. Not recommended in patients with advanced renal disease.†	Caution advised.	C*	Unknown
Piroxicam	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Caution advised.	Hepatic dose adjustment required.	C*	Yes (1% to 3%)
Propionic Acid Derivatives					
Fenoprofen calcium	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	No dosage adjustment required.	Caution advised.	C (D after 30 weeks of gestation)	Unknown
Flurbiprofen	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Caution advised.	Caution advised.	C*	Unknown
Ibuprofen	Caution advised when	Caution	Caution	C*	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	used in the elderly. FDA approved for the treatment of pain and fever reduction in children aged 6 months or older (IV solution [Caldolor®]);	advised.	advised.		
Ibuprofen lysine	Not studied in elderly patients. FDA approved for the closure of clinically significant PDA in premature infants.	Contraindicated in significant renal impairment.†	Not reported	Not reported	Not reported
Ketoprofen	Caution advised when used in the elderly. Safety and efficacy in pediatric patients have not been established.	Renal dose adjustment required.	Hepatic dose adjustment required.	C*	Unknown
Naproxen	Caution advised when used in the elderly. FDA approved for the treatment of juvenile rheumatoid arthritis in children 5 years of age and older. Safety and efficacy in children have not been established for other diagnoses.	Caution advised.	Caution advised.	C*	Unknown
Naproxen sodium	Caution advised when used in the elderly. FDA approved for the treatment of juvenile rheumatoid arthritis in children 2 years of age and older (tablet [Anaprox®, Anaprox DS®]). Safety and efficacy in children have not been established for other diagnoses.	Caution advised.	Caution advised.	C*	Unknown
Oxaprozin	Caution advised when used in the elderly.	Renal dose adjustment	Caution advised.	C*	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	FDA approved for the treatment of juvenile rheumatoid arthritis in children 6 years of age and older. Safety and efficacy in children have not been established for other diagnoses.	required.			
Selective COX-2 Inhibitors					
Celecoxib	Caution advised when used in the elderly. FDA approved for the treatment of juvenile rheumatoid arthritis in children 2 years of age and older. Safety and efficacy in children have not been established for other diagnoses.	Caution advised.	Caution advised.	C (D after 30 weeks gestation)	Unknown

ER=extended-release, FDA=Food and Drug Administration, PDA=patent ductus arteriosus
*Avoid use in late pregnancy, the third trimester, as NSAIDs are associated with premature closure of the ductus arteriosus.
†Specific level of renal dysfunction not defined.

Adverse Drug Events

The adverse event profiles of nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly related to their effects on prostaglandin synthesis. This includes common gastrointestinal adverse events including dyspepsia and nausea. More serious adverse effects can include gastrointestinal ulceration and bleeding, worsening of heart failure and acute renal failure. The common adverse drug events (>1%) associated with NSAID therapy are included below in table 6.

Table 6. Adverse Drug Events (%)[1-37,43]

Adverse reaction (%)	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin Indomethacin Sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calsium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
Cardiovascular System																		
Angina/angina pectoris	1 to 2*	-	-	-	< 1	-	-	-	-	< 2	-	-	< 1	-	-	-	-	< 2
Arrhythmia	-	< 1	< 1	-	< 1	< 1	-	-	< 1	< 2	< 1	-	< 1	< 1	< 1	-	-	
Hypertension	< 1 1 to 2*	< 1	< 1	1 to 3	< 1	< 1	3 to 9	-	< 1	< 2	< 1	-	< 1	< 1	< 1	-	-	< 2
Hypotension	< 1	-	< 1	-	-	-	-	-	< 1	< 2	< 1	-	-	-	-	-	-	
Myocardial infarction	< 1	< 1	-	-	< 1	-	-	-	< 1	< 2	< 1	-	< 1	-	< 1	-	-	< 2
Palpitations	< 1	< 1	< 1	< 1	< 1	< 1	-	< 1	< 1	< 2	< 1	2.5	-	< 1	< 1	1 to 3	< 1	< 2
Syncope	-	< 1	< 1	< 1	< 1	< 1	-	-	< 1	< 2	< 1	-	-	-	-	-	-	
Tachycardia	< 1	-	< 1	-	-	-	-	-	< 1	< 2	< 1	< 1	-	-	< 1	-	-	< 2
Vasculitis	-	< 1	-	-	< 1	-	-	-	< 1	< 2	-	-	-	-	-	< 1	-	
Ventricular Hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	29†				
Central Nervous System																		
Abnormal dreams/ dream abnormalities	-	-	-	< 1	-	-	-	-	< 1	< 2	< 1	-	-	< 1	-	< 1	-	
Anxiety	< 1	-	< 1	-	< 1	-	-	-	< 1	< 2	< 1	-	-	-	-	-	-	
Asthenia/malaise	< 1	3 to 9	-	< 1	< 1	-	3 to 9	< 1	< 1	< 2	< 1	1.0 to 5.4	-	-	-	< 1	< 1	
Central nervous system inhibition or excitation	-	-	-	-	-	-	-	-	-	-	-	-	1 to 3	-	3 to 9	-	1 to 3	
Confusion	-	< 1	< 1	-	< 1	-	-	-	< 1	< 2	< 1	1.4	< 1	< 1	< 1	-	-	
Convulsions	< 1	-	< 1	-	-	< 1	-	-	< 1	< 2	< 1	-	< 1	-	-	-	-	
Depression	< 1	1 to 3	1 to 3	< 1	< 1	< 1	1 to 3	< 1	< 1	< 2	< 1	< 1	-	< 1	-	< 1	-	< 2
Dizziness	1 to 3	3 to 9	3 to 9	7	3 to 9	3 to 9	3 to 9	3 to 9	1 to 10	1.1 to 3.8	1 to 10	6.5	1 to 3	3 to 9	1 to 3	3 to 9	-	2.0
Drowsiness	< 1	-	< 1	6	-	-	1 to 3	-	< 1	-	< 1	-	-	-	-	3 to 9	-	
Fatigue	-	-	1 to 3	-	1 to 3	-		< 1	-	< 2	-	1.7	-	-	-	-	-	< 2
Headache	3 to 9 0 to 7*	< 1	11.7	17	3 to 9	3 to 9	3 to 9	3 to 9	1 to 10	2.4 to 8.3	1 to 10	8.7	3 to 9	1 to 3	3 to 9	3 to 9	-	15.8
Hypesthesia	-	0 to 3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Hypokinesia	0 to 2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Insomnia	< 1	< 1	< 1	< 1	1 to 3	< 1	-	< 1	< 1	≤ 3.6	< 1	< 1	-	< 1	-	< 1	-	2.3
Lightheadedness	-	-	< 1	-	-	-	-	-	-	-	-	-	-	-	-	1 to 3	-	
Nervousness	-	1 to 3	< 1	< 1	1 to 3	1 to 3	-	-	< 1	< 2	< 1	5.7	1 to 3	1 to 3	-	-	-	< 2
Paresthesia	< 1 8 to 20*	< 1	< 1	< 1	< 1	< 1	-	< 1	< 1	< 2	< 1	-	< 1	< 1	< 1	-	-	< 2
Somnolence	-	< 1	1 to 3	-	1 to 3	< 1	-	-	< 1	< 2	< 1	8.5	-	< 1	-	-	-	< 2
Tremor	< 1	-	-	< 1	< 1	-	-	-	< 1	< 2	< 1	2.2	-	-	-	-	-	
Vertigo	-	-	1 to 3	< 1	< 1	< 1	-	-	< 1	2	< 1	-	-	-	< 1	1 to 3	-	< 2

Adverse reaction (%)	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin Indomethacin Sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calsium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
Dermatological																		
Alopecia/loss of hair	< 1 1 to 2*	< 1	< 1	-	< 1	< 1	-	< 1	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 2
Bullous eruption/rash	< 1 0 to 4*	-	-	-	< 1	-	-	-	-	< 2	-	-		-	< 1	-	-	
Burning/pain	15 to 26*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	< 2
Dry skin	25 to 27*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Edema	3 to 4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Exfoliation	6 to 24*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Exfoliative dermatitis	< 1 0 to 2*	-	< 1	-	-	< 1	-	< 1	< 1	-	< 1	< 1	< 1	-	< 1	-	< 1	< 2
Increased sweating	< 1	< 1	< 1	1 to 3	1 to 3	-	-	-	< 1	< 2	< 1	4.6	< 1	-	< 1	1 to 3	-	< 2
Photosensitivity/ photosensitivity reaction	< 1 0 to 3*	< 1	-	-	< 1	< 1	-	-	< 1	< 2	< 1	-	< 1	-	< 1	< 1	< 1	< 2
Pruritus	1 to 3 31 to 52*	1 to 4	< 1	1 to 3	3 to 9	1 to 3	-	1 to 3	1 to 10	≤ 2.4	1 to 10	4.2	< 1	1 to 3	< 1	3 to 9	< 1	< 2
Rash	1 to 3 35 to 46*	1 to 3	< 1	1 to 3	3 to 9	3 to 9	-	3 to 9	1 to 10	0.3 to 3.0	1 to 10	3.7	1 to 3	3 to 9	1 to 3	< 1	3 to 9	2.2
Skin carcinoma	0 to 2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Skin eruptions	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3 to 9	-	
Skin irritation	19 to 33*	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-	-	-	-	
Skin ulcer	1 to 2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Urticaria	< 1	< 1	< 1	< 1	< 1	-	< 1	1 to 3	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 2
Gastrointestinal																		
Abdominal distension	1 to 3	-	< 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Abdominal/ gastrointestinal distress	-	-	1 to 3	-	-	-	3 to 9	-	-	-	-	-	-	1 to 3	-	-	1 to 3	
Abdominal pain/cramps	3 to 9 1-2*	3 to 9	1 to 3	-	12	10	3 to 9	3 to 9	1 to 10	1.9 to 4.7	1 to 10	2	3 to 9	1 to 3	3 to 9	3 to 9	1 to 3	4.1
Anorexia/decreased appetite	-	< 1	< 1	< 1	< 1	1 to 3	-	1 to 3	-	-	1 to 10	< 1	-	1 to 3	1 to 3	-	1 to 3	< 2
Appetite increase	-	-	-	<1	<1	-	-	-	-	<2	-	-	-	-	<1	-	-	< 2
Bloating	-	-	< 1	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	
Colitis	<1	<1	-	-	-	<1	-	<1	-	<2	-	-	<1	-	-	<1	-	
Constipation	3 to 9	1 to 3	1 to 3	1 to 3	3 to 9	3 to 9	1 to 3	1 to 3	1 to 10	0.8 to 2.6	1 to 10	7	1 to 3	1 to 3	3 to 9	3 to 9	3 to 9	< 2
Diarrhea	3 to 9 2*	3 to 9	1 to 3	7	14	3 to 9	3 to 9	10 to 33	1 to 10	1.9 to 7.8	1 to 10	1.8	3 to 9	1 to 3	3 to 9	1 to 3	3 to 9	5.6
Dry mouth	<1	<1	-	<1	1 to 3	-	-	-	<1	<2	<1	<1	<1	<1	<1	-	-	< 2
Dysgeusia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dyspepsia/Indigestion	3 to 9 2-3*	10	3 to 9	12	13	3 to 9	3 to 9	-	1 to 10	3.8-= to 9.5	1 to 10	10.3	3 to 9	1 to 3	11	1 to 3	3 to 9	8.8
Epigastric/gastrointestinal	-	-	-	13	-	-	-	-	-	-	-	-	-	3 to 9	-	-	-	

Adverse reaction (%)	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin Indomethacin Sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calsium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
pain																		
Eructation	-	<1	-	<1	<1	-	-	-	<1	<2	<1	-	-	-	<1	-	-	
Esophagitis	-	<1	-	-	-	-	-	-	<1	<2	<1	-	-	-	-	-	-	< 2
Flatulence	1 to 3	3 to 9	< 1	1 to 3	3 to 9	1 to 3	3 to 9	3 to 9	1 to 10	0.4 to 3.2	1 to 10	< 1	1 to 3	1 to 3	3 to 9	-	1 to 3	2.2
Gastritis	-	1 to 3	-	< 1	1 to 3	< 1	1 to 3	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	-	-	< 2
Gastrointestinal bleeding	0.6	-	-	-	< 1	< 1	< 1	-	< 1	< 2	-	< 1	1 to 3	< 1	-	< 1	< 1	
Gastrointestinal fullness	-	-	-	1 to 3	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	
Gross bleeding/perforation	-	-	-	-	-	-	-	-	1 to 10	-	1 to 10	-	-	-	-	-	-	
Heartburn	-	-	-	-	-	-	-	3 to 9	1 to 10	-	1 to 10	-	-	3 to 9	-	3 to 9	-	
Hematemesis	-	-	-	-	-	-	-	-	<1	<2	<1	-	<1	-	<1	<1	-	
Hepatitis	<1	<1	-	-	-	<1	<1	-	<1	<2	<1	-	<1	<1	<1	-	<1	
Melena	< 1	1 to 3	-	-	< 1	-	-	-	< 1	< 2	< 1	-	-	< 1	< 1	< 1	-	
Nausea	3 to 9	3 to 9	3 to 9	12	3 to 9	3 to 9	11	11	1 to 10	2.4 to 7.2	1 to 10	7.7	3 to 9	3 to 9	3 to 9	3 to 9	3 to 9	3.5
Nausea and vomiting	-	-	1 to 3	-	-	1 to 3	-	11	-	-	-	-	-	1 to 3	-	-	-	
Pancreatitis	<1	<1	-	-	<1	<1	-	-	<1	<2	<1	<1	-	<1	<1	<1	<1	
Peptic ulcer	0.6	<1	<1	-	<1	<1	1 to 3	1 to 3	1 to 10	<2	1 to 10	<1	<1	-	<1	-	<1	
Peptic ulcer bleed	1 to 3	< 1	-	-	-	-	-	-	-	< 2	-	-	-	< 1	-	-	< 1	
Positive stool guaiac	-	-	-	-	3 to 9	-	-	-	-	-	-	< 1	-	-	-	-	-	
Stomatitis	-	-	-	1 to 3	1 to 3	< 1	< 1	1 to 3	< 1	-	< 1	-	< 1	-	1 to 3	1 to 3	< 1	
Vomiting	< 1	1 to 3	-	1 to 3	1 to 3	-	3 to 9	-	1 to 10	0.6-2.6	1 to 10	2.6	1 to 3	-	1 to 3	< 1	1 to 3	< 2
Genitourinary																		
Albuminuria	-	-	-	-	< 1	-	-	-	-	< 2	-	-	-	-	-	-	-	< 2
Dysuria	-	1 to 3	-	-	< 1	< 1	< 1	-	< 1	-	< 1	< 1	-	-	-	-	1 to 3	
Hematuria	< 1 0-2*	< 1	< 1	< 1	< 1	< 1	< 1	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 2
Renal failure	-	< 1	< 1	-	< 1	< 1	< 1	< 1	< 1	< 2	< 1	< 1	< 1	-	< 1	< 1	-	
Renal function impairment/ insufficiency	-	< 1	< 1	-	-	< 1	-	-	1 to 10	-	1 to 10	-	-	-	3 to 9	-	< 1	
Urinary frequency/ polyuria	< 1	1 to 3	< 1	< 1	-	-	-	-	< 1	0.1 to 2.4	< 1	-	-	< 1	-	-	1 to 3	
Urinary tract infection/ symptoms	-	-	-	-	-	-	1 to 3	-	-	0.3 to 6.9	-	-	3 to 9	-	1 to 3	-	-	
Hematologic/Lymphocytic																		
Anemia	-	< 1	-	< 1	< 1	-	-	-	1 to 10	≤ 4.1	1 to 10	-	-	-	< 1	-	< 1	< 2
Bleeding	-	-	-	-	-	-	-	-	-	-	-	-	-	32†	-	-	-	-
Ecchymosis	-	< 1	< 1	-	-	< 1	-	-	< 1	-	< 1	-	< 1	-	-	3 to 9	< 1	< 2
Leukopenia	< 1	< 1	< 1	-	< 1	< 1	-	< 1	< 1	< 2	< 1	-	< 1	-	-	< 1	< 1	
Purpura	< 1	-	-	1 to 3	-	< 1	< 1	-	< 1	< 2	< 1	< 1	-	-	< 1	1 to 3	-	
Thrombocytopenia	< 1	< 1	-	-	< 1	< 1	< 1	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 2
Hypersensitivity																		
Allergy/allergic reaction	0-1*	< 1	-	-	-	-	-	-	-	< 2	-	-	-	-	< 1	-	-	< 2
Angioedema/ angioneurotic edema	< 1	< 1	< 1	-	< 1	< 1	-	-	< 1	< 2	< 1	< 1	< 1	< 1	-	< 1	-	
Lab Test Abnormalities																		
ALT or AST elevations	2	-	-	-	-	-	-	-	-	< 2	-	< 1	-	-	-	-	-	

Adverse reaction (%)	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin Indomethacin Sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calsium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
	0 to 3*																	
Bleeding time increased	-	< 1	-	-	-	-	-	-	1 to 10	-	1 to 10	-	-	-	-	-	-	
Blood urea nitrogen increased	-	< 1	< 1	-	-	-	1 to 3	-	-	< 2	-	-	-	-	3 to 9	-	-	
Creatinine increase	0-4*	< 1	-	-	-	-	-	-	-	< 2	-	-	-	-	-	-	-	
Hemoglobin and hematocrit decreases	< 1	-	-	-	-	-	1 to 3	< 1	-	-	-	-	< 1	< 1	-	-	-	
Hypercholesterolemia	0 to 3*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Liver test abnormalities/elevations	3 to 9	< 1	-	-	< 1	< 1	< 1	< 1	1 to 10	-	1 to 10	-	1 to 3	< 1	-	< 1	< 1	
Metabolic and Nutritional																		
Body weight changes	-	< 1	-	-	-	-	3 to 9	-	< 1	< 2	< 1	-	1 to 3	-	< 1	-	< 1	< 2
Edema	-	< 1	< 1	4	3 to 9	1 to 3	3 to 9	1 to 3	1 to 10	0.5 to 4.5	1 to 10	-	3 to 9	1 to 3	3 to 9	3 to 9	< 1	< 2
Fluid retention	1 to 3	-	< 1	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	
Peripheral edema	-	-	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	2.1
Thirst	-	< 1	-	-	-	-	-	-	-	-	-	-	-	-	< 1	1 to 3	-	
Musculoskeletal System																		
Arthralgia	0 to 2*	-	-	-	-	-	-	-	-	≤ 5.3	-	-	-	-	-	-	-	< 2
Back pain	2 to 4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.8
Muscle weakness	0 to 2*	-	< 1	-	-	< 1	-	-	-	-	-	-	-	-	-	< 1	-	
Myalgia	2 to 3*	-	-	-	-	-	-	-	-	-	-	-	-	-	< 1	< 1	-	< 2
Respiratory System																		
Asthma	< 1 0 to 2*	< 1	< 1	-	< 1	-	-	-	< 1	< 2	< 1	-	< 1	-	-	-	-	
Bronchospasm	-	-	-	-	-	< 1	-	-	-	< 2	-	-	-	< 1	< 1	-	-	< 2
Coughing	-	-	-	< 1	< 1	-	-	-	-	0.2 to 2.4	-	-	-	-	-	-	-	< 2
Dyspnea	< 1 2*	< 1	< 1	< 1	< 1	< 1	-	-	< 1	< 2	< 1	2.8	< 1	-	< 1	3 to 9	-	
Pharyngitis	2*	< 1	-	-	-	-	-	-	-	0.6 to 3.2	-	-	-	-	< 1	-	-	2.3
Pneumonia	0 to 2*	-	-	-	-	-	-	-	< 1	-	< 1	-	-	-	-	-	-	< 2
Respiratory Failure	-	-	-	-	-	-	-	-	-	-	-	-	-	10†	-	-	-	-
Respiratory Infection	-	-	-	-	-	-	-	-	-	-	-	-	-	10†	-	-	-	-
Rhinitis	2*	< 1	-	< 1	-	-	-	-	-	-	-	-	1 to 3	< 1	< 1	-	-	2.0
Sinusitis	0 to 2*	< 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	< 1	5.0
Upper respiratory infection	-	-	-	-	-	-	-	-	-	≤ 8.3	-	1.5	-	-	-	-	< 1	8.1
Other																		
Accident, household	-	-	-	-	-	-	-	-	-	3.2 to 4.5	-	-	-	-	-	-	-	2.9
Back pain	-	-	-	-	-	-	-	-	-	0.4 to 3.0	-	-	-	-	-	-	-	
Blurred vision	< 1	1 to 3	< 1	< 1	-	< 1	-	< 1	< 1	-	< 1	2.2	-	-	-	-	< 1	
Chest pain	< 1	-	< 1	-	-	-	1 to 3	-	-	-	-	-	-	-	-	-	-	< 2
Chills	-	1 to 3	-	-	< 1	-	-	-	-	-	-	-	< 1	-	< 1	< 1	-	
Conjunctivitis	2 to 4*	< 1	-	-	-	-	-	< 1	< 1	< 2	< 1	-	< 1	< 1	< 1	-	< 1	

Adverse reaction (%)	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin Indomethacin Sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calsium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
Face edema	-	-	-	-	-	-	-	-	-	< 2	-	-	-	-	< 1	-	-	< 2
Fall	-	-	-	-	-	-	-	-	-	≤ 2.6	-	-	-	-	-	-	-	
Fever	-	1 to 3	< 1	< 1	< 1	-	< 1	-	< 1	< 2	< 1	< 1	< 1	-	-	< 1	-	< 2
Hearing disturbances	-	-	< 1	-	-	-	-	-	-	-	-	-	-	-	-	1 to 3	-	
Hearing loss/ impairment	< 1	-	-	< 1	-	< 1	-	-	< 1	-	< 1	1.6	-	< 1	< 1	< 1	< 1	
Infection	4*	< 1	-	< 1	-	-	-	-	< 1	-	< 1	-	-	-	< 1	-	-	
Influenza-like disease/ symptoms	1 to 10*	-	-	-	-	-	-	-	-	4.5 to 5.8	< 1	-	-	-	-	-	-	< 2
Injury, accidental	0 to 4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Neck pain	0 to 2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pain	-	-	-	-	-	-	-	-	-	0.9 to 5.2	-	-	-	-	< 1	-	-	
Sepsis	-	-	-	-	-	-	-	-	-	-	-	-	-	43†	-	-	-	-
Taste disorder/ perversion/ disturbance/alteration/changes	< 1	< 1	-	-	< 1	-	-	< 1	-	< 2	-	-	< 1	-	< 1	-	< 1	
Tinnitus	1 to 3	1 to 3	1 to 3	< 1	3 to 9	1 to 3	1 to 3	1 to 3	1 to 10	< 2	1 to 10	4.5	1 to 3	1 to 3	1 to 3	3 to 9	1 to 3	< 2
Visual disturbances/changes	-	< 1	-	-	< 1	< 1	1 to 3	-	-	-	-	-	1 to 3	-	1 to 3	1 to 3	-	

ALT=alanine aminotransferase, AST=aspartate transaminase
*Topical dosage form.
†Ibuprofen lysine IV injection.
- Event not reported.

Contraindications

Table 7. Contrainidcations[3-7]

Contraindication	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin/ Indomethacin sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calcium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
Concomitant use of aspirin or other NSAIDs.				a														
Concomitant use of pentoxifylline.				a														
Concomitant use of probenecid.				a														
History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
History of proctitis or recent rectal bleeding.			a	a														
Known hypersensitivity to bovine protein.	a *																	
Known hypersensitivity to ethylenediamine tetraacetic acid (EDTA).				a §														
Known hypersensitivity to the active drug or any components of	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a

Contraindication	Diclofenac/ Diclofenac sodium/ potassium	Etodolac	Indomethacin/ Indomethacin sodium	Ketorolac tromethamine	Nabumetone	Sulindac	Tolmetin sodium	Meclofenamate sodium	Mefenamic acid	Meloxicam	Piroxicam	Fenoprofen Calcium	Flurbiprofen	Ibuprofen/ Ibuprofen lysine	Ketoprofen	Naproxen/ Naproxen sodium	Oxaprozin	Celecoxib
the product.																		
Known hypersensitivity to sulfonamides.																		a
Neuraxial (epidural or intrathecal) administration due to its alcohol content				a														
Perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Pre-existing renal disease.									a									
Renal insufficiency, moderate to severe, in the perioperative period and who are at risk for volume depletion.	a †																	
Renal insufficiency, severe, or at risk for renal failure due to volume depletion				a								a		a ‖				
Use as prophylactic analgesia before major surgery.				a														
Use as treatment of perioperative pain analgesia before major surgery																		
Use during labor and delivery.				a														
Use in nursing mothers.				a														
Use in patients with active, acute ulceration or chronic inflammation of either the upper or lower gastrointestinal tract.									a									
Use in patients with active bleeding.														a ‖				
Use in patients with active gastrointestinal bleeding.																	a	a
Use in patients with active infection (known or suspected).														a ‖				
Use in patients with active peptic ulcer disease.				a														
Use in patients with coagulation defects.														a ‖				
Use in patients with congenital heart disease in whom patency of the PDA is necessary for satisfactory pulmonary or systemic blood flow														a ‖				
Use in patients with cerebrovascular bleeding (known or suspected), hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding				a														
Use in patients with necrotizing enterocolitis.														a ‖				
Use in patients with thrombocytopenia.														a ‖				

NSAID=nonsteroidal anti-inflammatory drug
*Zipsor®
†Dyloject®
‡Indocin® suppositories
§Sprix®
‖Neoprofen®

Almost all NSAIDs carry a black box warning for the risk of serious cardiovascular and gastrointestinal events. The two agents that do not have this black box warning are ibuprofen lysine solution (Neoprofen®) and indomethacin powder for solution. In addition to the standard warnings for NSAIDs, ketorolac tromethamine products have many additional black box warnings.[1-37]

Black Box Warning for NSAIDs[1-14,18-37]

WARNING
WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS **Cardiovascular Risk** · NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. · NSADS are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. **Gastrointestinal Risk** · NSAIDs cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal events.

Black Box Warning for ketorolac tromethamine (tablet, injection solution, nasal spray [Sprix®])[15-17]

WARNING
Ketorolac tromethamine tablets, a nonsteroidal anti-inflammatory drug (NSAID), are indicated for the short-term (up to 5 days in adults), management of moderately severe acute pain that requires analgesia at the opioid level and only as continuation treatment following IV or IM dosing of ketorolac tromethamine, if necessary. The total combined duration of use of ketorolac tromethamine should not exceed 5 days.* Ketorolac tromethamine tablets are not indicated for use in pediatric patients and it is NOT indicated for minor or chronic painful conditions.* **Gastrointestinal Risk*** · Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Elderly patients are at greater risk for serious gastrointestinal events **Cardiovascular Risk*** · Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. · Ketorolac tromethamine tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery. **Renal Risk*** · Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.

WARNING

Risk of Bleeding*

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding.

Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery.‡

Hypersensitivity†

- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine injection. Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Intrathecal or Epidural Administration†

- Ketorolac tromethamine is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

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 tromethamine is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs because of the cumulative risk 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.

Dosage and Administration‡

- Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine injection, and the combined duration of use of ketorolac tromethamine injection and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.
- The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine injection (maximum 120 mg).

*Black box warning for all products.
†Black box warning only injection solution formulation only.
‡Black box warning for tablet and injection solution formulation only.

Warnings/Precautions
All NSAIDs share similar warnings and precautions.[1-37]

Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Based on available data, it is unclear that the risk for cardiovascular thrombotic events is similar for all NSAIDs. The increase in cardiovascular thrombotic risk has been observed most consistently at higher doses. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for three to six months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Hepatotoxicity
Elevations of liver enzymes (three or more times the upper limit of normal) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Hypertension
NSAIDs, can lead to new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema
Several studies have implicated with an increased risk of myocardial infarction, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of NSAIDs may blunt the cardiovascular effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]). Monitor blood pressure during the initiation of NSAID treatment and throughout the course of therapy. Avoid the use of NSAIDs in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If NSAIDs are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy was usually followed by recovery to the pretreatment state. Limited or no information is available regarding the use of NSAIDs in patients with advanced renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating NSAIDs. Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Anaphylactic Reactions
NSAIDs have been associated with anaphylactic reactions in patients with and without known hypersensitivity.

Exacerbation of Asthma Related to Aspirin Sensitivity
A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported

in such aspirin-sensitive patients, NSAIDs are contraindicated in patients with this form of aspirin sensitivity asthma.

Serious Skin Reactions
NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning.

Fetal Toxicity
Starting at 30 weeks gestation, NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus.

Corticosteroid-Responsive Illness
NSAIDs cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Hematologic Toxicity (Anemia)
Anemia may occur in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients on long-term therapy with NSAIDs, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss.

Hematologic Toxicity (Prolonged Bleeding)
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Carefully monitor patients treated with NSAIDs who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

Masking of Inflammation and Fever
The pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically

Central Nervous System Effects
NSAIDs may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue the NSAID(s) if severe central nervous system adverse reactions develop.

Ocular Effects
Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with NSAIDs. Be alert to the possible association between the changes noted and the NSAID. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. TIVORBEX is not indicated for long-term treatment.

Eye Exposure (Sprix® [ketorolac tromethamine] nasal spray)[17]

Avoid contact of Sprix® with the eyes. If eye contact occurs, wash out the eye with water or saline, and consult a physician if irritation persists for more than an hour.

Drug Interactions

Table 8. Drug Interactions[1-37,42,43]

Generic Name	Interacting Medication or Disease	Potential Result
NSAIDs (all)	ACE inhibitors, ARBs	NSAIDs may decrease the antihypertensive effect of ACE inhibitors and ARBs and could precipitate renal failure. Monitor blood pressure and for hyperkalemia or acute renal failure.
NSAIDs (all)	Antiplatelet agents, clopidogrel, low molecular weight heparins, gingko biloba, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, warfarin	NSAIDs used concurrently with the interacting medication may result in an increased risk of bleeding. Monitor closely for bleeding, particularly gastrointestinal bleeding, which may be serious.
NSAIDs (all)	Aspirin	NSAIDs may reduce the cardioprotective effect of low-dose uncoated aspirin and may cause a higher risk of gastric irritation. Administer ibuprofen at least 8 hours before or 30 minutes after immediate-release aspirin. Administer an NSAID at least 1 hour after taking enteric-coated aspirin for cardioprotective action. Ketorolac is contraindicated for use with aspirin due to an increased risk of gastrointestinal adverse effects.
NSAIDs (all)	Azole antifungals (fluconazole, voriconazole)	Azole antifungals may increase the concentration of NSAIDs through CYP2C9 inhibition. Observe patients for an increase in NSAID adverse reactions and adjust the NSAID dose as needed.
NSAIDs (all)	Cyclosporine	NSAIDs used concurrently with cyclosporine may lead to additive nephrotoxicity. Monitor renal function.
NSAIDs (all)	Ketorolac	NSAIDs used concurrently with ketorolac may result in enhanced gastrointestinal adverse effects. This combination is contraindicated.
NSAIDs (all)	Loop diuretics, potassium sparing diuretics, thiazide diuretics	NSAIDs may reduce the effectiveness of diuretics and cause hyperkalemia or nephrotoxicity. Monitor blood pressure, weight changes, urine output, potassium levels, and creatinine levels.
NSAIDs (all)	Quinolone antibiotics	Concurrent use of NSAIDs and quinolone antibiotics may result in an increased risk of seizures. Caution is advised.
NSAIDs (all)	Sulfonylureas	NSAIDs used concurrently with sulfonylureas may result in an increased risk of hypoglycemia. Monitor closely for hypoglycemia.
NSAIDs (all)	Tacrolimus	NSAIDs used concurrently with tacrolimus

Generic Name	Interacting Medication or Disease	Potential Result
		may lead to additive nephrotoxicity resulting in acute renal failure. Monitor renal function.
NSAIDs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin sodium)	Methotrexate	NSAIDs used concurrently with methotrexate may result in methotrexate toxicity. Do not administer NSAIDs within 10 days of high-dose methotrexate. If concomitant administration is necessary, monitor closely for toxicity, especially myelosuppression and gastrointestinal toxicity. Lower doses have been tolerated with NSAID therapy, however caution is advised.
NSAIDs (indomethacin, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, tolmetin sodium)	Lithium	Concurrent use of indomethacin and lithium may result in an increased risk of lithium toxicity (weakness, tremor, excessive thirst, confusion). Monitor serum lithium levels for any symptoms of lithium toxicity.
NSAIDs (ibuprofen, indomethacin, naproxen, piroxicam)	β-blockers	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension and impair the antihypertensive effect of beta-blockers. Avoid using interacting NSAIDs if possible. Monitor blood pressure and adjust dose as needed.
NSAIDs (diclofenac, indomethacin)	Digoxin	NSAIDs used concurrently with digoxin may result in an increased risk of digoxin toxicity (nausea, vomiting and arrhythmias). Monitor the patient for signs of digoxin toxicity and if digoxin toxicity is suspected a digoxin serum concentration should be determined.
NSAIDs (ibuprofen)	Phenytoin	Ibuprofen used concurrently with phenytoin may result in an increased risk of phenytoin toxicity, especially in renally impaired patients. Monitor phenytoin serum concentrations and for signs and symptoms of phenytoin toxicity.
NSAIDs (indomethacin)	Potassium	Indomethacin used concurrently with potassium supplementation may result in hyperkalemia. Monitor serum potassium and if necessary discontinue potassium supplementation or decrease indomethacin dose.

ACE=angiotensin converting enzyme, ARB=angiotensin receptor blocker, NSAID=nonsteroidal anti-inflammatory drug

Dosage and Administration

Table 9. Dosing and Administration[1-37]

Generic Name	Adult Dose	Pediatric Dose	Availability
Acetic Acid Derivatives			
Diclofenac	Mild to Moderate Pain: Capsule: 18 to 35 mg TID Osteoarthritis: Capsule: 35 mg TID	Safety and efficacy in pediatric patients have not been established.	Capsule: 18 mg 35 mg
Diclofenac potassium	Acute Pain: Capsule, liquid filled: 25 mg QID Mild to Moderate Pain, Primary Dysmenorrhea: Tablet (sugar coated): 50 mg TID Osteoarthritis: Tablet (sugar coated): 50 mg BID to 50 mg TID Rheumatoid Arthritis: Tablet (sugar coated): 50 mg TID to 50 mg QID		Capsule, liquid filled (Zipsor®): 25 mg Tablet, sugar coated (Cataflam®): 50 mg
Diclofenac sodium	Acute Pain: Solution (injection): initial, 37.5 mg via IV bolus Q6H PRN for pain; maximum, 150 mg/day Ankylosing Spondylitis: DR tablet: initial, 100 to 125 mg/day (25 mg QID with an additional 25 mg PRN at bedtime); maximum, 125 mg/day Osteoarthritis: DR tablet: initial, 100 to 150 mg/day in divided doses (50 mg BID, 50 mg TID, 75 mg BID); maximum, 150 mg/day ER tablet: initial, maximum100 mg QD Rheumatoid Arthritis: DR tablet: initial,150 to 200 mg/day in divided doses (50 mg TID, 50 mg QID, 75 mg BID); maximum, 225 mg/day		Tablet, DR: 25 mg 50 mg 75 mg Tablet, film coated ER (Voltaren XR®): 100 mg Solution, injection (Dyloject®) 37.5 mg/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	ER tablet: initial mg QD; maximum, 100 mg BID if the benefits outweigh the risks		
Etodolac	Acute Pain: Capsule, tablet: initial, 200 mg to 400 mg Q6H to Q8H; maximum, 1,000 mg/day Osteoarthritis, Rheumatoid Arthritis: Capsule, tablet: initial, 300 mg BID, 300 mg TID, 400 mg BID, 500 mg BID; 600 mg/day may suffice for long-term administration; maximum, 1,000 mg/day ER tablet: initial, 400 mg to 1,000 mg QD; maximum, 1,000 mg QD	Juvenile Rheumatoid Arthritis (age six and older): ER tablet: initial, maximum, dose by body weight (400 mg QD [20 to 30 kg], 600 mg QD [31 to 45 kg], 800 mg QD [46 to 60 kg], 1,000 mg QD [>60kg])	Capsule: 200 mg 300 mg Tablet, ER: 400 mg 500 mg 600 mg Tablet, film coated: 400 mg 500 mg
Indomethacin	Acute Pain: Capsule (Tivorbex®): initial, maximum, 20 mg TID or 40 mg TID Acute Gouty Arthritis: Capsule, suppository*, oral suspension: initial, 50 mg TID for three to five days Acute Shoulder Pain: Capsule, suppository*, oral suspension: initial, 75 mg to 150 mg/day in three to four divided doses for seven to 14 days; maximum, 150 mg/day ER capsule: initial 75 mg QD or 150 mg BID for seven to 14 days; maximum, 150 mg BID Ankylosing Spondylitis, Rheumatoid Arthritis, Osteoarthritis: Capsule, suppository*, oral suspension: Initial, 25 mg BID or TID; maximum, 200 mg/day ER capsule: initial, 75 mg	Acute Gouty Arthritis, Acute Shoulder Pain, Ankylosing Spondylitis, Rheumatoid Arthritis, Osteoarthritis (FDA-approved for use in children 15 years of age or older): Capsule, suppository*, suspension: Refer to adult dosing	Capsule: 20 mg (Tivorbex®) 25 mg 40 mg (Tivorbex®) 50 mg Capsule, ER: 75 mg Suppository: 50 mg (Indocin®) Suspension, oral: 25 mg/5 mL (Indocin®)

Generic Name	Adult Dose	Pediatric Dose	Availability
	QD; maximum, 75 mg BID		
Indomethacin Na	Safety and efficacy have only been established in neonatal patients.	Closure of Patent Ductus Arteriosus (Neonatal patients): Injection: Administer one treatment course comprised of three IV injections at 12 to 24 hour intervals, dosed based on age at first dose. Age <48 hours: 1st: 0.2 mg/kg 2nd: 0.1 mg/kg 3rd: 0.1 mg/kg Age 2 to 7 days: 1st: 0.2 mg/kg 2nd: 0.2 mg/kg 3rd: 0.2 mg/kg Age over 7 days: 1st: 0.2 mg/kg 2nd: 0.25 mg/kg 3rd: 0.25 mg/kg If anuria or marked oliguria (urinary output <0.6 mL/kg/hr) is evident at the scheduled time of the second or third dose, do not give additional doses until laboratory studies indicate that renal function has returned to normal. If the ductus arteriosus re-opens, a second course of 1 to 3 doses may be given, each dose separated by a 12 to 24 hour interval as described above. If the neonate remains unresponsive to therapy with Indomethacin for	Solution, lyophilized powder for injection: 1 mg/vial

Generic Name	Adult Dose	Pediatric Dose	Availability
		Injection after two courses, surgery may be necessary for closure of the ductus arteriosus.	
Ketorolac tromethamine	Moderate to severe acute pain: Nasal spray: Patients <65 years of age, one spray (15.75 mg) in each nostril (total dose 31.5 mg) Q6H to Q8H; maximum, 126 mg/day (four doses); Patients ≥65 years of age, one spray in one nostril (total dose 15.75 mg) Q6H to Q8H Solution (injection): initial, single dose IM: Patients <65 years of age should be administered one 60 mg dose. Patients ≥65 years of age, renally impaired, or weighing <50 kg should be administered one 30 mg dose. Single dose IV: Patients <65 years of age should be administered one 30 mg dose. Patients ≥65 years of age, renally impaired, or weighing <50 kg should be administered 1 dose of 15 mg. Solution (multiple dose IV or IM): Patients <65 years of age should be administered 30 mg IV/IM every 6 hours. Patients ≥65 years of age, renally impaired, or weighing <50 kg and 15 mg IV/IM every 6 hours in; maintenance, not intended for use >5 days; maximum, 120 mg daily in patients< 65 years of age and 60 mg daily≥65 years of age, renally impaired, or weighing <50 kg Tablet: initial, patients <65 years of age: take 20 mg as first dose following 60 mg IM	Safety and efficacy of oral ketorolac has not been established in the pediatric population. Moderately severe, acute pain: Injection: initial, one dose of 1 mg/kg (IM) or 0.5 mg/kg (IV); maintenance, only intended for use as a single dose; maximum, 30 mg (IM) or 15 mg (IV)	Nasal Spray, metered: 15.75 mg/spray Solution, injection (vial): 15 mg/mL 30 mg/mL 60 mg/2 mL 300 mg/10 mL Tablet, film coated: 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	single dose, 30 mg IV single dose or 30 mg multiple dose. 10 mg every 4 to 6 hours thereafter; maintenance, not intended for use >5 days; maximum, 40 mg daily Patients >65 years of age, renally impaired, or weighing <50 kg: Take 10 mg as first dose following 30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose. 10 mg every 4 to 6 hours thereafter; maintenance, not intended for use >5 days; maximum, 40 mg daily		
Nabumetone	Osteoarthritis, Rheumatoid Arthritis: Tablet: initial 1,000 mg QD; maintenance, 1,500 to 2,000 mg QD or BID; maximum, 2,000 mg/day	Safety and efficacy has not been established in the pediatric population.	Tablet: 500 mg 750 mg
Sulindac	Acute Gouty Arthritis, Acute Shoulder Pain: Tablet: initial, 200 mg BID; maximum, 400 mg/day Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis: Tablet: initial, 150 mg BID; maximum, 400 mg/day	Safety and efficacy has not been established in the pediatric population.	Tablet: 150 mg 200 mg
Tolmetin Sodium	Osteoarthritis, Rheumatoid Arthritis: Capsule, tablet: initial, 400 mg TID; maintenance, 600 to 1,800 mg/day in divided doses; maximum, 1,800 mg/day	Juvenile Rheumatoid Arthritis (age 2 or older): Capsule and tablet: initial, 20 mg/kg/day TID or QID; maintenance, 15 to 30 mg/kg/day; maximum, 30 mg/kg/day	Capsule: 400 mg Tablet: 200 mg 600 mg
Anthranilic Acid (Fenamate) Derivatives			
Meclofenamate sodium	Fever Reduction: Capsule: No dosing recommendations provided for this diagnosis. Mild to moderate pain: Capsule: initial, 50 mg Q4H or Q6H; maximum, 400 mg/day	Safety and efficacy has not been established in the pediatric population in patients <14 years of age. Adolescent's ≥14 years of age may be	Capsule: 50 mg 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Primary dysmenorrhea: Capsule: initial/maintenance, 100 mg TID for up to six days starting at the onset of menstrual flow; maximum, 400 mg/day Rheumatoid arthritis, osteoarthritis: Capsule: initial/maintenance, 200 mg to 400 mg/day, administered in 3 or 4 equal doses; maximum, 400 mg/day	treated using adult dosing.	
Mefenamic acid	Mild to moderate pain: Capsule: initial, 500 mg x1 dose followed by 250 mg every Q6H PRN Primary dysmenorrhea: Capsule: initial, 500 mg x1 dose followed by 250 mg Q6H	Safety and efficacy has not been established in the pediatric population in patients <14 years of age. Adolescents aged 14 and above may be treated using adult dosing.	Capsule: 250 mg
Enolic Acid Derivatives			
Meloxicam	Osteoarthritis: Capsule: initial, 5 mg QD; maximum, 10 mg QD Oral suspension, tablet: initial, 7.5 mg QD; maximum, 15 mg QD Rheumatoid Arthritis: Oral suspension, tablet: initial, 7.5 mg QD; maximum, 15 mg QD	Juvenile Rheumatoid Arthritis (age 2 and older): Oral suspension: initial, 0.125 mg/kg QD; maximum, 7.5 mg QD	Capsule (Vivlodex®): 5 mg 10 mg Suspension, oral (Mobic®): 7.5 mg/5 mL Tablet (Mobic®): 7.5 mg 15 mg
Piroxicam	Osteoarthritis, Rheumatoid Arthritis: Capsule: initial/maintenance, 20 mg QD (may be divided) for 7 to 12 days	Safety and efficacy has not been established in the pediatric population.	Capsule: 10 mg 20 mg
Propionic Acid Derivatives			
Fenoprofen calcium	Mild to Moderate Pain: Capsule: initial/maintenance, 200 mg Q4H to Q6H PRN Osteoarthritis, Rheumatoid Arthritis: Capsule, tablet:	Safety and efficacy has not been established in the pediatric population.	Capsule: 200 mg 400 mg Tablet, film coated: 600 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	initial/maintenance, 400 mg to 600 mg TID or QID; maximum, 3,200 mg/day		
Flurbiprofen	Osteoarthritis, Rheumatoid Arthritis: Tablet: initial/maintenance, 200 mg to 300 mg/day administered BID, TID, or QID; maximum 100 mg/dose	Safety and efficacy has not been established in the pediatric population.	Tablet: 50 mg 100 mg
Ibuprofen	Fever Reduction: Injection: initial/maintenance, 400 mg IV x1 dose followed by 400 mg IV over at least 30 minutes Q4H to Q6H PRN or 400 mg IV x1 dose followed by 100 mg or 200 mg IV over at least 30 minutes Q4H PRN; maximum, 3,200 mg/day Mild to Moderate Pain: Injection: initial/maintenance, 400 mg to 800 mg IV over at least 30 minutes Q6H PRN; maximum, 3,200 mg/day Tablet: initial/maximum: 400 mg Q4H to Q6H PRN Moderate to Severe Pain: Injection: initial/maintenance, 400 mg to 800 mg IV over at least 30 minutes Q6H PRN; maximum, 3,200 mg/day Osteoarthritis, Rheumatoid Arthritis: Tablet: initial, 1,200 mg to 3,200 mg/day (400, 600, 800 mg TID or QID); maximum, 3,200 mg/day Primary Dysmenorrhea: Tablet: initial/maintenance, 400 mg Q4H PRN	Fever Reduction, Mild to Moderate Pain, Moderate to Severe Pain: Injection (12 to 17 years of age): initial/maintenance, 400 mg IV over at least 10 minutes Q4H to Q6H PRN; maximum, 2,400 mg/day Injection (6 months to 12 years of age): initial/maintenance, 10 mg/kg IV over at least 10 minutes Q4H to Q6H PRN; maximum, 40 mg/kg or 2,400 mg (whichever is less)	Injection (Caldolor®): 400 mg/mL 800 mg/mL Tablet, film coated: 400 mg 600 mg 800 mg
Ibuprofen Lysine	Safety and efficacy have only been established in neonatal patients.	Closure of Patent Ductus Arteriosus (Neonatal patients): Injection (500 to 1,500 grams, not less than 32 weeks gestational age):	Solution, injection: 10 mg/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
		initial, 10 mg/kg IV over 15 minutes on day 1, followed by 5 mg/kg IV over 15 minutes after 24 and 48 hours for a total of three doses (doses are based on birth weight) Injection (younger than 32 weeks gestation): 10 mg/kg continuous IV infusion (0.416 mg/kg/hr) on day 1, followed by 5 mg/kg continuous IV infusion (0.508 mg/kg/hr) on days 2 and 3	
Ketoprofen	Acute Pain, Primary Dysmenorrhea: Capsule: initial/maintenance, 25 mg to 50 mg every Q6H to Q8H PRN; maximum, 300 mg/day Osteoarthritis/Rheumatoid Arthritis: Capsule: initial/maintenance, 75 mg TID or 50 mg QID; maximum, 300 mg/day	Safety and efficacy has not been established in the pediatric population.	Capsule: 50 mg 75 mg
Naproxen	Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis: DR tablet: initial/maintenance, 375 mg or 500 mg BID; maximum, 1,500 mg/day Oral suspension, tablet: initial/maintenance, 250 mg, 375 mg, or 500 mg BID; maximum, 1,500 mg/day Acute Gouty Arthritis: Tablet: initial/maintenance, 750 mg followed by 250 mg Q8H; maximum, 1,500 mg daily	Juvenile rheumatoid arthritis (5 years of age and older): Oral suspension: initial/maintenance, 10 mg/kg/day in two divided doses	DR Tablet (EC-Naprosyn®): 375 mg Suspension, oral: 125 mg/5 mL Tablet (Naprosyn®): 250 mg 375 mg 500 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Acute Pain, Acute Shoulder Pain, Primary Dysmenorrhea: Oral suspension: initial/maintenance, 500 mg x1 dose followed by 500 mg Q12H or 250 mg Q6H or Q8H PRN; maximum, 1,250 mg (initial dose), 1,000 mg/day (maintenance doses)		
Naproxen sodium	Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis: Tablet (Anaprox®): initial/maintenance, 275 mg BID; maximum, 1,500 mg/day Tablet (Anaprox DS®): initial/maintenance, 550 mg BID; maximum, 1,500 mg/day Acute Gouty Arthritis: Tablet: initial/maintenance, 825 mg followed by 275 mg Q8H; maximum, 1,500 mg daily Acute Pain, Acute Shoulder Pain, Primary Dysmenorrhea: Tablet: initial/maintenance, 550 mg x1 dose, followed by 550 mg Q12 H or 275 mg Q6H to Q8H PRN; maximum, 1,375 mg	Not recommended for the treatment of Juvenile Rheumatoid Arthritis.	Tablet: 275 mg (Anaprox®) 550 mg (Anaprox DS®) ER tablet: 375 mg 500 mg 750 mg
Oxaprozin	Osteoarthritis: Tablet: initial/maintenance, 1,200 mg QD; maximum, 1,800 mg/day or 26 mg/kg (whichever is lower) Rheumatoid arthritis: Tablet: initial/maintenance, 1,200 mg QD; maximum, 1,800 mg/day	Juvenile Rheumatoid Arthritis (6 years of age and older): Tablet: initial, 600 mg QD (22 to 31 kg body weight), 900 mg QD (32 to 52 kg body weight), 1,200 mg QD (≥55 kg body weight)	Tablet: 600 mg
Selective COX-2 Inhibitors			
Celecoxib	Acute Pain, Primary Dysmenorrhea: Capsule: initial, 400 mg x1 dose followed by an additional 200 mg dose if needed on day one; maintenance, 200 mg BID	Juvenile Rheumatoid Arthritis (2 years of age and older): Tablet: initial, 50 mg BID (≥10 kg to ≤25 kg body weight), 100 mg BID (>25 kg body weight)	Capsule: 50 mg 100 mg 200 mg 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Ankylosing Spondylitis: Capsule: initial, 200 mg QD or 100 mg BID; maintenance, 200 mg/day to 400 mg/day; maximum, 400 mg/day Rheumatoid Arthritis: Capsule: initial/maintenance, 100 mg to 200 mg BID Osteoarthritis: Capsule: initial/maintenance, 200 mg QD or 100 mg BID		

Drug regimen abbreviations: BID=twice daily, PRN=as needed, Q12H=every 12 hours, Q4H=every four hours, Q6H=every six hours, Q8H=every eight hours, QD=once daily, QID=four times daily, TID=three times daily
Other Abbreviations: DR=delayed-release, ER=extended-release, IM=intramuscular, IV=intravenous
*Specific dosing not provided. FDA-approved label for indomethacin suppositories (Indocin®) lists dosing information for indomethacin capsules as guidance in using indomethacin suppositories.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[76]	Nonpharmacologic recommendations for the management of hand osteoarthritis · It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. Pharmacologic recommendations for the initial management of hand osteoarthritis · It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. · It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. · It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. Nonpharmacologic recommendations for the management of knee osteoarthritis

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	· It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> · It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with knee osteoarthritis not use

Clinical Guideline	Recommendations
	the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. · No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. Nonpharmacologic recommendations for the management of hip osteoarthritis · It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. Pharmacologic recommendations for the initial management of hip osteoarthritis · It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. · No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
American Academy of Orthopaedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[77]	Nonpharmacological/surgical therapy · Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. · Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. · Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. · Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use

Clinical Guideline	Recommendations
	of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. · It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. · Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. <u>Pharmacological therapy</u> · Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol. · There is a lack of compelling evidence to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. · There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
National Institute for Health and Clinical Excellence: **Osteoarthritis: Care and management in adults (2014)**[78]	· This summary will focus on pharmacologic therapy of osteoarthritis <u>Oral Analgesics</u> · Healthcare professionals should consider offering acetaminophen for pain relief in addition to core treatments; regular dosing may be required. Acetaminophen and/or topical NSAIDs should be considered ahead of oral NSAIDs, COX-2 inhibitors or opioids. · If acetaminophen or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in older people. <u>Topical Treatments</u> · Consider topical NSAIDs for pain relief in addition to core treatments for people with knee or hand osteoarthritis. Consider topical NSAIDs and/or acetaminophen ahead of oral NSAIDs, COX-2 inhibitors or opioids. · Topical capsaicin should be considered as an adjunct to core treatments for knee or hand osteoarthritis. · Do not offer rubefacients for treating osteoarthritis. <u>NSAIDs and Highly-Selective COX-2 Inhibitors</u> · Although NSAIDs and COX-2 inhibitors may be regarded as a single drug class of 'NSAIDs', these recommendations use the two terms for clarity and because of the differences in side-effect profile.

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	· Where acetaminophen or topical NSAIDs are ineffective for pain relief for people with osteoarthritis, then substitution with an oral NSAID/COX-2 inhibitor should be considered. · Use oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest possible period of time. · When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg). In either case, co-prescribe with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost. · All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. · If a person with osteoarthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient. <u>Intra-Articular Injections</u> · Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis. · Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.
American College of Rheumatology: **2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (2015)**[79]	<u>Recommendations for Early RA Patients</u> · We strongly recommend using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices. · For disease-modifying antirheumatic drug (DMARD)-naïve patients with early, symptomatic RA, we strongly recommend DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and conditionally recommend DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease. · For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), we strongly recommend treatment with a combination of DMARDs <u>or</u> a TNFi <u>or</u> a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy. · For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, we conditionally recommend adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent). Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the

Clinical Guideline	Recommendations
	duration of therapy is short. · For patients experiencing a flare of RA, we conditionally recommend adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient. Recommendations for Established RA Patients · We strongly recommend using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, however, another target may be chosen because tolerance by patients or comorbidities may mitigate the usual choices. · For DMARD-naïve patients with low disease activity, we strongly recommend using DMARD monotherapy over a TNFi. For DMARD-naïve patients with moderate or high disease activity, we conditionally recommend DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease. · For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, we strongly recommend using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy. · For all scenarios for established RA below, treatment may be with or without MTX. · For moderate or high disease activity despite TNFi therapy in patients currently not on a DMARD, we strongly recommend that one or two DMARDs be added to TNFi therapy rather than continuing TNFi therapy alone. · If disease activity is moderate or high despite single TNFi biologic therapy, we conditionally recommend using a non-TNF biologic. · If disease activity is moderate or high despite non-TNF biologic therapy, we conditionally recommend using another non-TNF biologic. However, if a patient has failed multiple non-TNF biologics and they are TNFi-naïve with moderate or high disease activity, we conditionally recommend treatment with a TNFi. · For patients with moderate or high disease activity despite prior treatment with at least one TNFi and at least one non-TNF-biologic (sequentially, not combined), we conditionally recommend first treating with another non-TNF biologic. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), we conditionally recommend treatment with tofacitinib. · If disease activity is moderate or high despite the use of multiple (2+) TNFi therapies (in sequence, not concurrently), we conditionally recommend non-TNF biologic therapy and then conditionally treating with tofacitinib when a non-TNF biologic is not an option. · If disease activity is moderate or high despite any of the above DMARD or biologic therapies, we conditionally recommend adding low-dose glucocorticoids. · If patients with established RA experience an RA flare while on DMARD,

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	TNFi, or non-TNF biologic therapy, we conditionally recommend adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient. · In patients with established RA and low disease activity but not remission, we strongly recommend continuing DMARD therapy, TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication. · In patients with established RA currently in remission, we conditionally recommend tapering DMARD therapy, TNFi, non-TNF biologic, or tofacitinib. · We strongly recommend not discontinuing all therapies in patients with established RA in disease remission. Recommendations for RA patients with High-risk comorbidities · Congestive Heart Failure o In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), we conditionally recommend using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNFi. o If patients in this population are treated with a TNFi and their CHF worsens while on the TNFi, we conditionally recommend switching to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNFi. · Hepatitis B o In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, we strongly recommend treating them the same as patients without this condition. o For a patient with natural immunity from prior exposure to hepatitis B (i.e., HB core antibody and HBS antibody positive and normal liver function tests), we recommend the same therapies as those without such findings as long as the patient's viral load is monitored. o For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy. · Hepatitis C o In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, we conditionally recommend treating them the same as the patients without this condition. o We recommend that rheumatologists work with gastroenterologists and/or hepatologists who would monitor patients and reassess the appropriateness of antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which may lead to a greater number of HCV patients being treated successfully. o If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, we conditionally recommend using DMARD therapy rather than TNFi. · Malignancy o Previous Melanoma and Non-Melanoma Skin Cancer o In patients with established RA and moderate or high disease activity

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	and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), we conditionally recommend the use of DMARD therapy over biologics or tofacitinib. o Previous Lymphoproliferative Disorders o In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, we strongly recommend using rituximab rather than a TNFi and conditionally recommend using combination DMARD therapy, abatacept or tocilizumab rather than TNFi. o Previous Solid Organ Cancer o In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, we conditionally recommend that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer. · Serious Infections o In patients with established RA with moderate or high disease activity and previous serious infection(s), we conditionally recommend using combination DMARD therapy or abatacept rather than TNFi. o Recommendations for the Use of Vaccines in RA patients on DMARD and/or biologic therapy o In early or established RA patients aged 50 and over, we conditionally recommend giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA. o In early or established RA patients who are currently receiving biologics, we conditionally recommend that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given. o In patients with early or established RA who are currently receiving biologics, we strongly recommend using appropriately indicated killed/inactivated vaccines.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis: The Management of Rheumatoid Arthritis in Adults (2009)**[80]	· In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. · In people with newly diagnosed rheumatoid arthritis for whom combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. · When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. · Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. · In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. · On the balance of its clinical benefits and cost-effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study; patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. · The anti-TNF agents adalimumab, etanercept and infliximab are

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	recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. · Anti-TNF agents should be used in combination with methotrexate. Adalimumab or etanercept may be given as monotherapy in patients with intolerance or contraindication to methotrexate. · After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. · An alternative anti-TNF agent may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy. · Escalation of dose of the anti-TNF agents above their licensed starting dose is not recommended. · Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. · Use of the anti-TNF agents for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. · Initiation of anti-TNF agents and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.
Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[81]	· Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. · Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. · Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. · Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. · Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic

Clinical Guideline	Recommendations
	disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. · Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. · Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence. · There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. · Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in AS. · Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.
National Comprehensive Cancer Network: **Adult Cancer Pain (2014)**[82]	· Pain is one of the most common symptoms associated with cancer. · The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine. · This guideline is unique it that it contains the following components: o In order to maximize patient outcomes, pain is an essential component of oncology management. o There is an increasing amount of evidence that survival is linked to effective pain control. o Analgesic therapy must be administered in conjunction with management of multiple symptoms or symptom clusters and complex pharmacologic therapies that patients with cancer are generally prescribed. o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect. o Persistent cancer pain often requires treatment with regularly

Clinical Guideline	Recommendations
	scheduled analgesics with supplemental doses of analgesics provided as needed to manage breakthrough pain. o A multidisciplinary team may be needed for comprehensive pain management. o Psychosocial support must be available. o Specific educational material must be provided to the patient. · The pain management algorithm distinguishes three levels of pain intensity, based on a zero to 10 numerical rating scale: severe pain (seven to 10), moderate pain (four to six) and mild pain (one to three). · Pain associated with oncology emergency should be addressed while treating the underlying condition. · Patients considered to be opioid tolerant are those who are taking >60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer. Patients not meeting this definition are considered opioid naïve. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as patient and family education. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. · Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. · Opioid-naïve patients experiencing mild pain intensity should receive nonopioids analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids. · Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long acting formulation opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration as preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. · Optimal analgesic selection will depend on the patient’s pain intensity, any current analgesic therapy, and concomitant medical illness(es). · In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice at an initial oral dose of 5 to 15 mg. · Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. · Pure agonists (fentanyl, morphine, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. · Due to the ease of titration, opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. · Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor

Clinical Guideline	Recommendations
	compliance. · Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid. · Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. Methadone use should be initiated by physicians with experience and expertise in its use. · At a maximum dose of 400 mg/day, tramadol is less potent than other opioids and is approximately 1/10 as potent as morphine. · Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration. · The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. · The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” · “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. · For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate, 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended. · Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. · If the pain decreases to 4 to 6, the same dose of opioid is repeated and reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered “as needed” over the initial 24 hours before proceeding

Clinical Guideline	Recommendations
	to subsequent management strategies. · No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse events, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. · For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new "rescue dose" must be increased by 10 to 20%. · Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families. · Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. · Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. · If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an ER oral medication (if feasible) or another ER formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by ER opioids. · Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. · Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. · Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. · The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. · Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant to opioids. · Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain.

Clinical Guideline	Recommendations
	· Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attention should also be focused on psychosocial support and providing education to patients and families.

Conclusions

NSAIDs are among the most commonly prescribed drugs worldwide to treat common pain and inflammatory conditions.[38] NSAIDS are FDA-approved to treat acute pain and inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, painful shoulder (bursitis and/or tendonitis), acute gouty arthritis, and postoperative pain. Additionally several agents are indicated for the treatment of primary dysmenorrhea, clinically significant patent ductus arterioles, or fever reduction.

NSAIDs have traditionally been grouped by their chemical characteristics. Currently available products have been derived from acetic acid, anthranilic acid, enolic acid, or propionic acid. However, with the development of products selective to COX-2, classification has begun to shift towards selectivity, rather than chemical structure.[41] There is only one selective COX-2 inhibitor currently available, celecoxib (Celebrex®). In addition, recent evidence suggests that some of the older NSAIDs such as diclofenac and meloxicam show some selectivity towards the COX-2 enzyme.[41] Due to the variability in NSAID half-life ($t_{1/2}$), a classification system has also been developed to group NSAIDs by half-life. Some NSAIDs such as ibuprofen and diclofenac are eliminated rapidly ($t_{1/2}$ of one to four hours), while other agents have a much greater half-life. Agents with $t_{1/2}$ greater than 10 hours include: celecoxib, naproxen, meloxicam, nabumetone, oxaprozin and piroxicam. Piroxicam has an estimated $t_{1/2}$ of 50 hours.[41-43] Agents with longer half-lives are generally given once per day.

Clinical trials have demonstrated NSAIDs to be more efficacious compared to placebo in the treatment of pain and inflammatory conditions. Although there are many head to head trials comparing various NSAIDs, there is no single agent that has been continuously found to be more efficacious or safe than the others.[44-75] Although the efficacy of NSAIDs appears to be similar at equipotent doses, there is a wide variability of response between individual patients, which is believed to be associated with non-prostaglandin-mediated NSAID-induced mechanisms of action. Thus, it is suggested that if a patient fails an NSAID of one class, an NSAID from a different class may be effective and is a reasonable option.[38] A summary of current clinical guidelines and NSAIDs place in therapy for specific disease states are listed in Table 10.[76-82]

References

1. Zorvolex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2014 Aug.
2. Zipsor® [package insert]. Newark (CA); Depomed, Inc.; 2015 Aug.
3. Cataflam® [package insert]. East Hanover (NJ); Novartis Pharmaceuticals Corp.; 2011 Feb.
4. Diclofenac sodium delayed release tablets, diclofenac sodium tablets [package insert]. Columbus (OH); Boehringer Ingelheim Roxane Laboratories; Aug 2006.
5. Dyloject® [package insert]. Lake Forest (IL); Hospira, Inc.; 2014 Dec.
6. Voltaren XR® [package insert]. East Hanover (NJ); Novartis Pharmaceuticals Corp.; 2011 Feb.
7. Etodolac capsule, etodolac film coated tablet [package insert]. Hawthorne (NY); Taro Pharmaceuticals U.S.A., Inc.; 2015 Dec.
8. Etodolac extended release tablet [package insert]. Hawthorne (NY); Taro Pharmaceuticals U.S.A., Inc.; 2015 Aug.
9. Tivorbex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2014 Feb.
10. Indomethacin capsule [package insert]. Piscataway (NJ); Camber Pharmaceuticals, Inc.; 2011 Oct.
11. Indomethacin extended release capsule [package insert]. Piscataway (NJ); Camber Pharmaceuticals, Inc.; 2011 Oct.
12. Indocin® (indomethacin suspension) [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2010 Jan.
13. Indocin® (indomethacin suppository) [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2015 Jul.
14. Indomethacin lyophilized powder for solution injection [package insert]. Lake Zurich (IL); Fresenius Kabi USA, LLC; 2013 Nov.
15. Ketorolac tromethamine film coated tablet [package insert]. Morgantown (WV; Mylan Pharmaceuticals Inc.; 2015 Jul.
16. Ketorolac tromethamine injection solution [package insert]. Schaumburg (IL)SAGENT Pharmaceuticals; 2015 Jul.
17. Sprix® [package insert]. Wayne (PA); Egalet US Inc.; 2015 Jun.
18. Nabumetone tablet [package insert]. Princeton (NJ); Sandoz Inc.; 2015 Jul.
19. Sulindac tablet [package insert]. Laurelton (NY); Epic Pharma, LLC; 2015 Jul.
20. Tolmetin sodium capsule, tolmetin sodium tablet [package insert]. Cranbury (NJ); Sun Pharmaceutical Industries, Inc.; 2015 Feb.
21. Meclofenamate sodium capsule [package insert]. Morgantown (WV); Mylan Pharmaceuticals Inc.; 2015 Jul.
22. Ponstel® [package insert]. Florham Park (NJ); Shionogi Inc.; May 2013.
23. Vivlodex® [package insert]. Philadelphia (PA); Iroko Pharmaceuticals, LLC; 2015 Oct.
24. Mobic® (meloxicam suspension), Mobic® (meloxicam tablet) [package insert]. Ridgefield (CT). Boehringer Ingelheim Pharmaceuticals, Inc.; 2012 Mar.
25. Feldene® [package insert]. New York (NY); Pfizer Inc.; 2015 Feb.
26. Nalfon® [package insert]. Ridgeland (MS); Xspire Pharma; 2012 Sept.
27. Fenoprofen calcium film coated tablet [package insert]. Morgantown (WV); Mylan Pharmaceuticals Inc.; 2015 Jul.
28. Flurbiprofen tablet [package insert]. Detroit (MI); Caraco Pharmaceutical Laboratories, LTC.; 2007 Aug.
29. Ibuprofen film coated tablet [package insert]. Princeton (NJ); Dr. Reddy's Laboratories, Inc.; 2007 Mar.
30. Caldolor® [package insert]. Nashville (TN); Cumberland Pharmaceuticals Inc.; 2015 Nov.
31. Neoprofen® [package insert]. Lebanon (NJ); Recordati Rare Diseases Inc.; 2013 Dec.
32. Ketoprofen capsule [package insert]. North Wales (PA); TEVA Pharmaceuticals USA, Inc.; 2015 Jul.
33. Naprosyn® (naproxen tablet), EC-Naprosyn® (naproxen delayed release tablet), Naprosyn® (napoxen suspension), Anaprox® (naproxen sodium tablet), Anaprox DS® (naproxen sodium tablet) [package insert]. South San Francisco (CA); Genentech USA, Inc.; 2013 Mar.
34. Naproxen suspension [package insert]. Greenville (SC); Palmetto Pharmaceuticals; 2013 May.
35. Naprelan® [package insert]. San Diego (CA); Victory Pharma, Inc.; 2009 Aug.
36. Daypro® [package insert]. New York (NY); G.D. Searle LLC Division of Pfizer Inc.; 2012 Dec.

37. Celebrex® [package insert]. New York (NY); G.D. Searle LLC Division of Pfizer Inc.; 2012 Dec.
38. Solomon DH. NSAIDs: Therapeutic use and variability of response in adults. In: Romain PL, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
39. Solomon DH. NSAIDs: mechanism of action. In: Romain PL (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2015 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
40. Feldman M. NSAIDs (including aspirin): pathogenesis of gastroduodenal toxicity. In: Grover S (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2016 Jan 12]. Available from: http://www.uptodate.com/contents/search.
41. Grosser T, Smyth E, FitzGerald GA. Chapter 34: Anti-inflammatory, Antipyretic, and Analgesic Agents; Pharmacotherapy of Gout. In: Brunton LL, Chabner BA, Knollmann BC (Eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011 [cited 2016 Jan 12]. Available from: http://accesspharmacy.mhmedical.com/.
42. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016 [cited 2016 Jan 12]. Available from: URL: http://www.clinicalpharmacology.com.
43. Micromedex® 2.0, (electronic version). Greenwood Village, CO: Truven Health Analytics; 2016 [citied 2016 Jan 12]. Available from: http://www.micromedexsolutions.com/.
44. Riff DS, Duckor S, Gottlieb I, Diamond E, Soulier S, Raymond G, et al. Diclofenac potassium liquid-filled soft gelatin capsules in the management of patients with postbunionectomy pain: a Phase III, multicenter, randomized, double-blind, placebo-controlled study conducted over 5 days. Clin Ther. 2009 Oct;31(10):2072-85. doi: 10.1016/j.clinthera.2009.09.011.
45. Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. Pain Med. 2009 Sep;10(6):1106-14. doi: 10.1111/j.1526-4637.2009.00647.x. Epub 2009 Jul 6.
46. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. Curr Med Res Opin. 2010 Aug;26(8):1915-23. doi: 10.1185/03007995.2010.495564.
47. Gan TJ, Daniels SE, Singla N, Hamilton DA, Carr DB. A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: a multicenter, double-blind, randomized, multiple-dose study. Anesth Analg. 2012 Nov;115(5):1212-20. doi: 10.1213/ANE.0b013e3182691bf9. Epub 2012 Aug 10.
48. Daniels S, Melson T, Hamilton DA, Lang E, Carr DB. Analgesic efficacy and safety of a novel injectable formulation of diclofenac compared with intravenous ketorolac and placebo after orthopedic surgery: a multicenter, randomized, double-blinded, multiple-dose trial. Clin J Pain. 2013 Aug;29(8):655-63. doi: 10.1097/AJP.0b013e318270f957.
49. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol. 2009 Mar;26(3):235-45. doi: 10.1055/s-0028-1103515. Epub 2008 Dec 9.
50. Kroll PB, Meadows L, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. Pain Pract. 2011 Jan-Feb;11(1):23-32. doi: 10.1111/j.1533-2500.2010.00402.x.
51. Southworth S1, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. Clin Ther. 2009 Sep;31(9):1922-35. doi: 10.1016/j.clinthera.2009.08.026.
52. Gibofsky A, Silberstein S, Argoff C, Daniels S, Jensen S, Young CL. Lower-dose diclofenac submicron particle capsules provide early and sustained acute patient pain relief in a phase 3 study. Postgrad Med. 2013 Sep;125(5):130-8. doi: 10.3810/pgm.2013.09.2693.
53. Gibofsky A, Hochberg MC, Jaros MJ, Young CL. Efficacy and safety of low-dose submicron diclofenac for the treatment of osteoarthritis pain: a 12 week, phase 3 study. Curr Med Res Opin. 2014 Sep;30(9):1883-93. doi: 10.1185/03007995.2014.946123. Epub 2014 Aug 6.

54. Altman R1, Daniels S, Young CL. Indomethacin submicron particle capsules provide effective pain relief in patients with acute pain: a phase 3 study. Phys Sportsmed. 2013 Nov;41(4):7-15. doi: 10.3810/psm.2013.11.2031.
55. ClinicalTrials.gov [internet]. Bethesda (MD): 2000- [cited 2015 Jun 5]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01543685?term=tivorbex&rank=24.
56. Altman R, Hochberg M, Gibofsky A, Jaros M, Young C. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin. 2015 Dec;31(12):2331-43. doi: 10.1185/03007995.2015.1112772.
57. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162(1):46.
58. Watson MC, Brookes ST, Kirwan JR, Faulkner A. Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee. Cochrane Database Syst Rev. 2000.
59. Towheed T, Shea B, Wells G, Hochberg M. Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. Cochrane Database Syst Rev. 2000.
60. 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.
61. Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev 2010; CD001751.
62. Owen PR. Prostaglandin synthetase inhibitors in the treatment of primary dysmenorrhea. Outcome trials reviewed. Am J Obstet Gynecol 1984; 148:96.
63. Zhang, WY, Li Wan, Po A. Efficacy of minor analgesics in primary dysmenorrhea: a systematic review. Br J Obstet Gynaecol 1998; 105;780.
64. Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception 2010; 81:185.
65. Budoff PW. Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA 1979; 241:2713.
66. Milsom I, Minic M, Dawood MY, et al. Comparison of the efficacy and safety of nonprescription doses of naproxen and naproxen sodium with ibuprofen, acetaminophen, and placebo in the treatment of primary dysmenorrhea: a pooled analysis of five studies. Clin Ther 2002; 24:1384.
67. Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout--a systematic review. Rheumatology (Oxford) 2006; 45:1422.
68. Schumacher HR Jr, Boice JA, Daikh DI, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002; 324:1488.
69. Rubin BR, Burton R, Navarra S, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis Rheum 2004; 50:598.
70. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Curr Med Res Opin 1991; 12:423.
71. Lomen PL, Turner LF, Lamborn KR, et al. Flurbiprofen in the treatment of acute gout. A comparison with indomethacin. Am J Med 1986; 80:134.
72. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. J Rheumatol 1988; 15:1422.
73. van Durme CM, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev 2014; 9:CD010120.
74. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol 2012; 39:1859.
75. Roelofs PD, Deyo RA, Koes BW, et al. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev 2008; CD000396.
76. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.

77. American Academy of Orthopedic Surgeons: Treatment of osteoarthritis of the knee. Rosemont (IL): 2013 [Guideline on the internet] [cited 2015 Feb 2]. Available from: http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf.
78. National Institute for Health and Clinical Excellence (NICE). Osteoarthritis: Care and management in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); Feb 2014 [cited 2015 Feb 2]. Available from: http://www.nice.org.uk/guidance/CG177.
79. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6.
80. National Institute for Health and Clinical Excellence (NICE). Rheumatoid Arthritis: The management of rheumatoid arthritis in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); Feb 2009 [cited 2015 Feb 2]. Available from: http://www.nice.org.uk/guidance/CG79.
81. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011 Jun;70(6):896-904.
82. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: adult cancer pain. Fort Washington (PA): 2014.version 1 [cited 2014 Apr 11]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
83. iCentra. iCentra: Making Drugs Better [webpage on the Internet]. King of Prussia (PA): SoluMatrix™; 2013 [cited 2016 Jan 12]. Available from: http://www.iceutica.com/solumatrix.