Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Non-Selective Oral Nonsteroidal Anti-Inflammatory Drugs

AHFS Classification: 28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents

Diclofenac
Etodolac
Fenoprofen
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Mefenamic Acid
Meloxicam
Nabumetone
Naproxen
Oxaprozin
Piroxicam
Sulindac
Tolmetin

Final Report
April 2018

Review prepared by:
Elena Martinez Alonso, B.Pharm., Medical Writer
Vicki Frydrych, B.Pharm., Pharm.D., Clinical Pharmacist
Valerie Gonzales, Pharm.D., Clinical Pharmacist
Joanita Lake, B.Pharm., MSc EBHC (Oxon), Research Assistant Professor, Clinical Pharmacist
Michelle Fiander, MA, MLIS, Research Assistant Professor, Evidence Synthesis Librarian
Joanne LaFleur, PharmD, MSPH, Associate Professor University of Utah College of Pharmacy

University of Utah College of Pharmacy, Drug Regimen Review Center
Copyright © 2018 by University of Utah College of Pharmacy
Salt Lake City, Utah. All rights reserved

Contents

Executive Summary 3
Introduction 6
Table 1. FDA-Approved Oral Non-selective NSAIDs 7
Table 2. FDA-Approved Indication for Oral Non-selective NSAIDs 13
Disease Overview and Guideline Recommendations 14
A) Disease Overview 14
B) Guideline Recommendations 17
Table 3. Guideline Recommendations for Oral NSAIDs 18
Table 4. Clinical Practice Guidance with Less Methodological Rigor than Guidelines Included in Table 3 24
Pharmacology & Special Populations 25
Table 5. *In Vitro* Selectivity Ratio for NSAIDs 25
Table 6. Pharmacokinetics for Oral Non-selective NSAIDs 26
Table 7. Special Population Considerations for Oral Non-selective NSAIDs 29
Methods 33
Clinical Efficacy 35
Figure 1. PRISMA flow diagram of the selection process 35
Figure 2. Head-to-Head Efficacy Evidence among Non-selective NSAIDs 36
Safety 46
Table 8. Gastrointestinal Toxicity Risk: NSAID Evidence 47
Table 9. Selection of NSAID agent based on patient´s cardiovascular and gastrointestinal risk 49
Table 10: Cardiovascular Toxicity Risk: NSAID Evidence 52
Table 11: Hepatic Toxicity Risk: NSAID Evidence 55
Summary 57
Table 12. Evidence-Based Findings on the Comparative Effectiveness among Oral nsNSAIDs 57
References 60
Appendix A. FDA-Approved Nonopioid Analgesics 73
Appendix B. NSAID Interactions 74
Appendix C. Literature Search Strategies 76
Appendix D. Key Findings Reported in Systematic Reviews/Meta-Analyses 91
Appendix E. Excluded References 100

Executive Summary

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used agents worldwide for the treatment of pain and inflammation associated with several inflammatory conditions such as osteoarthritis and low back pain. NSAIDs exhibit analgesic, anti-inflammatory, and antipyretic effects by inhibiting the action of cyclooxygenase (COX). Several safety concerns associated with the use of NSAIDs include gastrointestinal, cardiovascular, and renal adverse events. Most of the clinical guidelines for specific pain conditions (e.g., osteoarthritis, ankylosing spondylitis, gout, and low back pain) recommend the use of the NSAID class as efficacious, without specifying preference for any particular NSAID. NSAIDs differ in safety profiles and drug interaction. Guidelines emphasize that the selection of an NSAID should be based on the patient's comorbidities (gastrointestinal and/or cardiovascular diseases) and use of concomitant drugs.

The NSAID class includes the traditional agents (nonselective NSAIDs) such as ibuprofen and naproxen and the selective COX-2 inhibitors (coxibs) such as celecoxib. Among the nonselective NSAIDs, meloxicam, etodolac, and nabumetone are sometimes further classified as partially selective based on their partial selectivity to COX-2 over COX-1.

This report reviews the comparative efficacy and safety of 16 oral non-selective NSAIDs (nsNSAIDs) for the treatment of mild to moderate pain, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, bursitis, tendinitis, ankylosing spondylitis, dysmenorrhea, and gout: diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin. Diclofenac is available in 3 salt formulations (diclofenac acid, potassium, or sodium), and naproxen is available as naproxen and naproxen sodium. Each oral nsNSAID is available by prescription. Naproxen and ibuprofen are additionally available without prescription.

Efficacy: Following a systematic literature search for direct head-to-head comparisons among nsNSAIDs, 29 publications representing 20 systematic reviews/meta-analyses (SR/MAs), 8 randomized controlled trials (RCTs), and 1 substudy of an RCT were identified. Meta-analyses were generally not performed because RCTs used different nsNSAID comparators, as well as different pain outcome parameters and/or assessment tools. Evidence from the majority of studies showed no significant efficacy differences among the various nsNSAIDs. Listed below is a summary of the available evidence by indication:

Osteoarthritis: There was high-quality evidence (2 SR/MAs including many RCTs with consistent results) showing no significant differences in relieving osteoarthritis symptoms between partially selective NSAIDs (etodolac or meloxicam) compared to nsNSAIDs, or between various nsNSAIDs. One SR/MA showed less pain reduction with more withdrawals due to a lack of efficacy for meloxicam compared to nsNSAIDs (e.g., naproxen, diclofenac, nabumetone, or piroxicam). There was low-quality evidence from 2 short-term trials reporting no significant differences between nabumetome (partially selective NSAID) and nsNSAIDs.

Rheumatoid arthritis: There was low- to moderate-quality evidence from 2 SRs and 1 RCT reporting no significant efficacy differences among nsNSAIDs. However, some differences in

specific outcomes were found among nsNSAIDs in the 2 SRs. One SR reported higher withdrawal rates due to a lack of efficacy with meloxicam compared to other nsNSAIDs (e.g., naproxen, diclofenac, nabumetone). Another SR showed flurbiprofen is statistically superior to ibuprofen in terms of articular pain relief, to indomethacin in terms of articular swelling reduction, and to naproxen, indomethacin, and ibuprofen regarding articular stiffness reduction.

Juvenile arthritis (including juvenile idiopathic arthritis): There is insufficient evidence from 2 RCTs to confirm any difference among nsNSAID.

Ankylosing spondylitis: There was low- to moderate-quality evidence (2 SRs including small studies with imprecise estimate of effect) showing no significant differences in pain and stiffness reduction among the nsNSAIDs.

Acute gout: Moderate-quality evidence from 3 SRs showed similar efficacy in reducing acute gout pain among nsNSAIDs. Indomethacin, naproxen and sulindac are currently approved for acute gout pain. No studies directly comparing these agents were identified.

Low back pain: Moderate-quality evidence from 4 SRs and 1 RCT indicated that in the majority of studies all nsNSAIDs provide similar efficacy for acute low back pain. Regarding chronic low back pain, there was insufficient evidence from 1 small RCT to assess differences among nsNSAIDs.

Neck pain and associated disorders: There was insufficient evidence from a single RCT to confirm whether one nsNSAID differs from another nsNSAID.

Dysmenorrhea: Low-quality evidence for most nsNSAID comparisons suggested no significant efficacy differences among nsNSAIDs. Limitations of the evidence included small and underpowered studies, and poor reporting of study methods.

Dental postoperative pain: There was insufficient evidence from 2 multiple-dose RCTs to confirm whether one nsNSAID differs from other nsNSAIDs.

Influenza-like symptoms: Evidence is insufficient to confirm any difference among nsNSAID. A single RCT was identified in patients with influenza-like symptoms. No significant differences between diclofenac and ibuprofen were reported.

General pain: A low-quality SR/MA of RCTs in patients with several pain conditions (RA, OA, dysmenorrhea, traumatic injury, low back pain, and postoperative pain) suggested superior pain relief with ketoprofen compared to diclofenac or ibuprofen.

Evaluation of NSAIDs for other types of pain (e.g., migraine and cancer pain), was beyond the scope of this report.

Adverse Drug Reactions: NSAID use is associated with safety concerns, especially after exposure to high doses or long-term use. Prescription labeling states that NSAIDs should be used at the lowest effective dose for the shortest period of time to minimize the risk for an adverse event.

NSAID-related adverse events include gastrointestinal issues (nausea, vomiting, peptic ulcers, gastrointestinal bleed, abdominal pain, dyspepsia and perforation of the stomach or intestine),

cardiovascular effects (hypertension, edema, heart failure, myocardial infarction, stroke and death), renal effects (acute kidney injury, fluid retention, hyperkalemia, interstitial nephritis, and nephrotic syndrome), hepatic effects (elevations in aminotransferase levels, hepatitis, and hepatic failure), and allergic reactions (anaphylaxis). Some adverse events may be life threating. NSAID prescription class labeling includes two black box warnings, one concerning gastrointestinal (GI) bleeding, ulceration, and perforation, and one related to cardiovascular (CV) thrombotic events (myocardial infarction and stroke).

Partially selective NSAIDs such as etodolac and meloxicam are associated with lower risks of ulcer complications or symptomatic ulcers compared with other nsNSAIDs. No clear differences in GI risks were reported between other nsNSAIDs. Several studies support the association between the use of NSAIDs and the increased risk of heart attack or stroke. The CV risk varies among nsNSAIDs, doses, and clinical conditions. Nonselective NSAIDs (e.g., high-dose diclofenac or ibuprofen) seem to have similar risk of CV events compared to COX-2 selective NSAIDs (i.e. celecoxib). A recent, large RCT showed similar CV risk among naproxen, ibuprofen, and celecoxib in patients with CV disease or risk factors, based on the primary composite endpoint (CV death, nonfatal myocardial infarction, or nonfatal stroke). A meta-analysis of placebo-controlled trials and a systematic review of observational studies suggested naproxen may have less CV risk. Overall, evidence concerning CV risks is insufficient to strongly recommend one particular nsNSAID over another. Comparative safety evidence concerning renal and hepatic risks is limited. The incidence of renal adverse effects appears comparable among NSAIDs. Sulindac and diclofenac are associated with higher hepatotoxicity risk.

Summary: NSAIDs are effective to reduce pain and inflammation in several pain conditions. The majority of identified SR/MAs and RCTs studied the use of NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, low back pain, and acute gout. Overall, most evidence showed no significant efficacy differences among the different nsNSAIDs. However, the quality of evidence for the majority of indications was limited by small and underpowered studies with imprecise estimates of effect and the absence of several RCTs for the same nsNSAID comparison. Additionally, RCTs for every possible NSAID comparison are lacking. Guidelines, across indications, do not specify a preference for one nsNSAID over another. NSAIDs do differ in safety. Gastrointestinal, cardiovascular, renal, and hepatic adverse events may occur with the use of any NSAIDs. Among nsNSAIDs, naproxen seems to have less cardiovascular risk; however further evidence is needed. Partially selective NSAIDs (etodolac and meloxicam) seem to be associated with a lower incidence of gastrointestinal adverse events compared with other nsNSAIDs. Comparative safety evidence concerning renal and hepatic risks is limited.

The selection of an NSAID should be based on the benefit-risk balance for each patient. Factors to be considered include age (elderly populations are at higher risks of cardiovascular events, renal impairment, and bleeding), comorbidities (cardiovascular, renal, or gastrointestinal conditions), and the use of concomitant drugs (e.g., aspirin, anticoagulant agents).

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit antipyretic, anti-inflammatory, analgesic, and antiplatelet effects. NSAIDs are commonly used to reduce pain and inflammation associated with several inflammatory conditions such as osteoarthritis and rheumatoid arthritis. NSAIDs are also used to reduce the pain of acute gout, low back pain, and dysmenorrhea. NSAIDs may relieve symptoms, but do not delay disease progression or cure the underlying causes. Off-label uses include migraine prevention and pericarditis. The NSAID class includes the traditional agents (nonselective NSAIDs) such as ibuprofen and naproxen and the selective COX-2 inhibitors (coxibs) such as celecoxib. Among the nonselective NSAIDs, meloxicam, etodolac, and nabumetone are sometimes further classified as partially selective based on their partial selectivity to COX-2 over COX-1.

This report reviews the comparative efficacy and safety of 16 non-selective oral NSAIDs currently approved for the treatment of mild to moderate pain, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, bursitis, tendinitis, ankylosing spondylitis, dysmenorrhea, and gout. Non-selective NSAIDs (nsNSAIDs) include diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin. Diclofenac and naproxen are available in different salt formulations (diclofenac acid, potassium and sodium, and naproxen sosium). Salicylates (e.g., aspirin), diflunisal, and celecoxib are outside the scope of this report.

The present review addresses nsNSAIDs available as oral formulations. Some agents are additionally available as intramuscular or intravenous injections (e.g., ketorolac and diclofenac), nasal sprays (e.g., ketorolac), ophthalmic drops (e.g., flurbiprofen), or topical gels (e.g., diclofenac). All nsNSAIDs are available by prescription although ibuprofen and naproxen are also available without a prescription (over-the-counter, OTC). The OTC products are approved at lower strengths than prescription products and for durations of 10 days or less unless recommended by a doctor.[1]

Appendix A provides a list of the available FDA-approved nonopioid analgesic agents. **Table 1** provides specific information concerning labeled indications and dosing recommendation for the nsNSAIDs included in this report. **Table 2** includes product comparisons according to the labeled indications.

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
Diclofenac acid	Zorvolex Oral capsules[2]: • 18 mg • 35 mg	October 2013	Mild to moderate acute pain	18 mg or 35 mg 3 times daily
			Osteoarthritis	35 mg 3 times daily
Diclofenac potassium	Diclofenac Immediate-release oral tablets[3]: • 50 mg	November 1993 *(Cataflam - discontinued)* *(Only generic available)*	Mild to moderate pain	50 mg 3 times daily
			Dysmenorrhea	
			Osteoarthritis	50 mg 2 to 3 times daily
			Rheumatoid Arthritis	50 mg 3 to 4 times daily
	Cambia Powder for oral solution[4]: • 50 mg per packet	June 2009 *(Generic available)*	Acute treatment of migraine attacks with or without aura in adults ≥18 years of age	Single 50 mg dose
	Zipsor Oral liquid filled capsule[5]: • 25 mg	June 2009 *(Generic available)*	Mild to moderate acute pain	25 mg 4 times daily
Diclofenac sodium	Diclofenac Delayed-release tablets (enteric-coated)[6] • 25 mg • 50 mg • 75 mg	July 1988 *(Voltaren - discontinued)* *(Only generic available)*	Ankylosing Spondylitis	25 mg 4 times daily, with an extra 25 mg at bedtime if necessary
			Osteoarthritis	50 mg 2 to 3 times daily, or 75 mg twice daily
			Rheumatoid Arthritis	50 mg 3 to 4 times daily, or 75 mg twice daily
	Diclofenac Extended-release tablets[7]: • 100 mg	March 1996 *(Voltaren XR - discontinued)* *(Only generic available)*	Osteoarthritis	100 mg daily
			Rheumatoid Arthritis	100 mg daily (dose may be increased to 100 mg twice daily in some patients)
Etodolac	Etodolac Oral capsules[8]: • 200 mg • 300 mg Oral tablets[9]: • 400 mg • 500 mg	January 1991 *(Lodine - Discontinued)* *(Only generic available)*	Acute pain	200 to 400 mg every 6 to 8 hours
			Osteoarthritis:	300 mg 2 to 3 times daily, or 400 mg twice daily, or 500 mg twice daily
			Rheumatoid Arthritis	
	Etodolac XR Extended-release tablets[10]: • 400 mg • 500 mg • 600 mg	October 1996 *(Lodine XR – Discontinued)* *(Only generic available)*	Juvenile rheumatoid arthritis in patients 6 to 16 years of age	400 mg to 1000 mg daily
			Osteoarthritis	
			Rheumatoid Arthritis	

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
Fenoprofen calcium	Nalfon Oral capsules[11]: • 200 mg • 400 mg Fenoprofen calcium Film-coated tablets[12]: • 600 mg	March 1976 *(Generic available)* *Fenoprofen 600 mg – only generic available)*	Mild to moderate pain in adults	200 mg every 4 to 6 hours, as needed
			Osteoarthritis	400 to 600 mg, 3 or 4 times daily. Max dose: 3200 mg daily
			Rheumatoid Arthritis	
Flurbiprofen	Flurbiprofen Oral tablets[13]: • 50 mg • 100 mg	October 1988 (*Ansaid – Discontinued*) *(Only generic available)*	Osteoarthritis	200 to 300 mg/day in 2 to 4 divided doses. The max. single dose in a multiple-dose daily regimen is 100 mg
			Rheumatoid Arthritis	
Ibuprofen	**RX**:[14] - Ibuprofen oral suspensión 100 mg/5 ml - IBU-TAB tablets 400 mg, 600 mg - Ibuprofen tablets 400 mg, 600 mg, 800 mg **OTC**:[14] - Advil tablets 200mg - Advil Liqui-gels, capsules 200 mg - Advil Migraine Liqui-gels capsules 200 mg - IBU-TAB tablets 200 mg - Midol Liquid Gels, capsules 200 mg - Children's Advil: • Oral suspension 100 mg/5 ml • Oral chewable tablets 50 mg - Children's Advil-flavored • Children's Elixure, oral suspensión 100 mg/5 ml - Children's Motrin: • Oral suspensión 100 mg/5 ml • Oral chewable tablets 50 mg - Junior Strength Advil 100mg: • Oral tablets • Oral chewable tablets - Junior Strength Motrin 100 mg: • Oral tablets • Oral chewable tablets - Junior Strength Ibuprofen 100 mg - Motrin IB tablets 200 mg - Profen tablets 200 mg - TAB-Profen tablets 200 mg - Ibuprofen chewable tablets 50 mg, 100 mg	September 1974 (*Motrin and other Brand names– Discontinued*) *(Generic available)*	Mild to moderate pain	400 mg every 4 to 6 hours as needed. Max. dose: 3,200 mg/day
			Dysmenorrhea	400 mg every 4 hours as needed. Max. dose: 3,200 mg/day
			Osteoarthritis	400 to 800 mg 3 to 4 times daily. Max. dose: 3,200 mg/day
			Rheumatoid Arthritis	
			Note: Please refer to each drug label information for further information about recommended dosages in children *OTC labeling: Reduction of fever; management of pain due to headache, sore throat, arthritis, physical or athletic overexertion (e.g., sprains/strains), menstrual pain, dental pain, minor muscle/bone/joint pain, backache, pain due to the common cold and flu* - *Analgesic, antipyretic: 200 mg every 4 to 6 hours as needed. Max. dose: 1,200 mg/day. Treatment duration for >10 days as an analgesic or >3 days as an antipyretic is not recommended* - *Migraine: 400 mg at onset of symptoms*	

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
Indomethacin	Indocin Oral suspension[15]: • 25 mg/5 ml Indomethacin Oral capsules: • 25 mg • 50 mg	June 1965 *(Indocin and Indo-Lemon capsules – Discontinued)* *(Generic available)*	Rheumatoid arthritis	25 mg 2 or 3 times a day
			Ankylosing spondylitis	
			Osteoarthritis	
			Acute painful shoulder (bursitis and/or tendinitis)	75-150 mg daily in 3 or 4 divided doses
			Acute gouty arthritis	50 mg 3 times a day
			** Indomethacin suppositories 50 mg can be substituted for indomethacin capsules*	
	Indomethacin XR oral capsules[16]: 75 mg	February 1982 *(Indocin SR – Discontinued)* *(Only generic available)*	Rheumatoid arthritis	75 mg daily
			Ankylosing spondylitis	
			Osteoarthritis	
			** Indomethacin XR capsules may be substituted for all the indications for indomethacin IR capsules except acute gouty arthritis*	
	Tivorbex Oral capsules[17]: • 20 mg • 40 mg	February 2014	Mild to moderate acute pain in adults	20 mg 3 times daily or 40 mg orally 2 or 3 times daily
			**TIVORBEX capsules are not interchangeable with other formulations of oral indomethacin*	
Ketoprofen	Ketoprofen Oral capsule[18]: • 25 mg • 50 mg • 75 mg	January 1986 *(Orudis – Discontinued)* *(Only generic available)*	Pain, dysmenorrhea	25 to 50 mg every 6 to 8 hours as necessary. Max dose: 300 mg/day
			Osteoarthritis	75 mg 3 times or 50 mg 4 times a day. Max dose: 300 mg/day
			Rheumatoid Arthritis	
	Ketoprofen XR oral capsules[19]: • 100 mg • 150 mg • 200 mg	September 1993 *(Oruvail – Discontinued)* *(Only generic available)*	Osteoarthritis	200 mg once a day Max dose: 200 mg
			Rheumatoid Arthritis	
Ketorolac tromethamine	Ketorolac Oral tablets[20]: • 10 mg	December 1991 *(Toradol-Discontinued)* *(Only generic available)*	Acute Pain in Adult Patients	Following initial IM/IV dose, 20 mg once followed by 10 mg every 4 to 6 hours as needed, not to exceed 40 mg/day; total duration of IV/IM plus oral therapy is not to exceed 5 days
Mefenamic Acid	Ponstel Oral capsules[21]: • 250 mg	March 1967 *(Generic available)*	Mild to moderate pain in patients ≥ 14 years of age, when therapy will not exceed one week (7 days)	500 mg followed by 250 mg every 6 hours as needed
			Primary dysmenorrhea	

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
Meloxicam	Mobic Oral tablets[22]: • 7.5 mg • 15 mg	April 2000 *(Generic available)*	Osteoarthritis:	7.5 mg once daily. May increase to 15 mg once daily. Max dose: 15 mg
			Rheumatoid Arthritis	
			Juvenile rheumatoid arthritis in patients who weigh ≥60 kg	7.5 mg once daily
			* Mobic tablets are not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same	
	Vivlodex Oral capsules[23]: • 5 mg • 10 mg	October 2015	Osteoarthritis	Start with 5 mg once daily. May increase dose to 10 mg in patients who require additional analgesia * Vivlodex capsules are not interchangeable with other formulations of oral meloxicam even if the mg strength is the same
Nabumetone	Nabumetone Oral tablets[24]: • 500 mg • 750 mg	December 1991 *(Relafen – Discontinued)* *(Only generic available)*	Osteoarthritis	1,000 mg to 2,000 mg once daily or in 2 divided doses
			Rheumatoid arthritis	
Naproxen	**RX:** - Naprosyn oral suspension[25]: • 25 mg/ml - Naprosyn oral tablet[26]: • 250 mg • 375 mg • 500 mg - Generic: • oral tablets 250 mg, 375 mg, 500 mg, and oral suspension	March 1976 *(Generic available)*	Rheumatoid arthritis	250 to 500 mg twice daily
			Ankylosing spondylitis	
			Osteoarthritis	
			Polyarticular juvenile idiopathic arthritis (PJIA)	A liquid formulation may be more appropriate. 10 mg/kg/day given in 2 divided doses. Oral tablets are not appropriate for children weighing < 50 kg
			Pain	500 mg followed by 250 mg every 6 to 8 hours as required
			Primary dysmenorrhea	
			Acute tendonitis/bursitis	500 mg followed by 250 mg every 6 to 8 hours as required (Rx products only)
			Acute gout	750 mg followed by 250 mg every 8 hours until attack has subsided

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
	RX: - EC-Naprosyn delayed release tablet[26]: • 375 mg • 500 mg	October 1994 *(Generic available)*	Rheumatoid arthritis	375 mg or 500 mg twice daily * Delayed-release naproxen is not recommended for initial treatment of acute pain and for the treatment of acute gout because of the delay in absorption * A liquid formulation may be more appropriate for PJIA. Oral tablets are not appropriate for children weighing < 50 kg
			Ankylosing spondylitis	
			Osteoarthritis	
			Polyarticular juvenile idiopathic arthritis	
Naproxen sodium	**OTC:** - Aleve tablet 200 mg - Naproxen sodium tablet 200 mg	January 1994	OTC labeling: Pain, fever: 200 mg every 8 to 12 hours; if needed, may take 400 mg for the initial dose; maximum: 400 mg in any 8- to 12-hour period or 600 mg/24 hours.	
	RX: - Naprelan controlled-release tablet[27]: • 375 mg • 500 mg • 750 mg	January 1996 *(Generic available)*	Mild to moderate pain	Initial: 1,000 mg once daily; may temporarily increase to 1,500 mg once daily if greater pain relief is needed. Dose should be subsequently reduced to a maximum of 1,000 mg daily
			Dysmenorrhea	
			Acute tendonitis, bursitis	
			Ankylosing spondylitis	Two 375 mg or 500 mg tablets once daily, or one 750 mg tablet once daily
			Osteoarthritis	
			Rheumatoid arthritis	
			Acute gout	Initial: 1,000 to 1,500 mg once daily on the first day, followed by 1,000 mg once daily until attack subsides
	RX: - Anaprox oral tablet: • 275 mg - Anaprox DS oral tablet[26]: • 550 mg	September 1980 *(Generic available)*	Mild to moderate pain	550 mg of naproxen sodium followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as needed
			Dysmenorrhea	
			Acute tendonitis, bursitis	
			Ankylosing spondylitis	275 mg twice daily (Anaprox) 550 mg twice daily (Anaprox DS)
			Osteoarthritis	
			Rheumatoid arthritis	
			Acute gout	875 mg followed by 275 mg every 8 hours until attack has subsided

Table 1. FDA-Approved Oral Non-selective NSAIDs

Generic Name	*Brand Name* or *Generic Name* & Preparations Available[a]	Approval Date *(availability of generic)*[b]	Labeled Indications	Recommended Dosage[c]
Oxaprozin	Daypro Oral caplets[28]: • 600 mg	October 1992 *(Generic available)*	Osteoarthritis	1200 mg (two 600 mg caplets) once a day
			Rheumatoid Arthritis	
			Juvenile rheumatoid arthritis	Children 6 to 16 years: - 22 to 31 kg: 600 mg once daily - 32 to 54 kg: 900 mg once daily - ≥55 kg: 1,200 mg once daily
Piroxicam	Feldene Oral capsules[29]: • 10 mg • 20 mg	April 1982 *(Generic available)*	Osteoarthritis	20 mg once daily
			Rheumatoid arthritis	
Sulindac	Sulindac Oral tablets[30]: • 150 mg • 200 mg	September 1978 *(Clinoril – Discontinued)* *(Only generic available)*	Ankylosing spondylitis	150 mg twice a day. Max. dose: 400 mg daily
			Osteoarthritis	
			Rheumatoid arthritis	
			Acute painful shoulder (bursitis/tendinitis)	200 mg twice a day. Max. dose: 400 mg daily
			Acute gouty arthritis	
Tolmetin Sodium	Tolmetin Oral capsules[31]: • 400 mg Oral tablets: • 600 mg	March 1976 *(Tolectin, Tolectin DS, and Tolectin 600 – Discontinued)* *(Only generic available)*	Osteoarthritis	400 mg 3 times daily. Control is usually achieved at doses of 600 mg to 1800 mg daily in 3 divided doses. Max dose: 1800 mg daily
			Rheumatoid Arthritis	
			Juvenile rheumatoid arthritis	Children ≥2 years and Adolescents: - Initial: 20 mg/kg/day in 3 to 4 divided doses - Maintenance: 15 to 30 mg/kg/day in 3 to 4 divided doses

Abbreviations: IM/IV, intramuscular/intravenous; IR, immediate release; nsNSAIDs, nonselective non-steroidal anti-inflammatory drugs; OTC, over-the-counter drug; PJIA, polyarticular juvenile idiopathic arthritis; RX, prescription drug; XR, extended-release

[a] Some products may be also available as injections, nasal sprays, ophthalmic drops, and topical preparation

[b] Information regarding discontinued products and the availability of generics was collected from the Orange Book website (https://www.accessdata.fda.gov/scripts/cder/ob/), which is updated monthly

[c] All package inserts recommend using the lowest effective dose for the shortest possible duration

Table 2. FDA-Approved Indication for Oral Non-selective NSAIDs

Oral NSAIDs	FDA Approved Indications[a]									
	Pain	DYS	B/T	OA	RA	AS	JRA	PJIA	Gout	Migraine
Diclofenac acid	X			X						
Diclofenac potassium	X	X		X	X					X
Diclofenac sodium				X	X	X				
Etodolac	X			X	X		X			
Fenoprofen calcium	X			X	X					
Flurbiprofen				X	X					
Ibuprofen	X	X		X	X					X
Indomethacin	X		X	X	X	X			X	
Ketoprofen	X	X		X	X					
Ketorolac tromethamine	X									
Mefenamic acid	X	X								
Meloxicam				X	X		X			
Nabumetone				X	X					
Naproxen	X	X	X	X	X	X		X	X	
Naproxen sodium	X	X	X	X	X	X			X	
Oxaprozin				X	X		X			
Piroxicam				X	X					
Sulindac			X	X	X	X			X	
Tolmetin sodium				X	X		X			

Abbreviations: AS, ankylosing spondylitis; B/T, acute tendonitis/bursitis; DYS, dysmenorrhea; FDA, Food and Drug Administration; JRA, juvenile rheumatoid arthritis; nsNSAID, nonselective non-steroidal anti-inflammatory drug; OA, osteoarthritis; PJIA, polyarticular juvenile idiopathic arthritis; RA, rheumatoid arthritis

[a] Please refer to Table 1 for indications specific to each formulation

Disease Overview and Guideline Recommendations

A) Disease Overview

Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[32,33] The 2016 Institute of Medicine report, Relieving Pain in America, stated that more than 100 million Americans suffer from chronic pain.[34] Pain is a leading cause of disability and productivity loss.[34] In the United States, medical and societal costs associated with pain conditions approach 635 billion dollars annually.[34] In 2012, almost 55% of Americans 18 years old and older were diagnosed with a musculoskeletal pain condition, including low back pain, neck pain, arthritic and non-arthritic joint pain, and other musculoskeletal conditions.[35] The 2012 National Health Interview Survey, conducted by the Centers for Disease Control and Prevention (CDC), found 28% of adults reported low back pain, 26% chronic joint symptoms, 21% arthritis, rheumatoid arthritis (RA), gout, lupus, or fibromyalgia, 14% migraine or severe headache, 14% neck pain, and 5% face or jaw pain in the preceding 3 months.[36]

Several classification systems for pain exist. The most common is based on the underlying cause of pain (e.g., nociceptive and pathophysiologic pain), pain severity (e.g., mild, moderate, and severe pain), or pain duration (e.g., acute, subacute, and chronic).[32] Nociceptive pain is physiologic and protective. It occurs when the receptors of sensory nerves (i.e. nociceptors) are activated by substances released after tissue injury.[32] Nociceptive pain can be caused by damage to skin, muscle, ligament, bones or joints (i.e. somatic pain, also known as musculoskeletal pain) or by injury to visceral organs (i.e. visceral pain).[37] Pathophysiologic pain results from nerve damage in the peripheral and/or central nervous system (i.e. neuropathic pain) or impaired functioning of central nervous system pain processing.[32] Pathophysiologic pain conditions include fibromyalgia, diabetic neuropathy, postherpetic neuralgia, and drug-induced neuropathy, among others.[32]

The definition of acute pain includes a duration less than 3 to 6 months that subsides when the underlying tissue injury is resolved.[37] Nociceptive pain is the most common type of acute pain.[37] Typical causes of acute pain include fracture, burn, surgery, acute illness, trauma, labor, and cancer.[32,37] Depression, insomnia, and psychological issues are uncommon with acute pain.[32] An increased risk of developing chronic pain is associated with untreated, or inadequately treated acute pain.[32] Chronic pain is defined as pain that persists longer than 3 to 6 months or beyond the expected time for tissue damage resolution.[37] Some cases of chronic pain may not have an identified etiology. Chronic pain may be accompanied by depression, insomnia, and psychological problems.[32] Chronic pain is common in the setting of lower back pain, osteoarthritis, headaches, and peripheral neuropathy.[37]

Pain is subjective. Treatment decisions can be based on a patient's qualitative assessment of their pain with the use of assessment tools such as rating pain scales or pain questionnaires.[37] Patients' description of pain (type, location, duration, and severity) helps diagnosis and treatment decisions.[37]

Ideally, treating the underlying condition should eliminate pain. In some cases this does not eradicate pain.[38] Immediate symptomatic treatment of acute pain with analgesic therapy (NSAIDs, opioids) is the first-line option.[38] NSAIDs are effective for the management of pain and inflammation and are generally preferred as first-line options for the treatment of mild to moderate pain.[32] Treatment approaches should be individualized and the selection of an NSAID should be based on pain intensity, etiology, duration, comorbidities, and drug safety profile (gastrointestinal, cardiovascular, and renal risks).[39] If a patient does not respond to a particular NSAID, switching to another NSAIDs should be considered before progressing to more potent analgesics.[32]

NSAIDs are indicated for acute, mild to moderate pain (e.g., low back pain, headache, sore throat, dental pain, postoperative pain, post-traumatic pain, dysmenorrhea, etc.), and painful musculoskeletal conditions such as osteoarthritis (OA), rheumatoid arthritis (RA), childhood arthritis, bursitis/tendinitis, ankylosing spondylitis (AS), and gout.

Arthritis

Around 54 million adult Americans live with arthritis, a leading cause of chronic pain.[40] In 2014, around 410,000 (20.1%) adults lived with arthritis in Utah.[41] There are more than 100 types of arthritis including osteoarthritis, rheumatoid arthritis, childhood arthritis, and gout.[42,43] Typical symptoms of arthritis include pain and stiffness around joints, although some specific conditions also impair the immune system and internal organs.[42] Rheumatoid conditions may progress to severe complications causing disability and disturbing daily and work activities.[42] Advanced age, gender and genetic characteristics may increase the risk of arthritis.[42]

Osteoarthritis

Osteoarthritis (OA) is a musculoskeletal disease caused by joint cartilage degeneration and characterized by pain, inflammation, stiffness, and reduced movements.[44] It is the most common type of arthritis affecting nearby 30 million Americans.[44] OA primarily affects joints in hips and knees, and may progress to severe joint pain and inflammation.[44] Treatment includes non-pharmacological strategies (physical activity, physical therapy, weight loss) and pharmacological treatments (NSAIDs). Surgical interventions are recommended when medication therapy has failed.[44] The goals of osteoarthritis treatment include reducing pain, increasing function, and improving quality of life.[45]

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a systemic autoimmune disease that causes inflammation of the lining of joints in hands, wrists, and knees. RA also affects other organ tissues (e.g., lungs and heart), producing severe complications.[46] Signs and symptoms of RA include pain, inflammation, stiffness, tenderness, fever, fatigue, and weakness. Treatment approaches include agents to delay disease progression (i.e. disease-modifying antirheumatic drugs [DMARDs])[46] and NSAIDs for symptomatic pain relief.

Childhood Arthritis

Juvenile idiopathic arthritis (JIA), also called juvenile rheumatoid arthritis (JRA), is the most frequently diagnosed form of childhood arthritis.[47] It affects children of all ages. The specific cause remains unknown. Childhood arthritis may result in irreversible joint damage and disability.[47] Symptoms include joint pain, inflammation, fever, stiffness, rash, fatigue, loss of appetite, eye swelling, and difficulty in walking, playing and dressing.[47]

Ankylosing Spondylitis

Spondyloarthritis includes several types of inflammatory conditions.[48] Ankylosing Spondylitis (AS) is the most common type[49,50] and is classified as an axial spondyloarthritis because it affects spinal joints, particularly sacroiliac joints.[51,52] AS can also affect other parts of the body such as shoulders, hips, ribs, hands, feet, eyes, and bowel.[53,54] Disease progression may result in new bone formation (ankyloses), causing vertebral fusion and loss of spinal mobility.[50,51] Patients with AS typically have chronic back inflammation, pain, and stiffness.[54] The etiology of the disease is thought to relate to genetic factors.[19] Around 80-90% of AS patients have the presence of a genetic marker called human leukocyte antigen B27 (HLA-B27).[50] NSAIDs are the mainstay of pharmacological therapy for AS.[50-52]

The estimated prevalence of axial spondyloarthritis in adult Americans is between 0.9% and 1.4%.[48]

Gout

Gout is a painful and debilitating inflammatory arthritis associated with high serum uric acid (SUA) levels and triggered by deposition of monosodium urate crystals in joints, tendons, bursas and other tissues.[55] Gout is a major and increasing public health concern affecting 3.9% of adults in the United States,[56] especially middle-aged to elderly men and postmenopausal women.[57-59] The number of people with gout has increased in recent years,[56,60] especially in developed countries,[61] due to the growing aging population, dietary and lifestyle changes (e.g., high consumption of purine and fructose containing food and beverages, seafood, and alcohol), higher use of gout-inducing medications (e.g., diuretics), and comorbidities including hypertension, obesity, diabetes, renal impairment and cardiovascular disease.[61,62] A study that followed U.S. adult patients from 1987 to 2012 reported an incidence of gout of 0.84 cases per 1,000 person-years. Data also suggested an increasing incidence of gout over time.[61]

Three presentations of gout have been described: 1) acute gouty arthritis, 2) intercritical or the asymptomatic period between flares, and 3) chronic tophaceous gout. Acute gout is characterized by gout flares or episodic severe pain, redness, warmth, swelling and disability at the lower extremities. This generally occurs in a single joint, typically the great toe or knee with peak severity within 12-24 hours of onset, and commonly at night. Untreated gout flares can last a few days to several weeks, producing work limitations. Tophaceous gout is typified by longstanding accumulation of monosodium urate crystals (i.e. tophi) in tissues, which causes chronic inflammation, soft tissue destruction, joint deformities and impaired quality of life.[55,63,64]

Nephrolithiasis and chronic nephropathy are the two major renal complications of hyperuricemia and gout.[55]

The primary goals of gout treatment are to relieve pain associated with acute gout attacks, and to reduce SUA concentration to less than 6 mg/dL (360 µmol/L)[65,66] in order to prevent recurrent flares and the development of complications.[55] Pharmacologic approaches for acute gout attacks include NSAIDs, colchicine, corticosteroids and adrenocorticotropic hormone (ACTH).[57,67-69] Maintenance therapy for chronic gout includes xanthine oxidase inhibitors (i.e. allopurinol and febuxostat), uricosuric medications (i.e. probenecid and lesinurad), uricases (i.e. pegloticase) and a combination of probenecid plus colchicine.[66,69] Non-pharmacological approaches include lifestyle and dietary changes.[65,66,69]

Gout treatment should be individually tailored. Patient´s potential comorbidities, cardiovascular risk factors, contraindications to treatment alternatives for gout[65] and adherence barriers should be considered prior to the initiation of gout therapy.

Diverse guidelines for the management of acute and chronic gout have been developed by the American College of Physicians (ACP),[68] the European League Against Rheumatism (EULAR),[65] the 3e (Evidence, Expertise, Exchange) Initiative,[70] the American College of Rheumatology (ACR),[66,67] and the British Society for Rheumatology.[71] For the management of acute gout, guidelines recommend the use of colchicine, NSAIDs or corticosteroids as first-line treatment. Evidence-based ACP and ACR guidelines state no preference for one particular NSAID over another.[67,68]

B) Guideline Recommendations

Specific guidelines for various indications of the NSAIDs, in several treatment settings were identified. **Table 3** outlines guideline recommendations concerning the use of NSAIDs in the treatment of pain. Overall, guidelines recommend NSAIDs for the management of acute and chronic pain, including postoperative pain, low back pain, dysmenorrhea, and arthritis (OA, RA, AS, gout). Most guidelines do not support a preference for one NSAID over another.

Table 3. Guideline Recommendations for Oral NSAIDs

Guideline	Recommendation
Acute Pain	
American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management[72]	- The following drugs should be considered as part of a postoperative multimodal pain management regimen: o COX-2 selective NSAIDs (COXIBs) o Nonselective NSAIDs o Acetaminophen o Calcium channel α-2-antagonists (e.g.,gabapentin, pregabalin) - Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen
Chronic Pain	
CDC Guideline for prescribing opioids for chronic pain, 2016 [73](U.S. Department of Health and Human Services Centers for Disease Control and Prevention)	- Opioids are not first-line or routine therapy for chronic pain - Nonopioid choices include acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclics and serotonin and norepinephrine reuptake inhibitors). These are preferred for chronic pain and can be useful for arthritis and low back pain - NSAIDs and COX2 inhibitors are considered first-line treatment for osteoarthritis or low back pain but carry risk for gastrointestinal toxicity and renal and cardiovascular risk - Note the FDA has strengthened existing label warnings for NSAID risk in heart attack and stroke, especially with increase with longer use or at higher doses - Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain (category: A, evidence type: 3) ** The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care."*
Low Back Pain	
Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians (Qaseem 2017[74]) - Literature searches from January 2008 through November 2016	- Recommendations are based on 2 background evidence reviews[75,76] and a systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ)[77] General recommendations: - *Recommendation 1*: "If pharmacologic treatment is desired, clinicians and patients should select NSAIDs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)" - *Recommendation 3*: "In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with NSAIDs as first-line therapy, or tramadol or duloxetine as second-line therapy. (Grade: weak recommendation, moderate-quality evidence)" Acute or Subacute Low Back Pain: - "Moderate-quality evidence showed that **most head-to-head trials of one NSAID versus another showed no differences in pain relief** in patients with acute low back pain"[78] *** "**Treatment with NSAIDs resulted in a small improvement in both pain intensity (moderate-quality evidence) and function (low-quality evidence)

Table 3. Guideline Recommendations for Oral NSAIDs

Guideline	Recommendation
	* Clinicians should assess renovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend the lowest effective doses for the shortest periods necessary." Chronic Low Back Pain - "Moderate quality evidence showed that **most head-to-head trials of one NSAID versus another showed no differences in pain relief** in patients with chronic low back pain"[78] * "NSAIDs had a small to moderate effect on pain (moderate-quality evidence) and no to small effect on function (low-quality evidence) and should be the first option considered."
Osteoarthritis	
Management of osteoarthritis of the hip evidence-based clinical practice guideline, adopted by the American Academy of Orthopaedic Surgeons Board of Directors (March 2017) - Literature searches from January 1, 1990 to April, 15 2016	*NON-NARCOTIC MANAGEMENT* - **"**Strong evidence supports that NSAIDs improve short-term pain, function, or both in patients with symptomatic osteoarthritis of the hip. (Strength of Recommendation: Strong Evidence - Evidence from 2 or more "High" strength studies with consistent findings for recommending for or against the intervention)"
OARSI guidelines for the non-surgical management of knee Osteoarthritis (McAlindon,[79] 2014)	*"*NSAIDs (oral non-selective NSAIDs) Recommendations for NSAID use: - Appropriate: individuals without co-morbidities - Uncertain: individuals with moderate co-morbidity risk - Not appropriate: individuals with high co-morbidity risk Rationale*:* A 2011 comparative effectiveness review indicated that NSAIDs are associated with increased risk of serious GI, CV, and renal harms compared with placebo.[80] Nevertheless, the CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in two SRs of RCTs. Among currently marketed NSAIDs, diclofenac is associated with the highest rate of hepatic laboratory abnormalities. Due to serious safety risks associated with oral NSAID use, we recommend conservative dosing and treatment duration consistent with approved prescribing limits."
VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis. Department of Veterans Affairs Department of Defense (2014)[81]	Recommendations: - "In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral NSAIDs as first line treatment (Grade B: There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial) - In patients requiring treatment with oral NSAIDs and who are at high risk for serious adverse upper gastrointestinal (GI) events, clinicians should consider the addition of a proton-pump inhibitor (PPI) or misoprostol. (Grade A: There is high certainty that the net benefit is substantia) - Clinicians should consider the balance of benefit and potential harm in prescribing oral NSAIDs in patients at risk for or with known cardiovascular disease or renal injury/disease. (Grade B)" * Long-term use of oral NSAIDs is limited by adverse effects such as increased CV events, GI perforation, ulceration, and bleeding, and renal impairment.

Table 3. Guideline Recommendations for Oral NSAIDs

Guideline	Recommendation
	* All NSAIDs have the potential to increase the risk for cardiovascular events and therefore should be used at the lowest effective dose for the shortest possible duration. Naproxen has a neutral or lowest risk for adverse CV events.
American College of Rheumatology 2012 Recommendations for the Use of Non-pharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (Hochberg 2012[82]) - Literature searches up to December 31, 2010	"Oral NSAIDs are conditionally recommended for hand OA, knee OA, and hip OA, among other pharmacologic recommendations"
Osteoarthritis Care and management in adults, Clinical guideline CG177 Methods, evidence and recommendations, February 2014[83] (NICE Guideline)	- 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.
OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines (Zhang 2008[84]) - Literature searches from 1945 to January 2006	- "In patients with symptomatic hip or knee OA, NSAIDs should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a PPI or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with CV risk factors. (Level of evidence: Ia for Knee and hip – Meta-analysis of Randomized Controlled Trials)"
Rheumatoid Arthritis	
Rheumatoid arthritis in adults: management. Clinical guideline [CG79]. (NICE guideline, February 2009; last updated: December 2015)[85]	- Oral NSAIDs/COX-2 inhibitors should be used 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. In either case, these should be co-prescribed with a 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, healthcare professionals should take into account individual patient risk factors, including age. ** The above NSAID recommendations are based on RCTs (mostly moderate quality), case series, and the Guideline Development Group´s (GDG) opinion* - In people with newly diagnosed active RA, 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

Table 3. Guideline Recommendations for Oral NSAIDs

Guideline	Recommendation
Management of early rheumatoid arthritis. A national clinical guideline. Scottish Intercollegiate Guidelines Network. (February 2011)[86]	- There is **no difference in the efficacy of non-selective NSAIDs**. A health technology assessment concluded that selective COX-2 inhibitors have a similar efficacy to NSAIDs.[87] - "Cardiovascular side effects: Differences are shown between NSAIDs: diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk but naproxen (1 g daily) and lower doses of ibuprofen (1.2 g daily or less) are not. Data on other NSAIDs are, as yet, inconclusive. NSAIDs and COX-2 inhibitors should therefore be avoided in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate to severe heart failure."
Juvenile Rheumatoid Arthritis	
2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis (Ringold 2013[88]) - Literature searches up to January 2013	- NSAIDs are recommended in the 2011 and 2013 guidelines juvenile idiopathic arthritis. NSAIDs include all NSAIDs commonly used in clinical practice in the US, including selective cyclooxygenase 2 inhibitors. Maximum duration of NSAIDs monotherapy was 1 month.
Ankylosing Spondylitis	
Spondyloarthritis in over 16s: diagnosis and management (NICE guideline, February 2017[89])	NSAIDs: - "Offer NSAIDs at the lowest effective dose to people with pain associated with axial spondyloarthritis, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment - If an NSAID taken at the maximum tolerated dose for 2–4 weeks does not provide adequate pain relief, consider switching to another NSAID"
American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis (Ward 2016[90]) - Literature searches up to July 2014	"In adults with active AS: - We strongly recommend treatment with NSAIDs over no treatment with NSAIDs (PICO 2; low-quality evidence; vote 100% agreement). - We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs (PICO 1; very low-quality evidence; vote 90% agreement). - **We do not recommend any particular NSAID as the preferred choice** (PICO 3; moderate- to low-quality evidence; conditional recommendation; vote 100% agreement) * Evidence for the efficacy of NSAIDs in active AS comes from several placebo-controlled trials. The overall quality of evidence was low based on serious risk of bias and imprecision for several critical outcomes * We did not identify any formal comparative effectiveness analyses of different NSAIDs in AS. Evidence of the relative efficacy of NSAIDs was provided by several head-to-head controlled trials that used either indomethacin (n = 12), celecoxib (n = 2), or naproxen (n = 1) as the comparator drug. There was no evidence to suggest that indomethacin had different effects on pain or stiffness compared to other NSAIDs, nor differences in efficacy between celecoxib and either diclofenac or ketoprofen. Based on this evidence, **the panel recommended against designating any particular NSAIDs as the preferred treatment option.** Choice of

	NSAID should be based on consideration of the patient's past history of NSAID use, risk factors for adverse effects, and comorbidities."
2016 update of the ASAS/EULAR management recommendations for axial spondyloarthritis[91]	- "Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise."
2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis[92]	- NSAID, including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness. - Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease. - Cardiovascular, GI and renal risks should be taken into account when prescribing NSAID.
Acute Gout	
2016 updated EULAR evidence-based recommendations for the management of gout (Richette et al 2017[65]) Systematic literature review from January 2005 to May 2016	Recommendations (11 key recommendations): - "*Recommendation 2*: Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus PPIs if appropriate), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. - *Recommendation 3*: In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares. - *Recommendation 4*: Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered."
Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians (Qaseem et al 2017[68]) • Systematic literature review from January 2010 to March 2016	- Guideline recommendations based on: • 1 SR (Shekelle 2017)[93] • 1 systematic evidence review sponsored by AHRQ (Shekelle 2016)[69] - *Recommendation 1*: "ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout. (Grade: strong recommendation, high-quality evidence)" - *Comparative Effectiveness (Benefits and Harms) of Pharmacologic Treatments* • NSAIDs vs. NSAIDs: "Moderate-quality evidence from 16 RCTs showed **no clinically important differences in comparisons of different types of NSAIDs with one another in patients with gout**." - *Summary*: "Evidence showed that **NSAIDs are effective as a class, regardless of choice of the individual drug**"
The British Society for Rheumatology Guideline for the Management of Gout (Hui 2017[71]) Systematic literature search up to June 2015	- "An NSAID at maximum dose or colchicine in doses of 500 mg bd-qds is the drug of choice when there are no contraindications. Choice of first-line agent will depend on patient preference, renal function and co-morbidities. Patients on NSAIDs or cyclooxygenase-2 inhibitors (coxibs) should be co-prescribed a gastro-protective agent. (Level of evidence: Ia; strength of recommendation: 95% (range 80-100%)." - The efficacy of NSAIDs is supported by a single placebo-controlled RCT of tenoxicam 40 mg daily. **Most RCTs have been head-to-head comparisons with no single agent having greater efficacy**. There is, however, widespread

	expert consensus that, where there is no contraindication to do so, NSAIDs should be prescribed at high dose when treating patients with acute gout because of the severity of the pain and inflammation. NSAIDs are, however, frequently contraindicated in patients with renal insufficiency, peptic ulceration or a history of previous upper gastrointestinal haemorrhage or perforation."
3e (Evidence, Expertise, Exchange) initiative Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative (Sivera et al 2014[70]) - Systematic literature search from 2010 to 2011 - Panel of 78 international rheumatologists from 14 countries	• First-line therapy: low-dose colchicine (up to 2 mg/day), NSAIDs or corticosteroids (oral, intraarticular or IM) (Decision based on 25 trials: 21 for NSAIDs, 5 for CS and one for colchicine)
2012 American College of Rheumatology Guidelines for Management of Gout Part II: Therapy and Anti-inflammatory Prophylaxis of Acute Gouty Arthritis (Khanna et al 2012[67]) - Systematic literature search from 1950 to March 2011	• First line options for acute flare treatment include NSAIDs, colchicine and corticosteroids. • **"No preference between NSAIDs, although naproxen and indomethacin are approved by FDA for acute gout** (level of evidence A - high-quality evidence)"
General Guidelines	
Guidelines for prevention of NSAID-related ulcer complications. American College of Gastroenterology (Lanza 2009)[94]	• The American College of Gastroenterology offers guidance on the selection of an NSAID based on patient's gastrointestinal and cardiovascular risk

Abbreviations: ACP, American College of Physicians; COX-2; cyclooxygenase; CV, cardiovascular; DMARD, Disease-Modifying Antirheumatic Drugs; EULAR, European League Against Rheumatism; GI, gastrointestinal; IM, intramuscular; NSAID, non-steroidal anti-inflammatory drugs; OARSI, Osteoarthritis Research Society International; PPI, proton pump inhibitor; RA, rheumatoid arthritis; RCT, randomized controlled trial; SR, systematic review

Table 4. Clinical Practice Guidance with Less Methodological Rigor than Guidelines Included in Table 3

Guideline	Recommendation
Pharmacologic Therapy for Acute Pain. American Academy of Family Psysician (Blondell 2013[95])	"Key recommendations for practice: - Ibuprofen and naproxen (Naprosyn) are good, first-line NSAIDs for mild to moderate acute pain based on effectiveness, adverse effect profile, cost, and over-the-counter availability (Evidence A- consistent, good-quality patient-oriented evidence[78,96])"
Diagnosis and Treatment of Acute Low Back Pain (Casazza 2012)[97]	"NSAIDs are often first-line therapy for low back pain. Low-quality evidence suggests that they are effective for short-term symptom relief, compared with placebo. No patient characteristics at baseline can predict the success of NSAID therapy. **Moderate evidence suggests that no one NSAID is superior, and switching to a different NSAID may be considered if the first is ineffective**."
Diagnosis and Initial Management of Dysmenorrhea. American Academy of Family Psysician (Osayande 2014[98])	Key recommendations for practice: - Nonsteroidal anti-inflammatory drugs should be used as first-line treatment for primary dysmenorrhea (Evidence rating A: consistent, good-quality patient-oriented evidence[96]). A Cochrane review[96] of 73 randomized controlled trials (RCTs) demonstrated strong evidence to support nonsteroidal anti-inflammatory drugs (NSAIDs) as the first line treatment for primary dysmenorrhea. **The choice of NSAID should be based on effectiveness and tolerability for the individual patient, because no NSAID has been proven more effective than others.**
Analgesics for Osteoarthritis - Implementing AHRQ Effective Health Care Reviews. American Academy of Family Physicians (Fogleman 2013)[99]	• **Comparisons among various nonselective NSAIDs exhibit no differences in efficacy for the relief of osteoarthritic symptoms** (*SOE: **high** - There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions*) • The risk of serious GI adverse effects is higher with naproxen than with ibuprofen (*SOE: high*) • The partially selective NSAIDs meloxicam and etodolac are associated with lower risk of ulcer-related complications and symptomatic ulcers than nonselective NSAIDs (*SOE moderate - Findings are supported, but further research could change the conclusions*)
Diagnosis and Management of Rheumatoid Arthritis. American Academy of Family Physicians (Wasserman 2011)[100]	- Drug therapy for RA may involve NSAIDs and oral, intramuscular, or intra-articular corticosteroids for controlling pain and inflammation. Ideally, NSAIDs and corticosteroids are used only for short-term management. DMARDs are the preferred therapy.
Gout: Diagnosis and Management. Implementing AHRQ Effective Health Care Reviews (Noss 2017)[101]	Recommendations based on: o 1 systematic evidence review sponsored by AHRQ (Shekelle 2016)[69] • NSAIDs, colchicine, and corticosteroids all effectively treat acute gout. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.) • NSAIDs: 16 RCTs (1,280 patients). **No differences among NSAIDs in effectiveness** (Strength of Recommendation: B - Findings are supported, but further research could change the conclusions)

Abbreviations: DMARD, Disease-Modifying Antirheumatic Drugs; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SOE, strength of evidence

Pharmacology & Special Populations

Chemically, the NSAIDs are represented by a number of structural types, phenylacetic acids (diclofenac), salicylic acids/esthers (diflunisal), oxicams (piroxicam, meloxicam), carbo- and heterocyclic acids (etodolac, indomethacin, ketorolac, sulindac, tolmetin), propionic acids (fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin), non-acidic compounds (nabumetone) and fenamic acids (mefenamic acid).[102] The NSAIDs all act by the same mechanism of action, inhibition of cyclooxygenase (prostaglandin synthase, COX), which blocks the transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxanes.[103]

Prostaglandins generated by COX-1 enzymes function in gastric cytoprotection, vascular homeostasis, promotion of platelet aggregation, and controlling kidney function. Prostaglandins generated by COX-2 enzymes mediate pain, inflammation, and fever, and inhibit platelet aggregation. The inhibition of COX-2 enzymes is mainly associated with the anti-inflammatory and analgesic effects. The inhibition of COX-1 enzymes prevents clotting, but may result in gastrointestinal (GI) or renal toxicity.

The NSAIDs vary in selectivity for COX-1 and COX-2. Agents with higher COX-1 selectivity exhibit more adverse effects relating to COX-1 inhibition, while those with greater COX-2 specificity produce less COX-1-related adverse events and more COX-2 adverse effects. NSAIDs with greater COX-1 specificity are associated with greater risks for GI toxicity. NSAIDs with greater COX-2 specificity are associated with greater risks for cardiovascular toxicity. The selection of a patient-appropriate NSAID requires consideration of the cardiovascular-gastrointestinal risk-benefit tradeoff.

The *in vitro* selectivity ratio for NSAIDs may be classified as low, moderate, or high based on COX-2 selectivity, as shown in **Table 5**.[104-106]

Table 5. *In Vitro* Selectivity Ratio for NSAIDs[104-106]

COX-2 Selectivity (*in vitro*) ↓	Non-selective NSAIDs	
	Low	Flurbiprofen Indomethacin Ketoprofen Ketorolac Naproxen Oxaprosin Tolmetin
	Moderate	Diflusinal Fenoprofen Ibuprofen Nabumetone Piroxicam Sulindac
	High	Diclofenac Etodolac Mefenamic acid Meloxicam
	Selective NSAIDs	
	Highest	Celecoxib

Tables 6 and **7** include information concerning pharmacokinetics and special population considerations for oral nsNSAIDs. **Appendix B** outlines drug interactions with NSAIDs.

Table 6. Pharmacokinetics for Oral Non-selective NSAIDs[14,107]

NSAIDs	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-Life
Aspirin	Tmax: 1-2 hr	PB: variable (widely distributed)	Aspirin: Hepatic	Aspirin: Renal	Aspirin 15 min *salicylic acid 6 hr* Aspirin: 2-3 hr
Diclofenac	BA: 50% Tmax: 1 hr Diclofenac sodium: 1.5-6.5 hr	V_D: 1.3 L/kg PB: Over 99%	Liver: Extensive via CYP2C9 Active: 4'-hydroxydiclofenac CYP2C9, CYP3A4 Substrate CYP2C8, UGT2B7 Substrate (possible)	Renal 65% Bile 35%	1.9-2.2 hr Diclofenac potassium: 1-2 hr Metabolites: 1-3 hr
Etodolac	BA: ≥80% Tmax Capsule: 80 min Tablet: 1.4 hr Tablet (IR) hepatic impairment: 1.1 h Tablet (IR) renal impairment: 2.1 hr ER Tablet (18-44 yo): 4.5-6.7 hr ER tablet (55-88 yo): 6.2 hr	V_D Capsule: 0.362 L/kg Tablet: 393 mL/kg Tablet ER (18-44 yo): 459-580 mL/kg Tablet ER (66-88 yo): 552 mL/kg PB: 99%	Hepatic: Extensive Metabolites (inactive)	Renal: 72% Fecal: 16%	Capsule: 7.3 hr Tablet: 6.4 hr Tablet ER (18-44 yo): 7.6-8.4 hr Tablet ER (66-88 yo): 7.8 hr Hepatic impairment: 5.7 hr
Fenoprofen	BA: 80-85% Tmax: 2 hr	V_D: Not available PB: 99%	Hepatic: Extensive	Renal: 90%	3 hr
Flubriprofen	BA: 96% Tmax Healthy adults: 1.9 hr Elderly: 2.2 hr ESRD: 2.3 hr Alcoholic cirrhosis: 1.2 hr	V_D: 0.12 L/kg Healthy adults: 14 L Elderly, arthritis: 12 L ESRD: 10 L Alcoholic cirrhosis: 14 L PB: >99%	Hepatic via CYP2C9 CYP2C9, UGT2B7 Substrate	Renal: 70%	Healthy adults: 7.5 hr Geriatric, arthritis: 5.8 hr ESRD: 3.3 hr Alcoholic cirrhosis: 5.4 hr
Ibuprofen	BA: 80% Tmax: 1-2 hr	V_D 0.12-2 L/kg PB 99%	Hepatic; rapidly metabolized	Renal: 45-79%	Adults 1.8-2.44 hr Pediatrics: 1.5-1.8 hr
Indomethacin	BA: 100% Tmax: 1.3-2 hr	V_D: Not available PB: 99%	Hepatic: Extensive	Fecal: 33% Bile: Extensive enterohepatic circulation and some biliary excretion	Indocin: 4.5 hr Tivorbex™: 7.6 hr Capsules, IR: 7.2 hr

Table 6. Pharmacokinetics for Oral Non-selective NSAIDs[14,107]

Ketoprofen	BA: 90% Tmax Capsule: 1.2±0.6 hr Capsule ER: 6.8±2.1 hr	V_D: 0.1 L/kg PB: >99%	Hepatic: Glucuronide conjugation	Renal: 80%	Capsule: 2.1±1.2 hr NOTE: Geriatrics: Prolonged by 26% Capsule ER: 5.4±2.2 hr NOTE: Geriatrics: Prolonged by 54%
Ketoralac	BA: 100% Tmax: 44 min	V_D: 13 L PB: 99%	Hepatic: extensive via hydroxylation and conjugation	Renal: 92% Fecal: 6%	Healthy adults: 5.2-6.2 hr Healthy elderly: 6.1-7 hr Hepatic insufficiency: 4.5-5.4 hr Renal Insufficiency: 10.3-10.8 hr Renal dialysis: 13.6 hr Pediatrics: 5.8 hr
Mefenamic acid	BA: Well absorbed Tmax: 2-4 hr	V_D: 1.06 L/kg PB: >90%	Hepatic: Extensive via CYP2C9	Renal: 52% Fecal: 20%	2 hr
Meloxicam	BA: 89% Tmax Healthy adults (7.5 mg): 4.9 hr Healthy adults (15 mg): 4-8 hr Healthy adults (SoluMatrix 15mg): 2 hr Healthy adults: 30 mg: 8-11 hr Elderly men (15 mg): 5 hr Elderly women (15 mg): 6 hr Renal impairment (15 mg): 2.5-4 hr Hepatic impairment (15 mg): 10 hr	V_D 10-16 L PB: 99.4%	Hepatic: 99% via CYP2C9	Renal: 0.2% Fecal: 1.6%	Healthy Adults: 20.1-23.6 hr Renal failure: 18 hr Hepatic insufficiency: 16 hr
Nabumetone	BA: well absorbed (pro-drug) Tmax Active drug, young adults: 2.5-3 hr Active drug, elderly: 4 hr	V_D Young adults (1000 mg): 55.4±26.4 L Elderly (1000 mg): 50.2±25.3 L PB: >99%	Hepatic: Nabumetone (prodrug) Hepatic: Active metabolite (6-methoxy-2-napathylacetic acid, (6MNA), 35%	Renal Nabumetone 80% 6MNA: 75-80% Fecal: 6MNA: 9%	6MNA 24 h Young adults: 22.5±3.7 to 26.2±3.7 hr Elderly: 29.8±8.1 hr Renal insufficiency: 39.2±7.8 hr Severe renal dysfunction: increased

Table 6. Pharmacokinetics for Oral Non-selective NSAIDs[14,107]

Naproxen	BA: 95% Tmax Tablet: 2-4 hr Suspension: 1-4 hr Tablet DR: 4-6 hr	V_D: 016 L/kg PB: >99%	Hepatic: Extensive	Renal: 95%	12-17 hr
Naproxen Sodium	BA: 95% Tmax (IR): 1-2 hr Tmax (CR): 5 hr	V_D: 0.16 L/kg PB: >99%	Hepatic: Extensive	Renal 95% Fecal <3%	TBC: 0.13 mL/min/kg
Oxaprozin	BA: 95% Tmax: 2.44 to 3.09 hr	V_D: 11.7 to 16.7 L/70 kg PB: 99%	Hepatic: 95% via oxidation and conjugation Active metabolite Phenolic metabolite (<5%)	Renal: 65% Fecal: 35% Bile: Major (unchanged)	41.4 to 54.9 hr
Piroxicam	BA: Well absorbed Tmax: 3-5 hr	V_D: 0.1 to 0.2 L/kg PB: 99%	Hepatic: hydroxylation, conjugation, cyclodehydration, hydrolysis, decarboxylation, ring contraction and N-demethylation CYP2C9 Substrate NOTE: Genetic polymorphisms may lead to elevated levels and prolonged half-life	Renal: 5% unchanged "Piroxicam and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces"	50 hr
Sulindac	BA: 90% Tmax: 2 hr	V_D: Not available PB Sulindac 93.1% Sulfide metabolite: 97.9%	Hepatic: Extensive via enterohepatic recirculation; reversible & irreversible oxidation Metabolites sulfide (active), sulfones	Renal: 50% Fecal: 25%	Sulindac: 7.8 hr (mean) Sulfide metabolite: 16.4 hr (mean)
Tolmetin	BA: Well absorbed Tmax: 30 to 60 min Tmax (600 mg tablet): 20 min longer	V_D: Not available PB: 99%	Hepatic: Conjugation or oxidation	Renal	5 hr

Abbreviations: BA, bioavailability; CR, controlled release; DR, delayed release; ER, extended release; ESRD, end-stage renal disease; IR, immediate release; PB, protein binding; Susp, suspension; TBC, total body clearance; Tmax, time to maximum concentration; V_D, volume of distribution; yo, years of age.

Table 7. Special Population Considerations for Oral Non-selective NSAIDs[14,107]

NSAIDs	Pediatric	Geriatric	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy & Lactation
Diclofenac	Safety and efficacy not established	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Begin at the lower end of the dosing range	Initiate therapy with lowest recommended dose; monitor closely	Initiate therapy at 18 mg 3x daily; discontinue if not efficacious Potassium salt: Dosage reduction Sodium Salt: No adjustment necessary	Pregnancy: 1st & 2nd Trimester – category C 3rd Trimester – Category D May be used prior to 30 weeks is benefits to mother outweigh risks to the fetus. Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus. Crosses placenta Associated with reversible infertility
Etodolac	Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate No dose adjustment Elderly are more sensitive to side effects	Mild to moderate failure: no adjustment. Use with caution due to possible cumulative effects on renal function	Compensated hepatic disease: no adjustment Severe hepatic failure: dose reduction	Pregnancy: Category C Avoid use in late pregnancy due to the risk of premature closure of the ductus arteriosus Crosses placenta Lactation: Infant risk cannot be ruled out
Fenoprofen calcium	Safety and efficacy not established Weigh benefits vs risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Delayed Tmax Fenoprofen 300 mg TID = fenoprofen 600 mg TID x5 days in elderly OA patients; use smaller dose.	None required	No information	Pregnancy: Fetal risk cannot be ruled out Crosses placenta Lactation: Infant risk cannot be ruled out
Flurbiprofen	Safety and efficacy not established Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Due to higher incidence of GI side effects use the lowest effective dose for the shortest duration	Use with caution (88-98% of the daily dose is excreted in the urine); dosage reduction may be required to avoid accumulation of flurbiprofen metabolites	Use with caution	Pregnancy: Fetal risk cannot be ruled out May be used prior to 30 weeks is benefits to mother outweigh risks to the fetus. Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus. Crosses placenta Associated with reversible infertility

Table 7. Special Population Considerations for Oral Non-selective NSAIDs[14,107]

NSAIDs	Pediatric	Geriatric	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy & Lactation
Ibuprofen	Use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	None required	None required	Pregnancy: Fetal risk cannot be ruled out Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus. Crosses placenta Lactation: Infant risk cannot be ruled out
Indomethacin	Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Initiate therapy at the lower end of the dosage range	Advanced renal disease: not recommended unless benefits outweigh risks	No information	Pregnancy: 1st & 2nd Trimesters: category C 3rd Trimester: category D Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus. Crosses placenta Lactation: Infant risk cannot be ruled out
Ketoprofen	Safety and efficacy not established Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Age ≥75: Reduce initial dose	Renal impairment (mild): max. 150 mg/day CrCl<25 mL/min or ESRD: max. 100 mg/day Hypoalbuminemia & renal impairment: initiate with a lower dose	Hepatic impairment & serum albumin < 3.5 g/dL MAX 100 mg/day	Pregnancy: Category C Crosses placenta Lactation: Infant risk cannot be ruled out
Ketorolac	Safety and efficacy not established in children under 17 years of age	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Age ≥65 years: max. 40 mg/day	Renal impairment: max. 40 mg/day Advanced renal impairment or volume depletion: contraindicated	No recommendation Prolonged elimination half-life	Pregnancy: 1st & 2nd Trimester: Category C 3rd Trimester: Category D Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus. Crosses placenta Lactation: Infant risk has been demonstrated

Table 7. Special Population Considerations for Oral Non-selective NSAIDs[14,107]

NSAIDs	Pediatric	Geriatric	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy & Lactation
Mefenamic acid	Safety and efficacy not established in children under 14 years	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Start at lower end of dosing range and monitor for adverse effects	Preexisting renal disease or significant renal impairment: Do not use	Acute or chronic hepatic impairment: May require reduced doses	Pregnancy: Fetal risk cannot be ruled out Lactation: Infant risk cannot be ruled out
Meloxicam	Oral suspension dosing is weight based	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	CrCl > 15 mL/min: No adjustment needed CrCl < 15 mL/min: Use not recommended	Mild to moderate impairment (Child-Pugh Class I and II): No adjustment needed Severe hepatic impairment: Use caution and only if benefit outweighs risk	Pregnancy: Fetal risk cannot be ruled out Use caution in 1st and 2nd Trimester and avoid use in the 3rd Trimester Crosses placenta: Unknown; Breastfeeding: Infant risk cannot be ruled out
Nabumetone	Efficacy and safety in children not established Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	Monitor patient closely and reduce dosage if necessary	Monitor patient closely and reduce dosage if necessary	Pregnancy: Category C Crosses placenta Avoid use in late pregnancy due to the risk of premature closure of the ductus arteriosus Lactation: Infant risk cannot be ruled out
Naproxen	Safety and efficacy not established in children below 2 years of age Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate Use lowest effective dose; caution with high doses and dose adjustments may be required (consider 50% dosage reduction)	Moderate to severe renal impairment (CrCl<30 mL/min): Not recommended	Hepatic impairment: Use lowest effective dose; dose adjustments may be required	Pregnancy: Fetal risk cannot be ruled out Crosses placenta Lactation: Infant risk cannot be ruled out

Table 7. Special Population Considerations for Oral Non-selective NSAIDs[14,107]

NSAIDs	Pediatric	Geriatric	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy & Lactation
Oxaprozin	Safety and efficacy not established in children below 6 years of age Weigh benefits vs. risks; consider alternative therapy options; use the lowest dose for the shortest duration	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	Renal impairment: Initial 600 mg daily, monitor closely	Well-compensated hepatic cirrhosis: No adjustment Severe liver disease: Use with caution. Consider dose reduction	Pregnancy: Fetal risk cannot be ruled out Crosses placenta Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus Lactation: Infant risk cannot be ruled out
Piroxicam	Start at the low end of the dosing range	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	No adjustment needed Severe impairment: Not studied, recommend close monitoring	Liver dysfunction: consider dosage reductions	Pregnancy: 1st and 2nd Trimester – category C 3rd Trimester – category D Avoid use at 30 weeks due to the risk of premature closure of the ductus arteriosus Lactation: Infant risk cannot be ruled out
Sulindac	Safety and efficacy not established	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	Renal impairment: monitor patient closely and reduce dosage if necessary	Liver disease: Monitor patient closely and reduce dosage if necessary	Pregnancy: Category C Lactation: Infant risk cannot be ruled out
Tolmetin sodium	Safety and effectiveness not established in children less than 2 years of age	Beers Criteria[a]: Use caution or avoid use as potentially inappropriate	No adjustment needed	No adjustment needed	Pregnancy: Category C Avoid use in late pregnancy due to the risk of premature closure of the ductus arteriosus Lactation: Infant risk minimal

Abbreviation: CrCl, creatininve clearance; GI, gastrointestinal; OA, osteoarthritis; TID, three times daily; Tmax, time to maximum concentration
[a] Beers criteria for potentially inappropriate medication use in older adults[108]

Methods

Literature Search

1. Preliminary Search Strategy

Pharmacists conducted grey literature searching to identify high-quality systematic reviews such as Oregon and Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness reviews, and guidelines. Sources included:

- Agency for Healthcare Research and Quality (AHRQ): https://www.ahrq.gov/
- Oregon Health & Science University (OHSU): https://www.ohsu.edu/xd/
- Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cadth.ca/
- National Guideline Clearinghouse: https://www.guideline.gov/

For prescribing information package inserts and evidence-based drug information, the following sources were searched:

- The Food and Drug Administration website (Drugs@FDA: FDA Approved Drug Products: https://www.accessdata.fda.gov/scripts/cder/daf/)
- Evidence-based drug information databases (Micromedex and Lexicomp)

2. Systematic Search Strategy

Following the preliminary search, bibliographic database searches were conducted in February and March 2018. Search strategies were developed by an Information Scientist for OVID Medline and EMBASE.com. Strategies consisted of controlled vocabulary, such as MeSH and EMTREE, and keywords. Additionally, search strategies included vocabulary for individual drugs and drug class. Two methodological filters were used, one for SR/MAs, and another for RCTs.[109] Two main literature searches were performed, one for pain and oral formulations from 1996 to March 2018, and another search for certain indications and agents. In this last search, date restrictions based on references found in the preliminary search were applied. The complete search strategies and terms are available in **Appendix C**. We also screened the reference lists of related SR/MAs.

Screening

At least 2 review authors screened titles and abstracts. Conflicts were resolved via discussion or by third party. The full texts for all citations receiving 2 inclusion votes were retrieved; the lead author of this report determined final eligibility for inclusion.

Inclusion and Exclusion Criteria

Systematic reviews/meta-analyses (SR/MA) of RCTs and individual RCTs providing direct head-to-head efficacy or safety comparisons among the nsNSAIDs were included. For product

comparisons where a SR provided robust data, we examined only those trials or SRs published after the search date of the robust SR.

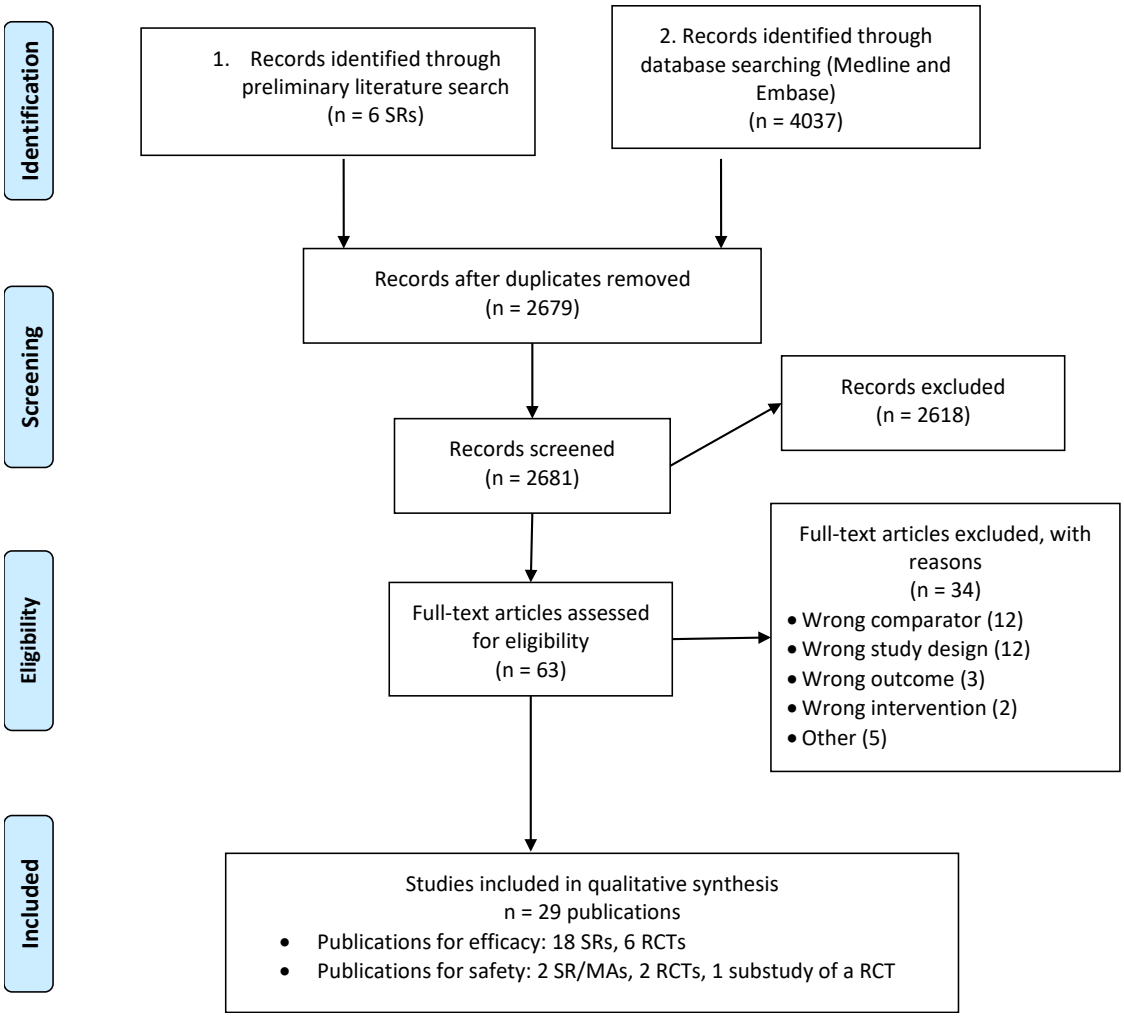
Excluded references met the following exclusion criteria:

- SR/MAs of observational studies, registries, and retrospective studies in the pooled analyses. Only SR/MA of RCTs or SR/MAs synthesizing the results from RCTs separately from observational studies were considered for the report
- Network meta-analyses, which are considered to have low quality according to the hierarchy of evidence because they include indirect comparisons
- SR/MAs or single studies comparing oral NSAIDs versus topical, transdermal, intramuscular, or intravenous NSAIDs
- Studies comparing nsNSAIDs versus placebo, paracetamol, aspirin, or cox-2 selective NSAIDs (i.e. celecoxib)
- Studies including NSAIDs combined with opioid drugs, or studies comparing NSAIDs versus opioid drugs
- Studies evaluating preventive analgesia (before pain onset) and pre-emptive analgesia (before the surgical event) with NSAIDs
- Studies evaluating single doses of NSAIDs for postoperative pain. Only multiple-dose studies for postoperative pain were considered, as NSAIDs are generally prescribed for several days following a surgery.
- Studies evaluating NSAID onset of action
- Single studies such as observational studies, pharmacodynamic studies, studies evaluating non-FDA approved doses, registries, pilot studies, or switching studies

Clinical Efficacy

After applying inclusion and exclusion criteria, 29 publications (20 SR/MAs, 8 RCTs, and 1 substudy of an RCT) evaluating the comparative efficacy or safety of the NSAIDs, listed in Table 1, were included in the qualitative synthesis. **Figure 1** shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart[110] for the review process of SRs and RCTs. The most commonly studied indications for NSAID use were OA, RA, AS, low back pain, and gout. Pain, physical function, and patient global assessment were the most frequently assessed efficacy outcomes in the studies identified.

Figure 1. PRISMA flow diagram of the selection process



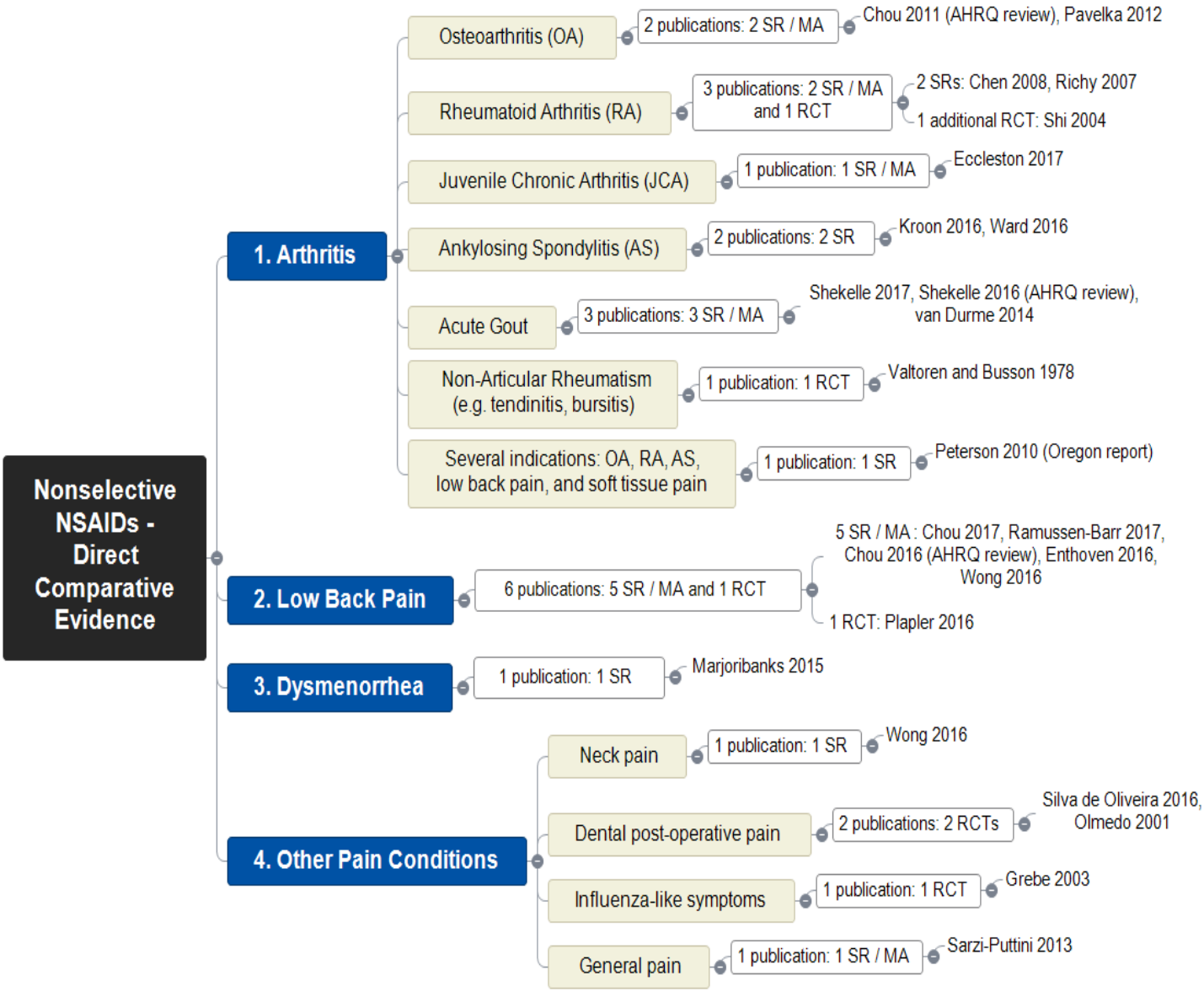
Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses (PRISMA); RCT, randomized controlled trial; SR, systematic review

Tables 1 to 10 of **Appendix D** include key findings reported in the SR/MAs identified. A list containing the excluded references is provided in **Appendix E**. A summary of the main efficacy findings can be found in the summary section (**Table 12**).

Summary of the Efficacy Evidence

Figure 2 presents head-to-head evidence identified from the literature search comparing nsNSAIDs.

Figure 2. Head-to-Head Efficacy Evidence among Non-selective NSAIDs



Abbreviations: AHRQ, Agency for Healthcare Research and Quality; NSAID, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial; SR / MA, systematic review/meta-analysis

1. ARTHRITIS

Osteoarthritis *(2 SR/MAs: Chou 2011 and Pavelka 2012)*

SYSTEMATIC REVIEWS

- AHRQ comparative effectiveness review (CER) on analgesics for osteoarthritis (**Chou et al**[111] 2011)

Chou et al performed a systematic literature search to update the 2006 AHRQ CER. Authors searched Medline up to 2011 and the Cochrane Central Register of Controlled Trials up to 2010. Etodolac, meloxicam and nabumetone were the included partially selective NSAIDs and diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin were the included nsNSAIDs. Overall, the majority of studies demonstrated no clear efficacy differences between the different types of NSAIDs in patients with OA, although some differences in safety (gastrointestinal events and cardiovascular risk) were found. A summary of the evidence reported by Chou et al is outlined in **Appendix D (Table 1)**.

<u>Partially selective NSAIDs versus nsNSAIDs</u>:

- *Etodolac versus nsNSAIDs (**high-strength evidence**)*: No significant efficacy differences were reported between groups in 3 Cochrane reviews, 1 SR, and 7 trials not included in the Cochrane reviews:
  - The original 2006 AHRQ CER included 3 good-quality Cochrane reviews[112-114] reporting no differences in efficacy for etodolac compared to several nsNSAIDs in patients with OA of the hip, knee, or back.
  - Seven additional RCTs not included in the Cochrane reviews were evaluated in the 2006 AHRQ CER. They consistently showed no differences in efficacy between etodolac and diclofenac, piroxicam, or naproxen for OA of the hip, knee, or foot. Five of the 7 trials included NSAIDs of interest for this report.[115-119] The remaining 2 studies included tenoxicam and nimesulide as comparators, which are not FDA-approved.
  - An additional SR/MA evaluating trials in OA and RA[87] was included in the 2011 AHRQ report. Literature searches were performed up to October-November 2003. Eighteen RCTs comparing etodolac with several nsNSAIDs in patients with OA were included. Results of the MA showed no differences in pain reduction and drug withdrawals due to lack of efficacy between groups.
- *Meloxicam versus nsNSAIDs (**high-strength evidence**)*
  - Eleven head-to-head RCTs in OA showed no clear efficacy differences between meloxicam (7.5 mg, 15 mg, or 25 mg) and nsNSAIDs (e.g., piroxicam, diclofenac). Two of the 11 trials studied patients with RA and were not included in this section.[120,121]
  - A SR/MA evaluating trials in OA and RA[87] was included in the 2011 AHRQ report. Eleven RCTs comparing meloxicam with several nsNSAIDs in patients with OA were included. Results showed significant lower pain reduction (mean difference on a 10

point VAS scale: 1.7 points, 95% confidence interval [CI] 0.8 to 2.8) and more withdrawals due to lack of efficacy (relative risk [RR] 1.5, 95% CI 1.2 to 1.7) with meloxicam compared to nsNSAIDs.

- *Nabumetone versus nsNSAIDs* ***(low-strength evidence)***: No significant efficacy differences were reported between nabumetone and sustained-released diclofenac or etodolac. This efficacy conclusion is based on 1 Cochrane review[114] that included 2 short-term trials on OA of the knee[122,123]

Non-selective NSAIDs versus non-selective NSAID

- The 2006 AHRQ CER showed no significant differences between nsNSAIDs regarding efficacy outcomes in patients with OA of the hip, knee, and back. This is supported by high-strength evidence from several Cochrane reviews.[112-114] No new RCTs were identified for inclusion in the 2011 AHRQ updated review.

- Systematic review of RCTs (**Pavelka et al[124]** 2012)

Pavelka et al conducted a SR concerning the efficacy of diclofenac in patients with osteoarthritis. Seven out of 12 RCTs included in the SR compared diclofenac versus another nsNSAID. Three of them were previously reported in the 2011 AHRQ CER for osteoarthritis (Liang and Hsu 2003, Valat 2001, and Yocum 2000).[118,125,126] Findings of the 4 new RCTs identified in this SR are described in **Appendix D (Table 2)**. Overall, the majority of studies showed similar efficacy outcomes between diclofenac compared to meloxicam, nabumetone, or ibuprofen.

Rheumatoid Arthritis *(2 SR/MAs: Chen 2008 and Richy 2007; and 1 RCT: Shi 2004)*

SYSTEMATIC REVIEWS

- Health Technology Assessment (HTA) report, prepared by **Chen et al**[87] (2008)

This HTA report evaluated the clinical effectiveness and cost-effectiveness of COX-2 selective NSAIDs for OA and RA. The review included trials identified up to October-November 2003 and included etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib. Eight trials compared etodolac or meloxicam versus different nsNSAIDs in patients with RA. The following findings were repored (see also **Appendix D, Table 3**):

  - *Etodolac versus nsNSAIDs* (naproxen, indomethacin, piroxicam, and ibuprofen) (5 trials).[127-131] No significant differences between groups were observed in terms of patient's assessment of arthritis pain (1 trial), patient´s assessment global efficacy (1 trial), and withdrawals due to lack of efficacy (3 trials).
  - *Meloxicam versus nsNSAIDs* (naproxen, diclofenac, and nabumetone) (3 trials)[121,132,133]: No significant differences between groups were observed in terms of pain reduction (3 trials) and patient´s assessment global efficacy (2 trials). Withdrawal rates due to lack of efficacy were higher in the meloxicam group compared to nsNSAIDs (RR 1.61, 95% CI [1.21 to 2.13]) (3 trials).

- Systematic review and meta-analysis of flurbiprofen in RA (**Richy et al**[134] 2007)

Richy et al searched the published literature from January 1975 to January 2006 and identified 14 RCTs comparing flurbiprofen versus placebo, aspirin (3 trials), indomethacin (7 trials), naproxen (4 trials), ibuprofen (1 trial), or ketoprofen (1 trial) in the management of RA. Results from the MA showed flurbiprofen is as effective as nsNSAIDs in RA. However, flurbiprofen was statistically superior to ibuprofen in terms of articular pain relief, to indomethacin in terms of articular swelling reduction, and to naproxen, indomethacin, and ibuprofen regarding articular stiffness reduction. Efficacy results for each specific endpoint are outlined in **Appendix D, Table 3**.

RANDOMIZED CONTROLLED TRIALS

One RCT (Shi et al[135]) not included in previous systematic reviews was identified in the systematic literature search.

- **Shi et al**[135] (2004) conducted a 6-month RCT in 461 Chinese subjects with RA to compare different type of NSAIDs (meloxicam, diclofenac, nabumetone, and celecoxib). No significant differences in efficacy (withdrawal rates due to lack of efficacy, clinical improvement, and clinical remission) were reported between the 4 NSAIDs at the end of the study.

Juvenile Arthritis *(1 SR/MA: Eccleston 2017)*

- Cochrane review on NSAIDs for chronic non-cancer pain in children and adolescents (**Eccleston et al**[136] 2017)

A literature search for RCTs published from 1946 to September 2016 was performed by Eccleston et al. Seven RCTs including NSAIDs were identified. Among them, only 2 studies evaluated 1 nsNSAID compared with another (Bhettay and Thomson[137] 1978 and Rupero et al[138] 2005). Bhettay 1978 compared ketoprofen versus indomethacin in patients with juvenile chronic arthritis. Rupero 2005 compared meloxicam versus naproxen in patients with juvenile idiopathic arthritis. The primary efficacy outcomes of "participant-reported pain relief of 30% or greater and participant-reported pain relief of 50% or greater" were evaluated in this SR. Rupero 2005 reported no significant differences between groups for both outcomes. No data related to this endpoint was available for Bhettay 1978. Evidence was rated as low-quality and authors mentioned they were not able to conclude on the efficacy and safety of NSAIDs in the treatment of non-cancer pain in children and adolescents.

Ankylosing Spondylitis *(2 SRs: Kroon 2016 and Ward 2016)*

SYSTEMATIC REVIEWS

- Cochrane review concerning NSAIDs in axial spondyloarthritis (**Kroon et al**[52] 2016)

Kroon et al performed literature searches up to June 2014. Moderate- to low-quality evidence was identified from 24 RCTs evaluating 1 NSAID compared to another NSAID. Most of the RCTs had several limitations such as small sample sizes and imprecision. Overall, no significant

differences in pain, stiffness, or safety were reported among NSAIDs. Eleven trials suggested a higher incidence of adverse events and neurological events (headache, dizziness) with indomethacin compared to other NSAIDs. However, withdrawal rates due to adverse events remained similar between groups and the incidence of adverse events was not significantly different when studies of high to unclear risk of bias were excluded. Among the 24 RCTs, 13 studies comparing different type of nsNSAIDs (See **Appendix D, Table 4**) were relevant for this report. The remaining 11 RCTs included aceclofenac or non-FDA approved NSAIDs compared to nsNSAIDs.

- Systematic review conducted by the American College of Rheumatology (**Ward et al**[90] 2016)

Ward et al conducted a SR to provide evidence-based recommendations for the management of AS. Literature searches up to 2014 were performed. Twelve studies compared indomethacin with naproxen, fenoprofen, aspirin, tolmetin, ibuprofen, etodolac, diclofenac, nabumetone, piroxicam, meclofenamate, sulindac, and flubiprofen. Naproxen was compared to flurbiprofen in a single study. Six additional head-to-head RCTs, not reported in the Cochrane review by Kroon et al[52] were identified (Sydnes 1981, Bacon 1990, Burry 1980, Sturrock 1974, Shipley 1980, and Gibson 1980). Authors reported no significant differences among NSAIDs based on moderate- to low-quality evidence. As a result, this evidence-based guideline includes the following recommendation: "We do not recommend any particular NSAID as the preferred choice (PICO 3; moderate- to low- quality evidence; conditional recommendation; vote 100% agreement".

Acute Gout *(3 SR/MAs: Shekelle 2016,[55] Shekelle 2017,[139] and Van Durme 2014[140])*

SYSTEMATIC REVIEWS

- Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review for the management of gout (**Shekelle et al**[55] 2016)

In the AHRQ report,[55] literature searches were performed from January 2010 to April 2015. Sixteen RCTs comparing NSAIDs with NSAIDs were identified. Results showed similar efficacy in acute gout pain reduction among NSAIDs. Evidence was rated as moderate-strength evidence, defined as follows: "we are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains." The majority of the RCTs identified had small sample sizes and were underpowered to identify differences. Of the 16 RCTs, 5 compared one nsNSAIDs versus other nsNSAIDs (see **Appendix D, Table 5**). Each study included between 29 and 61 patients and study treatment was administered for 7 days. The 5 studies found no significant efficacy differences between treatment groups for the management of pain associated with acute gout. The remaining 11 RCTs compared oral nsNSAIDs versus COX-2 selective inhibitors, non-FDA approved NSAIDs, or parenteral NSAIDs.

- Systematic review for the management of gout performed by the American College of Physicians (**Shekelle et al**[139] 2017)

In the American College of Physicians (ACP) systematic review,[139] a summary of findings reported in the aforementioned AHRQ report[55] was included. In addition, this SR reported findings from the updated search up to March 2016. Regarding comparisons among the NSAIDs, no additional head-to-head RCTs apart from the 16 RCTs described in the AHRQ report were identified.

- Cochrane review concerning NSAIDs in the management of acute gout (**Van Durme et al**[140] 2014).

Van Durme et al[140] (2014) performed a systematic review regarding NSAIDs versus placebo or other agents. Thirteen RCTs comparing NSAIDs versus NSAIDs were identified from a systematic search up to October 2013. All of them were reported in the aforementioned AHRQ and ACP systematic reviews. In this Cochrane review, a pooled analysis of 2 RCTs assessing naproxen versus etodolac was conducted. Results for 2 specific outcomes (patient's global assessment of treatment success and adverse events rate) were reported. No differences between groups were observed. The remainder of the individual studies comparing NSAIDs versus NSAIDs showed no differences between groups with respect to efficacy and safety results. Authors expressed concerns in interpreting the benefit and risk data in between NSAID comparisons as the evidence was low- to very low-quality.[139]

Non-Articular Rheumatism *(1 RCT: Valtoren and Busson 1978)*

One RCT comparing ibuprofen versus indomethacin in 60 patients with non-articular rheumatism (e.g., tendinitis, torticollis, bursitis, etc.) was performed by Valtoren and Busson in 1978.[141] No significant differences were found between groups for the efficacy parameters of pain, tenderness, and restriction of movements.

Arthritis (OA, RA, AS), Low Back Pain, Soft Tissue Pain *(1 SR: Peterson et al[142])*

SYSTEMATIC REVIEWS

- Oregon Drug Class Review on NSAIDs (**Peterson et al**[142] 2010)

Peterson et al evaluated the comparative effectiveness and safety of NSAIDs in the management of chronic pain associated with OA, RA, AS, back pain, and soft tissue pain. Literature searches were performed up to May-June 2010. Moderate to high strength of evidence from SRs and RCTs suggested similar efficacy outcomes in terms of pain relief between partially selective NSAIDs (meloxicam, nabumetone, and etodolac) and nonselective NSAIDs (diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin). High-strength evidence from 3 Cochrane reviews and 3 fair-quality RCTs showed no efficacy differences for the management of OA and low back pain among the nsNSAIDs. Two trials in patients with OA and RA reported less withdrawal rates due to lack of efficacy with

nsNSAIDs compared to meloxicam. Specific details concerning the references supporting these efficacy conclusions are included in **Appendix D, Tables 6 and 7.**

2. LOW BACK PAIN

SYSTEMATIC REVIEWS *(5 SR/MAs: Chou 2017, Ramussen-Barr 2017, Chou 2016, Enthoven 2016, and Wong 2016; and 1 RCT: Plapler 2016)*

- Systematic review on low back pain elaborated by **Chou et al**[75] (2017)

A SR on systemic pharmacologic therapies for low back pain was published in 2017 to support the American College of Physicians clinical practice guideline.[75] Literature searches were performed from January 2008 to November 2016. Regarding comparisons of NSAIDs versus NSAIDs, the authors reported "no clear differences" with respect to pain reduction in patients with acute low back pain (21 trials) or chronic low back pain (6 trials). This conclusion was supported by a Cochrane review published in 2008 by Roelofs et al,[78] including 33 individual studies that compared 2 or more types of NSAIDs. Twenty-seven trials reported no differences in efficacy outcomes for acute or chronic low back pain, while 6 studies in acute low back pain did identify differences between NSAIDs.[78] Eight of these 33 single trials evaluated the comparative efficacy among oral nsNSAIDs. The remaining studies included other type of NSAIDs not covered under the scope of this report such as injectable or topical formulations, and non-FDA approved agents. Regarding the 8 studies including oral nsNSAIDs (see **Appendix D, Table 8**), each comparison was assessed in 1 single study, except 2 trials[143,144] that compared the same nsNSAIDs (diclofenac versus meloxicam). Evidence from these 2 trials was rated as moderate evidence and showed no between-group efficacy differences in acute low back pain. The majority of the remaining 6 studies comparing nsNSAIDs on low back pain found no differences. Roelofs et al highlighted the presence of several limitations such as the low quality, the reduced number of participants, and the short treatment duration in most included studies.

- Cochrane review by **Ramussen-Barr et al**[145] (2017) concerning NSAIDs for acute sciatica

This review identified an RCT (Dreiser et al[144] 2001) already found in the Cochrane review performed by Roelofs et al[78] (2008). This trial reported no efficacy differences in acute sciatica between oral meloxicam and diclofenac.

- Cochrane review by **Enthoven et al**[146] (2016) concerning NSAIDs for chronic low back pain

This review is an update of the Cochrane review conducted by Roelofs et al[78] in 2008. It included RCTs published up to June 2015 and is focused on chronic low back pain. Three RCTs compared NSAIDs versus NSAIDs and reported no significant differences in efficacy. Only one trial of these 3 RCTs compared 1 nsNSAID with other nsNSAID (Videman et al[147] 1984: piroxicam vs. indomethacin). This short-term trial is already included in the SR by Chou 2017. See **Appendix D, Table 8** for further information about RCT findings.

- AHRQ CER on noninvasive treatments for low back pain (**Chou et al**[148] 2016)

This report performed literature searches from January 2008 to April 2015. It included the same Cochrane review,[78] mentioned in the SR conducted by Chou et al[75] (2017), to support efficacy and safety among nsNSAIDs for low back pain.

- Systematic review on NSAIDs for the management of neck pain, whiplash-associated disorders, or low back pain (**Wong et al**[149] 2016)

This SR performed literature searches from January 2000 to April 2014 to identify SRs comparing NSAIDs versus other interventions or no intervention for the management of neck pain, whiplash-associated disorders, or low back pain. Among the 7 SRs that met eligibility for inclusion, only 3 were relevant for this report (Roelofs et al 2008, Pinto et al 2012, and Keller et al[150] 2007). Findings from Roelofs et al were previously described. Pinto 2012, and Keller 2007 did not included additional RCTs not assessed in other SRs.

RANDOMIZED CONTROLLED TRIALS

An additional head-to-head RCT on low back pain (not included in the identified SR/MAs) was identified in the systematic literature search. Results are outlined below:

- In 2016, **Plapler et al**[151] conducted a 10-day, double-blind, non-inferiority trial to compare the efficacy of ketorolac trometamol versus naproxen in patients with acute low back pain. Results indicated ketorolac trometamol is not inferior in terms of low back pain relief (primary endpoint) compared to naproxen.

3. DYSMENORRHEA

SYSTEMATIC REVIEWS *(1 SR: Marjoribanks 2015)*

- Cochrane review concerning NSAIDs for dysmenorrhea (**Marjoribanks et al**[96] 2015)

In 2015, Marjoribanks et al[96] conducted a systematic review of 18 trials comparing NSAIDs versus NSAIDs in patients with primary dysmenorrhea. Among them, 11 trials included pain relief outcomes between nonselective NSAIDs (see **Appendix D, Table 9**). The majority of studies reported no between-group differences in menstrual pain relief. However, studies were small and underpowered to detect differences. Results from 2 individual studies indicated superiority in terms of pain relief using visual analog scales with diclofenac compared to meloxicam, or with naproxen compared to ketoprofen. Authors determined that there is insufficient evidence to confirm differences between NSAIDs for the treatment of primary dysmenorrhea.

4. OTHER PAIN CONDITIONS

Neck Pain and Associated Disorders (1 SR: Wong 2016)

- Systematic review on NSAIDs for the management of neck pain, whiplash-associated disorders, or low back pain (**Wong et al**[149] 2016)

This SR performed literature searches from January 2000 to April 2014 to identify SRs comparing NSAIDs versus other interventions or no intervention for the management of neck pain, whiplash-associated disorders, or low back pain. The following findings were reported:

  - Whiplash-associated disorders

Wong et al identified one SR (Hurwitz et al[152] 2008) that performed a literature search of published studies assessing NSAIDs for the treatment of whiplash-associated disorders. No studies pertinent to this review were identified.

  - Neck pain and associated disorders

Wong et al identified one SR (Hurwitz et al[152] 2008) including 1 relevant RCTs.[153] The RCT compared 2 nsNSAIDs (indomethacin versus piroxicam) in patients with cervicobrachial syndrome. No significant differences in pain relief were reported between the nsNSAIDs.

Post-operative Pain

SYSTEMATIC REVIEWS

No SR/MA comparing nsNSAIDs for postoperative pain were identified.

RANDOMIZED CONTROLLED TRIALS

Post-operative Pain after Dental surgery (2 multiple-dose RCTs)

- **Silva de Oliveira et al**[154] (2016)

This RCT compared ibuprofen (600 mg 3 times daily) versus etodolac (300 mg 3 times daily) administered for 3 days in 20 adolescents and adults with lower third molar surgery. Etodolac was more effective in reducing swelling, trismus, and pain compared to ibuprofen.

- **Olmedo et al**[155] (2001)

This RCT evaluated the efficacy of ketorolac (10 mg and 20 mg) versus ketoprofen 50 mg, administered for 2 days in 150 patients following a third molar surgery. Pain relief results and the percentage of patients taking rescue medications were significantly reduced with ketorolac versus ketoprofen.

Influenza-Like Symptoms

- **Grebe et al**[156] (2003) conducted a 3-day RCT to compare diclofenac potassium 12.5 mg with ibuprofen 200 mg in patients with influenza-like symptoms (fever, headache, and muscle or joint pain). Efficacy and safety results were similar between treatment groups.

Pain

- Systematic review and meta-analysis concerning the efficacy of ketoprofen versus ibuprofen and diclofenac (**Sarzi-Puttini et al**[157] 2013)

Sarzi-Puttini et al performed searches through June 2011 to identify RCTs comparing oral ketoprofen with either ibuprofen or diclofenac for pain relief. Thirteen RCTs were included in the meta-analysis (8 studies compared ketoprofen with ibuprofen and 5 compared ketoprofen with diclofenac). As outlined in **Appendix D (Table 10)**, several indications were addressed by the MA: arthritis (e.g., RA, OA, AS), low back pain, and painful shoulder (9 RCTs); postoperative pain (2 RCTs); dysmenorrhea (1 RCT); and traumatic sport injuries (1 RCT). Results of the MA indicated superior analgesic efficacy with ketoprofen compared to diclofenac or ibuprofen. Regarding individual studies, 4 RCTs showed no significant efficacy differences between ketoprofen and ibuprofen or diclofenac. Study limitations include methodological drawbacks and different treatment duration and efficacy parameters.

Safety

NSAIDs are associated with numerous adverse events including gastrointestinal, cardiovascular, renal, and hepatic adverse events, and allergic reactions. Most of the safety evidence identified is focused on cardiovascular (CV) and gastrointestinal (GI) risks. Safety finding from SR/MAs, RCTs, and observational studies are outlined in the following sections. One SR/MA evaluating the overall safety and tolerability of ketoprofen versus diclofenac or ibuprofen in patients with moderate to severe pain was identified. Similar safety results were reported between groups.[158]

1. Gastrointestinal Toxicity

NSAID prescription labeling includes a black box warning concerning gastrointestinal (GI) toxicity: "NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events."

Gastrointestinal side effects include nausea, vomiting, peptic ulcers, gastrointestinal bleed, abdominal pain, dyspepsia and perforation of the stomach or intestine. Gastrointestinal damage is correlated with COX-1 inhibition and may occur along the entire length of the gastrointestinal tract; esophagus, stomach, duodenum, small intestine or colon.[159] A number of pharmacologic mechanisms for gastrointestinal effects have been proven or postulated, including 1) non-COX-mediated topical irritation of the GI epithelium, 2) impaired mucosal barrier protections, 3) increased intestinal permeability alterations, 4) reduced prostaglandin synthesis, 5) reduced gastric mucosal blood flow, 6) reduced bicarbonate secretion, 7) increased acid secretion, and 8) interference with superficial injury repair mechanisms.[160] Ulcer risk increases as gastric protection against enzymes, acid and bile salts is impaired.[104]

Risk factors for gastrointestinal toxicity include male gender, older age (significant increases noted at 60 years of age), past history of ulceration (especially with bleeding), dyspepsia, cardiovascular disease, concomitant use of corticosteroids or anticoagulants, high-doses of NSAIDs, and concomitant use of multiple NSAIDs.[104,159,161] Gastrointestinal effects are common within the first 3 months of therapy and increase with extended duration of use, especially at higher doses.[161] NSAIDs should be prescribed at the lowest effective dose for the shortest duration of time, with instruction to take the medication with food or directly after a meal to minimize adverse events. The relative risk for a GI bleed or perforation is four-fold higher in patients who use an NSAID versus those that do not.[105,106]

Clinical evidence concerning GI risk and prevention is found in **Table 8**. All levels of evidence were included. Information relating to celecoxib is included for comparison purposes only.

Regarding evidence from several high-quality SRs (CADTH 2013, Chou 2011) and an RCT (Nissen 2016), nsNSAID use is associated with a higher incidence of gastrointestinal adverse events, but no significant differences in GI risks were reported among nsNSAIDs. The 2011 AHRQ review suggested a lower risk of ulcer complications or symptomatic ulcers with the partially selective NSAIDs (meloxicam or etodolac) compared to nsNSAIDs. A SR/MA of RCTs (Bhala 2013[162]) studied GI complications with high-doses of several nsNSAIDs (diclofenac, naproxen and ibuprofen). At higher ibuprofen doses (~2400 mg daily) the risk of GI events approached that of naproxen and was almost double the risk associated with celecoxib or diclofenac.[162]

Based on systematic reviews of observational studies and individual observational studies, the risk of gastrointestinal toxicity appears to be lowest with ibuprofen, highest with piroxicam and ketorolac, and moderate with naproxen.[163-166] Ibuprofen's lower risk likely reflects the use of relatively lower doses and the agent's shorter half-life.

Table 8. Gastrointestinal Toxicity Risk: NSAID Evidence

Relevant SRs/MAs of RCTs and/or Observational studies	
CADTH report,[167] 2013 (SR of RCTs and OS)	Literature search from 2008 to 2013 nsNSAIDs vs. nsNSAIDs: • GI risks: "Different non-selective NSAIDs appear to be associated with similar risks of serious gastrointestinal events." Etodolac or meloxicam vs. nsNSAIDs: • See Chou, 2011 (AHRQ review)
Bhala 2013[162] (SR/MA of RCTs)	Comparisons of NSAID vs. placebo or NSAID vs. NSAID were assessed for CV events and upper GI complications (perforation, obstruction or bleed) • Ibuprofen doses of 2400 mg daily yielded similar GI event rates as naproxen and were twice as high as with celecoxib or diclofenac • Upper GI complications (Rate Ratio, 95% CI, *p*-value) o Diclofenac vs. placebo: 1.89 (1.16 to 3.09, p=0.0106 o Ibuprofen vs. placebo: 3.97 (2.27 to 10, p<0.0001) o Naproxen vs. placebo: 4.22 (2.71 to 6.56, p<0.0001)
Chou,[111] 2011; AHRQ report (SR of RCTs and OS)	• Meloxicam and etodolac were associated with a < risk of ulcer complications or symptomatic ulcers compared to nsNSAIDs (based on a SR of RCTs [Chen 2008]): - Meloxicam (RR 0.53, 95% CI 0.29 to 0.97) (6 trials) - Etodolac (RR 0.32, 95% CI 0.15 to 0.71) (9 trials) - Differences in risk of ulcer complications alone did not reach statistical significance • Nabumetone: insufficient evidence • NsNSAIDs vs. nsNSAIDs: o No clear difference between nsNSAIDs at commonly used doses. o In large observational studies: naproxen was associated with a higher risk of serious GI harms than ibuprofen in 7 studies. Comparative data on GI harms with other nonselective NSAIDs was less consistent.
Peterson,[142] 2010 (SR of RCTs and OS)	• Meloxicam vs. nsNSAIDs: meloxicam did not demonstrate to offer an advantage over nsNSAIDs • Nabumetone vs. nsNSAIDs: nabumetone had a lower short-term risk of GI perforation, symptomatic ulcer, or bleeding events, but long-term comparative risks are unknown • Etodolac vs. nsNSAIDs: not evaluated • NsNSAIDs vs. nonuse: all nonselective NSAIDs are associated with relatively similar risks of serious GI events relative to nonuse (strong evidence from numerous RCTs and OS)
RCTs	
Nissen,[168] 2016 (PRECISION	GI events were a secondary outcome in this randomized head-to-head comparison of celecoxib, naproxen and ibuprofen (mean doses 209 mg, 852 mg and 2045 mg, respectively) in arthritis patients with CV

trial: non-inferiority RCT)	disease followed for a mean of 3 years. There was a low CV event rate and almost 70% of patients discontinued therapy • Celecoxib GI risk was significantly lower than naproxen or ibuprofen • Hazards ratio for GI event in **ibuprofen group vs. naproxen group** was 1.08 (95% CI, 0.85 to 1.39; P=0.53).
Network Meta-Analysis	
Systematic review & network meta-analysis of RCTs[169]	Comparison of effectiveness of clinical strategies to prevent NSAID-induced GI toxicity • 1st line: Selective COX-2 inhibitor + PPI [Risk ratio (RR), 95% Credible Interval (CrI): ulcer complications 0.07, 0.02-0.18] • 2nd line: Selective COX-2 inhibitor monotherapy (RR, 95% CrI: ulcer complications 0.25, 0.15-0.38; symptomatic ulcer 0.12, 0.04-0.30) • 3rd line: Nonselective NSAID + PPI (RR, 95% CrI: ulcer complications 0.28, 0.18-0.41; symptomatic ulcer 0.11, 0.04-0.23)
Observational Studies	
Systematic review of OS[163]	Risk of upper GI bleed/perforation • Not increased with celecoxib • RR low with ibuprofen (RR. 2.69) < diclofenac (RR 3.98) < meloxicam (RR 4.15) < indomethacin (RR 4.15) < ketoprofen (RR 5.4) < naproxen (RR 5.57) < piroxicam (RR 9.94) < ketorolac (RR 14.54)
Case-controlled study[164]	Relative risk from lowest to highest for upper gastrointestinal complications • Ibuprofen (RR 2.0) < meloxicam & celecoxib (RR 2.7) < diclofenac (RR 3.7) < ketoprofen (RR 5.4) < indomethacin (RR 7.2) < naproxen (RR 8.1)
Meta-analysis of case-control studies[165]	Risk rank for gastrointestinal complication • Ibuprofen < diclofenac < sulindac < diflusinal < naproxen < indomethacin (risk 2x ibuprofen) < piroxicam & ketoprofen (risk 4x ibuprofen)
Cohort study[166]	Risk rank for hospital admission for upper gastrointestinal bleed and perforation or other upper gastrointestinal diagnoses • Nabumetone < indomethacin < ibuprofen • Compared with ibuprofen the RR was 30-40% higher with ketoprofen, naproxen, immediate-release diclofenac • Compared with ibuprofen the RR was 63% higher with sustained-release diclofenac • Piroxicam RR was 3 times ibuprofen

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; MA, meta-analyses; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OS, observational studies; PPI, proton-pump inhibitor; RA, rheumatoid arthritis; RCT, randomized controlled trials; RR, relative risk; SR, systematic reviews

When an NSAID is required in a patient at risk of gastrointestinal complications, the use of a gastroprotective agent may reduce the risk (e.g., misoprostol, proton pump inhibitors or histamine-2 blockers).[170] The American College of Gastroenterology offers guidance on the selection of an NSAID based on patient's gastrointestinal and cardiovascular risk (**Table 9**).[94,168,171,172]

Table 9. Selection of NSAID agent based on patient´s cardiovascular and gastrointestinal risk (adapted from[94])

		Gastrointestinal Risk[a] NOTE: Patients with a history of ulcers should be tested for *H. pylori* and treated if positive		
Cardiovascular Risk[b]		**Low**	**Moderate**	**High**
	Low	COX-2 selective agent or other low-GI risk nsNSAID (*LOE[d] 1; SOR[e] A)*	COX-2 selective agent OR nsNSAID + PPI, misoprostol (*LOE[d] 1; SOR[e] B)*	Avoid NSAIDs where possible. If an NSAID is indicated, COX-2 selective agent + PPI or misoprostol *(LOE[d] 1; SOR[e] B)*
	High[b]	**Naproxen**[c] or low-dose COX-2 selective agent If receiving aspirin use: naproxen + PPI or misoprostol (*LOE[d] 2; SOR[e] C)*	**Naproxen**[c] + PPI or misoprostol (*LOE[d] 2; SOR[e] C)* Above options preferred to low-dose COX-2 selective agent	Avoid COX-2 selective agents or NSAIDs (*LOE[d] 2; SOR[e] C)*

Abbreviation: COX, cyclooxygenase enzyme; CV, cardiovascular; HR, hazards ratio; ITT, intent to treat; MI, myocardial infarction; nsNSAID, nonselective non-steroidal anti-inflammatory drug; OA, osteoarthritis; PPI, proton-pump inhibitor; RA, rheumatoid arthritis; RR, relative risk

[a] Levels of GI risk:

- Low risk: no risk factors
- Moderate risk: Presence of 1 or 2 risk factors
- High risk: History of complicated ulcer (especially recent), or use of anticoagulants or corticosteroids, or presence of more than 2 risk factors

* Risk factors: age > 65 years, high-dose NSAID, history of uncomplicated ulcer, use of aspirin or other antiplatelet agent

[b] Levels of CV risk:

- High risk: History of CV event, diabetes, hypertension, hyperlipidemia, obesity. Low-dose aspirin may be required
  - NOTE: After an MI, there does not seem to be a safe time frame for using NSAIDs

[c] Naproxen is preferred as it is not associated with an increase in CV events

[d] Levels of evidence (LOE): 1 (LOE strongly in favor of recommendation), 2 (LOE favors recommendation), 3 (LOE in favor of recommendation is equivocal), 4 (LOE against a recommendation)[94]

[e] Strength of recommendation (SOR): A (strong evidence from multiple RCTs, SR, MA), B (strong evidence from at least 1 RCT, cohort or case control studies), C (expert opinions based on clinical evidence or non-randomized clinical trials)[94]

2. Cardiovascular Toxicity

NSAID prescription labeling includes a black box warning concerning cardiovascular toxicity: "NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may be increased in patients with cardiovascular disease or risk factors for cardiovascular disease. NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery."[14]

Adverse cardiovascular events are associated with the use of NSAID therapy and are noted even in patients without prior cardiovascular disease.[173] A number of NSAID-related effects are thought to be responsible. Use of NSAID COX-1 and COX-2 inhibitors produces an imbalance between COX-1 medicated vasoconstriction, platelet aggregation via production of thromboxane A2 and COX-2 mediated production of vasodilating prostacyclin. The imbalance (COX-2 > COX-1 inhibition) is postulated to cause vasoconstriction, platelet aggregation and

thromobosis.[174] NSAID-related effects in heart failure, include the inhibition of prostaglandin function resulting in increased peripheral vascular resistance and decreased renal perfusion leading to sodium and water retention, hypertension and hemodynamic acute kidney injury.[175,176] COX-2 activity appears to correlate with cardiovascular risk, although not all COX-2 inhibitors produce the same pharmacologic effects.[177] A recent meta-analysis suggests that rofecoxib is positively correlated with CV toxicity while celecoxib is not, suggesting that COX-2 selectivity may not play a role in the CV risk of the NSAIDs.[178]

In 2015, the FDA advisory committee published these warnings concerning prescription NSAIDs and cardiovascular risk:[179]

- "The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use."

The aforementioned warnings were supported by a large pooled analysis of RCTs,[162] observational studies, and other publications.[179]

Cardiovascular toxicity events include hypertension, heart failure, myocardial infarction, stroke and death. Risk increases similarly in patients with and without CV risk factors, placing those with baseline risk at a higher risk.[180]

<u>Evidence from RCTs and systematic reviews/meta-analyses of RCTs and/or observational studies</u>

Evidence from several high-quality SRs (CADTH 2013, Bhala 2013, and Chou 2011) suggested a similar increase in CV risk (especially MI rate) with nsNSAIDs (e.g., high-dose diclofenac and ibuprofen) compared to celecoxib, whereas naproxen seemed to be associated

with less CV risk. A meta-analysis of placebo-controlled trials and a systematic review of observational studies suggested naproxen may have less CV risk.[162,181]

A large RCT, conducted by Nissen in 2016, [168] reported non-inferiority of ibuprofen compared to naproxen for the primary composite endpoint (CV death, nonfatal MI and nonfatal stroke). The incidence of nonfatal MI (one of the individual component of the primary endpoint) was significantly higher in the ibuprofen group versus naproxen group. Additionally, a substudy of this RCT showed an increased in ambulatory systolic blood pressure by 4mmHg with ibuprofen compared to naproxen.

Overall, evidence is unclear and insufficient to strongly recommend one particular nsNSAID over another.

Evidence from observational studies

The use of NSAIDs may double the risk of heart failure.[162,180] A case-control study found a dose-dependent, increased risk for heart failure hospital admissions in patients whom received NSAIDs in the 14 days prior.[175] The admission rate appeared to be dose dependent.[175]All NSAIDs demonstrated some effect. The risk doubled in patients receiving high dose diclofenac, indomethacin or piroxicam compared with those that did not receive an NSAID. Furthermore, the use of a current NSAIDs versus prior use increased risk by 20%.[175] A connection between heart failure and NSAIDs is reasonable based on the mechanism of action, although conflicting evidence is reported. One observational trial evaluating the use of NSAIDs and heart failure did not find a relationship[182] while another observational trial found higher rates of admission for heart failure in elderly patients receiving non-selective NSAIDs but not celecoxib.[183]

A time-dependent analysis of cardiovascular outcomes in outpatients with stable atherothrombotic disease, from the REduction of Atherothrombosis for Continued Health (REACH) registery found that use of a non-selective or COX-2 selective NSAID (yes/no) assessed yearly over 4 years was associated with adverse cardiovascular outcomes.[184] Patients taking NSAIDs were significantly more likely to be older, female, white, have higher baseline heart failure incidence, and more atherosclerotic risk factors. NSAID use was associated with an increased hazard for CV death/MI/stroke/ischemic hospitalizations; CV death/MI/stroke; MI; stroke; heart failure hospitalizations; and ischemic hospitalizations. The number needed to harm 1 patient was 33 for ischemic hospitalizations, 36 for CV death/MI/stroke/ischemic hospitalizations, and 61 for CV death/MI/stroke. Post-hoc analysis of the INternational VErapamil Trandolapril STudy (INVEST) found chronic, self-reported, NSAID use was associated with a 2-fold increase in CV death in the elderly.[185]

A recent meta-analysis using individual patient data found all NSAIDs to carry a risk for acute myocardial infarction.[186] The onset of risk occurred within the first week of therapy. The short-term (8-30 days) risk of harms correlated with daily dosage, for celecoxib > 200 mg, diclofenac > 100 mg, ibuprofen > 1200 mg, and naproxen > 750 mg. Risk did not appear to increase with continued use of the agent.[186]

Higher NSAID doses appear to confer greater cardiovascular risk,[179] although evidence for ibuprofen found no dose-dependent cardiovascular event increase,[180] an *almost* significant increase,[187] and an increase at doses above 1200 mg daily.[188]

The duration of NSAID therapy and cardiovascular risk has also been explored. In patients with a prior MI, the Danish National Registry found that risk begins early but at different times for various agents.[189] The risk of cardiovascular events occurs earliest with use of diclofenac (at the initiation of therapy), with ibuprofen at 1 week of therapy and with celecoxib at 14-30 days of therapy. It follows that the risk of death or MI within the first week of therapy was highest with diclofenac (HR 3.26, 95% CI 2.57 to 3.86). The risk of NSAID-induced cardiovascular events remained high during the first year of therapy and declined but remained elevated for at least 4 additional years.[190] The FDA reports that in the year following an MI, the mortality rate is higher for patients treated with an NSAID than not treated with an NSAID.[191]

Based on a systematic review of observational studies and RCTs, myocardial risk is increased with rofecoxib and diclofenac. No increase in myocardial risk was noted with meloxicam or naproxen. Data is insufficient for other agents. Vascular risk is higher with naproxen > diclofenac > ibuprofen > rofecoxib (inconclusive) > meloxicam > indomethacin > celecoxib.[192]

Evidence extracted from clinical trials concerning individual cardiovascular toxicity is found in **Table 10**. All levels of evidence were considered.

Table 10: Cardiovascular Toxicity Risk: NSAID Evidence

Relevant SRs of RCTs and/or observational studies	
CADTH report,[167] 2013 (SR of RCTs and OS)	• Literature search up to 2013: 5 SRs and 1 HTA were included nsNSAIDs vs. nsNSAIDs: • CV risks: "All non-selective NSAIDs except for naproxen were associated with similar risks of serious cardiovascular events."
Bhala 2013[162] (SR/MA of RCTs)	Comparisons of NSAID vs placebo or NSAID vs NSAID were assessed for GI and CV events including major vascular events (non-fatal MI, non-fatal stroke or vascular death); major coronary events (non-fatal MI or coronary death); stroke; mortality; heart failure. Rate Ratio (95% CI, *p*-value) High-dose diclofenac vs. placebo: • Major vascular events 1.41 (1.12 to 1.78, p=0.0038) • Major coronary events 1.70 (1.19 to 2.41, p=0.0032) • Vascular death 1.65 (0.95 to 2.85, p=0.0187) High-dose ibuprofen vs. placebo • Ibuprofen ((2400 mg/day) significantly increased major coronary events (Rate ratio 2.2, 95% CI 1.1 to 4.48; p=0.0253) but not major vascular events (Rate ratio 1.44, 95% CI 0.89 to 2.33) High-dose naproxen vs. placebo • Naproxen (1000 mg/day) did not significantly increase major vascular events (Rate ratio 0.93, 95% CI 0.69 to 1.27) or major coronary events (0·84, 0·52–1·35)
Chou,[111] 2011; AHRQ report (SR of RCTs and OS)	• The CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in 2 SR of RCTs • Most OS showed similar estimates of CV risk for naproxen, COX-2 selective NSAIDs, and other nonselective NSAIDs. • The CV safety of nsNSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs in a large SR of RCTs
Peterson,[142] 2010; Oregon report (SR of RCTs and OS)	• Meloxicam: No conclusive evidence regarding increased CV risk relative to nonuse or relative to diclofenac • NsNSAIDs: o "All nonselective NSAIDs except naproxen were associated with similar risks of clinically important cardiovascular events (primarily MI) compared with COX-2 inhibitors (data primarily on high-dose ibuprofen and diclofenac)

	o Naproxen was associated with a lower risk of MI compared with COX-2 inhibitors (relative risk, 2.04; 95% CI, 1.41 to 2.96; P=0.0002)" (based on Kearney, 2006)
Kearney, 2006[193] (MA of RCTs)	Cardiovascular event risk: • COX 2 inhibitor vs. placebo: 42% relative increase in the incidence of serious vascular events with COX 2 inhibitors • Diclofenac vs. placebo: RR 1.63, 95% CI 1.12 to 2.37 • Ibuprofen vs. placebo: RR 1.51 95% CI 0.96 to 2.37 • Naproxen vs. placebo: RR 0.92 95% CI 0.67 to 1.26 Authors's conclusion: "Selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess."
RCTs	
Nissen,[168] 2016 (PRECISION trial: non-inferiority RCT)	Randomized head-to-head comparison of **celecoxib, naproxen and ibuprofen** (mean doses 209 mg, 852 mg and 2045 mg, respectively) in 24,081 arthritis patients (OA and RA) with CV disease followed for a mean of 3 years. There was a low CV event rate and almost 70% of patients discontinued therapy • **Primary composite endpoint:** CV death, nonfatal MI and nonfatal stroke (ITT population): - Celecoxib was noninferior to ibuprofen and naproxen - Ibuprofen was noninferior to naproxen (HR 1.08; 95% CI, 0.90 to 1.31; P=0.02 for noninferiority) • Individual components of the primary outcome: ibuprofen vs. naproxen - The rate of **nonfatal MI** was **higher in the ibuprofen group** than in the naproxen group (HR, 1.39; 95% CI, 1.01 to 1.91; P=0.04) - No differences between groups for major adverse CV events and death from any cause • A prespecified substudy of PRECISION found **ibuprofen increased ambulatory systolic blood pressure** by 4mmHg, with naproxen and celecoxib not producing a significant change in SBP: o Change in ambulatory 24-h SBP from baseline at 4 months (3.7, 95% CI 1.72, 5.58)[194]
Solmaz,[195] 2012 (RCT)	• No significant differnces in endothelial function between the diclofenac and naproxen group at day 7 in patients with osteoarthritis.
ADAPT trial[196]	Randomized, placebo-controlled, parallel chemoprevention trial assessing COX-2 selective vs non-selective NSAID (naproxen) in dementia • Cardiovascular or cerebrovascular death, MI, stroke, CHF, TIA o 40/713 (8.25%), Hazard ratio 1.63 (95% CI 1.04 to 2.55)
SR of Observational Studies	
McGettigan,[181] 2011 (SR of OS)	Cardiovascular event risk (Ratio of RR [99% CI]): • Diclofenac vs. ibuprofen: 1.13 (1.03 -1.24) • Diclofenac vs. naproxen: 1.22 (1.11- 1.35) • Naproxen vs. ibuprofen: 0.92 (0.87- 0.99); • Naproxen vs. celecoxib: 0.96 (0.81-1.13) • Meloxicam vs. naproxen: 1.11 (1.0 – 1.23) • Indomethacin vs. naproxen: 1.23 (1.10 – 1.39) Author's conclusions: "naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Diclofenac in doses available without prescription elevates risk."
McGettigan, 2006 (SR of OS)	SR of case-control or cohort design to evaluate CV events: • Diclofenac had the highest risk with a RR of 1.40 (95% CI, 1.16-1.70). • Naproxen RR 0.97 (95% CI, 0.87-1.07); piroxicam RR 1.06 (95% CI, 0.70-1.59); and ibuprofen, RR 1.07 (95% CI, 0.97-1.18)

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CHF, congestive heart failure; HR, hazard ratio; HTA, health technology assessment; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug, OA, osteoarthritis; OR, adds ratio, OS, observational studies; RA, rheumatoid arthritis; RR, relative risk; SBP, systolic BP, blood pressure; TIA, transient ischemic attack

3. Renal Injury

Renal effects of NSAIDs include acute kidney injury, fluid retention, hyperkalemia, interstitial nephritis, and nephrotic syndrome. Pharmacologically, NSAIDs inhibit vasodilating prostaglandin production leading to a reduction in blood flow to the glomerulus.[197] This may lead to edema, sodium and water retention, and high blood pressure. The increased glomerular pressure and reduction in renal blood flow can cause permanent kidney damage. When compared

to hypertensive patients who do not use NSAIDs, those that use these drugs for 3 months or longer are 32% more likely to have chronic kidney disease.[198]

Risk factors for NSAID-induced nephrotoxicity include diabetes, renal insufficiency, heart failure and advanced age. [197] NSAIDs should be avoided in patients with underlying hypertension, heart failure, diabetes, or other chronic kidney disease, because they can increase blood pressure, cause fluid retention and worsen renal function.[199] NSAIDs are renally cleared and should be used with caution in the elderly due to an age-associated renal decline.[199,200] The risk of renal impairment is increased in patients receiving an ACE inhibitor, diuretic or other nephrotoxin.

In patients at risk of nephrotoxicity, avoid the use of NSAIDs with longer half-lives (e.g., oxaprozin, ketorolac, nabumetone, naproxen, meloxicam or piroxicam).[198,200-203] Short-term use of ibuprofen (OTC dosing), naproxen or daily low-dose aspirin are considered safe for most patients.[204,205] When an NSAID must be used in a high-risk patient (e.g., receiving an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or diuretic), check serum creatinine and potassium over several weeks.[206,207] Prescription NSAID labelling recommends a periodic chemistry profile.

Evidence from randomized controlled trials

The PRECISION trial compared 3 NSAIDs in patients with cardiovascular risk factors or disease; celecoxib, naproxen and ibuprofen at mean doses of 209 mg, 852 mg and 2045 mg, respectively.[168] The risk of a serious renal event was significantly lower in the celecoxib group than the ibuprofen group (hazard ratio, 0.61; 95% CI, 0.44 to 0.85; P=0.004), but not significantly different between the celecoxib and naproxen group (hazard ratio, 0.79; 95% CI, 0.56 to 1.12; P=0.19). Additionally, no significant differences in renal events was reported between ibuprofen and naproxen groups (hazard ratio, 1.29; 95% CI, 0.95 to 1.76; P=0.10). These findings must be interpreted with caution as it was not a primary outcome measure, the study did not have a placebo group and the dropout rate was ~70% over 10-years.

Evidence from observational studies

A nested, case-control study evaluated the association of NSAIDs with chronic kidney disease. As a class, no differences were noted. Long-term use of piroxicam, meloxicam and ketorolac was associated with an increased risk of chronic kidney disease with no increased risk noted for ibuprofen, diclofenac, ketoprofen or naproxen.[203]

Based on a systematic review of observational studies and RCTs, adverse renal outcomes are associated with use of rofecoxib, celecoxib, naproxen, diclofenac and indomethacin, while no increase in renal risk was noted with meloxicam, ibuprofen or etodolac (inconclusive).[192] A composite risk score, calculated by combining all the risk estimates for CV/renal outcomes yielded the following rank order: rofecoxib > diclofenac >indomethacin > celecoxib > naproxen > ibuprofen. A composite risk increase was not found for etodolac.[192]

4. Hepatic Injury

Hepatic injury may occur with NSAID use (~1-10 cases per 100,000 prescriptions) and represents 10% of all drug-induced hepatotoxicity.[208,209] Hepatotoxicity presents as acute hepatitis within 1-3 months of initiating therapy, with up to 18% of patients on long-term therapy demonstrating asymptomatic elevations in aminotransferase levels. Cases of fatal hepatitis have occurred, most commonly after 12-15 months of therapy. Injury is generally hepatocellular although cases of cholestatic jaundice has been noted with sulindac, and mixed injury with naproxen.[208,209] NSAID-induced hepatic toxicity is believed to represent an idiosyncratic hypersensitivity response versus intrinsic toxicity although toxic metabolite formation may be involved.[209,210] Risk factors for NSAID-induced hepatotoxicity include metabolic syndrome, hepatic steatosis, female sex, age above 50-75 years, autoimmune disease, and use of other potentially hepatotoxic drugs.[209,211] Acute hepatic injury risk with NSAID use is 10-fold higher in patients with rheumatoid arthritis vs osteoarthritis.[212] It is possible the difference reflects the difference in concomitant hepatotoxin exposure between patients with rheumatoid arthritis vs osteoarthritis. Additionally, it appears that systemic lupus erythematosus represents a disease-specific risk for hepatotoxicity.[212]

Evidence from systematic reviews of randomized controlled trials

Rostom et al[213] conducted a SR of RCTs and reported a higher incidence of elevated liver enzymes with diclofenac compared to ibuprofen and naproxen.

Evidence from observational studies

Sulindac hepatotoxic risk is higher than other NSAIDs with an incidence of 27 per 100,000 prescriptions.[209,212] Hepatic injury is considered an idiosyncratic hypersensitivity reaction that is mild and reversible. Risk factors include female gender and age above 50 years.

Diclofenac use is also associated with a higher risk of hepatic toxicity, 11 cases per 100,000 patients.[214] Findings include antinuclear antibody (ANA) positivity, histologic evidence of acute hepatitis and present within the first 6 months of therapy.[209] Patients may be managed by a switch to an alternative NSAID.[212]

Evidence extracted from SRs and observational studies concerning hepatic toxicity is found in **Table 11**.

Table 11: Hepatic Toxicity Risk: NSAID Evidence

SR of RCTs	
Rostom,[213] 2005 (SR of RCTs)	• "Diclofenac was associated with the highest rates of aminotransferase elevations >3 times the upper limit of normal (3.55%; 95% CI, 3.12 to 4.03) compared with ibuprofen (0.43%; 95% CI, 0.26 to 0.70) and naproxen (0.43%; 95% CI, 0.30 to 0.63)"
Observational Data	
Rubenstein,[215] 2004 (SR of 7 population-based epidemiological studies)	• Incidence of hepatic injury: 5-10 times higher for sulindac relative to other NSAIDs

5. Allergic Reactions

The use of NSAIDs is associated with allergic or pseudoallergic reactions. Allergic reactions, including anaphylaxis have been reported and are presumed to occur via an IgE-mediated immunological reaction.[216] Treatment may be re-attempted with a structurally dissimilar NSAID.

Pseudoallergic reactions are related to the inhibition of COX-1. The risk may be increased in the presence of the triad of asthma, sinus problems and nasal polyps.[159,216] No agent is safer than another and if a reaction occurs with one agent it is likely with alternatives.[216]

Summary

Non-steroidal anti-inflammatory drugs are commonly used to reduce pain and inflammation associated with several inflammatory conditions such as osteoarthritis and rheumatoid arthritis. Following a systematic literature search for direct head-to-head comparisons among the non-selective NSAIDs, 29 publications (20 SR/MAs, 8 RCTs, 1 substudy of an RCT) addressing efficacy and/or safety outcomes were identified. Overall, the majority of head-to-head RCTs showed no significant differences in efficacy among nsNSAIDs. A summary of efficacy findings is outlined in **Table 12**.

Table 12. Evidence-Based Findings on the Comparative Effectiveness among Oral nsNSAIDs

FDA-Approved Indication	Number of SR/MAs and RCTs	Efficacy Findings	Strength of Evidence[a]
Arthritis			
OA	**2 SRs:** AHRQ CER (Chou 2011): • Meloxicam vs. nsNSAIDs: - 1 SR (Chen 2008) including 11 head-to-head trials • Etodolac vs. nsNSAIDs: - 3 CRs - 1 SR (Chen 2008) including 18 trials - 1 additional trial (Liang 2003) not included in Chen 2008 and CRs • Nabumetone vs. nsNSAIDs: - 1 CR with 2 short-term trials • NsNSAIDs vs. nsNSAIDs: - 3 CRs Pavelka 2012: • Diclofenac vs. nsNSAID: 4 new RCTs not reported in previous SRs	The majority of studies showed **no significant efficacy differences** among NSAIDs: - Partially selective NSAIDs vs. nsNSAIDs: no significant differences. One SR showed less pain reduction and more withdrawals due to lack of efficacy for meloxicam compared to nsNSAIDs - NsNSAIDs vs. nsNSAIDs: no differences	High-quality evidence for etodolac, meloxicam, and nsNSAIDs (many RCTs reporting consistent evidence) Low-quality evidence for nabumetone (2 short-term RCTs with limitations)
RA	**2 SR/MAs**: • Chen 2008 (8 studies) • Richy 2007 (14 studies) **1 RCT** (Shi 2004): meloxicam vs. diclofenac and nabumetone	The majority of studies showed **no significant efficacy differences** among nsNSAIDs	Low- to moderate-quality evidence
JCA/JIA	**1 CR** (Eccleston 2017) including 2 RCTs	**No significant differences** in pain scores between meloxicam and naproxen	Low-quality evidence (lack of data)

FDA-Approved Indication	Number of SR/MAs and RCTs	Efficacy Findings	Strength of Evidence[a]
AS	**2 SRs**: • 1 CR (Kroon 2016) including 24 RCTs (13 RCTs comparing nsNSAIDs vs. nsNSAIDs) • 1 SR from ACR (Ward 2016) including 13 studies	The majority of studies showed **no significant differences** in pain and stiffness among the nsNSAIDs	Low- to moderate-quality evidence (small studies, imprecise estimate of effect, and serious risk of bias)
Acute Gout	**3 SRs**: • 1 SR from ACP (Shekelle 2017) • 1 AHRQ report (Shekelle 2016) • 1 CR (Van Durme 2014) 16 RCTs included in AHRQ and ACP reviews (5 out of 16 RCTs compared nsNSAIDs vs. nsNSAIDs in acute gout)	The majority of studies showed **no significant efficacy differences** in reducing acute gout pain among NSAIDs	Moderate-strength evidence (most of the studies were small and underpowered to detect differences)
Non-Articular Rheumatism (tendinitis, bursitis)	**1 RCT** (ibuprofen vs. indomethacin)	**No significant differences** in pain, tenderness, and restriction of movements	Low-quality evidence (a small RCT)
Arthritis, LBP, and STP	Oregon Report (Peterson 2010): • Meloxicam vs. nsNSAIDs: 9 RTC • Nabumetone vs. nsNSAIDs: 1 review including 2 double-blind RCTs • Etodolac vs. nsNSAIDs: 2 RCTs • NsNSAIDs vs. nsNSAIDs: 1 CR and 3 RCTs	The majority of studies showed **no significant efficacy differences** among NSAIDs: - Partially selective NSAIDs vs. nsNSAIDs: no significant differences - NsNSAIDs vs. nsNSAIDs: no significant differences	Moderate- to high-quality evidence from a Cochrane review and RCTs
Low Back Pain			
LBP	**5 SR/MAs**: • 1 SR for ACP- LBP (Chou 2017) • 1 CR - sciatica (Ramussen-Barr 2017) • 1 CR - chronic LBP (Enthoven 2016) • 1 AHRQ Report –LBP (Chou 2016) • 1 SR (Wong 2016) Roelofs 2008: main CR mentioned by the above SRs **1 RCTs:** Plapler 2016 (ketorolac vs. naproxen)	Most of the studies showed **no significant differences** in pain relief among nsNSAIDs for acute or chronic low back pain	Moderate-quality evidence for acute LBP Insufficient evidence for chronic LBP (1 small RCT)

FDA-Approved Indication	Number of SR/MAs and RCTs	Efficacy Findings	Strength of Evidence[a]
Dysmenorrhea			
Dysmenorrhea	**1 SR**: • 1 CR (Marjoribanks 2015) containing 18 RCTs (11 studies comparing nsNSAIDs vs. nsNSAIDs in pain relief)	The majority of studies showed **no significant efficacy differences** among NSAIDs	Low-quality evidence for most comparisons (small and underpowered studies, poor reporting of study methods)
Postoperative Pain			
Dental PO Pain	**2 multiple-dose RCTs:** - Ibuprofen vs. etodolac - Ketoprofen vs. ketorolac	- Etodolac was more effective in reducing swelling, trismus, and pain compared to ibuprofen - Ketorolac was superior in relieving pain to ketoprofen	Evidence from single, small studies
Neck Pain			
Neck Pain and Associated Disorders	**1 SR** (Wong 2016) including 1 relevant RCT of indomethacin vs. piroxicam	**No significant differences** between the NSAIDs	Low-quality evidence (lack of data)
General Pain			
Influenza-Like Symptoms	**1 RCT** (diclofenac potassium vs. ibuprofen)	**No significant differences** in efficacy	Low-quality evidence (lack of data)
Pain (RA, OA, DYS, trauma injury)	**1 SR/MA** (Sarzi-Puttini 2013) including 13 RCTs	**Superior** analgesic efficacy of ketoprofen compared to diclofenac or ibuprofen	Low-quality evidence (methodological drawbacks, different treatment duration and efficacy parameters)

Abbreviations: ACP, American College of Physicians; ACR, American College of Rheumatology; AHRQ; AS, ankylosing spondylitis; CER, comparative effectiveness review; CR, Cochrane review; DYS, dysmenorrhea; JCA, juvenile chronic arthritis; JIA, juvenile idiopathic arthritis; LBP, low back pain; PO, postoperative; RA, rheumatoid arthritis; RCT, randomized controlled trials; SR, systematic review; SR/MA, systematic review/meta-analysis; STP, soft-tissue pain

[a] Levels of evidence from very low-quality evidence: "we are very uncertain about the results" to high-quality evidence: "we are very confident in the results"

The selection of NSAIDs should be based on the benefit-risk balance for each patient. Factors to be considered include age (elderly populations are at higher risks of cardiovascular events, renal impairment, and bleeding), comorbidities (cardiovascular, renal, or gastrointestinal conditions), and the use of concomitant drugs (e.g., aspirin, anticoagulant agents).

References

1. U.S. Department of Health and Human Services. U.S. Food & Drug Administration. The Benefits and Risks of Pain Relievers: Q & A on NSAIDs with Sharon Hertz, M.D. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107856.htm. Accessed February 28, 2018.
2. Zorvolex (diclofenac) oral capsules [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; revised May 2016.
3. Diclofenac potassium oral tablets [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; revised August 2017.
4. Cambia (diclofenac potassium) oral solution [package insert]. Newark, CA: Depomed, Inc.; revised March 2017.
5. Zipsor (diclofenac potassium) oral liquid filled capsules [package insert]. Newark, CA: Depomed, Inc.; revised May 2016.
6. Diclofenac sodium delayed-release oral tablets [package insert]. Carlsbad, CA: Carlsbad Technology, Inc.; revised July 2017.
7. Diclofenac sodium extended-release oral tablet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; revised June 2017.
8. Etodolac oral capsules [package insert]. Weston, Florida: Apotex Corp.; revised November 2017.
9. Etodolac oral tablets [package insert]. Weston, Florida: Apotex Corp.; revised November 2017.
10. Etodolac extended-release oral tablets [package insert]. Ahmedabad, India: Cadila Healthcare Ltd.; revised November 2017.
11. Nalfon (fenoprofen) oral capsules [package insert]. Ridgeland, MS: Xspire Pharma; revised May 2016.
12. Fenoprofen calcium oral tablets [package insert]. Oklahoma City, OK: PD-Rx Pharmaceuticals, Inc.; revisede January 2017.
13. Flurbiprofen oral tablets [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; revised June 2017.
14. Drug Monographs. Lexi-Drugs. Lexicomp. Wolters Kluwer; 2018. https://online.lexi.com/lco/action/home. Accessed February 27, 2018.
15. Indocin (indomethacin) oral suspension [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; revised May 2016.
16. Indomethacin extended-release oral capsules [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; revised March 2017.
17. Tivorbex (indomethacin) oral capsules [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; revised May 2016.
18. Ketoprofen oral capsules [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; revised May 2017.
19. Ketoprofen extended-realease oral capsules [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; revised July 2015. .
20. Ketorolac tromethamine oral tablets [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; revised October 2016.
21. Mefenamic acid oral capsules [package insert]. Mason, OH: Prasco Laboratories; revised May 2016.
22. Mobic (meloxicam) oral tablets [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; revised May 2016.
23. Vivlodex (meloxicam) oral capsules [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; Revised October 2015.
24. Nabumetone oral tablets [package insert]. Lawrenceville, GA: Exelan Pharmaceuticals Inc.; revised December 2017.
25. Naprosyn (naproxen) oral suspension [package insert]. Alpharetta, GA: Canton Laboratories LLC; revised March 2017.
26. Naprosyn (naproxen) oral tablets, EC-Naprosyn (naproxen) delayed-release oral tablets, Anaprox DS (naproxen sodium) oral tablets [package insert]. Alpharetta, GA: Canton Laboratories LLC; revised August 2016.

27. Naprelan (naproxen sodium) controlled-release oral tablets [package insert]. Pine Brook, NJ: Almatica Pharma, Inc.; revised September 2017.
28. Daypro (oxaprozin) oral caplets [package insert]. New York, NY: Pfizer Inc.; revised May 2016.
29. Piroxicam oral capsules [package insert]. Sacramento, CA: Nivagen Pharmaceuticals, Inc; revised December 2017.
30. Sulindac oral tablets [package insert]. Laurelton, NY: Epic Pharma, LLC: revised December 2017.
31. Tolmetin sodium oral capsules and oral tablets [package insert]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; revised February 2015.
32. Herndon CM, Strickland JM, Ray JB. Pain Management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach, 10e.* New York, NY: McGraw-Hill Education; 2017.
33. U.S. Department of Health and Human Services. Research Portfolio Online Reporting Tools RePORT). Yesterday, Today & Tomorrow: NIH Research Timelines. NIH Fact Sheets Home. Pain Management. Accessed February 28, 2018.
34. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. *Military medicine.* 2016;181(5):397-399.
35. Clarke TC, Nahin RL, Barnes PM, Stussman BJ. Use of Complementary Health Approaches for Musculoskeletal Pain Disorders Among Adults: United States, 2012. *National health statistics reports.* 2016(98):1-12.
36. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. *Vital and health statistics Series 10, Data from the National Health Survey.* 2014(260):1-161.
37. National Pharmaceutical Council. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001.
38. Rathmell JP, Fields HL. Pain: Pathophysiology and Management. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e.* New York, NY: McGraw-Hill Education; 2015.
39. National Pharmaceutical Council. Management of Acute Pain and Chronic Noncancer Pain. Section IV: Management of Acute Pain and Chronic Noncancer Pain.
40. Arthritis. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/arthritis/index.htm. Updated February 21, 2018. Accessed March, 5, 2018.
41. Utah Department of Health. Utah Arthritis Program. An Assessment of the Burden of Arthritis in Utah. Findings from the 2013 and 2014 Behavioral Risk Factor Surveillance System. http://health.utah.gov/arthritis/pdf/Burden_Reports/2014%20Utah%20Burden%20Report.pdf. Accessed March 13, 2018.
42. Arthritis. Arthritis Basics. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/arthritis/basics/index.html. Updated February 21, 2018. Accessed March 5, 2018.
43. Arthritis. Public Health Indicator Based Information System (IBIS). Utah's Public Health Data Resource. Utah Department of Health. https://ibis.health.utah.gov/ibisph-view/topic/Arthritis.html. Updated November 17, 2017. Accessed March 13, 2018.
44. Arthritis. Osteoarthritis. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Updated March 15, 2018. Accessed March, 5, 2018.
45. Fendrick AM, Greenberg BP. A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. *Osteopathic medicine and primary care.* 2009;3:1.
46. Arthritis. Rheumatoid Arthritis. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html. Updated March 15, 2018. Accessed March 21, 2018.
47. Childhood Arthritis. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/arthritis/basics/childhood.htm. Updated August 4, 2017. Accessed March 21, 2018.

48. Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. *Arthritis care & research.* 2012;64(6):905-910.
49. Spondyloarthritis. Fast Facts. American College of Rheumatology Web site. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Spondyloarthritis. Updated November 2013. Accessed March 5, 2018.
50. Dougados M, Baeten D. Spondyloarthritis. *Lancet.* 2011;377(9783):2127-2137.
51. Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. *N Engl J Med.* 2016;375(13):1303.
52. Kroon FP, van der Burg LR, Ramiro S, et al. Nonsteroidal Antiinflammatory Drugs for Axial Spondyloarthritis: A Cochrane Review. *The Journal of rheumatology.* 2016;43(3):607-617.
53. Ankylosing Spondylitis. National Institute of Arthritis and Musculoskeletal and Skin Diseases. National Institue of Health (NIH) Web site. https://www.niams.nih.gov/health-topics/ankylosing-spondylitis#tab-overview. Updated June 30, 2016. Accessed March 21, 2018.
54. Ankylosing spondylitis. Symptoms. National Center for Advancing Translational Sciences. National Institue of Health Web site. https://rarediseases.info.nih.gov/diseases/9518/ankylosing-spondylitis. Updated September 2015. Accessed March 5, 2018.
55. Shekelle PG, FitzGerald J, Newberry SJ, Motala A, O'Hanlon CE, Okunogbe A, Tariq A, Han D, Dudley W, Shanman R, Booth M. Management of Gout. Comparative Effectiveness Review No. 176. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No.16-EHC017-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2016. Addendum October 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
56. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011;63(10):3136-3141.
57. Schumacher HR, Chen LX. Chapter 333. Gout and Other Crystal-Associated Arthropathies. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 18e.* New York, NY: The McGraw-Hill Companies; 2012.
58. Roddy E, Choi HK. Epidemiology of gout. *Rheumatic diseases clinics of North America.* 2014;40(2):155-175.
59. Seth R, Kydd AS, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. *Cochrane Database Syst Rev.* 2014(10):CD006077.
60. Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther.* 2010;12(6):223.
61. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nature reviews Rheumatology.* 2015;11(11):649-662.
62. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. *Vasc Health Risk Manag.* 2017;13:23-28.
63. Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep.* 2009;11(2):154-160.
64. Roddy E, Zhang W, Doherty M. Is gout associated with reduced quality of life? A case-control study. *Rheumatology (Oxford, England).* 2007;46(9):1441-1444.
65. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017;76(1):29-42.
66. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care and Research.* 2012;64(10):1431-1446.
67. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken).* 2012;64(10):1447-1461.
68. Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of P. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2017;166(1):58-68.

69. Shekelle PG, FitzGerald J, Newberry SJ, et al. AHRQ Comparative Effectiveness Reviews. In: *Management of Gout.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.
70. Sivera F, Andrés M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: Integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Annals of the Rheumatic Diseases.* 2014;73(2):328-335.
71. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology (Oxford, England).* 2017;56(7):1246.
72. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248-273.
73. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2016;65(1):1-49.
74. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Annals of internal medicine.* 2017;166(7):514-530.
75. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Annals of internal medicine.* 2017;166(7):480-492.
76. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Annals of internal medicine.* 2017;166(7):493-505.
77. Chou R, Deyo R, Friedly J, et al. AHRQ Comparative Effectiveness Reviews. In: *Noninvasive Treatments for Low Back Pain.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.
78. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *The Cochrane database of systematic reviews.* 2008(1):Cd000396.
79. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage.* 2014;22(3):363-388.
80. Chou R, McDonagh MS, Nakamoto E, Griffin J. AHRQ Comparative Effectiveness Reviews. In: *Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
81. VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis. Department of Veterans Affairs Department of Defense. Version 1.0, 2014. https://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf. Accessed February 28, 2018. .
82. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis care & research.* 2012;64(4):465-474.
83. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. In: *Osteoarthritis: Care and Management in Adults.* London: National Institute for Health and Care Excellence (UK) Copyright (c) National Clinical Guideline Centre, 2014.; 2014.
84. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and cartilage.* 2008;16(2):137-162.
85. National Collaborating Centre for Chronic C. National Institute for Health and Clinical Excellence: Guidance. In: *Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults.* London: Royal College of Physicians (UK). Royal College of Physicians of London.; 2009.
86. Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis. Edinburgh: SIGN; 2011. (SIGN publication no. 123). [cited February 2011]. Available from URL: http://www.sign.ac.uk.

87. Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2008;12(11):1-278, iii.
88. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis and rheumatism.* 2013;65(10):2499-2512.
89. National Institute for H, Care E. National Institute for Health and Care Excellence: Clinical Guidelines. In: *Spondyloarthritis in Over 16s: Diagnosis and Management.* London: National Institute for Health and Care Excellence (UK) Copyright (c) National Institute for Health and Care Excellence 2017.; 2017.
90. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis & rheumatology (Hoboken, NJ).* 2016;68(2):282-298.
91. van der Heijde D, Ramiro S, Landewe R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Annals of the rheumatic diseases.* 2017;76(6):978-991.
92. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Annals of the rheumatic diseases.* 2011;70(6):896-904.
93. Shekelle PG, Newberry SJ, FitzGerald JD, et al. Management of Gout: A Systematic Review in Support of an American College of Physicians Clinical Practice Guideline. *Annals of internal medicine.* 2017;166(1):37-51.
94. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *The American journal of gastroenterology.* 2009;104(3):728-738.
95. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. *American family physician.* 2013;87(11):766-772.
96. Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *The Cochrane database of systematic reviews.* 2010(1):Cd001751.
97. Casazza BA. Diagnosis and treatment of acute low back pain. *American family physician.* 2012;85(4):343-350.
98. Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. *American family physician.* 2014;89(5):341-346.
99. Fogleman CD. Analgesics for osteoarthritis. *American family physician.* 2013;87(5):354-356.
100. Wasserman AM. Diagnosis and management of rheumatoid arthritis. *American family physician.* 2011;84(11):1245-1252.
101. Noss MR, Saguil A. Gout: Diagnosis and Management. *American family physician.* 2017;96(10):668-670.
102. Crofford L. Prostanoid biology and its therapeutic targeting. In: *Kelley's Textbook of Rheumatology.* Saunders; 2012.
103. Grosser T, Smyth E, FitzGerald G. Pharmacotherapy of Inflammation, Fever, Pain, and Gout. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e.* New York, NY: McGraw-Hill Education; 2017.
104. Chou R, Helfand M, Peterson K, Dana T, Roberts C. Drug Class Reviews. In: *Drug Class Review: Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs): Final Report Update 3.* Portland (OR): Oregon Health & Science University Oregon Health & Science University, Portland, Oregon.; 2006.
105. Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2004;18(7):790-804.
106. Kawai S. Cyclooxygenase selectivity and the risk of gastro-intestinal complications of various non-steroidal anti-inflammatory drugs: a clinical consideration. *Inflammation research : official journal of the European Histamine Research Society [et al].* 1998;47 Suppl 2:S102-106.

107. Micromedex (electronic version). Truven Health Analytics; 2018. http://www.micromedexsolutions.com/. Accessed February 27, 2018.
108. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society.* 2015;63(11):2227-2246.
109. Ashbrook J, Rodgdakis N, Goodwin P, Yeowell G, Callaghan M. 43 Management of acute low back pain in the ED: a systematic review. *Emerg Med J.* 2017;34(12):A889.
110. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* 2009;6(7):e1000097.
111. Chou R, McDonagh MS, Nakamoto E, Griffin J. AHRQ Comparative Effectiveness Reviews. In: *Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
112. van Tulder MW, Scholten RJ, Koes BW, Deyo RA. WITHDRAWN: Non-steroidal anti-inflammatory drugs for low-back pain. *The Cochrane database of systematic reviews.* 2007(2):Cd000396.
113. Towheed TE, Hochberg MC, Shea BJ, Wells G. WITHDRAWN: Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. *The Cochrane database of systematic reviews.* 2007(1):Cd000517.
114. Watson M, Brookes ST, Faulkner A, Kirwan J. WITHDRAWN: Non-aspirin, non-steroidal anti-inflammatory drugs for treating osteoarthritis of the knee. *The Cochrane database of systematic reviews.* 2007(1):Cd000142.
115. Chikanza IC, Clarke B, Hopkins R, MacFarlane DG, Bird H, Grahame R. A comparative study of the efficacy and toxicity of etodolac and naproxen in the treatment of osteoarthritis. *The British journal of clinical practice.* 1994;48(2):67-69.
116. Freitas GG. A double-blind comparison of etodolac and piroxicam in the treatment of osteoarthritis. *Current medical research and opinion.* 1990;12(4):255-262.
117. Jennings M, Alfieri D. A controlled comparison of etodolac and naproxen in osteoarthritis of the foot. *Lower Extremity.* 1997;4:43-48.
118. Liang TH, Hsu PN. Double-blind, randomised, comparative trial of etodolac SR versus diclofenac in the treatment of osteoarthritis of the knee. *Current medical research and opinion.* 2003;19(4):336-341.
119. Rogind H, Bliddal H, Klokker D, Jensen F. Comparison of etodolac and piroxicam in patients with osteoarthritis of the hip or knee: a prospective, randomised, double-blind, controlled multicentre study. *Clinical drug investigation.* 1997;13(2):66-75.
120. Furst D, Hall DB, Roszko J, Leonard JP. Efficacy, safety and dose response of meloxicam up to 22.5 mg in the treatment of rheumatoid arthritis (RA): results of a phase III double-blind, placebo controlled trial. Zeitschrift fur Rheumatologie. 2001;60(Suppl 1):38.
121. Wojtulewski JA, Schattenkirchner M, Barcelo P, et al. A six-month double-blind trial to compare the efficacy and safety of meloxicam 7.5 mg daily and naproxen 750 mg daily in patients with rheumatoid arthritis. *British journal of rheumatology.* 1996;35 Suppl 1:22-28.
122. Alballa SR, Al-Arfaj H, Al-Sugair S, Al-Arfaj A, Al-Shammari SA. Randomized, double-blind, short-term trial of nabumetone versus diclofenac in osteoarthritis of the knee. *Current Therapeutic Research.* 1992;52(4):581-586.
123. Schnitzer TJ, Ballard IM, Constantine G, McDonald P. Double-blind, placebo-controlled comparison of the safety and efficacy of orally administered etodolac and nabumetone in patients with active osteoarthritis of the knee. *Clinical therapeutics.* 1995;17(4):602-612.
124. Pavelka K. A comparison of the therapeutic efficacy of diclofenac in osteoarthritis: a systematic review of randomised controlled trials. *Current medical research and opinion.* 2012;28(1):163-178.
125. Valat JP, Accardo S, Reginster JY, Wouters M, Hettich M, Lieu PL. A comparison of the efficacy and tolerability of meloxicam and diclofenac in the treatment of patients with osteoarthritis of the lumbar spine. *Inflammation research : official journal of the European Histamine Research Society [et al].* 2001;50 Suppl 1:S30-34.
126. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Archives of internal medicine.* 2000;160(19):2947-2954.

127. Taha AS, McLaughlin S, Sturrock RD, Russell RI. Evaluation of the efficacy and comparative effects on gastric and duodenal mucosa of etodolac and naproxen in patients with rheumatoid arthritis using endoscopy. *British journal of rheumatology.* 1989;28(4):329-332.
128. Delcambre B. Polyarthrite rhumatoide: efficacite, tolerance et benefice therapeutique compares de l'etodolac (600 mg/j) et de l'indometacine (100 mg/j) [in French]. Rhumatologie 1990; 42:213–8.
129. Taha AS, McLaughlin S, Holland PJ, Kelly RW, Sturrock RD, Russell RI. Effect on gastric and duodenal mucosal prostaglandins of repeated intake of therapeutic doses of naproxen and etodolac in rheumatoid arthritis. *Annals of the rheumatic diseases.* 1990;49(6):354-358.
130. Lightfoot R. Comparison of the efficacy and safety of etodolac and piroxicam in patients with rheumatoid arthritis. Etodolac Study 326 Rheumatoid Arthritis Investigators Group. *J Rheumatol Suppl.* 1997;47:10-16.
131. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. *J Rheumatol Suppl.* 1997;47:17-22.
132. Furst D, Hall D, Roszko J, Leonard J. Efficacy, safety and dose response of meloxicam up to 22.5 mg in the treatment of rheumatoid arthritis (RA): results of a phase III double-blind, placebo controlled trial. *Zeitschrift fur Rheumatologie.* 2001;60(Suppl 1):38.
133. Xu J-h, Ding C-h, Xu S-y. A double-blind, randomized controlled clinical study of meloxicam and nabumetone in the treatment of rheumatoid arthritis. *CHINESE PHARMACEUTICAL JOURNAL-BEIJING-.* 2002;37(4):310-311.
134. Richy F, Rabenda V, Mawet A, Reginster JY. Flurbiprofen in the symptomatic management of rheumatoid arthritis: a valuable alternative. *International journal of clinical practice.* 2007;61(8):1396-1406.
135. Shi W, Wang YM, Li LS, et al. Safety and efficacy of oral nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis : a six-month randomised study. *Clinical drug investigation.* 2004;24(2):89-101.
136. Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *The Cochrane database of systematic reviews.* 2017;8:CD012537.
137. Bhettay E, Thomson AJ. Double-blind study of ketoprofen and indomethacin in juvenile chronic arthritis. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* 1978;54(7):276-278.
138. Ruperto N, Nikishina I, Pachanov ED, et al. A randomized, double-blind clinical trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. *Arthritis and rheumatism.* 2005;52(2):563-572.
139. Shekelle PG, Newberry SJ, FitzGerald JD, et al. Management of gout: A systematic review in support of an american college of physicians clinical practice guideline. *Annals of internal medicine.* 2017;166(1):37-51.
140. van Durme CM, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewe RB. Non-steroidal anti-inflammatory drugs for acute gout. *The Cochrane database of systematic reviews.* 2014(9):CD010120.
141. Valtonen EJ, Busson M. A comparative study on ibuprofen (Brufen) and indomethacin in non-articular rheumatism. *Scandinavian journal of rheumatology.* 1978;7(3):183-187.
142. Peterson K, McDonagh M, Thakurta S, Dana T, Roberts C, Chou R, Helfand M. Drug class review: Nonsteroidal antiinflammatory drugs (NSAIDs). Update 4 final report. http://derp.ohsu.edu/about/final-document-display.cfm.
143. Colberg K, Hettich M, Sigmund R, Degner FL. The efficacy and tolerability of an 8-day administration of intravenous and oral meloxicam: a comparison with intramuscular and oral diclofenac in patients with acute lumbago. German Meloxicam Ampoule Study Group. *Current medical research and opinion.* 1996;13(7):363-377.
144. Dreiser RL, Le Parc JM, Velicitat P, Lleu PL. Oral meloxicam is effective in acute sciatica: two randomised, double-blind trials versus placebo or diclofenac. *Inflammation research : official journal of the European Histamine Research Society [et al].* 2001;50 Suppl 1:S17-23.

145. Rasmussen-Barr E, Held U, Grooten WJ, et al. Nonsteroidal Anti-inflammatory Drugs for Sciatica: An Updated Cochrane Review. *Spine.* 2017;42(8):586-594.
146. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *The Cochrane database of systematic reviews.* 2016;2:CD012087.
147. Videman T, Osterman K. Double-blind parallel study of piroxicam versus indomethacin in the treatment of low back pain. *Annals of clinical research.* 1984;16(3):156-160.
148. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain: a systematic review. *Agency for Healthcare Research and Quality (US).* 2016;see : https://effectivehealthcare.ahrq.gov/topics/back-pain-treatment/research:02.
149. Wong JJ, Cote P, Ameis A, et al. Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Eur Spine J.* 2016;25(1):34-61.
150. Keller A, Hayden J, Bombardier C, van Tulder M. Effect sizes of non-surgical treatments of non-specific low-back pain. *Eur Spine J.* 2007;16(11):1776-1788.
151. Plapler PG, Scheinberg MA, Ecclissato Cda C, Bocchi de Oliveira MF, Amazonas RB. Double-blind, randomized, double-dummy clinical trial comparing the efficacy of ketorolac trometamol and naproxen for acute low back pain. *Drug Des Devel Ther.* 2016;10:1987-1993.
152. Hurwitz EL, Carragee EJ, van der Velde G, et al. Treatment of neck pain: noninvasive interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine (Phila Pa 1976).* 2008;33(4 Suppl):S123-152.
153. Yamamoto M, Sugano T, Kashiwazaki S, Kageyama T, Mizushima Y, Kameyama M. Double-blind comparison of piroxicam and indomethacin in the treatment of cervicobrachial syndrome and periarthritis scapulohumeralis (stiff shoulder). *European journal of rheumatology and inflammation.* 1983;6(3):266-273.
154. Silva de Oliveira JC, Grossi de Oliveira GA, Bassi AP. Comparative Assessment of the Effect of Ibuprofen and Etodolac on Edema, Trismus, and Pain in Lower Third Molar Surgery: A Randomized Clinical Trial. *J Oral Maxillofac Surg.* 2016;74(8):1524-1530.
155. Olmedo MV, Galvez R, Vallecillo M. Double-blind parallel comparison of multiple doses of ketorolac, ketoprofen and placebo administered orally to patients with postoperative dental pain. *Pain.* 2001;90(1-2):135-141.
156. Grebe W, Ionescu E, Gold MS, Liu JM, Frank WO. A multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group comparison of diclofenac-K and ibuprofen for the treatment of adults with influenza-like symptoms. *Clinical therapeutics.* 2003;25(2):444-458.
157. Sarzi-Puttini P, Atzeni F, Lanata L, Bagnasco M. Efficacy of ketoprofen vs. ibuprofen and diclofenac: a systematic review of the literature and meta-analysis. *Clin Exp Rheumatol.* 2013;31(5):731-738.
158. Sarzi-Puttini P, Atzeni F, Lanata L, et al. Safety of ketoprofen compared with ibuprofen and diclofenac: A systematic review and meta-analysis. *Trends in Medicine.* 2014;14(2):17-26.
159. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Comparison. 2018; http://www.emedexpert.com/compare/nsaids.shtml.
160. Wallace JL. How do NSAIDs cause ulcer disease? *Bailliere's best practice & research Clinical gastroenterology.* 2000;14(1):147-159.
161. Wong JJ, Cote P, Sutton DA, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Eur J Pain.* 2017;21(2):201-216.
162. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013;382(9894):769-779.
163. Masso Gonzalez EL, Patrignani P, Tacconelli S, Garcia Rodriguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis and rheumatism.* 2010;62(6):1592-1601.
164. Garcia Rodriguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology.* 2007;132(2):498-506.

165. Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ (Clinical research ed).* 1996;312(7046):1563-1566.
166. MacDonald TM, Morant SV, Robinson GC, et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ (Clinical research ed).* 1997;315(7119):1333-1337.
167. CADTH Rapid Response Reports, in Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Safety. 2013, Canadian Agency for Drugs and Technologies in Health.: Ottawa (ON).
168. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med.* 2016;375(26):2519-2529.
169. Yuan JQ, Tsoi KK, Yang M, et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. *Alimentary pharmacology & therapeutics.* 2016;43(12):1262-1275.
170. Chan FK, Graham DY. Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications--review and recommendations based on risk assessment. *Alimentary pharmacology & therapeutics.* 2004;19(10):1051-1061.
171. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Annals of internal medicine.* 1995;123(4):241-249.
172. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet (London, England).* 2007;369(9573):1621-1626.
173. Antman EM. Evaluating the Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs. *Circulation.* 2017;135(21):2062-2072.
174. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation.* 2007;115(12):1634-1642.
175. Arfe A, Scotti L, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ (Clinical research ed).* 2016;354:i4857.
176. Medicine TUSo. Major Side Effects of NSAIDs & COX-2 Selective Inhibitors. 2017; http://tmedweb.tulane.edu/pharmwiki/doku.php/nsaid_side_effects.
177. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Annals of internal medicine.* 2005;142(3):157-164.
178. Gunter BR, Butler KA, Wallace RL, Smith SM, Harirforoosh S. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. *Journal of clinical pharmacy and therapeutics.* 2017;42(1):27-38.
179. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. U.S. Food and Drug Administration Web site. https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm. Updated February 26, 2018. Accessed March 21, 2018.
180. Fosbol EL, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. *Circulation Cardiovascular quality and outcomes.* 2010;3(4):395-405.
181. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS medicine.* 2011;8(9):e1001098.
182. Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Archives of internal medicine.* 2002;162(3):265-270.
183. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet (London, England).* 2004;363(9423):1751-1756.

184. Kohli P, Steg PG, Cannon CP, et al. NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. *The American journal of medicine.* 2014;127(1):53-60.e51.
185. Bavry AA, Khaliq A, Gong Y, Handberg EM, Cooper-Dehoff RM, Pepine CJ. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *The American journal of medicine.* 2011;124(7):614-620.
186. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ (Clinical research ed).* 2017;357:j1909.
187. Fosbol EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clinical pharmacology and therapeutics.* 2009;85(2):190-197.
188. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation.* 2006;113(25):2906-2913.
189. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation.* 2011;123(20):2226-2235.
190. Olsen AM, Fosbol EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. *Circulation.* 2012;126(16):1955-1963.
191. communication Fds. FDA strengthens warning that non-aspirin nonsteroidal anit-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. In.
192. Asghar W, Jamali F. The effect of COX-2-selective meloxicam on the myocardial, vascular and renal risks: a systematic review. *Inflammopharmacology.* 2015;23(1):1-16.
193. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ (Clinical research ed).* 2006;332(7553):1302-1308.
194. Ruschitzka F, Borer JS, Krum H, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. *Eur Heart J.* 2017;38(44):3282-3292.
195. Solmaz D, Sari I, Can G, et al. The effect of non-steroidal anti-inflammatory drugs on the endothelial function of patients with osteoarthritis in short term. *International journal of rheumatic diseases.* 2012;15(2):207-211.
196. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS clinical trials.* 2006;1(7):e33.
197. Mulnar MY BD. Acute Kidney Injury. In: Alldredge BK CR, Ernst ME, et al. , ed. *Koda-Kimble & Young's Applied Therapeutics: the clinical use of drugs.* Philadelphia, PA: Lippincott Willams & Wilkins; 2013:743-763.
198. Hsu CC, Wang H, Hsu YH, et al. Use of Nonsteroidal Anti-Inflammatory Drugs and Risk of Chronic Kidney Disease in Subjects With Hypertension: Nationwide Longitudinal Cohort Study. *Hypertension (Dallas, Tex : 1979).* 2015;66(3):524-533.
199. Nephrology ASo. Choosing Wisely. . *Avoid nonsteroidal antiinflammatory drugs (NSAIDs) in individuals with hypertension or heart failure of CKD of all causes, includeing diabetes.* 2018; http://www.choosingwisely.org/.
200. DP T. In: Alldredge BK CR, Ernst ME, et al, ed. *Koda-Kimble & Young's Applied Therapeutics: the clinical use of drugs* Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
201. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ (Clinical research ed).* 2013;346:e8525.
202. Clinical Resource, Common Questions About Ketorolac. In. *Pharmacist's Letter/Prescriber's Letter*2012.

203. Ingrasciotta Y, Sultana J, Giorgianni F, et al. Association of individual non-steroidal anti-inflammatory drugs and chronic kidney disease: a population-based case control study. *PloS one.* 2015;10(4):e0122899.
204. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Archives of internal medicine.* 2009;169(2):141-149.
205. Bouvy ML, Heerdink ER, Hoes AW, Leufkens HG. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. *Drug safety.* 2003;26(13):983-989.
206. Fournier JP, Lapeyre-Mestre M, Sommet A, Dupouy J, Poutrain JC, Montastruc JL. Laboratory monitoring of patients treated with antihypertensive drugs and newly exposed to non steroidal anti-inflammatory drugs: a cohort study. *PloS one.* 2012;7(3):e34187.
207. Chen SW OCR, Reta AM. Rheumatoid Arthritis. In: Alldredge BK CR, Ernst ME, et al, ed. *Koda-Kimble and Young's applied therpeutics: the clinical use of drugs.* Philadelphia, PA: Lippincott Williams & Wilkins; 2013:1002-1038.
208. Nonsteroidal Antiinflammatory Drugs. 2018. https://livertox.nih.gov/NonsteroidalAntiinflammatoryDrugs.htm)
209. Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? *World journal of gastroenterology.* 2010;16(45):5651-5661.
210. Roth SH, Fuller P. Pooled safety analysis of diclofenac sodium topical solution 1.5% (w/w) in the treatment of osteoarthritis in patients aged 75 years or older. *Clinical interventions in aging.* 2012;7:127-137.
211. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. *QJM : monthly journal of the Association of Physicians.* 2003;96(11):787-791.
212. Nonselective NSAIDs:Overview of Adverse Effects. Wolters Kluwer; 2018. https://www.uptodate.com/contents/nonselective-nsaids-overview-of-adverse-effects?search=nsaid%20hepatotoxicity&sectionRank=1&usage_type=default&anchor=H6&source=machineLearning&selectedTitle=1~150&display_rank=1#H6.
213. Rostom A, Goldkind L, Laine L. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2005;3(5):489-498.
214. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology.* 2013;144(7):1419-1425, 1425.e1411-1413; quiz e1419-1420.
215. Rubenstein JH, Laine L. Systematic review: the hepatotoxicity of non-steroidal anti-inflammatory drugs. *Alimentary pharmacology & therapeutics.* 2004;20(4):373-380.
216. Simon RA. NSAIDs (including aspirin): Allergic and pseudoallergic reactions. 2018.
217. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *The Cochrane database of systematic reviews.* 2015(7):Cd001751.
218. Chang DM, Young TH, Hsu CT, Kuo SY, Hsieh TC. Endoscopic comparison of the gastroduodenal safety and the effects on arachidonic acid products between meloxicam and piroxicam in the treatment of osteoarthritis. *Clinical rheumatology.* 2001;20(2):104-113.
219. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. *British journal of rheumatology.* 1998;37(9):946-951.
220. Goei The HS, Lund B, Distel MR, Bluhmki E. A double-blind, randomized trial to compare meloxicam 15 mg with diclofenac 100 mg in the treatment of osteoarthritis of the knee. *Osteoarthritis and cartilage.* 1997;5(4):283-288.
221. Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment. *British journal of rheumatology.* 1998;37(9):937-945.

222. Hosie J, Distel M, Bluhmki E. Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium. *British journal of rheumatology.* 1996;35 Suppl 1:39-43.
223. J. Hosie D, Distel M, Bluhmki E. *Efficacy and Tolerability of Meloxicam versus Piroxicam in Patients with Osteoarthritis of the Hip or Knee.* Vol 131997.
224. Linden B, Distel M, Bluhmki E. A double-blind study to compare the efficacy and safety of meloxicam 15 mg with piroxicam 20 mg in patients with osteoarthritis of the hip. *British journal of rheumatology.* 1996;35 Suppl 1:35-38.
225. CHOPRA A, BICHILE L, RAJADHYAKSHA AG, et al. Randomized double-blind clinical drug trials of meloxicam in rheumatoid arthritis and osteoarthritis knees: an Indian experience. *APLAR Journal of Rheumatology.* 2004;7(2):108-116.
226. Scott DL, Palmer RH. Safety and efficacy of nabumetone in osteoarthritis: emphasis on gastrointestinal safety. *Alimentary pharmacology & therapeutics.* 2000;14(4):443-452.
227. Morgan GJ, Jr., Kaine J, DeLapp R, Palmer R. Treatment of elderly patients with nabumetone or diclofenac: gastrointestinal safety profile. *Journal of clinical gastroenterology.* 2001;32(4):310-314.
228. Lomen PL, Turner LF, Lamborn KR, Winblad MA, Sack RL, Brinn EL. Flurbiprofen in the treatment of acute gout. A comparison with indomethacin. *Am J Med.* 1986;80(3a):134-139.
229. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. *The Journal of rheumatology.* 1988;15(9):1422-1426.
230. Lederman R. A double-blind comparison of etodolac (Lodine) and high doses of naproxen in the treatment of acute gout. *Adv Ther.* 1990;7(344):54.
231. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. *Current medical research and opinion.* 1991;12(7):423-429.
232. Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. *Arzneimittel-Forschung.* 1983;33(4a):641-643.
233. Jenner PN. Nabumetone in the treatment of skin and soft tissue injury. *Am J Med.* 1987;83(4b):101-106.
234. Herrera JA, Millan A, Ramos R, Fuentes P, Gonzalez M. Evaluation of the effectiveness and tolerability of controlled-release diclofenac-potassium versus immediate-release diclofenac-potassium in the treatment of knee osteoarthritis. *Current therapeutic research, clinical and experimental.* 2007;68(2):82-93.
235. Prabhu VV. A comparative clinical trial evaluating efficacy and safety of fixed dose combination of nimesulide (100 mg) and racemethionine (50 mg) (namsafe) versus reference drug (nimesulide) and other NSAIDs in the treatment of osteoarthritis. *Journal of the Indian Medical Association.* 2008;106(6):402-404.
236. Wagenitz A, Mueller EA, Frentzel A, Cambon N. Comparative efficacy and tolerability of two sustained-release formulations of diclofenac: results of a double-blind, randomised study in patients with osteoarthritis and a reappraisal of diclofenac's use in this patient population. *Current medical research and opinion.* 2007;23(8):1957-1966.
237. Aoki T, Kuroki Y, Kageyama T, Irimajiri S, Mizushima Y, Yamamoto K. Multicentre double-blind comparison of piroxicam and indomethacin in the treatment of lumbar diseases. *European journal of rheumatology and inflammation.* 1983;6(3):247-252.
238. Dreiser RL, Marty M, Ionescu E, Gold M, Liu JH. Relief of acute low back pain with diclofenac-K 12.5 mg tablets: a flexible dose, ibuprofen 200 mg and placebo-controlled clinical trial. *International journal of clinical pharmacology and therapeutics.* 2003;41(9):375-385.
239. Matsumo S, Kaneda K, Norhara Y. Clinical evaluation of ketoprofen (Orudis) in lumbago - a double-blind comparison with diclofenac sodium. *The British journal of clinical practice.* 1981;35(7-8):266.
240. Pena M. Etodolac: analgesic effects in musculoskeletal and postoperative pain. *Rheumatology international.* 1990;10 Suppl:9-16.
241. Siegmeth W, Sieberer W. A comparison of the short-term effects of ibuprofen and diclofenac in spondylosis. *The Journal of international medical research.* 1978;6(5):369-374.
242. Marchini M, Tozzi L, Bakshi R, Pistai R, Fedele L. Comparative efficacy of diclofenac dispersible 50 mg and ibuprofen 400 mg in patients with primary dysmenorrhea. A randomized, double-blind, within-

patient, placebo-controlled study. *International journal of clinical pharmacology and therapeutics.* 1995;33(9):491-497.
243. Chantler I, Mitchell D, Fuller A. The effect of three cyclo-oxygenase inhibitors on intensity of primary dysmenorrheic pain. *The Clinical journal of pain.* 2008;24(1):39-44.
244. Dawood, M. Y. (1999). Efficacy and Safety of Piroxicam- beta-Cyclodextrin(PBCD, Brexidol registered)--Comparison Studies with Ibuprofen, Naproxen Sodium and Placebo in the Relief of Moderate or Severe Abdominal Pain Associated with Primary Dysmenorrhea. Journal of New Developments in Clinical Medicine, 17(4), 273.
245. Martinez Alcala FO, Aldrete Velasco JA, Risco Cortes RJ, et al. Efficacy and safety of COX-2 selective inhibitor versus non selective NSAID in the symptomatic treatment of primary dysmenorrhea. *Revista Brasileira de Medicina.* 2003;60(11):882-887.
246. Kintigh J. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Diclofenac Potassium Versus Naproxen Sodium in the Treatment of Primary Dysmenorrhea. *TODAYS THERAPEUTIC TRENDS.* 1995;12:47-47.
247. Milsom I, Andersch B. Ibuprofen and naproxen-sodium in the treatment of primary dysmenorrhea: a double-blind cross-over study. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 1985;23(4):305-310.
248. Ingemanson C-A, Sikstrom B, Bjorkman R. Comparison between diclofenac and naproxen in the treatment of primary dysmenorrhoea. *Current therapeutic research.* 1984;36(6):1203-1209.
249. Åkerlund M, Strömberg P. Comparison of ketoprofen and naproxen in the treatment of dysmenorrhoea, with special regard to the time of onset of pain relief. *Current medical research and opinion.* 1989;11(8):485-490.
250. Mehlisch D. Double-blind crossover comparison of ketoprofen, naproxen, and placebo in patients with primary dysmenorrhea. *Clinical therapeutics.* 1990;12(5):398-409.
251. Wilhelmsson L, Jonsson K, Hailing L, et al. Piroxicam in the treatment of primary dysmenorrhea. *Acta obstetricia et gynecologica Scandinavica.* 1985;64(4):317-321.
252. Andersch B, Milsom I. A double-blind cross-over study comparing flurbiprofen with naproxen-sodium for the treatment of primary dysmenorrhea. *Acta obstetricia et gynecologica Scandinavica.* 1989;68(6):555-558.

Appendix A. FDA-Approved Nonopioid Analgesics

Table 1. FDA-Approved Nonopioid Analgesics[32,102]

Chemical Class	Generic Name
Salicylates	Acetylsalicylic acid Choline and magnesium trisalicylate Diflunisal Salsalate
Para-aminophenol	Acetaminophen
Fenamates	Meclofenamate Mefenamic acid
Pyranocarboxylic acid	Etodolac
Acetic acid	Diclofenac
Oxicams	Meloxicam Piroxicam
Propionic acids	Ibuprofen Fenoprofen Ketoprofen Naproxen Naproxen sodium Oxaprozin
Carbo- and heterocyclic acids	Etodolac Indomethacin Ketorolac Sulindac Tolmetin
Non-acidic compounds	Nabumetone
Pyrazoles	Celecoxib

Appendix B. NSAID Interactions

Table 1. NSAID Interactions[14,107]

Interacting medication(s)	Interaction	Severity	All NSAIDS	Specific NSAID
NSAIDs	**Additive GI effects (peptic ulcers, GI blessing and/or perforation**	**C**	**X**	
Aminolevulinic acid	**Increased photosensitizing effects of Aminolevulinic acid**	**C**	**X**	
Calcium polystyrene sulfonate, Sodium polystyrene sulfonate	**Meloxicam oral suspension (containing sorbitol) increases the risk for intestinal necrosis**	**C**		**Meloxicam**
NSAID Cox-2 inhibitors	**Increased risk of bleeding and GI toxicity**	**C**	**X**	
Omacetaxine	**Increased risk for bleeding, avoid use in patients with PLT < 50,000/uL**	**C**	**X**	
Urokinase agents	**Enhanced anticoagulant effect**		**X**	
Alcohol (Ethyl)	Enhanced adverse/toxic effects, e.g. GI bleeding	M	X	
Aliskiren	Diminished antihypertensive effect and enhanced nephrotoxic effects of Aliskiren	M	X	
Amikacin	Increased amikacin exposure	M		Ibuprofen, Indomethacin
Aminoglycosides (gentamicin, tobramycin)	Decreased excretion of aminoglycoside (data in premature infants only)	M	X	Indomethacin
Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers	Increased renal dysfunction and/or increased blood pressure	M	X	
Anisindione	Increased risk of bleeding	M	X	
Anticoagulants (dicumarol)	Increased risk of bleeding, enhanced anticoagulant effects	M	X	
Antiplatelet agents (e.g. P2Y12 inhibitors, ticlodipine, clopidigrel, prasugrel, ticagrelor, cangrelor	Increased risk of bleeding	S	X	
Aspirin	Decreased antiplatelet effect of aspirin; increased risk of bleeding	S	X	
Beta-adrenergic blockers	Increased blood pressure	M		Ibuprofen
Betrixaban	Increased risk of bleeding	S	X	
Bile acid sequestrants	Decreased absorption of NSAIDs	S	X	
Bisphosphonates	Increased GI ulceration, increased risk of nephrotoxicity	M	X	
Cephalothin	Increased risk of bleeding	M	X	
Ceritinib			X	
Collagenase	Increased risk of injection site bruising and/or bleeding	M	X	
Corticosteroids	Increased risk of GI ulcer or bleeding	S	X	
CYP2C9 Substrates (e.g. Ceritinib, Enzalutamide, Lumacaftor, Mifepristone, Rifapentine)	Increased serum concentration of substrates	M	X	
CYP2C9 Inducers	May decrease the serum concentration of the CYP2C9 substrates		X	
CYP2C9 Inhibitors	May decrease the metabolism of CYP2C9 substrates	M (moderate inhibitors) S (strong inhibitors)	X	
Cyclosporine	Increased risk of cyclosporine nephrotoxicity	S	X	
Dasatinib	Enhanced anticoagulant effects	M	X	
Deferasirox	Increased risk for GI ulceration/irritation or GI bleeding	M	X	
Deoxycholic acid	Increased risk for bleeding and bruising in the treatment area	M	X	
			X	
Desmopressin	Increased risk of hyponatremia	S	X	
Digoxin	Increased digoxin serum concentrations; prolonged digoxin half-life	S	X	
Direct oral anticoagulants (e.g. Apixaban, Betrixaban, Dabigatran etexilate, Edoxaban, Rivaroxaban)	Increased bleeding risk	M	X	
Diuretics, Thiazides, Thiazide-like, and Loops	Reduced diuretic effectiveness, possible nephrotoxicity	S	X	
Drospirenone	Enhanced hyperkalemic effect	M	X	
Enzalutamide	Decreased serum concentrations of enzalutamide	S	X	

Eplerenone	Decreased antihypertensive effect, increased hypokalemic effect	M	X	
Feverfew	Increased risk of NSAID adverse effects (e.g. GI, renal)	S	X	
Ginkgo	Increased risk of bleeding	S	X	
Glucosamine	Enhanced antiplatelet effects	M	X	
Gossypol	Increased risk of adverse GI effects	S	X	
Haloperidol	Increase haloperidol adverse/toxic effects (e.g. drowsiness, confusion)	M	X	
Herbs: anticoagulant/antiplatelet (e.g. alfalfa, anise, bilberry)	Increased risk of bleeding, IF used together (not recommended) monitor for bleeding, bruising, altered mental status from possible CNS bleeds.	S	X	
Hydralazine	Reduced antihypertensive effect		X	
Ibritumomab, Ibrutinib	Increased risk of bleeding; impaired platelet function	M	X	
L-methylfolate	Decreased L-methylfolate effiacy	M	X	
Lithium	May result in lithium toxicity	S	X	
Low molecular weight heparins	Increased risk of bleeding	S	X	
Ma Huang	Increased risk of developing gastric mucosal lesions.	M	X	
Meadowsweet	Increased risk of bleeding	S	X	
Methotrexate	Increased risk of methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)	S		Ibuprofen
Mifepristone	Increased exposure to NSAID	M	X	
Multivitamins with minerals/fluoride	Enhanced antiplatelet effect	M	X	
Naftazone	Enhanced antiplatelet effect	M	X	
Obinutuzumab	Increased adverse/toxic effects of obinutuzumab, especially bleeding	M	X	
Omega-3 fatty acids	Enhanced antiplatelet effects		X	
Pentosan polysulfate sodium	Increased risk of bleeding	S	X	
Pentoxifylline	Increased risk of bleeding	S	X	
Pemetrexed	Pemetrexed toxicity (myelosuppression, renal toxicity, GI toxicity)	S	X	
Porfimer	Enhanced photosensitizing effects	M	X	
Potassium sparing diuretics	Reduced diuretic effectiveness, hyperkalemia, possible nephrotoxicity	S	X	
Pralatrexate	Increased pralatrexate exposure, monitor for decreased pralatrexate levels with NSAID discontinuation	S	X	
Probenecid	Increased NSAID serum concentrations	M	X	
Prostacyclin analogues	Enhanced antiplatelet effects	M	X	
Prostaglandins, ophthalmic	Increased or decreased therapeutic effect of prostaglandin	M	X	
Quinolones (e.g Ciprofloxacin, Levofloxacin, Ofloxacin, Norfloxacin)	Increased risk of seizures	M	X	
Rifapentine			X	
Salicylates	Increased risk of bleeding	S		Diclofenac, Indomethacin
Selective serotonin reuptake inhibitors	Increased risk of bleeding	S	X	
Serotonin-norepinephrine reuptake inhibitors	Increased risk of bleeding	S	X	
Sodium phosphates	Enhanced nephrotoxic effects of NSAIDs (e.g. acute phosphate nephropathy)	M	X	
Tacrolimus	May result in acute renal failure	S	X	
Tenofivir	Enhanced nephrotoxic effects (avoid use with multiple NSAIDS or a single NSAID at high dose)	S	X	
Thrombolytic agents	Enhanced anticoagulant effects	M	X	
Tipranavir	Enhanced antiplatelet effeccts	M	X	
Tricyclic Antidepressants	Increased risk of bleeding	M	X	
Vancomycin	Increased vancomycin serum levels	M	X	
Verteporfin	Enhanced photosensitizine effects	M	X	
Vitamin E	Enhanced antiplatelet effects	M	X	
Vitamin K analogs	Enhanced anticoagulant effects	S	X	
Voriconazole	Increased meloxicam serum concentration	M		Naproxen, Meloxicam, Diclofenac

Abbreviations: C, contraindicated; S, Major interaction; M, Moderate interaction, GI, gastrointestinal; CNS, central nervous system

Appendix C. Literature Search Strategies

Two main literature searches were performed, one for pain and oral formulations from 1996 to March 2018, and another search for specific indications, agents, and dates. In this last search, the following criteria for searching was followed:

1. Based on an Oregon report on NSAIDs[142] with systematic literature searches up to May 2010, a search from 2010 to March 2018 was developed for the following concepts:
    - All NSAIDs listed in Table 1, plus terminology for relevant indications (osteoarthritis, rheumatoid arthritis, low back pain, bursitis, tendinitis, and ankylosing spondylitis)
2. Based on an AHRQ comparative effectiveness report on gout management[55] and 1 systematic reviews conducted by the American College of Physicians,[93] with systematic searches up to March 2016, a search from 2016 to January 2018 was developed for the following concepts:
    - Specific agents approved for gout (indomethacin, naproxen, and sulindac) and terminology for the gout indication
3. Based on a Cochrane review[217] on dysmenorrhea with systematic searches up to January 2015, a search from 2015 to January 2018 was developed for:
    - Specific agents approved for dysmenorrhea (diclofenac, ibuprofen, ketoprofen, mefenamic acid, naproxen), plus terminology of dysmenorrhea indication

Tables 1 and 2 include Medline and EMBASE strategies, respectively.

Table 1. Medline Literature Search Strategy for SRs and RCTs

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2014 to Daily Update, **Ovid MEDLINE(R) without Revisions** 1996 to January Week 3 2018
1 Anti-Inflammatory Agents, Non-Steroidal/ (61470)
2 (nsaid or nsaids or 'nonsteroid* antiinflammatory' or 'non steroid* antiinflammatory' or 'nonsteroid* anti-inflammatory').ti,ab,kw,kf,rn. (34455)
3 or/1-2 [NSAIDs] (77820)
4 (NABUMETONE* or aflex or anfer or arthaxan or balmox or brl14777 or bumeton or consolan or diosmal or goflex or labuton or listran or mebutan or nabentac or nabon or nabonet or nabuco or nabucox or nabuflam or nabumeton or naburen or nabuser or nadorex or naflex or nameton or no ton or prodac or relafen or relif or relifen or relifex or reliflex or relisan or reliton or subuton or tanleeg or tontec or unimeton).ti,ab,kw,kf,rn. (510)
5 TOLMETIN/ or (tolmetin or midocil* or reutol* or tolectin* or tolmetin sodium* or tolmetin*).ti,ab,kw,kf,rn. (1441)
6 (MELOXICAM* or acticam? or aflamid? or artrilox? or contacera? or dormelox? or ecax? or emdocam? or exel or flexicam? or flodin? or rafre? or recocam? or revitacam? or rheumocam? or rumonal? or vivlod? or hexaphlogin? or inflacam? or loxibest? or loxicam? or loxicom? or masflex? or mecox? or melcox or mowin? or muvera? or ostelox? or parocin? or melicam? or melocam? or melocox? or melosolut? or melosteral? or melosus? or melovem? or melox? or meloxidolor? or meloxidyl? or meloxin? or meloxivet? or meloxoral? or merapiran? or mesoxicam? or metacam? or mevamox? or mexpharm? or miloxam? or mobec? or mobic? or mobicox? or mopik? or movalis? or movatec? or movicox?).ti,ab,kw,kf,rn. (2262)
7 PIROXICAM/ or (piroxicam? or alganpar? or antiflog? or apopiroxicam? or arpyrox? or artrilas? or artroxicam? or atidem? or baxo or benoxicam? or brexic? or brexodin? or camrox? or capxidin? or cp16171 or dacam or desinflam? or dixonal? or doblexan? or dolonex? or erazon? or exipan? or facicam? or felcicam? or felden? or felrox? or felxicam? or flamic? gel? or flaxin? or flexirox? or floglugen? or flogoben? or flogosan? or fulden? or hotemin? or infeld? or inflamen? or konshien? or

kydoflam? or larapam? or leciva? or macroxam? or movon gel? or movon 20? or moxicam? or novopirocam? or nu pirox? or osteral? or parixam? or piralden? or piram? or pirax? or pirkam? or pirocutan? or piroftal? or pirohexal d? or pirom? or pirox? or piroxan? or piroxedol? or piroxen? or piroxim? or piroxton? or pixicam? or posiden? or priorheum? or proxalyoc? or proxicam? or pyrocaps? or pyroxy? or raxicam? or rexicam? or rheugesic? or riacen? or rosic or rosiden or rosig or roxal? or roxicam? or roxium? or ruvamed? or scanden? or sefden? or sinalgico? or sofden? or sotilen? or stopen? or tropiden? or unicam? or vidapirocam? or xicalom? or xicam? or xycam? or zitumex? or zunden?).ti,ab,kw,kf,rn. (7923)
8 (OXAPROZIN* or benilas or danaprox* or danoprox* or daypro or dayrun or deflam or durapro or duraprox or unaprin or wy21743).ti,ab,kw,kf,rn. (155)
9 DICLOFENAC/ or (diclofenac? or abdiflam or abitren or acuflam or akis or algipatch or algistick or "algopain eze" or algoplast or allvoran or almiral or alonpin or antalcalm or "apo-diclofenac ec" or arcanafenac or arthrifen or artren or artrenac or artrites or assaren or athrofen or "berafen gel" or berifen or betaren or bolabomin or calozan or catanac or catas or cencenag or "clo far" or clofec or clofen or clonac or clonaren or clonodifen or cordralan or curinflam or "ddl plaster" or declophen or decrol or "deflam k" or deflamat or delphinac or denaclof or depain or diceus or dicipan or diclac or diclax or diclo or diclobasan or diclobene or diclod or diclodent or diclodoc or diclodolor or diclofen or diclofenac or dicloflam or diclohexal or dicloin or diclomax or diclomol or diclon or diclopax or "diclophenac sodium" or diclopuren or dicloral or "dicloran gel" or diclorecip or dicloren or dicloreum or "diclosan sr" or diclosian or diclotec or diclowal or dicsnal or difen or difena or difenac or "difenol gel" or "difnal k" or dioxaflex or divoltar or dixol or doflastad or doflex or dolaren or "dolflam retard" or "dolo voltaren" or doloflam or dolotren or doragon or dosanac or duravolten or "dycon sr" or dyloject or ecofenac or econac or effekton or eflagen or epifenac or eslofen or evadol or evinopon or feloran or fenac or fenadium or fenaspec or flameril or flexagen or flogofenac or "flogosin d" or flogozan or "fortfen sr" or freejex or "gp 45840" or grofenac or hizemin or imflac or "inac gel" or indicam or inflamac or inflanac or "isv 205" or isv205 or "jonac gel" or kadiflam or kinespir or "klofen l" or klotaren or kriplex or lesflam or leviogel or lifenac or lofenac or lotirac or magluphen or merflam or modifenac or monoflam or motifene or naboal or "nac gel" or naclof or nacoflar or nadifen or novapirina or "novo difenac" or novolten or ofenac or olfen or "olfen-75 sr" or optanac or orthophen or osteoflam or painstop or panamor or pennsaid or profenac or "relaxyl gel" or remethan or "renvol emulgel" or rewodina or rheufenac or rheumafen or rheumatac or rhewlin or rhumalgan or rolactin or sailib or savismin or sefnac or slofenac or solaraze or sophenoderm or soproxen or spraymik or "sr 318t" or staren or "sting gel" or tabiflex or "tigen plaster" or toraren or traulen or tsudohmin or uniclonax or uniren or valentac or vartelon or veral or voldal or voldic or volero or volfenac or "volna k" or volsaid or volta or "voltadex emulgel" or voltadvance or voltalen or voltalgan or voltaren or "voltaren xr" or voltarene or voltarenspe or voltarol or voltine or voltral or voltrix or "voren emulgel" or votalen or voveran or "voveran emulgel" or vurdon or wergyl or xenid or yuren or zolterol or zorvolex).ti,ab,kw,kf,rn. (13058)
10 ETODOLAC/ or (etodolac? or "ay 24, 236" or "ay 24236" or "ay24,236" or ay24236 or ecridoxan or edolan or entrang or etodin or "etodolic acid" or etonox or etopan or hypen or lodine or lonene or lonine or osteluc or ramodar or "sdx 101" or sdx101 or tedolan or toselac or ultradol or zedolac).ti,ab,kw,kf,rn. (674)
11 FENOPROFEN/ or (fenoprofen* or fenprofen or fepron or feprona or 'lilly 53858' or phenoprofen).ti,ab,kw,kf,rn. (481)
12 FLURBIPROFEN/ or (ansaid or antadys or "apo flurbiprofen" or arflur or "bifen cataplasma" or "bts 18, 322" or "bts 18322" or "bts18, 322" or bts18322 or cebutid or "clinadol forte" or evril or florphen or flubiprofen or flugalin or fluorbiprofen or flupen or "flur di fen" or flurben or flurbiprofene or flurbiprophen or flurofen or flurozin or "fp 70" or fp70 or froben or lapole or "ly 112101" or ly112101 or mirafen or ocufen or ocuflur or strepfen or tolerane or "u 27182" or u27182 or zepolas).ti,ab,kw,kf,rn. (2689)
13 Ibuprofen/ (7891)
14 ibuprofen?.ti,ab,kw,kf,rn. (13104)
15 ("aches n pain" or adex or advil or afebril or aktren or algifor or algofen or algoflex or allipen or am-fam 400 or anadvil or analgyl or anbifen or anco or andran or anflagen or antarene or antiflam or atril 300 or attritin or balkaprofen or bestafen or betaprofen or bifen or bluton or brufanic or brufen or brufort or brugesic or brumed or buburone or bufect or bufohexal or bupogesic or burana or butacortelone or caldolor or cap profen or cenbufen or elixsure or codral period pain or combiflam or contraneural or cuprofen or dc 7034 or dc7034 or dg 7034 or dg7034 or dibufen or diffutab sr 600 or dolan fp or dolgit or dolocyl or dolodolgit or dolofen f or dolomax or dolormin or dolval or donjust or dorival or druisel or easifon or ecoprofen or emflam or emflam 200 or epobron or exidol or expanfen or febratic or febryn or femapirin or fenalgic or fenbid or flamicon or gyno neuralgin or "h loniten" or halprin or haltran or ibu slow or ibu tab or ibuberl or ibudak or ibufen or ibuflam or ibufug or ibugel or ibugesic or ibulgan or ibuloid or ibumetin or ibupen or ibupirac or ibuprin or ibuprocin or ibuprofene or ibuprohm or iburon or ibusal or ibustar or ibusynth or ibutop or "idyl sr" or infibu or ipren or irfen or junifen or kontraneural or lamidon or librofem or lidifen or liptan or lopane or malafene or maxagesic or "mcn r 1451" or medicol or medipren or mediprin or mensoton or midol or motrin or mynosedin or nagifen d or napacetin or neobrufen or nerofen or neutropain or nobfelon or nobgen or norflam t or noritis or norton or novogent or novoprofen or nugin or nuprin or nureflex or nurofen or optifen or opturem or ostarin or ostofen or paduden or panafen or pedea or pediacare fever or perofen or proartinal or profen or profeno or proflex or proris or provon or quadrax or rafen or ranofen or rebugen or renidon or reuvol or rhelafen or roidenin or solufen

lidose or spedifen or spifen or syntofene or tab profen or tabalon or taskine or tatanal or tofen or trendar or umafen or unipro or upfen or uprofen or urem or zofen).ti,ab,kw,kf,rn. (1746)
16 or/13-15 [IBUPROFEN] (14584)
17 Indomethacin/ (27616)
18 (indometacin or algiflam or algometacin or amuno or antalgin dialicels or apo indomethacin or areumatin or argilex or arthrexin or articulen or artracin or artrilona or artrinovo or artrocid or asimet or benocid or betacin or bonidon or boutycin or catlep or chrono indocid or chronoindocid or confortid or docin or dolazal or dolazol or dolcidium or dometin or durametacin or elmego spray or elmetacin or endometacin or flamaret or flexin continus or grindocin or helvecin or idicin or "im 75" or imbrilon or imet or inacid or indacin or indalgin or inderapollon or indicin or indo lemmon or indo phlogont or indo tablinen or indocap or indocid or indocin or indocolir or indocollyre or indogesic or indolag or indolar sr or indolemmon or indomecin or indomed or indomee or indomelan or indomelol or indomet retard or indometacin or indometacine or indomethacin or indomethacine or indomethacinum or indomethegan or indometicina mckesson or indometin or indomexum or indomin or indono or indoptic or indoptol or indorektal or indorem or indos or indosan or indosima or indosmos or indotard or indovis or indoxen or indoy or indren or indrenin or indylon or inflazon or inmetsin or inteban or lauzit or luiflex or lyo indometacin trihydrate or malival or "mcn r 1166" or "mcn r1166" or metacen or methacin or methindol or methindole or methocaps or metindol or mezolin or miometacen or "mk 615" or mk615 or mobilan or novomethacin or osmogit or osmosin or reumacid or reusin or rheumacid or rheumacin sr or salinac or servimeta or sidocin or tannex or tivorbex or "vi gel" or vonum).ti,ab,kw,kf,rn. (42230)
19 or/17-18 [INDOMETHACIN] (42230)
20 Ketoprofen/ (2556)
21 (ketoprofen or alreumat or alrhemun or alrheumat or alrheumin or alrheumun or alrhumat or aneol or anzema or "apo keto" or arcental or begsan or bi profenid or bi rofenid or biprofenid or capisten or cetoprofen or diractin or dolofar or drastirel or efiken or epatec or fastum or fetik or floramil or gabrilen or "gesicpad k" or helenil or ibifen or jomezal or kaltrofen or kebanon or keduril or kefen or kehancer or kenhancer or kenofen gel or keotsan or keplat or keprofen or ketadom or ketin or "keto film" or ketofarm or ketofen or ketoflam or ketolgin or ketomex or ketonal or ketoprofene or ketores or ketorin or ketosolan or ketospray or ketum or knavon or "kpl 202" or liotondol or "lisactiv gola" or mohrus or naxal or novo keto ec or opokan keto or orochet or orucote or orudis or oruvail or oscorel or ovurila or oxoprofene or phardol or profecom or profenid or profika or prontoflex or protofen or "provail cr" or rematof or rhetoflam or "rheuna pap" or rofenid or rofixdol or "rp 19, 583" or "rp 19583" or siduro or spondylon or tiloket or toprec or treosin or yerasel).ti,ab,kw,kf,rn. (3974)
22 or/20-21 [KETOPROFEN] (3974)
23 exp KETOROLAC/ or (ketorolac? or droal or ketocol or "rs 37619" or taradyl or toradol or torate).ti,ab,kw,kf,rn. (2745)
24 MEFENAMIC Acid/ or (MEFENAMIC? or Pontal? or Coslan? or Dysman? or Mefac? or Mefacit? or Nu-Mefenamic? or Nu Mefenamic? or NuMefenamic? or Pinalgesic? or PMS-Mefenamic Acid? or Ponalar? or Ponalgic? or Ponmel? or Ponstan? or Mefic? or Parkemed? or Ponsyl? or Ponstel? or Apo-Mefenamic? or ApoMefenamic? or Contraflam?).ti,ab,kw,kf,rn. (1611)
25 NAPROXEN/ or (naproxen$ or Methoxypropiocin? or Anaprox? or Aleve or Proxen or Synflex? or Naprosin? or Naprosyn?).ti,ab,kw,kf,rn. (6294)
26 SULINDAC/ or (Apo Sulin? or Arthrobid? or Clinoril? or Arthrocine? or Klinoril? or Sulindal? or Chibret? or Kenalin? or MK-231? or "MK 231" or MK231 or Novo-Sundac? or Novo Sundac? or Nu-Sulindac? or "Nu Sulindac" or Aclin? or Copal?).ti,ab,kw,kf,rn. (1472)
27 or/4-12,16,19,22-26 [All agents] (88524)
28 Low back pain/ or ((low$ adj2 back pain?) or backach$ or back ache?).ti,ab,kw,kf. (34008)
29 exp arthritis, rheumatoid/ or (rheum$ adj2 arthrit$).ti,ab,kw,kf. (136089)
30 osteoarthritis/ or osteoarthri$.ti,ab,kw,kf. (68547)
31 spondylitis, ankylosing/ or (ankylos$ adj2 spondyl$).ti,ab,kw,kf. (17179)
32 Bursitis/ or bursiti$.ti,ab,kw,kf. (4291)
33 Tendinopathy/ or (tendinopath$ or tendinit$ or tendonit$).ti,ab,kw,kf. (8231)
34 Dysmenorrhea/ or (dysmenorrhe* or (pain* adj3 (menstrual or period?))).ti,ab,kw,kf. (8145)
35 Migraine Disorders/ or migraine?.ti,ab,kw,kf. (34724)
36 Gout/ or gout?.ti,ab,kw,kf. (14790)
37 pain, postoperative/ or post-op$ pain.ti,ab,kw,kf. (34981)
38 or/28-37 [SELECTED INDICATIONS] (338188)
39 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (1135325)
40 exp animals/ not humans.sh. (4430459)

41	(39 not 40) and English.la. [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] (959693)
42	(animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or feline? or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or simian? or thoroughbred).ti. or veterinar$.ti,ab,kw,kf,hw. (2179792)
43	(cochrane? or systematic review?).jn. (1032)
44	meta-analysis/ (85299)
45	(metaanaly$ or meta-analy$).ti,ab,kw,kf. (124656)
46	((systematic adj3 review?) or (overview adj4 review?)).ti,kw,kf. (86345)
47	((or/43-46) not (or/40,42)) and English.la. [SR Filter -ad hoc] (180664)
48	(((or/3,27) and (or/28-33) and 47) not (or/40,42)) and (2014$ or 2015$ or 2016$ or 2017$ or 2018$).dp,yr,ed. [All & Osteo, Back, Rheum,Burs,Tend,Ankol] (123)
49	((or/9,16,22,24-25) and 34 and 47 and (2015$ or 2016$ or 2017$ or 2018$).ed,yr,dp.) not (or/40,42) [Dysmenorrhea] (2)
50	((or/19,25-26) and 36 and 47 and (2016$ or 2017$ or 2018$).ed,yr,ed.) not (or/40,42) [Gout] (3)
51	((or/9,16) and 35 and 47 and (2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).ed,yr,dp.) not (or/40,42) [Migraine] (23)
52	((or/3,27) and 37 and 47 and (2016$ or 2017$ or 2018$).ed,yr,dp.) not (or/40,42) [Post-op Pain] (34)
53	or/48-52 [SR Results] (179)
54	remove duplicates from 53 (178)
55	(((or/3,27) and (or/28-33) and 41) not 42) and (2014$ or 2015$ or 2016$ or 2017$ or 2018$).dp,yr,ed. [All & Osteo, Back, Rheum,Burs,Tend,Ankol] (379)
56	((or/9,16,22,24-25) and 34 and 41 and (2015$ or 2016$ or 2017$ or 2018$).ed,yr,dp.) not 42 [Dysmenorrhea] (33)
57	((or/19,25-26) and 36 and 41 and (2016$ or 2017$ or 2018$).ed,yr,ed.) not 42 [Gout] (4)
58	((or/9,16) and 35 and 41 and (2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).ed,yr,dp.) not 42 [Migraine] (37)
59	((or/3,27) and 37 and 41 and (2016$ or 2017$ or 2018$).ed,yr,dp.) not 42 [Post-op Pain] (222)
60	or/55-59 [RCT Results] (662)
61	administration, oral/ or administration, buccal/ or administration, sublingual/ (133693)
62	((adminis$ or dose? or dosage?) adj2 (oral$ or mouth or buccal$ or subling$ or sub-ling$)).ti,ab,kw,kf. (127172)
63	(oral$ adj2 drug?).ti,ab,kw,kf. (10401)
64	"by mouth".ti,ab,kw,kf. (3138)
65	((oral adj2 (preparat$ or formul$ or suspension? or powder?)) or pill or pills or tablet? or capsule?).ti,ab,kw,kf. (134960)
66	Capsules/ or Powders/ (23483)
67	(liquid adj2 (preparat$ or formul$)).ti,ab,kw,kf. (2810)
68	(liquid adj2 suspension?).ti,ab,kw,kf. (830)
69	or/61-68 [Oral] (365808)
70	exp Pain/ (354156)
71	pain.ti,ab,kw,kf. (532850)
72	70 or 71 [Pain] (678028)
73	or/9-11,16,19,22-25 [Selected Agents] (76086)
74	69 and 72 and 73 (1613)
75	74 and 47 and (1996$ or 1997$ or 1998$ or 1999$ or 20$).dp,yr. [Pain & Oral & Selected NSAIDs & SR] (79)
76	74 and 47 and (2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).yr,dp. (40)
77	74 and 47 and (2008$ or 2009$ or 201$).yr,dp. (58)
78	(1996$ or 1997$ or 1998$ or 1999$ or 20$).dp,yr. (16632809)
79	(2008$ or 2009$ or 201$).yr,dp. (9867341)
80	(2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).yr,dp. (5696216)
81	and/3,47,69,72,78 [NSAIDS & Oral & Pain & SR & 1996-] (104)
82	and/3,47,69,72,79 [NSAIDS & Oral & Pain & SR & 2008-] (72)
83	and/3,47,69,72,80 [NSAIDS & Oral & Pain & SR & 2013-] (41)

84	from 81 keep 1-104 (104)
85	(or/3,73) and 69 and 72 and 41 [Agent/Class & Pain & Oral RCT] (1294)
86	remove duplicates from 85 (1274)

Table 2. EMBASE Literature Search Strategy for SRs and RCTs

** EMBASE strategies followed same combinations as Medline strategies*	
No. Query	**Results**
#48 **#31 OR #32 OR #33 OR #34 OR #35 OR #36 [ORAL FORMULATION]**	**361969**
#47 **'pill'/mj OR 'lozenge'/de OR 'microcapsule'/mj OR 'oral drops'/de OR 'oral spray'/de OR 'troche'/de**	**4762**
#46 **((oral NEAR/2 (preparat* OR formul* OR suspension* OR powder*)):ti,ab,kw) OR pill:ti,ab,kw OR pills:ti,ab,kw OR tablet*:ti,ab,kw OR capsule*:ti,ab,kw**	**195253**
#45 **'by mouth':ti,ab,kw**	**4149**
#44 **(oral* NEAR/2 drug?):ti,ab,kw**	**8020**
#43 **((adminis* OR dose* OR dosag* OR dosing?) NEAR/2 (oral* OR mouth OR buccal* OR subling* OR 'sub ling*')):ti,ab,kw**	**165887**
#42 **'oral drug administration'/mj**	**1571**
#41 **#35** AND **#40**	**490**
#40 (**'clinical study'**/mj OR **'clinical trial'**/mj OR **'controlled clinical trial'**/mj OR **'controlled study'**/mj OR **'major clinical study'**/mj OR **'randomized controlled trial'**/mj OR **'control group'**/mj OR (((**clinical** OR **randomi*** OR **controlled** OR **multicentre** OR **multicenter** OR **'multi centre'** OR **'multi center'**) NEAR/3 (**study** OR **trial**)):ti,ab) OR **placebo**:ab,ti OR **'head to head'**:ti,ab) NOT (**'conference abstract'**/it OR **'conference paper'**/it) NOT **#39** AND [english]/lim	**593,363**
#39 **#37** OR **#38**	**6,845,115**
#38 **animal***:ti OR **beaver***:ti OR **beef**:ti OR **bovine**:ti OR **breeding**:ti OR **canine**:ti OR **castoris**:ti OR **cat**:ti OR **cattle**:ti OR **cats**:ti OR **chicken***:ti OR **cow**:ti OR **dog**:ti OR **dogs**:ti OR **equine**:ti OR **foal**:ti OR **foals**:ti OR **fish**:ti OR **insect***:ti OR **livestock**:ti OR **mice**:ti OR **mouse**:ti OR **murine**:ti OR **plant**:ti OR **plants**:ti OR **pork**:ti OR **porcine**:ti OR **protozoa***:ti OR **purebred**:ti OR **rabbit***:ti OR **rat**:ti OR **rats**:ti OR **rodent***:ti OR **sheep**:ti OR **thoroughbred**:ti OR **veterinar***:ti,ab,de	**2,531,033**
#37 (**'animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) NOT (**'animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) AND (**'human'**/exp OR **'human cell'**/de))	**6,119,907**
#36	**143**

#19 AND **#35**	
#35 **#30** OR **#31** OR **#32** OR **#33** OR **#34**	**3,051**
#34 (**2016**:py OR **2017**:py OR **2018**:py) AND (**#17** OR **#18**) AND **#29**	**647**
#33 (**2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py) AND (**#1** OR **#5**) AND **#27**	**139**
#32 (**2016**:py OR **2017**:py OR **2018**:py) AND (**#6** OR **#12** OR **#15**) AND **#28**	**18**
#31 (**2015**:py OR **2016**:py OR **2017**:py OR **2018**:py) AND (**#1** OR **#5** OR **#7** OR **#9** OR **#12**) AND **#26**	**42**
#30 (**2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py) AND (**#17** OR **#18**) AND (**#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25**)	**2,230**
#29 **'postoperative pain'**/mj OR (((**postop*** OR **'post-op*'**) NEAR/3 **pain***):ti,ab,kw)	**54,048**
#28 **'gout'**/mj OR gout$:ti,ab,kw	**18,709**
#27 **'migraine'**/exp/mj OR migraine$:ti,ab,kw	**49,916**
#26 **'dysmenorrhea'**/mj OR **dysmenorrhe***:ti,ab,kw OR (**pain***:ti,ab,kw AND **near3**:ti,ab,kw AND (**menstrual**:ti,ab,kw OR period$:ti,ab,kw))	**7,448**
#25 **'tendinitis'**/mj OR **tendinit***:ti,ab,kw	**5,409**
#24 **'bursitis'**/mj OR **bursiti***:ti,ab,kw	**3,981**
#23 **'ankylosing spondylitis'** OR (**ankylos***:ti,ab,kw AND **near2**:ti,ab,kw AND **spondyl***:ti,ab,kw)	**28,701**
#22	**99,995**

'osteoarthritis'/exp/mj OR **osteoarthri***:ti,ab,kw

109,685

#21

'rheumatoid arthritis'/mj OR (**rheum***:ti,ab,kw AND **near2**:ti,ab,kw AND **arthrit***:ti,ab,kw)

23,300

#20

'low back pain'/mj OR ((**low***:ti,ab,kw AND **near2**:ti,ab,kw AND **back**:ti,ab,kw AND pain$:ti,ab,kw OR **backach***:ti,ab,kw OR **back**:ti,ab,kw) AND ache$:ti,ab,kw)

169,592

#19

(**cochrane***:jt OR **'systematic review*'**:jt OR **'meta analysis'**/mj OR **'systematic review'**/mj OR ((**systematic** NEAR/3 **review**):ti) OR **'meta analys*'**:ti,ab,kw OR **metaanalys***:ti,ab,kw OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)) NOT (**'conference abstract'**/it OR **'conference paper'**/it OR (**('animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) NOT (**('animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) AND (**'human'**/exp OR **'human cell'**/de)))) AND [english]/lim

66,248

#18

'nonsteroid antiinflammatory agent'/mj OR **nsaid**:ti,ab,kw,dn,mn,rn,tn OR **nsaids**:ti,ab,kw,dn,mn,rn,tn OR **'nonsteroid* antiinflammatory'**:ti,ab,kw,dn,rn,tn,mn OR **'non steroid* antiinflammatory'**:ti,ab,kw,dn,rn,tn,mn OR **'nonsteroid* anti-inflammatory'**:ti,ab,kw,dn,rn,tn,mn

123,792

#17

#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16**

1,554

#16

'tolmetin'/mj OR **tolmetin**:kw OR **'mcn 2559'**:ti,ab,dn,mn,rn,tn OR **'mcn 2559 21 98'**:ti,ab,dn,mn,rn,tn OR **midocil**:ti,ab,dn,mn,rn,tn OR **reutol**:ti,ab,dn,mn,rn,tn OR **tolectin**:ti,ab,dn,mn,rn,tn OR **'tolmetin sodium'**:ti,ab,dn,mn,rn,tn OR **tolmetine**:ti,ab,dn,mn,rn,tn

3,698

#15

'sulindac'/mj OR **'sulindac'**:ti,ab,dn,mn,rn,tn,kw OR **aclin**:ti,ab,dn,mn,rn,tn OR **aflodac**:ti,ab,dn,mn,rn,tn OR **algocetil**:ti,ab,dn,mn,rn,tn OR **'apo sulin'**:ti,ab,dn,mn,rn,tn OR **arthrocine**:ti,ab,dn,mn,rn,tn OR **artribid**:ti,ab,dn,mn,rn,tn OR **cenlidac**:ti,ab,dn,mn,rn,tn OR **citireuma**:ti,ab,dn,mn,rn,tn OR **clidol**:ti,ab,dn,mn,rn,tn OR **clinoril**:ti,ab,dn,mn,rn,tn OR **dometon**:ti,ab,dn,mn,rn,tn OR **dorindac**:ti,ab,dn,mn,rn,tn OR **imbaral**:ti,ab,dn,mn,rn,tn OR **imbaron**:ti,ab,dn,mn,rn,tn OR **kenalin**:ti,ab,dn,mn,rn,tn OR **klimacobal**:ti,ab,dn,mn,rn,tn OR **lyndak**:ti,ab,dn,mn,rn,tn OR **'mk 231'**:ti,ab,dn,mn,rn,tn OR **mk231**:ti,ab,dn,mn,rn,tn OR **norilafin**:ti,ab,dn,mn,rn,tn OR **'novo sundac'**:ti,ab,dn,mn,rn,tn OR **sudac**:ti,ab,dn,mn,rn,tn OR **sulen**:ti,ab,dn,mn,rn,tn OR **sulic**:ti,ab,dn,mn,rn,tn OR **'sulindaco lisan'**:ti,ab,dn,mn,rn,tn OR **sulindal**:ti,ab,dn,mn,rn,tn OR **sulindec**:ti,ab,dn,mn,rn,tn OR **sulinol**:ti,ab,dn,mn,rn,tn OR **suloril**:ti,ab,dn,mn,rn,tn OR **sulreuma**:ti,ab,dn,mn,rn,tn OR **zirofalen**:ti,ab,dn,mn,rn,tn

6,489

#14

'piroxicam'/mj OR **piroxicam**:ti,ab,dn,mn,rn,tn,kw OR **alganpar**:ti,ab,dn,mn,rn,tn OR **antiflog**:ti,ab,dn,mn,rn,tn OR **'apo piroxicam'**:ti,ab,dn,mn,rn,tn OR **apopiroxicam**:ti,ab,dn,mn,rn,tn OR **arpyrox**:ti,ab,dn,mn,rn,tn OR **artrilase**:ti,ab,dn,mn,rn,tn

OR **artroxicam**:ti,ab,dn,mn,rn,tn OR **atidem**:ti,ab,dn,mn,rn,tn OR **baxo**:ti,ab,dn,mn,rn,tn OR **benoxicam**:ti,ab,dn,mn,rn,tn OR **brexic**:ti,ab,dn,mn,rn,tn OR **brexodin**:ti,ab,dn,mn,rn,tn OR **camrox**:ti,ab,dn,mn,rn,tn OR **'candyl d'**:ti,ab,dn,mn,rn,tn OR **capxidin**:ti,ab,dn,mn,rn,tn OR **'citoken t'**:ti,ab,dn,mn,rn,tn OR **'cp 16, 171'**:ti,ab,dn,mn,rn,tn OR **'cp 16171'**:ti,ab,dn,mn,rn,tn OR **'cp16,171'**:ti,ab,dn,mn,rn,tn OR **cp16171**:ti,ab,dn,mn,rn,tn OR **dacam**:ti,ab,dn,mn,rn,tn OR **desinflam**:ti,ab,dn,mn,rn,tn OR **dixonal**:ti,ab,dn,mn,rn,tn OR **doblexan**:ti,ab,dn,mn,rn,tn OR **dolonex**:ti,ab,dn,mn,rn,tn OR **erazon**:ti,ab,dn,mn,rn,tn OR **exipan**:ti,ab,dn,mn,rn,tn OR **facicam**:ti,ab,dn,mn,rn,tn OR **felcicam**:ti,ab,dn,mn,rn,tn OR **felden***:ti,ab,dn,mn,rn,tn OR **felrox**:ti,ab,dn,mn,rn,tn OR **felxicam**:ti,ab,dn,mn,rn,tn OR **'flamic* gel'**:ti,ab,dn,mn,rn,tn OR **flaxine**:ti,ab,dn,mn,rn,tn OR **flexirox**:ti,ab,dn,mn,rn,tn OR **floglugen**:ti,ab,dn,mn,rn,tn OR **flogobene**:ti,ab,dn,mn,rn,tn OR **flogosan**:ti,ab,dn,mn,rn,tn OR **fulden**:ti,ab,dn,mn,rn,tn OR **hotemin**:ti,ab,dn,mn,rn,tn OR **infeld**:ti,ab,dn,mn,rn,tn OR **inflamene**:ti,ab,dn,mn,rn,tn OR **konshien**:ti,ab,dn,mn,rn,tn OR **kydoflam**:ti,ab,dn,mn,rn,tn OR **larapam**:ti,ab,dn,mn,rn,tn OR **leciva**:ti,ab,dn,mn,rn,tn OR **macroxam**:ti,ab,dn,mn,rn,tn OR **'movon gel'**:ti,ab,dn,mn,rn,tn OR **'movon 20'**:ti,ab,dn,mn,rn,tn OR **moxicam**:ti,ab,dn,mn,rn,tn OR **novopirocam**:ti,ab,dn,mn,rn,tn OR **'nu pirox'**:ti,ab,dn,mn,rn,tn OR **osteral**:ti,ab,dn,mn,rn,tn OR **parixam**:ti,ab,dn,mn,rn,tn OR **piraldene**:ti,ab,dn,mn,rn,tn OR **piram**:ti,ab,dn,mn,rn,tn OR **pirax**:ti,ab,dn,mn,rn,tn OR **pirkam**:ti,ab,dn,mn,rn,tn OR **pirocutan**:ti,ab,dn,mn,rn,tn OR **piroftal**:ti,ab,dn,mn,rn,tn OR **'pirohexal d'**:ti,ab,dn,mn,rn,tn OR **pirom**:ti,ab,dn,mn,rn,tn OR **pirox**:ti,ab,dn,mn,rn,tn OR **piroxan**:ti,ab,dn,mn,rn,tn OR **piroxedol**:ti,ab,dn,mn,rn,tn OR **piroxene**:ti,ab,dn,mn,rn,tn OR **piroxim**:ti,ab,dn,mn,rn,tn OR **piroxton**:ti,ab,dn,mn,rn,tn OR **pixicam**:ti,ab,dn,mn,rn,tn OR **posidene**:ti,ab,dn,mn,rn,tn OR **priorheum**:ti,ab,dn,mn,rn,tn OR **proxalyoc**:ti,ab,dn,mn,rn,tn OR **proxicam**:ti,ab,dn,mn,rn,tn OR **pyrocaps**:ti,ab,dn,mn,rn,tn OR **pyroxy**:ti,ab,dn,mn,rn,tn OR **raxicam**:ti,ab,dn,mn,rn,tn OR **rexicam**:ti,ab,dn,mn,rn,tn OR **rheugesic**:ti,ab,dn,mn,rn,tn OR **riacen**:ti,ab,dn,mn,rn,tn OR **rosic**:ti,ab,dn,mn,rn,tn OR **rosiden**:ti,ab,dn,mn,rn,tn OR **rosig**:ti,ab,dn,mn,rn,tn OR **'rosig d'**:ti,ab,dn,mn,rn,tn OR **roxal**:ti,ab,dn,mn,rn,tn OR **roxicam**:ti,ab,dn,mn,rn,tn OR **roxium**:ti,ab,dn,mn,rn,tn OR **ruvamed**:ti,ab,dn,mn,rn,tn OR **scandene**:ti,ab,dn,mn,rn,tn OR **sefdene**:ti,ab,dn,mn,rn,tn OR **sinalgico**:ti,ab,dn,mn,rn,tn OR **sofden**:ti,ab,dn,mn,rn,tn OR **sotilen**:ti,ab,dn,mn,rn,tn OR **stopen**:ti,ab,dn,mn,rn,tn OR **tropidene**:ti,ab,dn,mn,rn,tn OR **unicam**:ti,ab,dn,mn,rn,tn OR **vidapirocam**:ti,ab,dn,mn,rn,tn OR **xicalom**:ti,ab,dn,mn,rn,tn OR **xicam**:ti,ab,dn,mn,rn,tn OR **xycam**:ti,ab,dn,mn,rn,tn OR **zitumex**:ti,ab,dn,mn,rn,tn OR **zunden**:ti,ab,dn,mn,rn,tn

317

#13

'oxaprozin'/mj OR **oxaprozin**:kw OR **benilas**:ti,ab,dn,mn,rn,tn OR **danaprox**:ti,ab,dn,mn,rn,tn OR **danoprox**:ti,ab,dn,mn,rn,tn OR **daypro**:ti,ab,dn,mn,rn,tn OR **dayrun**:ti,ab,dn,mn,rn,tn OR **deflam**:ti,ab,dn,mn,rn,tn OR **durapro**:ti,ab,dn,mn,rn,tn OR **duraprox**:ti,ab,dn,mn,rn,tn OR **'oxaprozin potassium'**:ti,ab,dn,mn,rn,tn OR **unaprin**:ti,ab,dn,mn,rn,tn OR **'wy 21743'**:ti,ab,dn,mn,rn,tn OR **wy21743**:ti,ab,dn,mn,rn,tn

12,058

#12

'naproxen'/mj OR **naproxen**:kw OR **acusprain**:ti,ab,dn,mn,rn,tn OR **aflamax**:ti,ab,dn,mn,rn,tn OR **aflaxen**:ti,ab,dn,mn,rn,tn OR **agilex**:ti,ab,dn,mn,rn,tn OR **agilxen**:ti,ab,dn,mn,rn,tn OR **aleve**:ti,ab,dn,mn,rn,tn OR **alpoxen**:ti,ab,dn,mn,rn,tn OR **alpron**:ti,ab,dn,mn,rn,tn OR **'anaprox ds'**:ti,ab,dn,mn,rn,tn OR **anexopen**:ti,ab,dn,mn,rn,tn OR **apranax**:ti,ab,dn,mn,rn,tn OR **apraxin**:ti,ab,dn,mn,rn,tn OR **apronax**:ti,ab,dn,mn,rn,tn OR **artagen**:ti,ab,dn,mn,rn,tn OR **artron**:ti,ab,dn,mn,rn,tn OR **artroxen**:ti,ab,dn,mn,rn,tn OR **'axer alfa'**:ti,ab,dn,mn,rn,tn OR **bipronyl**:ti,ab,dn,mn,rn,tn OR **bonyl**:ti,ab,dn,mn,rn,tn OR **congex**:ti,ab,dn,mn,rn,tn OR **crysanal**:ti,ab,dn,mn,rn,tn OR **dafloxen**:ti,ab,dn,mn,rn,tn OR **daprox**:ti,ab,dn,mn,rn,tn OR **deflamox**:ti,ab,dn,mn,rn,tn OR **diferbest**:ti,ab,dn,mn,rn,tn OR **diocodal**:ti,ab,dn,mn,rn,tn OR **dysmenalgit**:ti,ab,dn,mn,rn,tn OR **'ec naprosyn'**:ti,ab,dn,mn,rn,tn OR **equiproxen**:ti,ab,dn,mn,rn,tn OR **femex**:ti,ab,dn,mn,rn,tn OR **flanax**:ti,ab,dn,mn,rn,tn OR **floginax**:ti,ab,dn,mn,rn,tn OR **flonax**:ti,ab,dn,mn,rn,tn OR **floxene**:ti,ab,dn,mn,rn,tn OR **fuxen**:ti,ab,dn,mn,rn,tn OR **gibixen**:ti,ab,dn,mn,rn,tn OR **headlon**:ti,ab,dn,mn,rn,tn OR **iraxen**:ti,ab,dn,mn,rn,tn OR **laraflex**:ti,ab,dn,mn,rn,tn OR **lefaine**:ti,ab,dn,mn,rn,tn OR **leniartil**:ti,ab,dn,mn,rn,tn OR **licorax**:ti,ab,dn,mn,rn,tn OR **'methoxypropiocin sodium'**:ti,ab,dn,mn,rn,tn OR **nafasol**:ti,ab,dn,mn,rn,tn

OR **naixan**:ti,ab,dn,mn,rn,tn OR **napolon**:ti,ab,dn,mn,rn,tn OR **naposin**:ti,ab,dn,mn,rn,tn OR **naprelan**:ti,ab,dn,mn,rn,tn
OR **napren**:ti,ab,dn,mn,rn,tn OR **naprium**:ti,ab,dn,mn,rn,tn OR **naprius**:ti,ab,dn,mn,rn,tn OR **naproflam**:ti,ab,dn,mn,rn,tn
OR **naprogesic**:ti,ab,dn,mn,rn,tn OR **naprong**:ti,ab,dn,mn,rn,tn OR **naprontag**:ti,ab,dn,mn,rn,tn
OR **naprorex**:ti,ab,dn,mn,rn,tn OR **naprosyn**:ti,ab,dn,mn,rn,tn OR **naprosyne**:ti,ab,dn,mn,rn,tn
OR **naprovite**:ti,ab,dn,mn,rn,tn OR **'naproxi 250'**:ti,ab,dn,mn,rn,tn OR **'naproxi 500'**:ti,ab,dn,mn,rn,tn
OR **naproxen**:ti,ab,dn,mn,rn,tn OR **naproxyn**:ti,ab,dn,mn,rn,tn OR **naprozyne**:ti,ab,dn,mn,rn,tn OR **naprux**:ti,ab,dn,mn,rn,tn
OR **napxen**:ti,ab,dn,mn,rn,tn OR **narma**:ti,ab,dn,mn,rn,tn OR **narocin**:ti,ab,dn,mn,rn,tn OR **narox**:ti,ab,dn,mn,rn,tn
OR **naxen**:ti,ab,dn,mn,rn,tn OR **naxopren**:ti,ab,dn,mn,rn,tn OR **naxyn**:ti,ab,dn,mn,rn,tn OR **neprossin**:ti,ab,dn,mn,rn,tn
OR **norswel**:ti,ab,dn,mn,rn,tn OR **'novo naprox'**:ti,ab,dn,mn,rn,tn OR **novonaprox**:ti,ab,dn,mn,rn,tn
OR **novuran**:ti,ab,dn,mn,rn,tn OR **nuprafem**:ti,ab,dn,mn,rn,tn OR **nycopren**:ti,ab,dn,mn,rn,tn OR **pactens**:ti,ab,dn,mn,rn,tn
OR **prexan**:ti,ab,dn,mn,rn,tn OR **priaxen**:ti,ab,dn,mn,rn,tn OR **primeral**:ti,ab,dn,mn,rn,tn OR **prodilor**:ti,ab,dn,mn,rn,tn
OR **pronaxen**:ti,ab,dn,mn,rn,tn OR **proxen**:ti,ab,dn,mn,rn,tn OR **proxidol**:ti,ab,dn,mn,rn,tn OR **rahsen**:ti,ab,dn,mn,rn,tn
OR **'rs 3540'**:ti,ab,dn,mn,rn,tn OR **'rs 3650'**:ti,ab,dn,mn,rn,tn OR **rs3540**:ti,ab,dn,mn,rn,tn OR **rs3650**:ti,ab,dn,mn,rn,tn
OR **sanomed**:ti,ab,dn,mn,rn,tn OR **saritilron**:ti,ab,dn,mn,rn,tn OR **seladin**:ti,ab,dn,mn,rn,tn OR **shiprosyn**:ti,ab,dn,mn,rn,tn
OR **sutolin**:ti,ab,dn,mn,rn,tn OR **synaprosyn**:ti,ab,dn,mn,rn,tn OR **synflex**:ti,ab,dn,mn,rn,tn OR **tohexen**:ti,ab,dn,mn,rn,tn
OR **'u ritis'**:ti,ab,dn,mn,rn,tn OR **uniflam**:ti,ab,dn,mn,rn,tn OR **velsay**:ti,ab,dn,mn,rn,tn OR **veradol**:ti,ab,dn,mn,rn,tn
OR **vinsen**:ti,ab,dn,mn,rn,tn OR **wintrex**:ti,ab,dn,mn,rn,tn OR **xenar**:ti,ab,dn,mn,rn,tn OR **xenobid**:ti,ab,dn,mn,rn,tn

2,005

#11

'nabumetone'/de OR **nabumetone**:ti,ab,dn,mn,rn,tn,kw OR **aflex**:ti,ab,dn,mn,rn,tn OR **anfer**:ti,ab,dn,mn,rn,tn
OR **arthaxan**:ti,ab,dn,mn,rn,tn OR **balmox**:ti,ab,dn,mn,rn,tn OR **'brl 14777'**:ti,ab,dn,mn,rn,tn OR **brl14777**:ti,ab,dn,mn,rn,tn
OR **bumetone**:ti,ab,dn,mn,rn,tn OR **consolan**:ti,ab,dn,mn,rn,tn OR **diosmal**:ti,ab,dn,mn,rn,tn OR **goflex**:ti,ab,dn,mn,rn,tn
OR **labuton**:ti,ab,dn,mn,rn,tn OR **listran**:ti,ab,dn,mn,rn,tn OR **mebutan**:ti,ab,dn,mn,rn,tn OR **nabentac**:ti,ab,dn,mn,rn,tn
OR **nabone**:ti,ab,dn,mn,rn,tn OR **nabonet**:ti,ab,dn,mn,rn,tn OR **nabuco**:ti,ab,dn,mn,rn,tn OR **nabucox**:ti,ab,dn,mn,rn,tn
OR **nabuflam**:ti,ab,dn,mn,rn,tn OR **nabumeton**:ti,ab,dn,mn,rn,tn OR **naburen**:ti,ab,dn,mn,rn,tn
OR **nabuser**:ti,ab,dn,mn,rn,tn OR **nadorex**:ti,ab,dn,mn,rn,tn OR **naflex**:ti,ab,dn,mn,rn,tn OR **nametone**:ti,ab,dn,mn,rn,tn
OR **'no ton'**:ti,ab,dn,mn,rn,tn OR **prodac**:ti,ab,dn,mn,rn,tn OR **relafen**:ti,ab,dn,mn,rn,tn OR **relif**:ti,ab,dn,mn,rn,tn
OR **relifen**:ti,ab,dn,mn,rn,tn OR **relifex**:ti,ab,dn,mn,rn,tn OR **reliflex**:ti,ab,dn,mn,rn,tn OR **relisan**:ti,ab,dn,mn,rn,tn
OR **relitone**:ti,ab,dn,mn,rn,tn OR **subuton**:ti,ab,dn,mn,rn,tn OR **tanleeg**:ti,ab,dn,mn,rn,tn OR **tontec**:ti,ab,dn,mn,rn,tn
OR **unimetone**:ti,ab,dn,mn,rn,tn

3,087

#10

'meloxicam'/mj OR **meloxicam**:ti,ab,dn,mn,rn,tn,kw OR **acticam**:ti,ab,dn,mn,rn,tn OR **aflamid**:ti,ab,dn,mn,rn,tn
OR **artrilox**:ti,ab,dn,mn,rn,tn OR **contacera**:ti,ab,dn,mn,rn,tn OR **dormelox**:ti,ab,dn,mn,rn,tn OR **ecax**:ti,ab,dn,mn,rn,tn
OR **emdocam**:ti,ab,dn,mn,rn,tn OR **exel**:ti,ab,dn,mn,rn,tn OR **flexicam**:ti,ab,dn,mn,rn,tn OR **flodin**:ti,ab,dn,mn,rn,tn
OR **hexaphlogin**:ti,ab,dn,mn,rn,tn OR **inflacam**:ti,ab,dn,mn,rn,tn OR **loxibest**:ti,ab,dn,mn,rn,tn OR **loxicam**:ti,ab,dn,mn,rn,tn
OR **loxicom**:ti,ab,dn,mn,rn,tn OR **masflex**:ti,ab,dn,mn,rn,tn OR **mecox**:ti,ab,dn,mn,rn,tn OR **'mel od'**:ti,ab,dn,mn,rn,tn
OR **melcox**:ti,ab,dn,mn,rn,tn OR **melicam**:ti,ab,dn,mn,rn,tn OR **melocam**:ti,ab,dn,mn,rn,tn OR **melocox**:ti,ab,dn,mn,rn,tn
OR **melosolute**:ti,ab,dn,mn,rn,tn OR **melosteral**:ti,ab,dn,mn,rn,tn OR **melosus**:ti,ab,dn,mn,rn,tn
OR **melovem**:ti,ab,dn,mn,rn,tn OR **melox**:ti,ab,dn,mn,rn,tn OR **meloxidolor**:ti,ab,dn,mn,rn,tn
OR **meloxidyl**:ti,ab,dn,mn,rn,tn OR **meloxin**:ti,ab,dn,mn,rn,tn OR **meloxivet**:ti,ab,dn,mn,rn,tn
OR **meloxoral**:ti,ab,dn,mn,rn,tn OR **merapiran**:ti,ab,dn,mn,rn,tn OR **mesoxicam**:ti,ab,dn,mn,rn,tn
OR **metacam**:ti,ab,dn,mn,rn,tn OR **mevamox**:ti,ab,dn,mn,rn,tn OR **mexpharm**:ti,ab,dn,mn,rn,tn
OR **miloxam**:ti,ab,dn,mn,rn,tn OR **mobec**:ti,ab,dn,mn,rn,tn OR **mobic**:ti,ab,dn,mn,rn,tn OR **mobicox**:ti,ab,dn,mn,rn,tn
OR **mopik**:ti,ab,dn,mn,rn,tn OR **movalis**:ti,ab,dn,mn,rn,tn OR **movatec**:ti,ab,dn,mn,rn,tn OR **'movi cox'**:ti,ab,dn,mn,rn,tn

OR **movicox**:ti,ab,dn,mn,rn,tn OR **mowin**:ti,ab,dn,mn,rn,tn OR **muvera**:ti,ab,dn,mn,rn,tn OR **ostelox**:ti,ab,dn,mn,rn,tn OR **parocin**:ti,ab,dn,mn,rn,tn OR **rafree**:ti,ab,dn,mn,rn,tn OR **recocam**:ti,ab,dn,mn,rn,tn OR **revitacam**:ti,ab,dn,mn,rn,tn OR **rheumocam**:ti,ab,dn,mn,rn,tn OR **rumonal**:ti,ab,dn,mn,rn,tn OR **vivlode**:ti,ab,dn,mn,rn,tn

2,725

#9

'mefenamic acid'/mj OR **'mefenamic acid'**:kw OR **algastel**:ti,ab,dn,mn,rn,tn OR **algifort**:ti,ab,dn,mn,rn,tn OR **alpain**:ti,ab,dn,mn,rn,tn OR **aprostal**:ti,ab,dn,mn,rn,tn OR **atmose**:ti,ab,dn,mn,rn,tn OR **beafemic**:ti,ab,dn,mn,rn,tn OR **benostan**:ti,ab,dn,mn,rn,tn OR **bonabol**:ti,ab,dn,mn,rn,tn OR **'ci 473'**:ti,ab,dn,mn,rn,tn OR **ci473**:ti,ab,dn,mn,rn,tn OR **'cn 35355'**:ti,ab,dn,mn,rn,tn OR **cn35355**:ti,ab,dn,mn,rn,tn OR **coslan**:ti,ab,dn,mn,rn,tn OR **dolfenal**:ti,ab,dn,mn,rn,tn OR **dysman**:ti,ab,dn,mn,rn,tn OR **dyspen**:ti,ab,dn,mn,rn,tn OR **ecopan**:ti,ab,dn,mn,rn,tn OR **eurostan**:ti,ab,dn,mn,rn,tn OR **femen**:ti,ab,dn,mn,rn,tn OR **fenalac**:ti,ab,dn,mn,rn,tn OR **fenamic**:ti,ab,dn,mn,rn,tn OR **fenamin**:ti,ab,dn,mn,rn,tn OR **fenamol**:ti,ab,dn,mn,rn,tn OR **fendol**:ti,ab,dn,mn,rn,tn OR **fengic**:ti,ab,dn,mn,rn,tn OR **gardan**:ti,ab,dn,mn,rn,tn OR **hamitan**:ti,ab,dn,mn,rn,tn OR **hispen**:ti,ab,dn,mn,rn,tn OR **hostan**:ti,ab,dn,mn,rn,tn OR **'inf 3355'**:ti,ab,dn,mn,rn,tn OR **inf3355**:ti,ab,dn,mn,rn,tn OR **johnstal**:ti,ab,dn,mn,rn,tn OR **kemostan**:ti,ab,dn,mn,rn,tn OR **lysalgo**:ti,ab,dn,mn,rn,tn OR **manomic**:ti,ab,dn,mn,rn,tn OR **masafen**:ti,ab,dn,mn,rn,tn OR **'mecid a'**:ti,ab,dn,mn,rn,tn OR **mefac**:ti,ab,dn,mn,rn,tn OR **mefacap**:ti,ab,dn,mn,rn,tn OR **mefacit**:ti,ab,dn,mn,rn,tn OR **mefalqic**:ti,ab,dn,mn,rn,tn OR **'mefanamic acid'**:ti,ab,dn,mn,rn,tn OR **mefast**:ti,ab,dn,mn,rn,tn OR **mefen**:ti,ab,dn,mn,rn,tn OR **mefenamate**:ti,ab,dn,mn,rn,tn OR **mefic**:ti,ab,dn,mn,rn,tn OR **meftal**:ti,ab,dn,mn,rn,tn OR **mephenamate**:ti,ab,dn,mn,rn,tn OR **'mephenamic acid'**:ti,ab,dn,mn,rn,tn OR **'mephenaminic acid'**:ti,ab,dn,mn,rn,tn OR **metmic**:ti,ab,dn,mn,rn,tn OR **namic**:ti,ab,dn,mn,rn,tn OR **napan**:ti,ab,dn,mn,rn,tn OR **parkemed**:ti,ab,dn,mn,rn,tn OR **passton**:ti,ab,dn,mn,rn,tn OR **pefamic**:ti,ab,dn,mn,rn,tn OR **ponalar**:ti,ab,dn,mn,rn,tn OR **poncofen**:ti,ab,dn,mn,rn,tn OR **pondex**:ti,ab,dn,mn,rn,tn OR **pondnadysmen**:ti,ab,dn,mn,rn,tn OR **ponlar**:ti,ab,dn,mn,rn,tn OR **ponser**:ti,ab,dn,mn,rn,tn OR **'ponstan forte'**:ti,ab,dn,mn,rn,tn OR **'ponstan 500'**:ti,ab,dn,mn,rn,tn OR **'ponstel kapseals'**:ti,ab,dn,mn,rn,tn OR **ponstil**:ti,ab,dn,mn,rn,tn OR **ponstyl**:ti,ab,dn,mn,rn,tn OR **pontacid**:ti,ab,dn,mn,rn,tn OR **pontal**:ti,ab,dn,mn,rn,tn OR **pontyl**:ti,ab,dn,mn,rn,tn OR **potarlon**:ti,ab,dn,mn,rn,tn OR **pynamic**:ti,ab,dn,mn,rn,tn OR **ralgec**:ti,ab,dn,mn,rn,tn OR **sefmic**:ti,ab,dn,mn,rn,tn OR **selmac**:ti,ab,dn,mn,rn,tn OR **sicadol**:ti,ab,dn,mn,rn,tn OR **solasic**:ti,ab,dn,mn,rn,tn OR **tanston**:ti,ab,dn,mn,rn,tn OR **tropistan**:ti,ab,dn,mn,rn,tn OR **vandifen**:ti,ab,dn,mn,rn,tn OR **youfenam**:ti,ab,dn,mn,rn,tn OR **zerrmic**:ti,ab,dn,mn,rn,tn

4,433

#8

'ketorolac'/mj OR **ketorolac**:ti,ab,dn,mn,rn,tn,kw OR **droal**:ti,ab,dn,mn,rn,tn OR **ketocol**:ti,ab,dn,mn,rn,tn OR **'rs 37619'**:ti,ab,dn,mn,rn,tn OR **taradyl**:ti,ab,dn,mn,rn,tn OR **toradol**:ti,ab,dn,mn,rn,tn OR **torate**:ti,ab,dn,mn,rn,tn

12,251

#7

'ketoprofen'/de OR **ketoprofen**:kw OR **alreumat**:ti,ab,dn,mn,rn,tn OR **alrhemun**:ti,ab,dn,mn,rn,tn OR **alrheumat**:ti,ab,dn,mn,rn,tn OR **alrheumin**:ti,ab,dn,mn,rn,tn OR **alrheumun**:ti,ab,dn,mn,rn,tn OR **alrhumat**:ti,ab,dn,mn,rn,tn OR **aneol**:ti,ab,dn,mn,rn,tn OR **anzema**:ti,ab,dn,mn,rn,tn OR **'apo keto'**:ti,ab,dn,mn,rn,tn OR **arcental**:ti,ab,dn,mn,rn,tn OR **begsan**:ti,ab,dn,mn,rn,tn OR **'bi profenid'**:ti,ab,dn,mn,rn,tn OR **'bi rofenid'**:ti,ab,dn,mn,rn,tn OR **biprofenid**:ti,ab,dn,mn,rn,tn OR **capisten**:ti,ab,dn,mn,rn,tn OR **cetoprofen**:ti,ab,dn,mn,rn,tn OR **diractin**:ti,ab,dn,mn,rn,tn OR **dolofar**:ti,ab,dn,mn,rn,tn OR **drastirel**:ti,ab,dn,mn,rn,tn OR **efiken**:ti,ab,dn,mn,rn,tn OR **epatec**:ti,ab,dn,mn,rn,tn OR **fastum**:ti,ab,dn,mn,rn,tn OR **fetik**:ti,ab,dn,mn,rn,tn OR **floramil**:ti,ab,dn,mn,rn,tn OR **gabrilen**:ti,ab,dn,mn,rn,tn OR **'gesicpad k'**:ti,ab,dn,mn,rn,tn OR **helenil**:ti,ab,dn,mn,rn,tn OR **ibifen**:ti,ab,dn,mn,rn,tn OR **jomezal**:ti,ab,dn,mn,rn,tn OR **kaltrofen**:ti,ab,dn,mn,rn,tn OR **kebanon**:ti,ab,dn,mn,rn,tn OR **keduril**:ti,ab,dn,mn,rn,tn OR **kefen**:ti,ab,dn,mn,rn,tn OR **kehancer**:ti,ab,dn,mn,rn,tn OR **kenhancer**:ti,ab,dn,mn,rn,tn OR **'kenofen gel'**:ti,ab,dn,mn,rn,tn OR **keotsan**:ti,ab,dn,mn,rn,tn OR **keplat**:ti,ab,dn,mn,rn,tn OR **keprofen**:ti,ab,dn,mn,rn,tn

OR **ketadom**:ti,ab,dn,mn,rn,tn OR **ketin**:ti,ab,dn,mn,rn,tn OR **'keto film'**:ti,ab,dn,mn,rn,tn OR **ketofarm**:ti,ab,dn,mn,rn,tn OR **ketofen**:ti,ab,dn,mn,rn,tn OR **ketoflam**:ti,ab,dn,mn,rn,tn OR **ketolgin**:ti,ab,dn,mn,rn,tn OR **ketomex**:ti,ab,dn,mn,rn,tn OR **ketonal**:ti,ab,dn,mn,rn,tn OR **ketoprofene**:ti,ab,dn,mn,rn,tn OR **ketores**:ti,ab,dn,mn,rn,tn OR **ketorin**:ti,ab,dn,mn,rn,tn OR **ketosolan**:ti,ab,dn,mn,rn,tn OR **ketospray**:ti,ab,dn,mn,rn,tn OR **ketum**:ti,ab,dn,mn,rn,tn OR **knavon**:ti,ab,dn,mn,rn,tn OR **'kpl 202'**:ti,ab,dn,mn,rn,tn OR **liotondol**:ti,ab,dn,mn,rn,tn OR **'lisactiv gola'**:ti,ab,dn,mn,rn,tn OR **mohrus**:ti,ab,dn,mn,rn,tn OR **naxal**:ti,ab,dn,mn,rn,tn OR **'novo keto ec'**:ti,ab,dn,mn,rn,tn OR **'opokan keto'**:ti,ab,dn,mn,rn,tn OR **orochet**:ti,ab,dn,mn,rn,tn OR **orucote**:ti,ab,dn,mn,rn,tn OR **orudis**:ti,ab,dn,mn,rn,tn OR **oruvail**:ti,ab,dn,mn,rn,tn OR **oscorel**:ti,ab,dn,mn,rn,tn OR **ovurila**:ti,ab,dn,mn,rn,tn OR **oxoprofene**:ti,ab,dn,mn,rn,tn OR **phardol**:ti,ab,dn,mn,rn,tn OR **profecom**:ti,ab,dn,mn,rn,tn OR **profenid**:ti,ab,dn,mn,rn,tn OR **profika**:ti,ab,dn,mn,rn,tn OR **prontoflex**:ti,ab,dn,mn,rn,tn OR **protofen**:ti,ab,dn,mn,rn,tn OR **'provail cr'**:ti,ab,dn,mn,rn,tn OR **rematof**:ti,ab,dn,mn,rn,tn OR **rhetoflam**:ti,ab,dn,mn,rn,tn OR **'rheuna pap'**:ti,ab,dn,mn,rn,tn OR **rofenid**:ti,ab,dn,mn,rn,tn OR **rofixdol**:ti,ab,dn,mn,rn,tn OR **'rp 19, 583'**:ti,ab,dn,mn,rn,tn OR **'rp 19583'**:ti,ab,dn,mn,rn,tn OR **siduro**:ti,ab,dn,mn,rn,tn OR **spondylon**:ti,ab,dn,mn,rn,tn OR **tiloket**:ti,ab,dn,mn,rn,tn OR **toprec**:ti,ab,dn,mn,rn,tn OR **treosin**:ti,ab,dn,mn,rn,tn OR **yerasel**:ti,ab,dn,mn,rn,tn

57,543

#6

'indometacin'/mj OR **indometacin**:kw OR **algiflam**:ti,ab,dn,mn,rn,tn OR **algometacin**:ti,ab,dn,mn,rn,tn OR **amuno**:ti,ab,dn,mn,rn,tn OR **'antalgin dialicels'**:ti,ab,dn,mn,rn,tn OR **'apo indomethacin'**:ti,ab,dn,mn,rn,tn OR **areumatin**:ti,ab,dn,mn,rn,tn OR **argilex**:ti,ab,dn,mn,rn,tn OR **arthrexin**:ti,ab,dn,mn,rn,tn OR **articulen**:ti,ab,dn,mn,rn,tn OR **artracin**:ti,ab,dn,mn,rn,tn OR **'artrilona'**:ti,ab,dn,mn,rn,tn OR **artrinovo**:ti,ab,dn,mn,rn,tn OR **artrocid**:ti,ab,dn,mn,rn,tn OR **asimet**:ti,ab,dn,mn,rn,tn OR **benocid**:ti,ab,dn,mn,rn,tn OR **betacin**:ti,ab,dn,mn,rn,tn OR **bonidon**:ti,ab,dn,mn,rn,tn OR **boutycin**:ti,ab,dn,mn,rn,tn OR **catlep**:ti,ab,dn,mn,rn,tn OR **'chrono indocid'**:ti,ab,dn,mn,rn,tn OR **chronoindocid**:ti,ab,dn,mn,rn,tn OR **confortid**:ti,ab,dn,mn,rn,tn OR **docin**:ti,ab,dn,mn,rn,tn OR **dolazal**:ti,ab,dn,mn,rn,tn OR **dolazol**:ti,ab,dn,mn,rn,tn OR **dolcidium**:ti,ab,dn,mn,rn,tn OR **dometin**:ti,ab,dn,mn,rn,tn OR **durametacin**:ti,ab,dn,mn,rn,tn OR **'elmego spray'**:ti,ab,dn,mn,rn,tn OR **elmetacin**:ti,ab,dn,mn,rn,tn OR **endometacin**:ti,ab,dn,mn,rn,tn OR **flamaret**:ti,ab,dn,mn,rn,tn OR **'flexin continus'**:ti,ab,dn,mn,rn,tn OR **grindocin**:ti,ab,dn,mn,rn,tn OR **helvecin**:ti,ab,dn,mn,rn,tn OR **idicin**:ti,ab,dn,mn,rn,tn OR **'im 75'**:ti,ab,dn,mn,rn,tn OR **imbrilon**:ti,ab,dn,mn,rn,tn OR **imet**:ti,ab,dn,mn,rn,tn OR **inacid**:ti,ab,dn,mn,rn,tn OR **indacin**:ti,ab,dn,mn,rn,tn OR **indalgin**:ti,ab,dn,mn,rn,tn OR **inderapollon**:ti,ab,dn,mn,rn,tn OR **indicin**:ti,ab,dn,mn,rn,tn OR **'indo lemmon'**:ti,ab,dn,mn,rn,tn OR **'indo phlogont'**:ti,ab,dn,mn,rn,tn OR **'indo tablinen'**:ti,ab,dn,mn,rn,tn OR **indocap**:ti,ab,dn,mn,rn,tn OR **indocid**:ti,ab,dn,mn,rn,tn OR **indocin**:ti,ab,dn,mn,rn,tn OR **indocolir**:ti,ab,dn,mn,rn,tn OR **indocollyre**:ti,ab,dn,mn,rn,tn OR **indogesic**:ti,ab,dn,mn,rn,tn OR **indolag**:ti,ab,dn,mn,rn,tn OR **'indolar sr'**:ti,ab,dn,mn,rn,tn OR **indolemmon**:ti,ab,dn,mn,rn,tn OR **indomecin**:ti,ab,dn,mn,rn,tn OR **indomed**:ti,ab,dn,mn,rn,tn OR **indomee**:ti,ab,dn,mn,rn,tn OR **indomelan**:ti,ab,dn,mn,rn,tn OR **indomelol**:ti,ab,dn,mn,rn,tn OR **'indomet retard'**:ti,ab,dn,mn,rn,tn OR **indometacin**:ti,ab,dn,mn,rn,tn OR **indometacine**:ti,ab,dn,mn,rn,tn OR **indomethacin**:ti,ab,dn,mn,rn,tn OR **indomethacine**:ti,ab,dn,mn,rn,tn OR **indomethacinum**:ti,ab,dn,mn,rn,tn OR **indomethegan**:ti,ab,dn,mn,rn,tn OR **'indometicina mckesson'**:ti,ab,dn,mn,rn,tn OR **indometin**:ti,ab,dn,mn,rn,tn OR **indomexum**:ti,ab,dn,mn,rn,tn OR **indomin**:ti,ab,dn,mn,rn,tn OR **indono**:ti,ab,dn,mn,rn,tn OR **indoptic**:ti,ab,dn,mn,rn,tn OR **indoptol**:ti,ab,dn,mn,rn,tn OR **indorektal**:ti,ab,dn,mn,rn,tn OR **indorem**:ti,ab,dn,mn,rn,tn OR **indos**:ti,ab,dn,mn,rn,tn OR **indosan**:ti,ab,dn,mn,rn,tn OR **indosima**:ti,ab,dn,mn,rn,tn OR **indosmos**:ti,ab,dn,mn,rn,tn OR **indotard**:ti,ab,dn,mn,rn,tn OR **indovis**:ti,ab,dn,mn,rn,tn OR **indoxen**:ti,ab,dn,mn,rn,tn OR **indoy**:ti,ab,dn,mn,rn,tn OR **indren**:ti,ab,dn,mn,rn,tn OR **indrenin**:ti,ab,dn,mn,rn,tn OR **indylon**:ti,ab,dn,mn,rn,tn OR **inflazon**:ti,ab,dn,mn,rn,tn OR **inmetsin**:ti,ab,dn,mn,rn,tn OR **inteban**:ti,ab,dn,mn,rn,tn OR **lauzit**:ti,ab,dn,mn,rn,tn OR **luiflex**:ti,ab,dn,mn,rn,tn OR **'lyo indometacin trihydrate'**:ti,ab,dn,mn,rn,tn OR **malival**:ti,ab,dn,mn,rn,tn OR **'mcn r 1166'**:ti,ab,dn,mn,rn,tn OR **'mcn r1166'**:ti,ab,dn,mn,rn,tn OR **metacen**:ti,ab,dn,mn,rn,tn OR **methacin**:ti,ab,dn,mn,rn,tn OR **methindol**:ti,ab,dn,mn,rn,tn

OR **methindole**:ti,ab,dn,mn,rn,tn OR **methocaps**:ti,ab,dn,mn,rn,tn OR **metindol**:ti,ab,dn,mn,rn,tn OR **mezolin**:ti,ab,dn,mn,rn,tn OR **miometacen**:ti,ab,dn,mn,rn,tn OR **'mk 615'**:ti,ab,dn,mn,rn,tn OR **mk615**:ti,ab,dn,mn,rn,tn OR **mobilan**:ti,ab,dn,mn,rn,tn OR **novomethacin**:ti,ab,dn,mn,rn,tn OR **osmogit**:ti,ab,dn,mn,rn,tn OR **osmosin**:ti,ab,dn,mn,rn,tn OR **reumacid**:ti,ab,dn,mn,rn,tn OR **reusin**:ti,ab,dn,mn,rn,tn OR **rheumacid**:ti,ab,dn,mn,rn,tn OR **'rheumacin sr'**:ti,ab,dn,mn,rn,tn OR **salinac**:ti,ab,dn,mn,rn,tn OR **servimeta**:ti,ab,dn,mn,rn,tn OR **sidocin**:ti,ab,dn,mn,rn,tn OR **tannex**:ti,ab,dn,mn,rn,tn OR **taye**:ti,ab,dn,mn,rn,tn OR **tivorbex**:ti,ab,dn,mn,rn,tn OR **'vi gel'**:ti,ab,dn,mn,rn,tn OR **vonum**:ti,ab,dn,mn,rn,tn

23,586

#5

'ibuprofen'/mj OR **ibuprofen**:kw OR **'aches n pain'**:ti,ab,dn,mn,rn,tn OR **'act 3'**:ti,ab,dn,mn,rn,tn OR **'adex 200'**:ti,ab,dn,mn,rn,tn OR **'adex liqui-gels'**:ti,ab,dn,mn,rn,tn OR **advil**:ti,ab,dn,mn,rn,tn OR **afebril**:ti,ab,dn,mn,rn,tn OR **aktren**:ti,ab,dn,mn,rn,tn OR **algifor**:ti,ab,dn,mn,rn,tn OR **algofen**:ti,ab,dn,mn,rn,tn OR **algoflex**:ti,ab,dn,mn,rn,tn OR **allipen**:ti,ab,dn,mn,rn,tn OR **'am-fam 400'**:ti,ab,dn,mn,rn,tn OR **anadvil**:ti,ab,dn,mn,rn,tn OR **analgyl**:ti,ab,dn,mn,rn,tn OR **anbifen**:ti,ab,dn,mn,rn,tn OR **anco**:ti,ab,dn,mn,rn,tn OR **andran**:ti,ab,dn,mn,rn,tn OR **anflagen**:ti,ab,dn,mn,rn,tn OR **antarene**:ti,ab,dn,mn,rn,tn OR **antiflam**:ti,ab,dn,mn,rn,tn OR **'apo ibuprofen'**:ti,ab,dn,mn,rn,tn OR **'atril 300'**:ti,ab,dn,mn,rn,tn OR **attritin**:ti,ab,dn,mn,rn,tn OR **balkaprofen**:ti,ab,dn,mn,rn,tn OR **bestafen**:ti,ab,dn,mn,rn,tn OR **betaprofen**:ti,ab,dn,mn,rn,tn OR **bifen**:ti,ab,dn,mn,rn,tn OR **bluton**:ti,ab,dn,mn,rn,tn OR **brufanic**:ti,ab,dn,mn,rn,tn OR **brufen**:ti,ab,dn,mn,rn,tn OR **brufort**:ti,ab,dn,mn,rn,tn OR **brugesic**:ti,ab,dn,mn,rn,tn OR **brumed**:ti,ab,dn,mn,rn,tn OR **buburone**:ti,ab,dn,mn,rn,tn OR **bufect**:ti,ab,dn,mn,rn,tn OR **bufohexal**:ti,ab,dn,mn,rn,tn OR **bupogesic**:ti,ab,dn,mn,rn,tn OR **burana**:ti,ab,dn,mn,rn,tn OR **butacortelone**:ti,ab,dn,mn,rn,tn OR **caldolor**:ti,ab,dn,mn,rn,tn OR **'cap profen'**:ti,ab,dn,mn,rn,tn OR **cenbufen**:ti,ab,dn,mn,rn,tn OR **elixsure**:ti,ab,dn,mn,rn,tn OR **'codral period pain'**:ti,ab,dn,mn,rn,tn OR **combiflam**:ti,ab,dn,mn,rn,tn OR **contraneural**:ti,ab,dn,mn,rn,tn OR **cuprofen**:ti,ab,dn,mn,rn,tn OR **'dc 7034'**:ti,ab,dn,mn,rn,tn OR **dc7034**:ti,ab,dn,mn,rn,tn OR **'dg 7034'**:ti,ab,dn,mn,rn,tn OR **dg7034**:ti,ab,dn,mn,rn,tn OR **dibufen**:ti,ab,dn,mn,rn,tn OR **'diffutab sr 600'**:ti,ab,dn,mn,rn,tn OR **'dolan fp'**:ti,ab,dn,mn,rn,tn OR **dolgit**:ti,ab,dn,mn,rn,tn OR **dolocyl**:ti,ab,dn,mn,rn,tn OR **dolodolgit**:ti,ab,dn,mn,rn,tn OR **'dolofen f'**:ti,ab,dn,mn,rn,tn OR **dolomax**:ti,ab,dn,mn,rn,tn OR **dolormin**:ti,ab,dn,mn,rn,tn OR **dolval**:ti,ab,dn,mn,rn,tn OR **donjust**:ti,ab,dn,mn,rn,tn OR **dorival**:ti,ab,dn,mn,rn,tn OR **druisel**:ti,ab,dn,mn,rn,tn OR **easifon**:ti,ab,dn,mn,rn,tn OR **ecoprofen**:ti,ab,dn,mn,rn,tn OR **emflam**:ti,ab,dn,mn,rn,tn OR **'emflam 200'**:ti,ab,dn,mn,rn,tn OR **epobron**:ti,ab,dn,mn,rn,tn OR **exidol**:ti,ab,dn,mn,rn,tn OR **expanfen**:ti,ab,dn,mn,rn,tn OR **febratic**:ti,ab,dn,mn,rn,tn OR **febryn**:ti,ab,dn,mn,rn,tn OR **femapirin**:ti,ab,dn,mn,rn,tn OR **fenalgic**:ti,ab,dn,mn,rn,tn OR **fenbid**:ti,ab,dn,mn,rn,tn OR **flamicon**:ti,ab,dn,mn,rn,tn OR **'gyno neuralgin'**:ti,ab,dn,mn,rn,tn OR **'h loniten'**:ti,ab,dn,mn,rn,tn OR **halprin**:ti,ab,dn,mn,rn,tn OR **haltran**:ti,ab,dn,mn,rn,tn OR **'ib 100'**:ti,ab,dn,mn,rn,tn OR **ibofen**:ti,ab,dn,mn,rn,tn OR **ibosure**:ti,ab,dn,mn,rn,tn OR **ibu**:ti,ab,dn,mn,rn,tn OR **'ibu 4'**:ti,ab,dn,mn,rn,tn OR **'ibu 6'**:ti,ab,dn,mn,rn,tn OR **'ibu 8'**:ti,ab,dn,mn,rn,tn OR **'ibu slow'**:ti,ab,dn,mn,rn,tn OR **'ibu tab'**:ti,ab,dn,mn,rn,tn OR **ibuberl**:ti,ab,dn,mn,rn,tn OR **ibudak**:ti,ab,dn,mn,rn,tn OR **ibufen**:ti,ab,dn,mn,rn,tn OR **ibuflam**:ti,ab,dn,mn,rn,tn OR **ibufug**:ti,ab,dn,mn,rn,tn OR **ibugel**:ti,ab,dn,mn,rn,tn OR **ibugesic**:ti,ab,dn,mn,rn,tn OR **ibulgan**:ti,ab,dn,mn,rn,tn OR **ibuloid**:ti,ab,dn,mn,rn,tn OR **ibumetin**:ti,ab,dn,mn,rn,tn OR **ibupen**:ti,ab,dn,mn,rn,tn OR **ibupirac**:ti,ab,dn,mn,rn,tn OR **ibuprin**:ti,ab,dn,mn,rn,tn OR **ibuprocin**:ti,ab,dn,mn,rn,tn OR **ibuprofen**:ti,ab,dn,mn,rn,tn OR **ibuprofene**:ti,ab,dn,mn,rn,tn OR **ibuprohm**:ti,ab,dn,mn,rn,tn OR **iburon**:ti,ab,dn,mn,rn,tn OR **ibusal**:ti,ab,dn,mn,rn,tn OR **ibustar**:ti,ab,dn,mn,rn,tn OR **ibusynth**:ti,ab,dn,mn,rn,tn OR **ibutop**:ti,ab,dn,mn,rn,tn OR **'idyl sr'**:ti,ab,dn,mn,rn,tn OR **infibu**:ti,ab,dn,mn,rn,tn OR **ipren**:ti,ab,dn,mn,rn,tn OR **irfen**:ti,ab,dn,mn,rn,tn OR **junifen**:ti,ab,dn,mn,rn,tn OR **kontraneural**:ti,ab,dn,mn,rn,tn OR **lamidon**:ti,ab,dn,mn,rn,tn OR **librofem**:ti,ab,dn,mn,rn,tn OR **lidifen**:ti,ab,dn,mn,rn,tn OR **liptan**:ti,ab,dn,mn,rn,tn OR **lopane**:ti,ab,dn,mn,rn,tn OR **malafene**:ti,ab,dn,mn,rn,tn OR **maxagesic**:ti,ab,dn,mn,rn,tn OR **'mcn r 1451'**:ti,ab,dn,mn,rn,tn OR **medicol**:ti,ab,dn,mn,rn,tn OR **medipren**:ti,ab,dn,mn,rn,tn OR **mediprin**:ti,ab,dn,mn,rn,tn OR **mensoton**:ti,ab,dn,mn,rn,tn OR **'midol'**:ab,dn,mn,rn,tn OR **motrin**:ti,ab,dn,mn,rn,tn OR **mynosedin**:ti,ab,dn,mn,rn,tn OR **'nagifen d'**:ti,ab,dn,mn,rn,tn OR **napacetin**:ti,ab,dn,mn,rn,tn

OR **neobrufen**:ti,ab,dn,mn,rn,tn OR **nerofen**:ti,ab,dn,mn,rn,tn OR **neutropain**:ti,ab,dn,mn,rn,tn
OR **nobfelon**:ti,ab,dn,mn,rn,tn OR **nobgen**:ti,ab,dn,mn,rn,tn OR **'norflam t'**:ti,ab,dn,mn,rn,tn OR **noritis**:ti,ab,dn,mn,rn,tn
OR **norton**:ti,ab,dn,mn,rn,tn OR **novogent**:ti,ab,dn,mn,rn,tn OR **novoprofen**:ti,ab,dn,mn,rn,tn OR **nugin**:ti,ab,dn,mn,rn,tn
OR **nuprin**:ti,ab,dn,mn,rn,tn OR **nureflex**:ti,ab,dn,mn,rn,tn OR **nurofen**:ti,ab,dn,mn,rn,tn OR **optifen**:ti,ab,dn,mn,rn,tn
OR **opturem**:ti,ab,dn,mn,rn,tn OR **ostarin**:ti,ab,dn,mn,rn,tn OR **ostofen**:ti,ab,dn,mn,rn,tn OR **paduden**:ti,ab,dn,mn,rn,tn
OR **panafen**:ti,ab,dn,mn,rn,tn OR **pedea**:ti,ab,dn,mn,rn,tn OR **'pediacare fever'**:ti,ab,dn,mn,rn,tn
OR **perofen**:ti,ab,dn,mn,rn,tn OR **proartinal**:ti,ab,dn,mn,rn,tn OR **profen**:ti,ab,dn,mn,rn,tn OR **profeno**:ti,ab,dn,mn,rn,tn
OR **proflex**:ti,ab,dn,mn,rn,tn OR **proris**:ti,ab,dn,mn,rn,tn OR **provon**:ti,ab,dn,mn,rn,tn OR **quadrax**:ti,ab,dn,mn,rn,tn
OR **rafen**:ti,ab,dn,mn,rn,tn OR **ranofen**:ti,ab,dn,mn,rn,tn OR **rebugen**:ti,ab,dn,mn,rn,tn OR **renidon**:ti,ab,dn,mn,rn,tn
OR **reuvol**:ti,ab,dn,mn,rn,tn OR **rhelafen**:ti,ab,dn,mn,rn,tn OR **roidenin**:ti,ab,dn,mn,rn,tn OR **rufen**:ti,ab,dn,mn,rn,tn
OR **'rupan or schufen or seclodin or sodium ibuprofen or solufen lidose or spedifen or spifen or syntofene'**:ti,ab,dn,mn,rn,tn OR **'tab profen'**:ti,ab,dn,mn,rn,tn OR **tabalon**:ti,ab,dn,mn,rn,tn OR **taskine**:ti,ab,dn,mn,rn,tn
OR **tatanal**:ti,ab,dn,mn,rn,tn OR **tofen**:ti,ab,dn,mn,rn,tn OR **trendar**:ti,ab,dn,mn,rn,tn OR **umafen**:ti,ab,dn,mn,rn,tn
OR **unipro**:ti,ab,dn,mn,rn,tn OR **upfen**:ti,ab,dn,mn,rn,tn OR **uprofen**:ti,ab,dn,mn,rn,tn OR **urem**:ti,ab,dn,mn,rn,tn
OR **zofen**:ti,ab,dn,mn,rn,tn

3,391

#4

'flurbiprofen'/mj OR **flurbiprofen**:kw OR **ansaid**:ti,ab,dn,mn,rn,tn OR **antadys**:ti,ab,dn,mn,rn,tn OR **'apo flurbiprofen'**:ti,ab,dn,mn,rn,tn OR **arflur**:ti,ab,dn,mn,rn,tn OR **'bifen cataplasma'**:ti,ab,dn,mn,rn,tn OR **'bts 18, 322'**:ti,ab,dn,mn,rn,tn OR **'bts 18322'**:ti,ab,dn,mn,rn,tn OR **'bts18, 322'**:ti,ab,dn,mn,rn,tn OR **bts18322**:ti,ab,dn,mn,rn,tn
OR **cebutid**:ti,ab,dn,mn,rn,tn OR **'clinadol forte'**:ti,ab,dn,mn,rn,tn OR **evril**:ti,ab,dn,mn,rn,tn OR **florphen**:ti,ab,dn,mn,rn,tn
OR **flubiprofen**:ti,ab,dn,mn,rn,tn OR **flugalin**:ti,ab,dn,mn,rn,tn OR **fluorbiprofen**:ti,ab,dn,mn,rn,tn
OR **flupen**:ti,ab,dn,mn,rn,tn OR **'flur di fen'**:ti,ab,dn,mn,rn,tn OR **flurben**:ti,ab,dn,mn,rn,tn
OR **flurbiprofene**:ti,ab,dn,mn,rn,tn OR **flurbiprophen**:ti,ab,dn,mn,rn,tn OR **flurofen**:ti,ab,dn,mn,rn,tn
OR **flurozin**:ti,ab,dn,mn,rn,tn OR **'fp 70'**:ti,ab,dn,mn,rn,tn OR **fp70**:ti,ab,dn,mn,rn,tn OR **froben**:ti,ab,dn,mn,rn,tn
OR **lapole**:ti,ab,dn,mn,rn,tn OR **'ly 112101'**:ti,ab,dn,mn,rn,tn OR **ly112101**:ti,ab,dn,mn,rn,tn OR **mirafen**:ti,ab,dn,mn,rn,tn
OR **ocufen**:ti,ab,dn,mn,rn,tn OR **ocuflur**:ti,ab,dn,mn,rn,tn OR **strepfen**:ti,ab,dn,mn,rn,tn OR **tolerane**:ti,ab,dn,mn,rn,tn OR **'u 27182'**:ti,ab,dn,mn,rn,tn OR **u27182**:ti,ab,dn,mn,rn,tn OR **zepolas**:ti,ab,dn,mn,rn,tn

2,633

#3

'fenoprofen'/de OR **fenprofen**:ti,ab,kw,dn,mn,rn,tn OR **fepron**:ti,ab,dn,mn,rn,tn OR **feprona**:ti,ab,dn,mn,rn,tn OR **'lilly 53858'**:ti,ab,dn,mn,rn,tn OR **phenoprofen**:ti,ab,dn,mn,rn,tn

985

#2

'etodolac'/mj OR **etodolac**:kw OR **'ay 24, 236'**:ti,ab,dn,mn,rn,tn OR **'ay 24236'**:ti,ab,dn,mn,rn,tn
OR **'ay24,236'**:ti,ab,dn,mn,rn,tn OR **ay24236**:ti,ab,dn,mn,rn,tn OR **ecridoxan**:ti,ab,dn,mn,rn,tn OR **edolan**:ti,ab,dn,mn,rn,tn
OR **entrang**:ti,ab,dn,mn,rn,tn OR **etodin**:ti,ab,dn,mn,rn,tn OR **'etodolic acid'**:ti,ab,dn,mn,rn,tn OR **etonox**:ti,ab,dn,mn,rn,tn
OR **etopan**:ti,ab,dn,mn,rn,tn OR **hypen**:ti,ab,dn,mn,rn,tn OR **lodine**:ti,ab,dn,mn,rn,tn OR **lonene**:ti,ab,dn,mn,rn,tn
OR **lonine**:ti,ab,dn,mn,rn,tn OR **osteluc**:ti,ab,dn,mn,rn,tn OR **ramodar**:ti,ab,dn,mn,rn,tn OR **'sdx 101'**:ti,ab,dn,mn,rn,tn
OR **sdx101**:ti,ab,dn,mn,rn,tn OR **tedolan**:ti,ab,dn,mn,rn,tn OR **toselac**:ti,ab,dn,mn,rn,tn OR **ultradol**:ti,ab,dn,mn,rn,tn
OR **zedolac**:ti,ab,dn,mn,rn,tn

20,176

#1

'diclofenac'/mj OR **diclofenac**:kw OR **abdiflam**:ti,ab,dn,mn,rn,tn OR **abitren**:ti,ab,dn,mn,rn,tn OR **acuflam**:ti,ab,dn,mn,rn,tn
OR **akis**:ti,ab,dn,mn,rn,tn OR **algipatch**:ti,ab,dn,mn,rn,tn OR **algistick**:ti,ab,dn,mn,rn,tn OR **'algopain eze'**:ti,ab,dn,mn,rn,tn

OR **algoplast**:ti,ab,dn,mn,rn,tn OR **allvoran**:ti,ab,dn,mn,rn,tn OR **almiral**:ti,ab,dn,mn,rn,tn OR **alonpin**:ti,ab,dn,mn,rn,tn
OR **antalcalm**:ti,ab,dn,mn,rn,tn OR **'apo-diclofenac ec'**:ti,ab,dn,mn,rn,tn OR **arcanafenac**:ti,ab,dn,mn,rn,tn
OR **arthrifen**:ti,ab,dn,mn,rn,tn OR **artren**:ti,ab,dn,mn,rn,tn OR **artrenac**:ti,ab,dn,mn,rn,tn OR **artrites**:ti,ab,dn,mn,rn,tn
OR **assaren**:ti,ab,dn,mn,rn,tn OR **athrofen**:ti,ab,dn,mn,rn,tn OR **'berafen gel'**:ti,ab,dn,mn,rn,tn OR **berifen**:ti,ab,dn,mn,rn,tn
OR **betaren**:ti,ab,dn,mn,rn,tn OR **bolabomin**:ti,ab,dn,mn,rn,tn OR **calozan**:ti,ab,dn,mn,rn,tn OR **catanac**:ti,ab,dn,mn,rn,tn
OR **catas**:ti,ab,dn,mn,rn,tn OR **cencenag**:ti,ab,dn,mn,rn,tn OR **'clo far'**:ti,ab,dn,mn,rn,tn OR **clofec**:ti,ab,dn,mn,rn,tn
OR **clofen**:ti,ab,dn,mn,rn,tn OR **clonac**:ti,ab,dn,mn,rn,tn OR **clonaren**:ti,ab,dn,mn,rn,tn OR **clonodifen**:ti,ab,dn,mn,rn,tn
OR **cordralan**:ti,ab,dn,mn,rn,tn OR **curinflam**:ti,ab,dn,mn,rn,tn OR **'ddl plaster'**:ti,ab,dn,mn,rn,tn
OR **declophen**:ti,ab,dn,mn,rn,tn OR **decrol**:ti,ab,dn,mn,rn,tn OR **'deflam k'**:ti,ab,dn,mn,rn,tn OR **deflamat**:ti,ab,dn,mn,rn,tn
OR **delphinac**:ti,ab,dn,mn,rn,tn OR **denaclof**:ti,ab,dn,mn,rn,tn OR **depain**:ti,ab,dn,mn,rn,tn OR **diceus**:ti,ab,dn,mn,rn,tn
OR **dicipan**:ti,ab,dn,mn,rn,tn OR **diclac**:ti,ab,dn,mn,rn,tn OR **diclax**:ti,ab,dn,mn,rn,tn OR **diclo**:ti,ab,dn,mn,rn,tn
OR **diclobasan**:ti,ab,dn,mn,rn,tn OR **diclobene**:ti,ab,dn,mn,rn,tn OR **diclod**:ti,ab,dn,mn,rn,tn OR **diclodent**:ti,ab,dn,mn,rn,tn
OR **diclodoc**:ti,ab,dn,mn,rn,tn OR **diclodolor**:ti,ab,dn,mn,rn,tn OR **diclofen**:ti,ab,dn,mn,rn,tn OR **diclofenac**:ti,ab,dn,mn,rn,tn
OR **dicloflam**:ti,ab,dn,mn,rn,tn OR **diclohexal**:ti,ab,dn,mn,rn,tn OR **dicloin**:ti,ab,dn,mn,rn,tn OR **diclomax**:ti,ab,dn,mn,rn,tn
OR **diclomol**:ti,ab,dn,mn,rn,tn OR **diclon**:ti,ab,dn,mn,rn,tn OR **diclopax**:ti,ab,dn,mn,rn,tn OR **'diclophenac sodium'**:ti,ab,dn,mn,rn,tn OR **diclopuren**:ti,ab,dn,mn,rn,tn OR **dicloral**:ti,ab,dn,mn,rn,tn OR **'dicloran gel'**:ti,ab,dn,mn,rn,tn
OR **diclorecip**:ti,ab,dn,mn,rn,tn OR **dicloren**:ti,ab,dn,mn,rn,tn OR **dicloreum**:ti,ab,dn,mn,rn,tn OR **'diclosan sr'**:ti,ab,dn,mn,rn,tn OR **diclosian**:ti,ab,dn,mn,rn,tn OR **diclotec**:ti,ab,dn,mn,rn,tn OR **diclowal**:ti,ab,dn,mn,rn,tn
OR **dicsnal**:ti,ab,dn,mn,rn,tn OR **difen**:ti,ab,dn,mn,rn,tn OR **difena**:ti,ab,dn,mn,rn,tn OR **difenac**:ti,ab,dn,mn,rn,tn
OR **'difenol gel'**:ti,ab,dn,mn,rn,tn OR **'difnal k'**:ti,ab,dn,mn,rn,tn OR **dioxaflex**:ti,ab,dn,mn,rn,tn
OR **divoltar**:ti,ab,dn,mn,rn,tn OR **dixol**:ti,ab,dn,mn,rn,tn OR **doflastad**:ti,ab,dn,mn,rn,tn OR **doflex**:ti,ab,dn,mn,rn,tn
OR **dolaren**:ti,ab,dn,mn,rn,tn OR **'dolflam retard'**:ti,ab,dn,mn,rn,tn OR **'dolo voltaren'**:ti,ab,dn,mn,rn,tn
OR **doloflam**:ti,ab,dn,mn,rn,tn OR **dolotren**:ti,ab,dn,mn,rn,tn OR **doragon**:ti,ab,dn,mn,rn,tn OR **dosanac**:ti,ab,dn,mn,rn,tn
OR **duravolten**:ti,ab,dn,mn,rn,tn OR **'dycon sr'**:ti,ab,dn,mn,rn,tn OR **dyloject**:ti,ab,dn,mn,rn,tn
OR **ecofenac**:ti,ab,dn,mn,rn,tn OR **econac**:ti,ab,dn,mn,rn,tn OR **effekton**:ti,ab,dn,mn,rn,tn OR **eflagen**:ti,ab,dn,mn,rn,tn
OR **epifenac**:ti,ab,dn,mn,rn,tn OR **eslofen**:ti,ab,dn,mn,rn,tn OR **evadol**:ti,ab,dn,mn,rn,tn OR **evinopon**:ti,ab,dn,mn,rn,tn
OR **feloran**:ti,ab,dn,mn,rn,tn OR **fenac**:ti,ab,dn,mn,rn,tn OR **fenadium**:ti,ab,dn,mn,rn,tn OR **fenaspec**:ti,ab,dn,mn,rn,tn
OR **flameril**:ti,ab,dn,mn,rn,tn OR **flexagen**:ti,ab,dn,mn,rn,tn OR **flogofenac**:ti,ab,dn,mn,rn,tn OR **'flogosin d'**:ti,ab,dn,mn,rn,tn OR **flogozan**:ti,ab,dn,mn,rn,tn OR **'fortfen sr'**:ti,ab,dn,mn,rn,tn OR **freejex**:ti,ab,dn,mn,rn,tn OR **'gp 45840'**:ti,ab,dn,mn,rn,tn OR **grofenac**:ti,ab,dn,mn,rn,tn OR **hizemin**:ti,ab,dn,mn,rn,tn OR **imflac**:ti,ab,dn,mn,rn,tn OR **'inac gel'**:ti,ab,dn,mn,rn,tn OR **indicam**:ti,ab,dn,mn,rn,tn OR **inflamac**:ti,ab,dn,mn,rn,tn OR **inflanac**:ti,ab,dn,mn,rn,tn OR **'isv 205'**:ti,ab,dn,mn,rn,tn OR **isv205**:ti,ab,dn,mn,rn,tn OR **'jonac gel'**:ti,ab,dn,mn,rn,tn OR **kadiflam**:ti,ab,dn,mn,rn,tn
OR **kinespir**:ti,ab,dn,mn,rn,tn OR **'klofen l'**:ti,ab,dn,mn,rn,tn OR **klotaren**:ti,ab,dn,mn,rn,tn OR **kriplex**:ti,ab,dn,mn,rn,tn
OR **lesflam**:ti,ab,dn,mn,rn,tn OR **leviogel**:ti,ab,dn,mn,rn,tn OR **lifenac**:ti,ab,dn,mn,rn,tn OR **lofenac**:ti,ab,dn,mn,rn,tn
OR **lotirac**:ti,ab,dn,mn,rn,tn OR **magluphen**:ti,ab,dn,mn,rn,tn OR **merflam**:ti,ab,dn,mn,rn,tn OR **modifenac**:ti,ab,dn,mn,rn,tn
OR **monoflam**:ti,ab,dn,mn,rn,tn OR **motifene**:ti,ab,dn,mn,rn,tn OR **naboal**:ti,ab,dn,mn,rn,tn OR **'nac gel'**:ti,ab,dn,mn,rn,tn
OR **naclof**:ti,ab,dn,mn,rn,tn OR **nacoflar**:ti,ab,dn,mn,rn,tn OR **nadifen**:ti,ab,dn,mn,rn,tn OR **novapirina**:ti,ab,dn,mn,rn,tn
OR **'novo difenac'**:ti,ab,dn,mn,rn,tn OR **novolten**:ti,ab,dn,mn,rn,tn OR **ofenac**:ti,ab,dn,mn,rn,tn OR **olfen**:ti,ab,dn,mn,rn,tn
OR **'olfen-75 sr'**:ti,ab,dn,mn,rn,tn OR **optanac**:ti,ab,dn,mn,rn,tn OR **orthophen**:ti,ab,dn,mn,rn,tn
OR **osteoflam**:ti,ab,dn,mn,rn,tn OR **painstop**:ti,ab,dn,mn,rn,tn OR **panamor**:ti,ab,dn,mn,rn,tn OR **pennsaid**:ti,ab,dn,mn,rn,tn
OR **profenac**:ti,ab,dn,mn,rn,tn OR **'relaxyl gel'**:ti,ab,dn,mn,rn,tn OR **remethan**:ti,ab,dn,mn,rn,tn OR **'renvol emulgel'**:ti,ab,dn,mn,rn,tn OR **rewodina**:ti,ab,dn,mn,rn,tn OR **rheufenac**:ti,ab,dn,mn,rn,tn OR **rheumafen**:ti,ab,dn,mn,rn,tn
OR **rheumatac**:ti,ab,dn,mn,rn,tn OR **rhewlin**:ti,ab,dn,mn,rn,tn OR **rhumalgan**:ti,ab,dn,mn,rn,tn OR **rolactin**:ti,ab,dn,mn,rn,tn
OR **sailib**:ti,ab,dn,mn,rn,tn OR **savismin**:ti,ab,dn,mn,rn,tn OR **sefnac**:ti,ab,dn,mn,rn,tn OR **slofenac**:ti,ab,dn,mn,rn,tn
OR **solaraze**:ti,ab,dn,mn,rn,tn OR **sophenoderm**:ti,ab,dn,mn,rn,tn OR **soproxen**:ti,ab,dn,mn,rn,tn

OR **spraymik**:ti,ab,dn,mn,rn,tn OR **'sr 318t'**:ti,ab,dn,mn,rn,tn OR **staren**:ti,ab,dn,mn,rn,tn OR **'sting gel'**:ti,ab,dn,mn,rn,tn OR **tabiflex**:ti,ab,dn,mn,rn,tn OR **'tigen plaster'**:ti,ab,dn,mn,rn,tn OR **toraren**:ti,ab,dn,mn,rn,tn OR **traulen**:ti,ab,dn,mn,rn,tn OR **tsudohmin**:ti,ab,dn,mn,rn,tn OR **uniclonax**:ti,ab,dn,mn,rn,tn OR **uniren**:ti,ab,dn,mn,rn,tn OR **valentac**:ti,ab,dn,mn,rn,tn OR **vartelon**:ti,ab,dn,mn,rn,tn OR **veral**:ti,ab,dn,mn,rn,tn OR **voldal**:ti,ab,dn,mn,rn,tn OR **voldic**:ti,ab,dn,mn,rn,tn OR **volero**:ti,ab,dn,mn,rn,tn OR **volfenac**:ti,ab,dn,mn,rn,tn OR **'volna k'**:ti,ab,dn,mn,rn,tn OR **volsaid**:ti,ab,dn,mn,rn,tn OR **volta**:ti,ab,dn,mn,rn,tn OR **'voltadex emulgel'**:ti,ab,dn,mn,rn,tn OR **voltadvance**:ti,ab,dn,mn,rn,tn OR **voltalen**:ti,ab,dn,mn,rn,tn OR **voltalgan**:ti,ab,dn,mn,rn,tn OR **voltaren**:ti,ab,dn,mn,rn,tn OR **'voltaren xr'**:ti,ab,dn,mn,rn,tn OR **voltarene**:ti,ab,dn,mn,rn,tn OR **voltarenspe**:ti,ab,dn,mn,rn,tn OR **voltarol**:ti,ab,dn,mn,rn,tn OR **voltine**:ti,ab,dn,mn,rn,tn OR **voltral**:ti,ab,dn,mn,rn,tn OR **voltrix**:ti,ab,dn,mn,rn,tn OR **'voren emulgel'**:ti,ab,dn,mn,rn,tn OR **votalen**:ti,ab,dn,mn,rn,tn OR **voveran**:ti,ab,dn,mn,rn,tn OR **'voveran emulgel'**:ti,ab,dn,mn,rn,tn OR **vurdon**:ti,ab,dn,mn,rn,tn OR **wergyl**:ti,ab,dn,mn,rn,tn OR **xenid**:ti,ab,dn,mn,rn,tn OR **yuren**:ti,ab,dn,mn,rn,tn OR **zolterol**:ti,ab,dn,mn,rn,tn OR **zorvolex**:ti,ab,dn,mn,rn,tn

Appendix D. Key Findings Reported in Systematic Reviews/Meta-Analyses

Osteoarthritis

- AHRQ Comparative Effectiveness Review (Chou,[111] 2011)
  - Literature searches in Medline up to 2011 and the Cochrane Central Register of Controlled Trials up to 2010
  - Conclusions:
    - ✓ "Partially selective NSAIDs versus nonselective NSAIDs: Meloxicam, etodolac, and nabumetone were associated with no clear differences in efficacy compared to nonselective NSAIDs in patients with osteoarthritis
    - ✓ Nonselective NSAIDs versus nonselective NSAIDs: There were no clear differences in efficacy between various non-aspirin, nonselective NSAIDs"

Table 1. Evidence comparing nsNSAIDs for Osteoarthritis (identified by Chou et al[111])

Study Reference	Intervention	Condition/Efficacy Results[a]
Etodolac versus nsNSAIDs		
Systematic reviews		
Watson, 2005 (**CR**)[b]	• Etodolac (600 mg and 800 mg) vs. diclofenac (100-150 mg), naproxen (1000 mg), piroxicam (20 mg), indomethacin (150 mg), nabumetone (1500 mg) • Nabumetone (1000 mg) vs. diclofenac (100 mg) • Flurbiprofen (150 mg) vs. diclofenac (150 mg) • Naproxen (750 mg) vs. diclofenac (150 mg)	OA of the knee Withdrawal due to lack of efficacy: MA of 9 trials showed no differences between etodolac, diclofenac or naproxen Patient Global Assessment: "Favored etodolac in two trials however results are questionable due to nonequivalent dose comparisons" Pain: "Only 2 of 14 trials assessed pain measurement with adequate power (70%) to detect minimum clinical difference between treatments. Both trials favored etodolac over the comparator drug. Nonequivalent dose comparisons resulted in questionable validity of results."
Towheed,[113] 2006 (**CR**)[b]	- 29 trials evaluated NSAIDs: 6 NSAIDs were included in at least 5 trials. Of these, indomethacin was rated more effective in 5 of its 7 comparisons, but more toxic in 7 of 12 comparisons. - Only 5 of the 29 (17%) NSAID comparisons found statistically significant differences in efficacy - "In head to head trials, no significant difference amongst any of the compared interventions (no RR provided)"	OA of the hip "Author's conclusion: NSAID trials in patients with OA of the hip appear to be weakened by the lack of standardization of case definition of OA, and also by the lack of standardization of outcome assessments. No clear recommendations for the choice of specific NSAID therapy in hip OA can be offered at this time based on this analysis."
van Tulder,[112] 2005 (**CR**)[b]	See updated information in Roelofs,[78] 2008 (low back pain section)	

Chen,[87] 2008 (**HTA report**)	Etodolac versus other nsNSAIDs on OA (18 trials) Summary of efficacy results: • Pain score: Mean difference (95% CI) [2 trials]: 2.06 (–2.09 to 6.22) • Global efficacy: mean difference (95% CI) [2 trials]: -0.00 (–0.22 to 0.22) • Withdrawals due to lack of efficacy: RR (95% CI) [13 trials]: 1.14 (0.72 to 1.78)	OA **No difference**s in pain reduction, global efficacy, and withdrawals due to lack of efficacy
Additional RCTs		
Liang and Hsu,[118] 2003	Etodolac sustained release 400 mg QD (4 weeks) vs. diclofenac 50 mg BID (4 weeks)	OA of the knee **No differences** in pain and functional improvements
Freitas,[116] 1990	Etodolac 300 mg BID vs. piroxicam 20 mg QD, 8 weeks	OA of the knee **No differences** in efficacy
Rogind,[119] 1997	Etodolac 600 mg/day vs. piroxicam 20 mg/day, 8 weeks	OA of the hip and knee **No differences** in efficacy
Chikanza,[115] 1994	Etodolac 300 mg BID vs. naproxen 500 mg BID, 4 weeks	OA of the knee and/or hip **No differences** in pain and stiffness reduction
Jennings,[117] 1997	Etodolac 400 mg BID vs. naproxen 500 mg BID, 5 weeks	OA of the foot **No differences** in efficacy
Meloxicam versus nsNSAIDs		
Systematic reviews		
Chen,[87] 2008 (**HTA report**)	Meloxicam versus other nsNSAIDs on OA (11 trials) Summary of efficacy results: • Pain score (VAS): mean difference (95% CI) [7 trials]: 1.7 (**0.80 to 2.8**) • Global efficacy: mean difference (95% CI) [3 trials]: -0.06 (-0.28 to 0.16) • Withdrawals due to lack of efficacy: RR (95% CI) [8 trials]: 1.40 (**1.14 to 1.72**)	**No differences** in global efficacy. **Significant lower pain reduction and higher withdrawal rates with meloxicam** compared to NSAIDs.
RCTs		
Chang,[218] 2001	Meloxicam 7.5 mg QD vs. piroxicam 20 mg QD, 4 weeks	OA of the knee **No differences** in pain relief (VAS score)
Dequeker,[219] 1998	Meloxicam 7.5 mg QD vs. piroxicam 20 mg QD, 28 days	OA **No differences** in efficacy
Goei,[220] 1997	Meloxicam 15 mg vs. diclofenac 100 mg (slow release), 6 weeks	OA of the knee **No differences** in pain, global efficacy and paracetamol consumption
Hawkey,[221] 1998	Meloxicam 7.5 mg vs. diclofenac 100 mg (slow release)	OA/Pain reduction (VAS scale): **Statistically but not clinically significant differences** in favor of diclofenac. Significantly **more withdrawals due to lack of efficacy with meloxicam**
Hosie,[222] 1996	Meloxicam 7.5 mg QD vs. diclofenac 100 mg (slow release) QD, 6 months	OA of the hip or knee **No differences** in pain, global efficacy, and quality of life

Hosie,[223] 1997	Meloxicam 15 mg QD vs. Piroxicam 20 mg QD, 6 months	OA of the hip or knee **No differences** in pain, joint stiffness, global efficacy, and quality of life
Linden,[224] 1996	Meloxicam 15 mg QD vs. Piroxicam 20 mg, 6 weeks	OA of the hip **No differences** in pain and global efficacy
Valat,[125] 2001	• Meloxicam 7.5 mg/day, 14 days • Diclofenac 100 mg slow release, 14 days	OA of the lumbar spine **No differences** in reducing pain
Yocum,[126] 2000	• Meloxicam 3.75 mg/day, 7.5 mg/day, 15 mg/day, 12 weeks • Diclofenac 50 mg BID, 12 weeks	OA of the hip or knee **No differences** between meloxicam 7.5 or 15 mg/day and diclofenac for all primary and secondary endpoints
Nabumetone versus nsNSAIDs		
Watson 2005 (**CR**)[b]	2 trials were included in the Cochrane review: Nabumetone vs. diclofenac (Alballa,[122] 1992) Nabumetone vs. etodolac (Schnitzer,[123] 1995)	OA of the knee **No differences** in efficacy

Abbreviations: BID, twice daily; CI, confidence interval; CR, Cochrane review; HTA, Health Technology Assessment, nsNSAIDs, non-selective non-steroidal anti-inflammatory drugs; QD, once daily; RCT, randomized controlled trial; RR, relative risk; VAS, visual analog scale

[a] Include statistically significant results. "No differences" means "no statistically significant differences"

[b] Cochrane reviews withdrawn from publication "until an update can be undertaken to reflect the current evidence". No full text is available for withdrawn articles

- Systematic review of RCTs (Pavelka,[124] 2012)
  - Literature search for RCTs published from 1999 to September 2010

Table 2. RCTs comparing nsNSAIDs not reported in Chou, 2011

Study Reference	Intervention	Condition/Efficacy Results[a]
Chopra,[225] 2004	• Diclofenac 100 mg slow release QD, N=68, 4 weeks • Meloxicam 7.5 mg/day, N=65, 4 weeks	OA (knee)/**No differences** in pain relief and WOMAC physical function-(Pain reduction on the VAS was marginally better with diclofenac)
Scott and Palmer, 2000[226]	• Diclofenac 100 mg SR QD, N=199, 6 months • Nabumetone 1500 mg/day, N=200, 6 months	OA (knee or hip)/**Significant differences in VAS pain score** in favor of diclofenac. No differences in other efficacy assessments
Morgan,[227] 2001	• Diclofenac 50 mg BID to TID, N=168, 12 weeks • Nabumetone 1000–2000 mg/day, N=167, 12 weeks	OA (knee or hip, ≥65 years)/**No differences** for all efficacy endpoints
Prabhu, 2008	• Diclofenac 50 mg, N=12, 3 months • Ibuprofen 400 mg, N=12, 3 months • Acetaminophen • Nimesulide • Nimesulide+racemethionine	OA/**No differences** in pain refief (pain intensity reduction: 49.35% for ibuprofen and 50.63% for diclofenac)

Abbreviations: BID, twice daily nsNSAID; non-selective non-steroidal anti-inflammatory drugs; OA, osteoarthritis; QD, once daily; RCT, randomized controlled trials; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; TID, three times daily

[a] Include statistically significant results. "No differences" means "no statistically significant differences"

Rheumatoid Arthritis

Table 3. Evidence comparing nsNSAIDs in Rheumatoid Arthritis

Study Reference	Intervention	Efficacy Results in RA[a]
	Systematic Reviews	
Chen, 2008 (**HTA**) • Searches up to November 2003	Etodolac vs. nsNSAIDs (**5 trials**) • Etodolac 300 mg BID vs. naproxen 500 mg BID, 4 weeks (Taha,[127] 1989 and Taha[129] 1990) • Etodolac 600 mg/day vs. indomethacin 100 mg/day (Delcambre,[128] 1990) • Etodolac 200 mg or 300 mg BID vs. piroxicam 20 mg QD, 12 weeks (Lightfoot,[130] 1997) • Etodolac 150-500 mg BID vs. ibuprofen 600 QID, 3 years (Neustadt,[131] 1997)	**No differences** for etodolac vs. nsNSAID
	Meloxicam vs. nsNSAIDs (**3 trials**) • Meloxicam 7.5 mg QD vs. naproxen 750 mg (Wojtulewski,[121] 1996) • Meloxicam 7.6 mg/day, 15 mg/day, 22.5 mg/day vs. diclofenac 150 mg/day (Furst,[132] 2002) • Meloxicam 15 mg/day vs. nabumetone 1000 mg/day (Xu,[133] 2002)	**No differences** in pain reduction and global efficacy for meloxicam vs. nsNSAID, but **withdrawal rates due to lack of efficacy were significantly higher with meloxicam** Withdrawal rates: RR [95% CI] 1.61, 1.21 to 2.13) (3 trials)
Richy, 2007 (**SR/MA**) • Literature searches from January 1975 to January 2006	14 trials: • F vs. I (Fixed effects model) • F vs. Ibu (Fixed effects model) • F vs. N (Random model)	Global symptomatic efficacy • F superior to I • F vs. Ibu: no significant differences • F superior to N Efficacy on articular pain • F vs. I: no differences • F superior to Ibu • F vs. N: no differences Efficacy on articular swelling • F superior to I • F vs. Ibu: no differences • F vs. N: no differences Efficacy on articular stiffness • F superior to I • F superior to Ibu • F superior to N
	RCTs	
Shi,[135] 2004 (**RCT**)	Meloxicam vs. diclofenac vs. nabumetone vs. celecoxib	No differences between groups

Abbreviations: BID, twice daily; F, flurbiprofen; HTA; health technology assessment; I, indomethacin; Ibu, ibuprofen; N, naproxen; QD, once daily; RA, rheumatoid arthritis; SR/MA, systematic reviews/meta-analyses
[a] Include statistically significant results. "No differences" means "no statistically significant differences"

Ankylosing Spondylitis

- Cochrane Review (Kroon,[52] 2016)
  - Literature searches up to June 2014
  - Conclusions: "High-quality evidence indicates that both traditional and COX-2 NSAID are efficacious for treating axSpA, and harms are not different from placebo in the short term. Various NSAID are equally effective."

Table 4. RCTs comparing nsNSAIDs for Ankylosing Spondylitis (identified by Kroon,[52] 2016)

Study Reference	Intervention	Efficacy Results[a]
Calabro 1986, Khan 1985, Khan 1987	Diclofenac vs. indomethacin	No differences in efficay
Caldwell 1986	Oxaprozin vs. indomethacin	
Calin 1979	Sulindac vs. indomethacin	
Good 1977, Lomen 1986, Mena 1977	Flurbiprofen vs. indomethacin	
Myklebust 1986	Naproxen vs. piroxicam	
Nahir 1980	Diclofenac vs. sulindac	
Palferman 1991	Nabumetome vs. indomethacin	
Santo 1988	Oxaprozin vs. diclofenac	
Tannenbaum 1984	Piroxicam vs. indomethacin	

[a] Include statistically significant results. "No differences" means "no statistically significant differences"

Acute Gout

- AHRQ Comparative Effectiveness Report (Shekelle,[55] 2016)
  - Literature searches from January 2010 to April 2015
  - Conclusions:
    - ✓ "High-strength evidence supports the efficacy of NSAIDs to reduce pain in acute gout
    - ✓ Moderate-strength evidence supports a lack of difference among NSAIDs in effectiveness"

Table 5. Findings from RCTs comparing nsNSAIDs for acute gout (identified by Shekelle,[55] 2016)

Study Reference	Intervention	Condition/Efficacy Results[a]
Lomen,[228] 1986	Flubiprofen 400 mg QD, then 200 mg QD vs. indomethacin 200 mg QD, then 100 mg QD N=29	Monoarticular gouty arthritis **No differences** in pain, swelling, erythema reduction
Altman,[229] 1988	Ketoprofen 100 mg TID vs. indomethacin 50 mg TID, 7 days, N=59	Acute gouty arthritis **No differences** in pain relief
Lederman,[230] 1990	Etodolac 300 mg BID vs. naproxen 500 mg TID, 7 days, N= 60	Acute gout **No differences** in pain relief
Maccagno,[231] 1991	Etodolac 300 mg BID vs. naproxen 500 mg BID, 7 days, N= 61	Acute gouty arthritis **No differences** at day 7. Etodolac was significantly better than naproxen in overall improvement and joint swelling at day 2
Eberl,[232] 1983	Meclofenamate 800mg/day, then 100mg/TID vs. indomethacin 200mg/day, then 50mg/TID	Acute gout **No differences** in improving pain, inflammation, and function

Abbreviations: nsNSAIDs, non-selective non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial;
[a] Include statistically significant results. "No differences" means "no statistically significant differences"

Arthritis (OA, RA, AS), Low Back Pain, Soft Tissue Pain

- Oregon Drug Class Review (Peterson, 2010l[142])
  - Literature searches up to May-June 2010
  - Conclusions:
    - ✓ "Partially selective NSAIDs compared with nonselective NSAIDs: Partially selective NSAIDs (meloxicam, nabumetone, and etodolac) were associated with similar pain reduction effects relative to nonselective NSAIDs in short-term randomized controlled trials
    - ✓ Comparisons among nonselective NSAIDs: Good-quality Cochrane reviews and more recent trials found no clear differences among nonselective NSAIDs in efficacy for treating osteoarthritis of the knee or hip or for low-back pain"

Table 6. Evidence of partially selective NSAIDs versus nsNSAIDs (identified by Peterson et al[142])

Study Type (# of studies)	References	Intervention	Condition/Efficacy Results[a]
Double-blind RCTs (9)[120,121,125,219-224]	9 RCTs[120,121,125,132,219-224]: Dequeker 1998 Furst 2001 Goei 1997 Hawkey 1998 Hosie 1996 Hosie 1997 Linden 1996 Valat 2001 Wojtulewski 1996	Meloxicam 7.5 mg, 15 mg, and 25 mg vs. nsNSAIDs (piroxicam, diclofenac, slow release diclofenac, naproxen)	OA (7 RCTs)[125,219-224]/RA (2 RCTs)[120,121] **No differences** in efficacy (pain, function and/or global efficacy)[b]
	2 RCTs[121,221]: Hawkey 1998 Wojtulewski 1996	Meloxicam 7.5 mg, 15 mg, and 25 mg vs. nsNSAIDs (diclofenac and naproxen)	OA (1)/RA (1) **Less withdrawal rates** due to lack of efficacy with nsNSAIDs vs. meloxicam
Review of 2 RCTs[233]	Jenner 1987[233]	Nabumetone vs. ibuprofen or naproxen	Skin and soft tissue injury **No differences** in pain reduction
Cochrane Review (1)[114] and short-term RCTs (1)[119]	Watson 2006[114 c] Rogind 1997[119]	Etodolac vs. nsNSAIDs	OA of knee and/or hip **No differences** in withdrawals due to lack of efficacy and pain improvements
Small RCT (1)[118]	Liang 2003[118]	Etodolac (sustained-release) vs. diclofenac	OA of the knee **No differences** in pain reduction

Abbreviations: nsNSAID, nonselective non-steroidal anti-inflammatory drugs; RCT, randomized controlled trials; OA, osteoarthritis

[a] Include statistically significant results. "No differences" means "no statistically significant differences"

[b] Not all RCTs evaluated all 3 efficacy parameters (pain, physical function, and/or global efficacy)

[c] Cochrane reviews withdrawn from publication "until an update can be undertaken to reflect the current evidence". No full text is available for withdrawn articles

Table 7. Evidence of nsNSAIDs versus nsNSAIDs (identified by Peterson et al[142])

Study Type (# of studies)	References	Intervention	Conditions/Efficacy Results[a]
Cochrane Reviews (3)[78,113,114]	Watson 2006[b] Towheed 2007[b] Roelofs 2008	nsNSAIDs vs. nsNSAIDs	OA of knee, hip, or LBP **No differences**
3 fair-quality RCTs[234-236]	Herrera 2007 Prabhu 2008 Wagenitz 2007	nsNSAIDs vs. nsNSAIDs	OA **No differences**

Abbreviation: LBP, low back pain; NSAID, non-steroidal anti-inflammatory drugs; nsNSAIDS, nonselective non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomized controlled trials

[a] Include statistically significant results. "No differences" means "no statistically significant differences"

[b] Cochrane reviews withdrawn from publication "until an update can be undertaken to reflect the current evidence". No full text is available for withdrawn articles

Low Back Pain

- Systematic review to support the American College of Physicians clinical practice guideline (Chou,[75] 2017)
  - Literature searches from January 2008 to November 2016
  - Conclusions: "There were no clear differences in pain relief between different NSAIDs for acute or chronic low back pain (21 and 6 trials, respectively)"

Table 8. Evidence of nsNSAIDs versus nsNSAIDs for low back pain (identified by Chou 2017)

Study Reference	Intervention	Efficacy Results[a]
Systematic Reviews		
Roelofs,[78] 2008 (**CR**)	NSAIDs vs. NSAIDs (33 RCTs) NsNSAIDs vs. nsNSAIDs (8 trials, see list below)	Results: "there is strong evidence that various types of NSAIDs, including COX-2 NSAIDs, are equally effective for acute low-back pain" Conclusions: "there does not seem to be a specific type of NSAID which is clearly more effective than others". Limitations: studies with small number of patients
RCTs included in Roelofs 2008		
Aoki 1983[237] 2-week, double-blind, parallel, multicenter study	• Piroxicam 20 mg capsules QD (N=116) vs. • Indomethacin 25 mg capsules TID (N=114)	"Numerical **superiority** was evident **for piroxicam** in most efficacy parameters" in the treatment of lumbar diseases." However, duration of back pain is unclear

Colberg 1996[143] RCT, parallel and open multicenter study	• Meloxicam IV 1.5 ml (= 15 mg) 1 injection day 1 plus 15 mg tablets once a day, 7 days (N=92) vs. • Diclofenac IM 3 ml (= 75 mg) 1 injection day 1 plus 100 mg tablets once a day, 7 days (N=91)	During oral therapy: meloxicam showed the **same activity of effective pain reduction** and improvement of daily activities as diclofenac for each time point. Global efficacy (primary efficacy endpoint) at the end of the trial was **significantly in favour of meloxicam** in patients with acute lumbago
Dreiser 2001[144] RCT; double-blind; double-dummy; multicentre	• Meloxicam 7.5 mg/ day, 14 days (N=164) • Meloxicam 15 mg/ day, 14 days (N=163) • Diclofenac 150 mg, daily, 14 days (N=162).	**No differences.** Meloxicam is as effective as diclofenac, in acute sciatica
Dreiser 2003[238] RCT double-blind, double-dummy	• Diclofenac-K 12.5 mg, initial dose 2 tablets, 7 days flexible dose 4 to 6 tablets/ day (N=124) • Ibuprofen 200 mg, initial dose 2 tablets, days flexible dose 4 to 6 tablets/ day (N=122) • Placebo	Diclofenac-K is effective and at least comparable to ibuprofen 200 mg in acute LBP
Matsumo 1991[239] RCT, double-blind	• Ketoprofen 25 mg capsules, 150 mg per day, duration not given (N=77) • Diclofenac sodium 25 mg capsules, 75 mg per day, duration not given (N=78)	**No differences** in patients with lumbago
Pena 1990[240]	• Etodolac 200 mg TID, 5 days • Diclofenac 50 mg TID, 5 days	**No differences** in acute LBP
Siegmeth 1978[241] Controlled, single-blind parallel group study	• Ibuprofen, 1200 mg per day, 14 days (N=15) • Diclofenac, 75 mg per day, 14 days (N=15).	Patients with spondylosis: "Statistically significant improvement was shown by patients receiving ibuprofen for the degree of pain relief at rest and improvement was also shown for the degree of pain at rest and during exercise, for pain relief during exercise and for spinal flexion. Patients who received diclofenac showed statistically significant improvement for forward flexion, together with improvement for the degree of pain on exercise."
Videman 1984[147] Double-blind comparative trial	• Piroxicam 20 mg QD, 6 weeks (N=14) • Indomethacin 25 mg capsules TID, 6 weeks (N=14)	No differences in **chronic** LBP

Abbreviations: CR, Cochrane review; IM, intramuscular; IV, intravenous; LBP, low back pain; QD, once daily; TID, three times daily

[a] Include statistically significant results. "No differences" means "no statistically significant differences

Dysmenorrhea

- Cochrane Review (Marjoribanks,[96] 2015)
  - Literature searches through January 2015
  - Conclusions: "there was little evidence of the superiority of any individual NSAID for either pain relief or safety. However, the available evidence had little power to detect such differences, as most individual comparisons were based on very few small trials."

Table 9. Efficacy findings for RCTs comparing nsNSAIDs for dysmenorrhea (identified by Marjoribanks et al)

Study Reference	Intervention	Efficacy Results[a]
Marchini,[242] 1995	Diclofenac vs. ibuprofen	No differences in pain relief (binary outcome)
Chantler,[243] 2008	**Diclofenac vs.meloxicam**	**Diclofenac better than meloxican in pain relief (VAS, mean differences change scores)**
Dawood,[244] 1999	Ibuprofen vs. piroxicam	No differences in pain relief (binary outcome)
De Mello,[245] 2004	Mefenamic acid vs. meloxicam	No differences in pain relief (binary outcome)
Kintigh,[246] 1995	Naproxen vs. diclofenac	No differences in pain relief (continuous data: mean difference final scores [1-5 scale])
Milsom,[247] 1985 Ingemanson,[248] 1984	Naproxen vs. ibuprofen or diclofenac	No differences in pain relief (mean difference final scores [1-5 scale])
Akerlund,[249] 1989	**Naproxen vs. ketoprofen**	**Naproxen better than ketoprofen in pain relief (VAS, mean differences change scores)**
Mehlisch,[250] 1990 Wilhelmsson,[251] 1985	Naproxen vs. ketoprofen or piroxicam	No differences in pain relief (binary outcome)
Andersch,[252] 1989	Naproxen vs. flurbiprofen	No differences in pain intensity

Abbreviations: AE, adverse events; GI, gastrointestinal; VAS, visual analog scale
[a] Include statistically significant results. "No differences" means "no statistically significant differences"

General Pain

- Systematic review and meta-analysis (Sarzi-Puttini,[157] 2013). Literature searches through June 2011

Table 10. RCTs of ketoprofen versus ibuprofen or diclofenac for pain (identified by Sarzi-Puttini, 2013)

Study Reference	Condition
Ketoprofen vs. ibuprofen	
Calin 1977	RA
Giaccai 1978	OA
Huskisson 1976	RA
Mehlisch 1988	DYS
Mills 1973	RA
Montrone 1979	RA
Robbins 1990	Traumatic injury
Saxena 1978	RA/OA
Ketoprofen vs. diclofenac	
Matsumo 1981	LBP
Boey 1988	RA
Hynninen 2000	PO Pain
Cherubino 1997	LBP
Tai 1992	PO Pain

Abbreviations: DYS, dysmenorrhea, LBP, low back pain, OA, osteoarthritis, PO, postoperative, RA, rheumatoid arthritis

Appendix E. Excluded References

Table 1. List of Excluded References

Wrong study design (12)
1. Collins SL, Moore RA, McQuay HJ, et al. Single dose oral ibuprofen and diclofenac for postoperative pain. Cochrane database of systematic reviews.(2000)(2):CD001548. 2. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis.[Republished from Lancet. 2016 May 21;387(10033):2093-2105; PMID: 26997557]. Lancet. 2017;390(10090):e21-e33. 3. Kaplan V, Eroglu CN. Comparison of the Effects of Daily Single-Dose Use of Flurbiprofen, Diclofenac Sodium, and Tenoxicam on Postoperative Pain, Swelling, and Trismus: A Randomized Double-Blind Study. J Oral Maxillofac Surg. 2016;74(10):1946.e1941-1946. 4. McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. Health technology assessment (Winchester, England). 1998;2(12):1-236. 5. Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L. Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews. The Cochrane database of systematic reviews. 2015(11):CD010794. 6. Wong JJ, Cote P, Sutton DA, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur J Pain. 2017;21(2):201-216.
Single-dose studies 7. Ahlstrom U, Bakshi R, Nilsson P, Wahlander L. The analgesic efficacy of diclofenac dispersible and ibuprofen in postoperative pain after dental extraction. Eur J Clin Pharmacol. 1993;44(6):587-588. 8. Bakshi R, Frenkel G, Dietlein G, Meurer-Witt B, Schneider B, Sinterhauf U. A placebo-controlled comparative evaluation of diclofenac dispersible versus ibuprofen in postoperative pain after third molar surgery. J Clin Pharmacol. 1994;34(3):225-230. 9. Collins SL, Moore RA, McQuay HJ, et al. Single dose oral ibuprofen and diclofenac for postoperative pain. Cochrane database of systematic reviews.(2000)(2):CD001548. 10. Gazal G, Al-Samadani KH. Comparison of paracetamol, ibuprofen, and diclofenac potassium for pain relief following dental extractions and deep cavity preparations. Saudi Med J. 2017;38(3):284-291. 11. Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. Pharmacotherapy. 1990;10(6 (Pt 2)):94S-105S. 12. Seymour RA, Hawkesford JE, Weldon M, Brewster D. An evaluation of different ibuprofen preparations in the control of postoperative pain after third molar surgery. Br J Clin Pharmacol. 1991;31(1):83-87.
Wrong comparator (12)
13. Billy CA, Lim RT, Ruospo M, Palmer SC, Strippoli GFM. Corticosteroid or Nonsteroidal Antiinflammatory Drugs for the Treatment of Acute Gout: A Systematic Review of Randomized Controlled Trials. The Journal of rheumatology. 2017:01.
14. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain physician. 2013;16(6):E685-704.
15. Myers J, Wielage RC, Han B, et al. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. BMC Musculoskelet Disord. 2014;15:76.
16. Mkontwana N, Novikova N. Oral analgesia for relieving post-caesarean pain. The Cochrane database of systematic reviews. 2015(3):CD010450.
17. Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. The Cochrane database of systematic reviews. 2013(5):CD003686.
18. Secrist ES, Freedman KB, Ciccotti MG, Mazur DW, Hammoud S. Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials. Am J Sports Med. 2016;44(9):2435-2447.
19. Shirvani A, Shamszadeh S, Eghbal MJ, Asgary S. The efficacy of non-narcotic analgesics on post-operative endodontic pain: A systematic review and meta-analysis: The efficacy of non-steroidal anti-inflammatory drugs and/or paracetamol on post-operative endodontic pain. J Oral Rehabil. 2017;44(9):709-721.

20. Solomon DH, Husni ME, Wolski KE, et al. Differences in Safety of Non-Steroidal Anti-Inflammatory Drugs in Patients with Osteoarthritis and Rheumatoid Arthritis: A Randomized Clinical Trial. Arthritis & rheumatology (Hoboken, NJ). 2017:20.
21. Torabinejad M, Dorn SO, Eleazer PD, et al. Effectiveness of various medications on postoperative pain following root canal obturation. J Endod. 1994;20(9):427-431.
22. Van den berg R, Baraliakos X, Braun J, Van der heijde D. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: A systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Rheumatology (United Kingdom). 2012;51(8):1388-1396.
23. Wang J, Liu GT, Mayo HG, Joshi GP. Pain Management for Elective Foot and Ankle Surgery: A Systematic Review of Randomized Controlled Trials. J Foot Ankle Surg. 2015;54(4):625-635.
24. Zhu A, Benzon HA, Anderson TA. Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. Anesth Analg. 2017;125(5):1569-1587.
Wrong outcomes (3)
25. Olson NZ, Otero AM, Marrero I, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharmacol. 2001;41(11):1238-1247.
26. Schleier P, Prochnau A, Schmidt-Westhausen AM, et al. Ibuprofen sodium dihydrate, an ibuprofen formulation with improved absorption characteristics, provides faster and greater pain relief than ibuprofen acid. International journal of clinical pharmacology and therapeutics. 2007;45(2):89-97.
27. Lawati HA, Jamali F. Onset of Action and Efficacy of Ibuprofen Liquigel as Compared to Solid Tablets: A Systematic Review and Meta-Analysis. J Pharm Pharm Sci. 2016;19(3):301-311.
Wrong intervention (2)
28. Boric K, Dosenovic S, Jelicic Kadic A, et al. Interventions for postoperative pain in children: An overview of systematic reviews. Paediatr Anaesth. 2017;27(9):893-904. 29. Forrest JB, Camu F, Greer IA, et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. Br J Anaesth. 2002;88(2):227-233.
Other (5)
<u>Newer more robust SRs (3)</u> 30. Rasmussen-Barr E, Held U, Grooten WJ, et al. Non-steroidal anti-inflammatory drugs for sciatica. The Cochrane database of systematic reviews. 2016;10:CD012382. 31. 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). The Cochrane database of systematic reviews. 2015(7):CD010952. 32. Wechalekar MD, Vinik O, Moi JH, et al. The efficacy and safety of treatments for acute gout: results from a series of systematic literature reviews including Cochrane reviews on intraarticular glucocorticoids, colchicine, nonsteroidal antiinflammatory drugs, and interleukin-1 inhibitors. J Rheumatol Suppl. 2014;92:15-25.
<u>Full text not available (1)</u> 33. Ashbrook J, Rodgdakis N, Goodwin P, Yeowell G, Callaghan M. 43 Management of acute low back pain in the ED: a systematic review. Emerg Med J. 2017;34(12):A889.
<u>Non-English studies (1)</u> 34. Kreutzkamp B, Author A, Hamburg G, Correspondence A, B. Kreutzkamp G. Pains in hip and knee osteoarthritis. Meta-analysis: Diclofenac is the most suitable ORIGINAL (NON-ENGLISH) TITLE Metaanalyse: Diclofenac am besten geeignet. Medizinische Monatsschrift fur Pharmazeuten. 2017;40(4):186-187.