OSTEOARTHRITIS

The Osteoarthritis Research Society International (OARSI) defines osteoarthritis as "a disorder involving movable joints characterized by cell stress and extracellular matrix degradations initiated by micro and macro injury that activates maladaptive repair responses, including pro-inflammatory pathways of innate immunity. The disease manifests by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation) and loss of normal joint function."

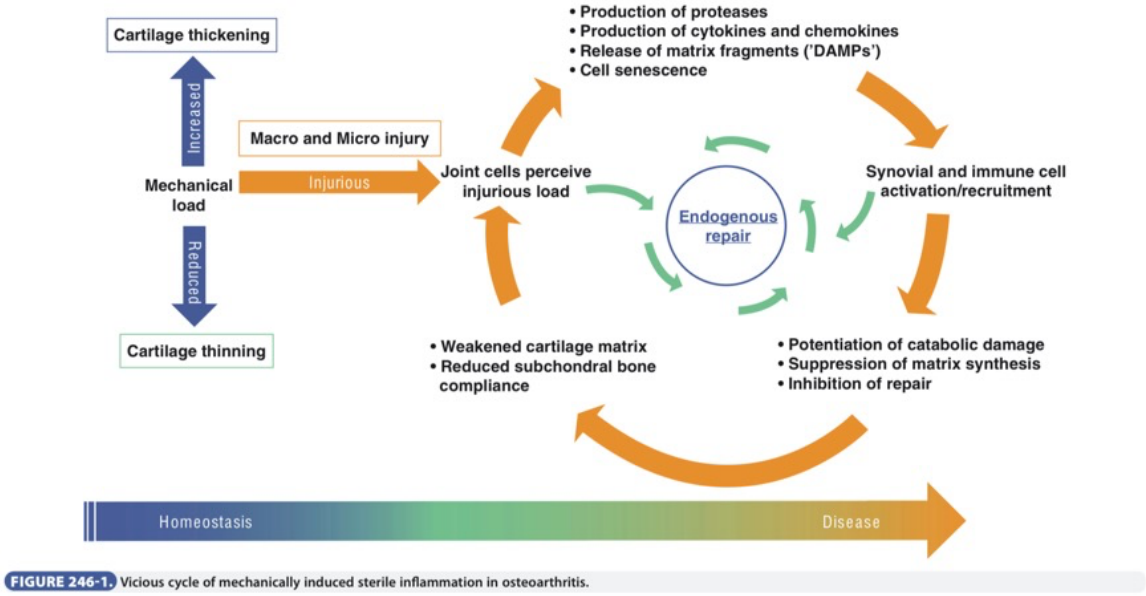
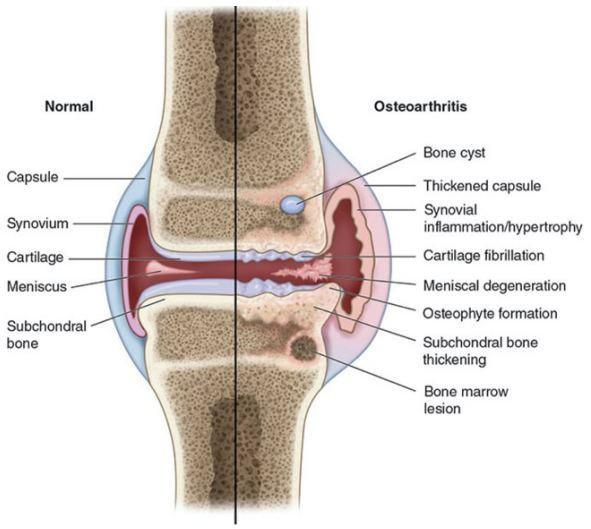


FIGURE 246-1. Vicious cycle of mechanically induced sterile inflammation in osteoarthritis.

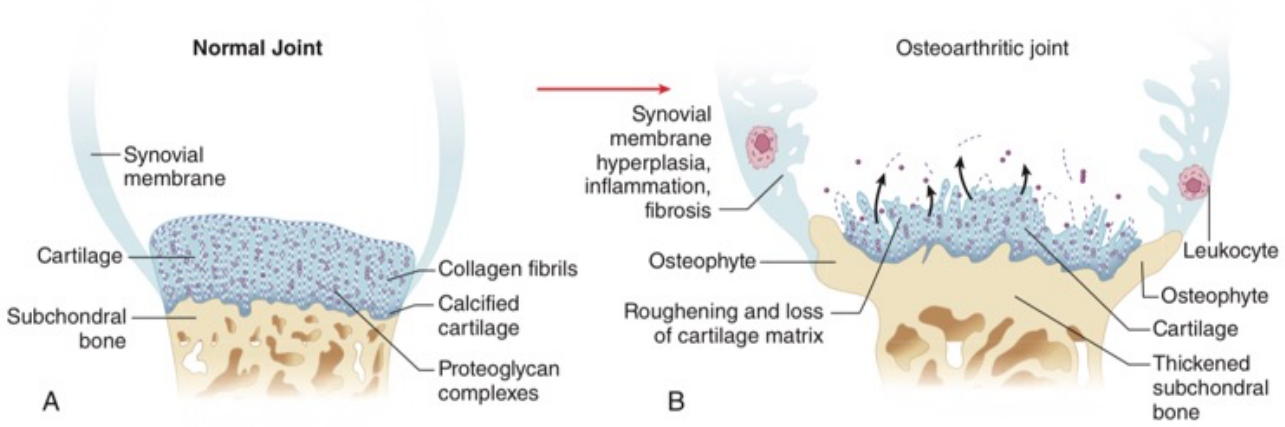
- Mechanical factors appear to be the most important etiological factors in OA development.
- As we age, our ability to reduce the impact of joint loading during normal activities is reduced by loss of muscle mass (e.g., quadriceps strength across the knee), loss of gait reflexes, and poor response times
- Osteoarthritis (OA) will occur when abnormal loads are imposed on a normal joint or when normal loads are experienced by a joint that has lost its mechano-protective mechanisms.
- Repetitive or traumatic injury to the articular surfaces initiates the cascade leading to release of inflammatory cytokines (tumor necrosis factor [TNF], IL-1), nitric oxide, and proteolytic enzymes that break down the extracellular matrix of cartilage.
- Proinflammatory factors and proteolytic enzymes responsible for the degradation of the extracellular matrix also result in joint tissue destruction.
- Although destruction and loss of the articular cartilage is a central component of OA, all joint tissues are affected in some way, indicating that OA is a disease of

TABLE 246-2 MECHANICAL ETIOLOGIES OF OSTEOARTHRITIS

ABNORMAL LOAD ON NORMAL JOINT	NORMAL LOAD ON AN UNPROTECTED JOINT
Direct articular trauma	Aging by loss of muscle support and gait reflexes
Obesity	Chondrodysplasia through maladapted joint shape and weakened joint tissues
Repetitive occupational load, e.g., "coal miner's back," "cotton-picker's thumb"	Joint destabilization, e.g., ruptured anterior cruciate ligament, meniscal tear
Joint malalignment, e.g., valgus and varus deformities	Cartilage weakened by previous arthritis, e.g., gout, rheumatoid arthritis, sepsis (in the past referred to as *secondary osteoarthritis*)



the joint as an organ, affecting bone, synovium, ligaments, joint capsule, meniscus (knee), and periarticular muscles / nerves.



Cartilage

- OA begins with damage to articular cartilage, through trauma or other injury, excess joint loading from obesity or other reasons --> chondrocyte activity increases in an attempt to remove and repair the damage.
- Depending on the degree of damage, the balance between breakdown (catabolism) and resynthesis of cartilage (anabolism) is lost, and a vicious cycle of increasing breakdown leads to further cartilage loss and apoptosis of chondrocytes.
- Joint space narrows as a result from loss of cartilage, which leads to painful deformed joint.
- Remaining cartilage softens and develops cartilage fibrillations (vertical clefts into the cartilage), followed by splitting off of more cartilage and exposure of underlying bone.

Bone

- Thickening of the subchondral bone (bone sclerosis) occurs due to increased production of collagen that is improperly mineralized.
- Osteophytes (bone spurs) form at the joint margins in an attempt to stabilize the joint by providing an increased surface area over which to distribute the load across the joint.
- Bone cysts, observed on MRI, occur in more advanced disease.
- Subchondral bone releases vasoactive peptides and MMPs (matrix metalloproteinases) --> further damage articular cartilage.

Synovium

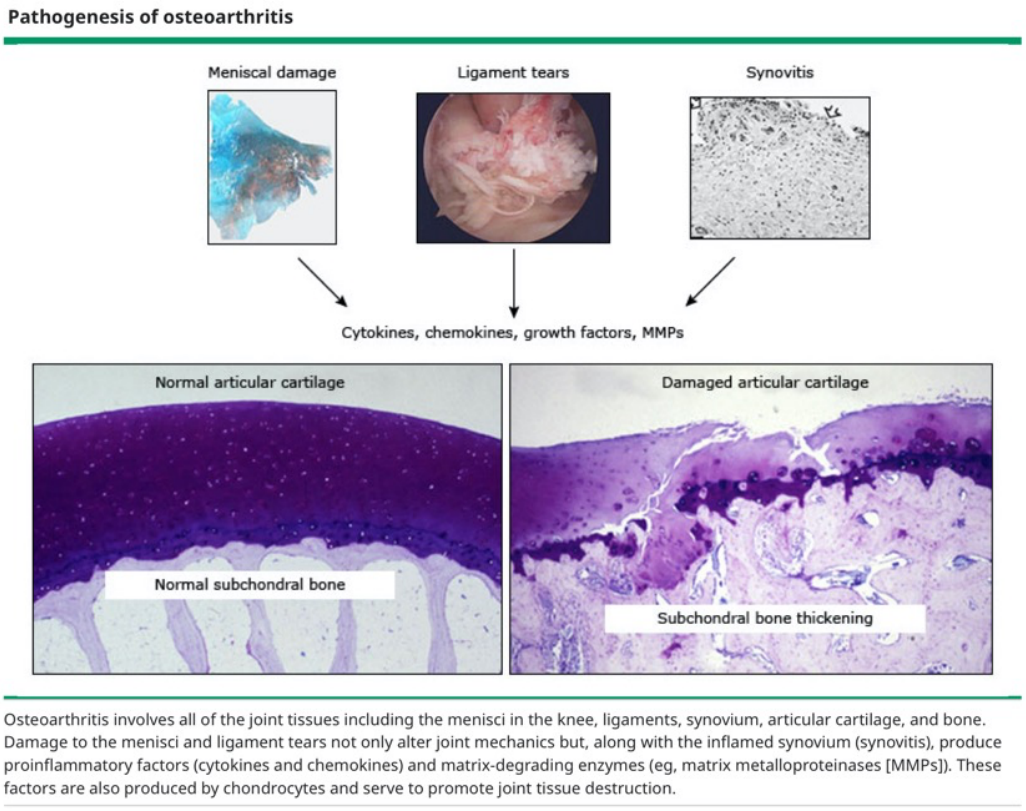
- Synovitis (synovial inflammation) and/or synovial hypertrophy are mediated by the production of proinflammatory factors and proteins.
- Synovitis contributes to pain and disease progression.

Soft Tissues

- Ligaments, joint capsule, and meniscus (knee) are commonly affected by OA.
- Thickening of the joint capsule along with osteophytes contribute to the enlargement of osteoarthritic joints.
- In older adults with established OA, it's common to find tears in ligaments and the meniscus --> contribute to inflammatory mediators in the affected joint.

Periarticular Muscles / Nerves

- Periarticular muscles and nerves are also affected by OA, resulting in muscle weakness and pain via activation of nociceptive nerve endings within the joint.



Osteoarthritis involves all of the joint tissues including the menisci in the knee, ligaments, synovium, articular cartilage, and bone. Damage to the menisci and ligament tears not only alter joint mechanics but, along with the inflamed synovium (synovitis), produce proinflammatory factors (cytokines and chemokines) and matrix-degrading enzymes (eg, matrix metalloproteinases [MMPs]). These factors are also produced by chondrocytes and serve to promote joint tissue destruction.

Post-Traumatic Osteoarthritis

- OA that develops after injury to a joint is called post-traumatic OA.
- The pathologic changes of post-traumatic OA are often evident within 10 years after injury, with the time of onset influenced in part by the age of the individual at the time of injury.
- OA can develop after injuries that result in ligament and/or meniscal tears, or after injuries such as fracture that involve the joint.
- Tears include acute inflammation with joint swelling that is particularly severe.
- Studies have shown a host of inflammatory mediators, include TNF (elevated sixfold) and IL-6 (elevated 1000-fold) are present shortly after injury.
- The risk of developing OA after a significant ligament/meniscal tear is the same whether the ligament is repaired or not, which suggests that either the mechanics of the joint are not completed restored after reconstruction/repair or that the acute inflammation that occurs with the injury puts the OA process in motion.

Overview of Management

- Available treatments for OA target pain since no treatment has been proven to alter the progression of the disease.
    - As our understanding of the mechanisms underlying OA improves, treatments are being developed that target specific mediators thought to promote joint tissue destruction.
    - Since OA results from a change in the balance of catabolic and anabolic activity in the joint, both anti-catabolic agents and pro-anabolic agents are being developed and tested.
    - Since joint tissues, including cartilage, are not capable of intrinsic repair and that advanced disease involves damage to the entire joint, it is unlikely that treatment of advanced disease will be successful in reversing OA --> targeting specific mediator(s) at earlier stages of OA will need to be successful.

Overview of Management (cont.)

- OA pain results from a multifactorial biopsychosocial process in which non-cartilaginous structures, including the subchondral bone, synovium, and periarticular structures, are involved.
    - Note: Peripheral and central sensitization of nociceptive pathways also play a role in chronic pain associated with OA.
- The goals of OA management are to minimize pain, optimize function, and beneficially minimize the process of joint damage (e.g., weight management, exercises, walking aids, joint splints & braces).

Overview of Drug Therapy

- The initial treatment for OA pain and stiffness is acetaminophen (APAP) on a routine basis for a 2-3 week trial in doses typically less than 4 gm/day, or less than 3 gm/day in patients > 65 years-old, unless contraindicated.
    - APAP offers a considerable degree of safety over NSAIDs for mild to moderate OA disease.
    - Clinical trials have demonstrated significantly better efficacy of NSAIDs, compared with APAP in patients with both pain and inflammation, since APAP lacks significant anti-inflammatory properties.
- NSAIDs are considered in patients with inadequate response to APAP or patients who present with pain and inflammation.
    - A careful risk versus benefit analysis must be individualized for each patient started on an NSAID, with consideration given to adverse effects (GI bleeding, reduced renal function, cardiovascular risk) and drug-drug interactions or drug-disease interactions.
- Topical therapies may be selected for patients unable to tolerate oral NSAIDs: capsaicin (Zostrix^{R}) cream/patch and diclofenac (Voltaren^{R}) cream/patch.
- In patients presenting with effusions of the knee, aspiration of the affected joint and intra-articular injections of corticosteroids may be therapeutic once infectious etiologies have been rules out.
- Intra-articular injections of hyaluronic acid derivatives are the last of the conservative strategies before surgical interventions.
- Tramadol (Ultram^{R}) may represent a useful option for many patients unless precluded due to seizures or misuse history or drug-drug interaction potential.
- There are currently no recommendations for the use of oral glucocorticoids in the treatment of OA.
- The use of oral or transdermal opioids or opioid/acetaminophen combinations of pain management should be discouraged because of the limited evidence demonstrating benefit and the high potential for adverse effects and opioid dependence.

Topical NSAID: Diclofenac (Voltaren) 1% Gel

- In patients with one or a few joints affected, especially knee and/or hand OA, topical NSAIDs are recommended due to their similar efficacy compared with oral NSAIDs and their better safety profile.
- Diclofenac (Voltaren) 1% gel (OTC) for hip OA is not recommended since topical pharmacologic therapies are unable to penetrate and reach the hip joint.
- Topical NSAIDs are excellent options for hand and knee OA in patients who have a history of GI bleed, are aged 75 years or older, or have any other reason to avoid the risks of oral NSAIDs.
- SEs are limited to localized reactions: dry skin, redness, and pruritus.

Topical Capsaicin (Zostrix Cream)

- Capsaicin depletes substance P from afferent nociceptive nerve fibers (substance P is implicated in the transmission of pain).
- Capsaicin is considered to have moderate efficacy in knee/hand OA, but ineffective in hip OA due to limited penetration into deeper regions of the hip joints.
- SEs are limited to localized reactions: burning, stinging, and erythema.

Oral NSAIDs

- Oral NSAIDs are preferred in patients with inadequate symptoms relief from topical NSAIDs, symptomatic OA in multiple joints, and/or patients with hip OA.
- The lowest dose of an NSAID is recommended to control the patient's symptoms on an as-needed "PRN" basis.
- The use of NSAIDs is limited by the increased risk of GI, cardiovascular, and renal complications.
- In patients with low cardiovascular risk and **moderate-to-high risk of GI bleeding**, celecoxib (Celebrex) OR NSAID plus PPI OR misoprostol (Cytotec) is recommended.
    - **Cardiovascular risks of NSAIDs** are associated with hypertension (HTN) and volume expansion (due to renal PGI inhibition --> Na/H_2O retention).
        - Naproxen (Naprosyn) presents less cardiovascular risk than celecoxib (Celebrex) and non-selective NSAIDs (e.g., ibuprofen, diclofenac, ketorolac, indomethacin, etc…).
    - **GI bleeding risk of NSAIDs** are caused by PGE inhibition.
        - Higher relative risk for GI bleeding is associated with indomethacin (Indocin), ketorolac (Toradol), and naproxen (Naprosyn).
        - Lower relative risk for GI bleeding is associated with ibuprofen (Motrin), diclofenac (Voltaren), meloxicam (Mobic), and celecoxib (Celebrex).
- In patients with **mild cardiovascular disease**, consider the use of tramadol (Ultram) or naproxen.
- **NSAIDs are not recommended** in patients with a high comorbidly risk, i.e., patients with previous GI bleeding, mod-severe cardiovascular disorders, or chronic kidney disease (CKD).

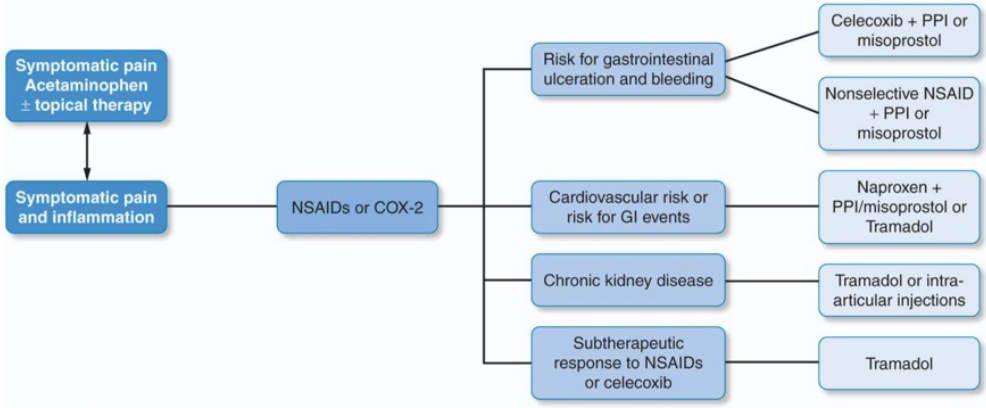
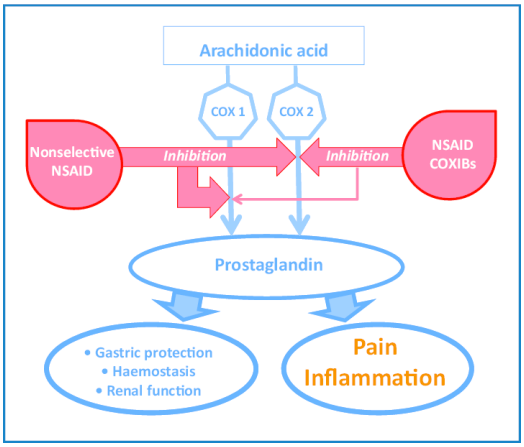


Figure 43-2 Overview of pharmacologic therapy for treatment of osteoarthritis. (Adapted from multiple references.)[11,12,14,18,30]

NSAIDs: Selective COX-2 Inhibitors → Celecoxib (Celebrex)

- Selective COX-2 inhibitors, or coxibs, were developed an attempt to inhibit PG synthesis by COX-2 at the site of inflammation without affecting the action of the "housekeeping" COX-1 isoenzyme found in the GI tract and platelets.
- Celecoxib is 10-20 times more selective for COX-2 than for COX-1; however, celecoxib does not offer cardioprotective effects since it inhibits COX-2 mediated prostacyclin synthesis in the vascular endothelium --> increases vasoconstriction --> increases BP --> increases cardiovascular risk.



NSAIDs: Selective COX-2 Inhibitors (cont.)

- Celecoxib also inhibits COX-2 medicated prostacyclin in the renal vascular endothelium --> decreases renal blood flow --> decreases GFR --> increases Na/H_20 retention --> increases BP and cardiovascular risk.
- Dose: Celecoxib 100 - 200 mg daily (or in divided doses, Q12H).

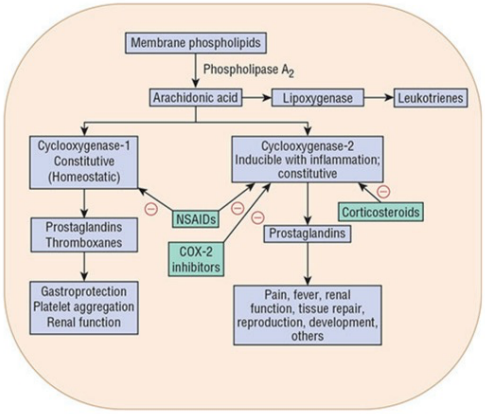


FIGURE 106-6 Pathway of synthesis for prostaglandins and leukotrienes. COX-1 and COX-2 are cyclooxygenase-1 and cyclooxygenase-2 enzymes, respectively. The minus (–) sign indicates inhibitory influence. Prostaglandins include PGE_2 and PGI_2; the latter is also known as prostacyclin.

NSAIDs: "Preferential" COX-2 Inhibitor (Meloxicam)

- Meloxicam (Mobic) preferentially inhibits COX-2 over COX-1, particularly at its lowest dose of 7.5 mg/day.
- Since meloxicam is not as selective as celecoxib, it is considered "preferentially" selective rather than "highly" selective for COX-2.
- Diclofenac (Voltaren) is also considered a "preferential" COX-2 inhibitor, but approx. 50% less selective as meloxicam.
- Meloxicam is associated with fewer GI symptoms and complications, compared to non-selective NSAIDs (e.g., naproxen, ibuprofen, diclofenac).
- Similar to celecoxib, meloxicam has minimal effects on blocking thromboxane A_2 and causing antiplatelet effects.
- Dose: Meloxicam 7.5 – 15 mg PO daily.

Indomethacin (Indocin)

- Indomethacin differs somewhat from other NSAIDs in its high potency, indications (e.g., gout), and CNS toxicities, namely headache (15-20%), dizziness, confusion, and depression.

Oral nonsteroidal antiinflammatory drugs (NSAIDs)

Applies to all:

- Due to increased side effects in older adults, use should be limited to brief course(s) in selected patients for painful flare-ups at lowest effective dose
- Avoid use of NSAIDs in older adults with renal insufficiency (CrCl <50 mL/min), GI bleeding, platelet dysfunction, reduced cardiac output, hypovolemic state, hyponatremia, hepatic impairment, or receiving an anticoagulant
- Dose- and age-associated risk of gastropathy; pharmacologic gastroprotection may be indicated even with COX-2 selective therapy (refer to UpToDate topic on prevention of NSAID-associated gastroduodenal toxicity)
- Can cause or worsen renal insufficiency, including age-associated decline in renal function
- Traditional NSAIDs (eg, ibuprofen, naproxen) reversibly inhibit platelet functioning and may alter cardioprotective effects of aspirin
- Use with serotonin reuptake inhibitor antidepressants (eg, SSRIs, nortriptyline, venlafaxine) additively decreases platelet functioning

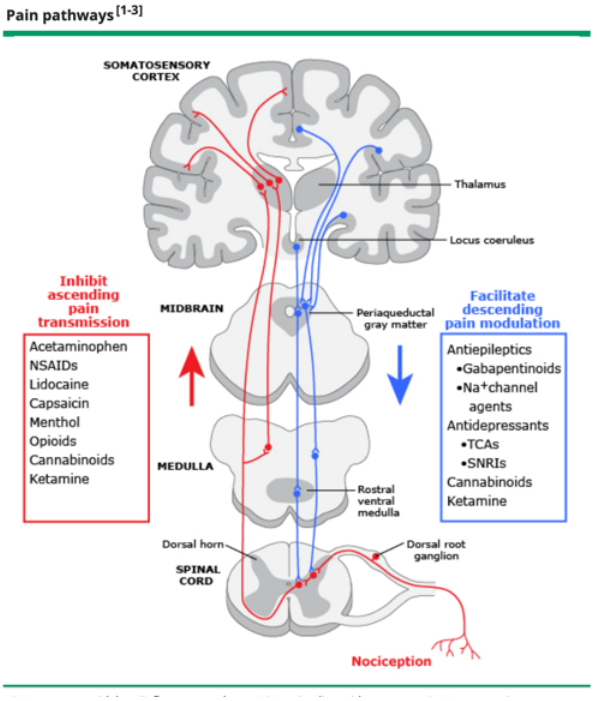
Naproxen sodium	220 mg twice per day (equivalent to 200 mg naproxen base twice per day)	▪ Less cardiovascular toxicity than other nonselective NSAIDs ▪ Naproxen sodium has better absorption and more rapid onset than naproxen base
Ibuprofen	200 mg 3 times per day	▪ Short half-life may be advantageous in older adults ▪ Avoid combined use with cardioprotective (low-dose) aspirin therapy
Celecoxib	100 mg per day	▪ Relative reduction in GI toxicity compared with nonselective NSAIDs ▪ No effect on platelet functioning ▪ Patients taking cardioprotective aspirin may still need concurrent gastroprotection (eg, proton pump inhibitor)

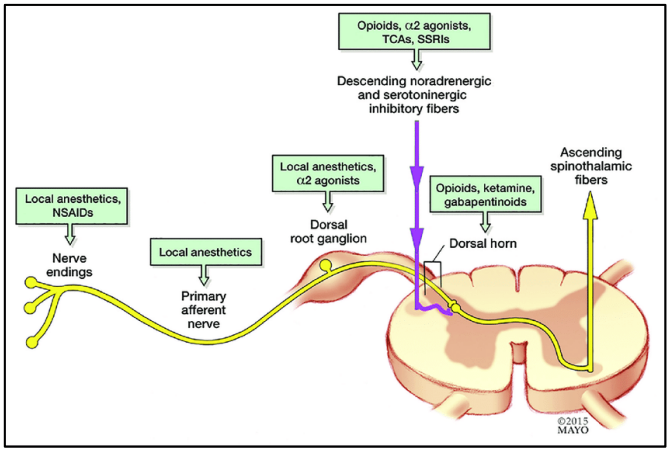
Tramadol (Ultram)

- The ACR (American College of Rheumatology) recommends tramadol in patients have failed or have contraindications to NSAIDs.
- MOA: Tramadol is a centrally acting analgesic that binds to the mu-opioid receptor and also inhibits the reuptake of norepinephrine (NE) and serotonin (SE).
- Tramadol can also be used with APAP for a combined analgesic effect:
  Ultracet® = Tramadol 37.5 mg + APAP 325 mg
- SEs: nausea, constipation, dizziness, drowsiness, headache, seizures (most serious)
  - Tramadol has a lower risk of constipation and dependence than traditional opioids, but it carries the risk of serotonin syndrome when combined with other serotonergic agents (e.g., TCAs, SSRIs, SNRIs).
  - Tramadol can lower the seizure threshold in patient with seizure disorders or patients who are predisposed to seizures.
  - Tramadol is a Schedule IV (CIV) controlled substance → potential risk of dependence & addiction
- Short-term use of an opioid or opioid/APAP combination (Norco-5, Percocet-5) may be considered for severe pain in patients in whom the use of tramadol is ineffective or contraindicated.
- Dose: Tramadol (Ultram) 25 – 100 mg PO QID PRN pain.

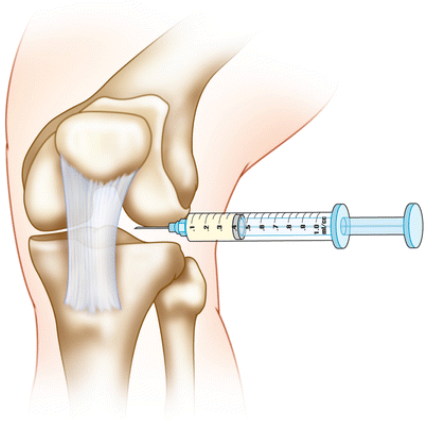
Duloxetine (Cymbalta)

- Duloxetine was approved by the FDA in 2012 for treatment of chronic musculoskeletal pain, including OA.
- MOA: duloxetine is a centrally-acting SNRI, although NE reuptake inhibition does not occur until doses reach 60 mg/day.
- Dose: Duloxetine 60 mg PO daily (contraindicated in patients with CrCl < 30 ml/min).
- Note: The analgesic effects of duloxetine are independent of its antidepressant effect.
- While the most common pain in OA is peripheral nociceptive pain, there is some evidence that chronic nociceptive pain leads to central pain sensitization.
  - Duloxetine provides pain relief through descending noradrenergic and serotoninergic inhibitory fibers (i.e., modulation) that innervate the dorsal horn and reduce ascending pain transmission.
- Duloxetine is preferred over tramadol in patients for whom there is a concern over the possibility of drug abuse or misuse.
- OA and coexisting depression: since depression is common in patients with chronic OA, there may be an additional indication for use in patients with OA and coexisting depression.
- SEs: nausea, dry mouth, constipation, anorexia, fatigue, drowsiness, dizziness, liver failure (in predisposed patients with liver dysfunction, e.g., alcohol liver disease).





Intra-Articular (IA) Corticosteroids



- When patients fail oral or topical therapies, intra-articular (IA) injections of corticosteroids represent the last conservative effect before surgical intervention of the knee (note: efficacy has not been demonstrated with hip OA).
  - Systemic corticosteroid therapy (PO/IV) is not recommended in OA, given the lack of proven benefit and well-known adverse effects with long-term use (HPA-suppression, osteoporosis, cataracts, hyperglycemia, hypertension, immunosuppression).
- Note: Recent evidence suggests that routine use of IA glucocorticoids may exert harmful effects on hyaline cartilage and may accelerate OA progression.
- Typically, IA corticosteroids of **triamcinolone (Kenalog)** and **methylprednisolone (Medrol)** with lidocaine 1% have been shown to be effective in reducing knee pain and stiffness for approx. 4 weeks --> benefits of IA corticosteroids tend to be limited with a relatively short duration, and IA injections cannot be administered more frequently than every 3 months.
- Intra-articular injection of glucocorticoid (triamcinolone, methylprednisolone) is carried out after aspiration and inspection of synovial fluid to rule out infection (septic arthritis)
- SEs (transient): hyperglycemia, hypertension, post-injection flare (5%).
  - Post-injection flare is characterized by a localized inflammatory response that typically occurs and resolves within 48 hours after injection and may be due to the corticosteroid solubility factor.
  - Triamcinolone (Kenalog) is less soluble than methylprednisolone (Medrol) and is associated with more post-injection flare.

Depot glucocorticoid suspension	Dose according to joint size or extraarticular site			Average duration of action (days)	Available strengths
	Small*	Medium ¶	Large Δ		
Methylprednisolone acetate	10 to 20 mg	40 to 60 mg	40 to 80 mg	7 to 84	20 mg/mL 40 mg/mL 80 mg/mL
Triamcinolone acetonide ◊	8 to 10 mg	20 to 30 mg	20 to 40 mg	14	10 mg/mL 40 mg/mL 80 mg/mL

Intra-Articular Hyaluronic Acid (HA)

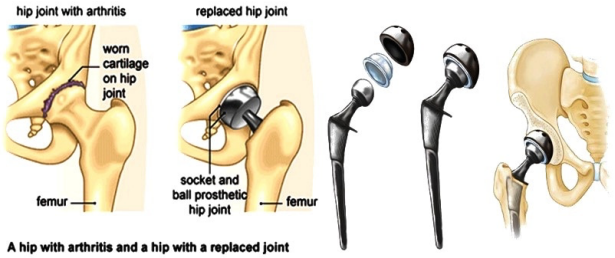
- HA is naturally occurring component of cartilage and synovial fluid and may have anti-inflammatory, analgesic, and chondroprotective effects on the articular cartilage and joint synovium.
- The goal of intra-articular hyaluronic acid (HA) is to provide and maintain IA lubrication; however, IA injections of HA are not widely recommended and not routinely used due to the lack of robust evidence demonstrating clinically benefits.
- Most HA products are injected once weekly for 3-5 weeks, and repeated every 6 months if patients report satisfactory results.
- HA products are expensive since drug costs are added to administrative costs.
- SEs: acute joint swelling, effusion, joint stiffness.
- Conclusion: Patients' expectation and cost effectiveness must be considered before choosing HA injections.

Pharmacologic Agents in Osteoarthritis

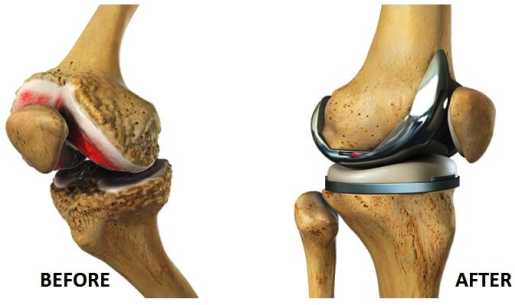
Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral Analgesics			
Acetaminophen	Hepatotoxicity	Total daily dose limits	Use caution with multiple acetaminophen-containing products—total 4 g limit (or less in patients with hepatic dysfunction)
Tramadol	Nausea, vomiting, somnolence	No routine labs recommended	Drug–drug interaction with other serotonergic medications
Opioids	Sedation, constipation, nausea, dry mouth, hormonal changes	No routine labs recommended	Risks of addiction, dependence, and drug diversion
NSAIDs	Dyspepsia, CV events, GI bleeding, renal impairment	BUN/Creatinine, Hgb/Hct, blood pressure	Risks higher in those older than 75 years of age
Topical Analgesics			
Capsaicin	Skin irritation and burning	Inspection of areas of application	Wash hands thoroughly after application
NSAIDs	Skin itching, rash, irritated Dyspepsia, CV events, GI bleeding, renal impairment	Inspection of areas of application. As needed: BUN/Creatinine, Hgb/Hct, blood pressure	Wash hands thoroughly after application. Avoid oral NSAID or aspirin other than cardioprotective dose. Ensure patient applying gel, solution, or patch correctly
Injectable drugs			
Intra-articular corticosteroids	Hypertension, hyperglycemia	Glucose, blood pressure	HPA axis suppression if used too frequently
Intra-articular hyaluronates	Local joint swelling, stiffness, pain	No routine labs recommended	Less effective than intra-articular corticosteroids; expensive

Surgery

- Total/Partial joint replacement in advanced knee and hip OA is highly effective in patients when conservative therapies have failed to provide adequate pain relief.
- A systemic review of 14 studies demonstrated that 20% of patients with total knee replacement and 9% of patients hip replacement reported moderate-severe long-term pain postoperatively.
    - Unfavorable pain outcomes after surgery may be related to pre-operative levels of pain, presence of comorbidities and depression, and the presence of concomitant pain at other joints.



A hip with arthritis and a hip with a replaced joint



Nutritional Supplement: Glucosamine and Chondroitin

- Glucosamine and chondroitin have been promoted for their ability to simulate synthesis of articular cartilage in OA.
- The American College of Rheumatology recommends against use of glucosamine and chondroitin since neither agent had demonstrated clinical efficacy.
- Most clinicians do not recommend glucosamine/chondroitin, but do not discourage their use for patients who are intent on using them if they report some symptomatic benefit with their use.

Commonly Prescribed Opioids

TABLE 27-4 FORMULATIONS, DOSAGES, AND PHARMACOLOGIC INFORMATION ON COMMONLY PRESCRIBED OPIOIDS

DRUG	EQUI-ANALGESIC DOSAGE (ORAL UNLESS SPECIFIED)	READILY AVAILABLE ROUTES OF ADMINISTRATION	DURATION OF ACTION	COMMENTS
PURE OPIOID AGONISTS				
Morphine	30 mg	IV, IM, PO, PR; SR formulation	3-6 h for short-acting, 8-12 h for SR	Reference standard for all opioids. Renally excreted active metabolite.
Oxycodone	20 mg	PO, PR; SR formulation	3-6 h for short-acting, 8-12 h for SR	Widely available in combination form with nonopioid analgesics. Greater euphoric effects than morphine. Popular among recreational users.
Hydromorphone	3-6 mg	PO, PR, IV, IM, SR formulation	3-6 h, 18-24 h for SR	Higher PO:IV conversion ratio than other opioids. SR form reserved for opioid-tolerant patients and contraindicated in patients with recent monoamine oxidase inhibitor use.
Hydrocodone	30-60 mg	PO, SR formulation	3-6 h, 12-24 h for SR	Wide variation in morphine equivalent dose. Most commonly prescribed opioid in U.S. Typically used in combination form with nonopioid analgesic acetaminophen. SR form available without acetaminophen.
Oxymorphone	10 mg	PO, IV, IM, PR; SR formulation	4-8 h, 8-12 h for SR	Co-ingestion of alcohol with SR formulation can lead to rapid increase in plasma levels and overdose. Very low (10%) oral bioavailability.
Methadone	2-20 mg	PO, PR, IV	6-12 h for pain	Morphine:methadone conversion varies according to dose and length of opioid use, ranging from 2 : 1 to >20 : 1 in patients on very high doses. Any physician with a schedule II DEA license may prescribe for pain. May take 5-7 days to reach steady state due to long half-life. EKG monitoring recommended with higher doses. Other properties such as NMDA receptor antagonism and reuptake inhibition of serotonin and norepinephrine may slow tolerance and increase efficacy for neuropathic pain.
Levorphanol	4 mg	PO, IM, V	4-10 h	2 : 1 oral to IV conversion ratio. Agonist at mu, kappa and delta receptors. Multiple mechanisms of action including inhibition of serotonin and norepinephrine reuptake, NDMA receptor antagonism and sigma receptor agonism. Long half-life exceeded only by methadone.
Fentanyl	12.5 µg/hr (TD) 100-300 µg (TM)	TD, TM	72 hours for TD; 1.5-3 h for TM	TD, TM and B formulations may be useful in patients with poor bowel function. Rapid onset (<10 min) iontophoretic TD system available for postoperative pain. TD: Wide variation in conversion ratios and doses depending on route. Delivery system may be associated with fewer gastrointestinal side effects and include buccal, sublingual, and intranasal routes. TM delivery associated with more rapid (10 min) onset than immediate release oral opioids. FDA approved for breakthrough cancer pain in opioid-tolerant patients. Approximately 40% greater bioavailability for transmucosal films and sprays than lozenges and tablets.
Sufentanil	15-30 µg	TM	1.5-3 h	Rapid onset, wide variation in conversion ratio. For use only in health care and battlefield settings. 15 and 30 µg dosages approved in Europe; 15 µg dosage approved in the United States.
Codeine	200 mg	PO, PR, IM, SR codeine combination product available as cough suppressant	3-6 h, 8-12 h for SR	Often used in combination with nonopioid analgesics. Efficacy and side effects may be affected by rate of metabolism to active metabolite morphine, which varies significantly. Popular as cough suppressant.
Propoxyphene	200 mg	PO, PR	3-6 h	Removed from market in U.S. Wide variation in morphine equivalent dose. Often used in combination form with nonopioid analgesic. Toxic metabolite may accumulate with excessive use, especially in elderly. Weak antagonist at NMDA receptor.
Meperidine	300 mg	PO, PR, IM, IV	2-4 h	Toxic metabolite may accumulate with excessive use, especially in patients with renal insufficiency. Associated with tachycardia and hypertension. Concurrent use with monoamine oxidase inhibitors may result in fatal reactions. May cause more "euphoria" than other opioids. IM absorption erratic.
AGONIST-ANTAGONISTS, PARTIAL AGONISTS				
Buprenorphine Buprenorphine/ Naloxone (4 : 1 ratio for opioid addiction)	0.3-24 mg SL 5-70 µg/h (TD) 2-24 mg/d	TM, PR, IV, TD	8-12 h for TM, 7 d for SR, once daily for stable buprenorphine/ naloxone combination	Partial µ-agonist κ-antagonist that may precipitate withdrawal in opioid-dependent patients on high doses. Lower abuse potential and fewer side effects than pure agonists. Not readily reversed by naloxone. Schedule III drug in U.S. Primarily used in combination with naloxone as sublingual or buccal tablets and films for opioid dependence. May prolong QT interval.
Butorphanol	1 mg/spray, repeat after 60-90 min (IN) 1-2 mg (IV/IM)	IN, IM, IV, PO	3-5 h	Mixed agonist and antagonist at µ-receptor and antagonist at κ-receptor. Commonly used as nasal spray to treat migraine headache and less commonly for labor pain. Significant abuse potential.
Nalbuphine	1 : 1 parenteral ratio	SC, IM, IV	3-6 h	Mixed agonist-antagonist, often used for labor and delivery. Sometimes used to treat refractory opioid-induced pruritus.
Pentazocine Pentazocine/ Naloxone (Talwin) (100 : 1 ratio of pentazocine to	90 mg	PO, SC, IM, IV	3-4 h parenteral, 3-8 h PO	Mixed agonist-antagonist. Negative entantiomer is kappa agonist. Naloxone added in 1970s (e.g., Talwin) to prevent abuse. Commonly prescribed in preparation with acetaminophen. Schedule IV controlled substance in the United States.

Commonly Prescribed Opioids (cont.)

TABLE 27-4 FORMULATIONS, DOSAGES, AND PHARMACOLOGIC INFORMATION ON COMMONLY PRESCRIBED OPIOIDS—cont'd

DRUG	EQUI-ANALGESIC DOSAGE (ORAL UNLESS SPECIFIED)	READILY AVAILABLE ROUTES OF ADMINISTRATION	DURATION OF ACTION	COMMENTS
WEAK, DUAL-ACTION OPIOID AGONISTS				
Tramadol	150-300 mg	PO	4-6 h, 24 h for SR	Dual action involves inhibition of serotonin and norepinephrine reuptake. Affinity for μ-opioid receptor 6000× less than morphine. Analogue of codeine with active metabolite in which differences in metabolism may influence drug effects. Available in combination form with acetaminophen. Maximum recommended dose of 400 mg/d. Avoid concurrent use of monoamine oxidase inhibitors. Recently moved to FDA category schedule IV in U.S.
Tapentadol	75-110 mg	PO	4-6 h, 12 h for SR	Dual action involves inhibition of norepinephrine reuptake. May have fewer of certain side effects than morphine, such as gastrointestinal and respiratory depression. Maximum dose 600 mg/d. Avoid concurrent use of monoamine oxidase inhibitors. Schedule II in U.S. Approved for diabetic neuropathy.

PO = oral; PR = rectal; IV = intravenous; IM = intramuscular; IN = intranasal; SL = sublingual; TD = transdermal; TM = transmucosal; B = buccal; NMDA = *N*-methyl-D-aspartate; SR = sustained release