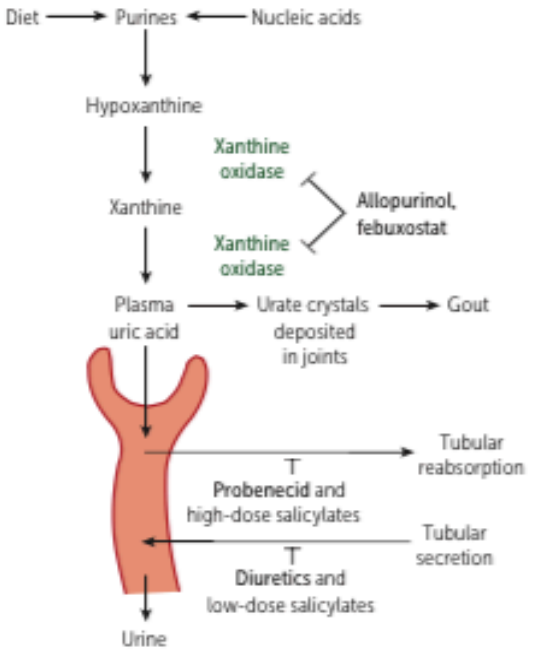
Gout drugs

Chronic gout drugs (preventive)	
Allopurinol	Inhibits xanthine oxidase after being converted to alloxanthine, ↓ conversion of xanthine to uric acid. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. ↑ concentrations of azathioprine and 6-MP (both normally metabolized by xanthine oxidase).
Febuxostat	Inhibits xanthine oxidase.
Pegloticase	Recombinant uricase that catalyze metabolism of uric acid to allantoin (a more water-soluble product).
Probenecid	Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.
Acute gout drugs	
NSAIDs	Naproxen, indomethacin.
Glucocorticoids	Oral or intra-articular.
Colchicine	Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI side effects.
	Do not give salicylates; all but the highest doses depress uric acid clearance. Even high doses (5–6 g/day) have only minor uricosuric activity.



TNF-α inhibitors — All TNF-α inhibitors predispose to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

DRUG	MECHANISM	CLINICAL USE
Etanercept	Fusion protein (receptor for TNF-α + IgG_1 Fc), produced by recombinant DNA. Etanercept is a TNF decoy receptor.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis
Infliximab, adalimumab	Anti-TNF-α monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis

ACUTE GOUT: *rapid onset* of excruciating pain, swelling, inflammation
- Monoarticular (1st metatarsopharangeal joint)
- ***Non-salicylate NSAIDs**, NSAIDs + Cochicine, Corticosteroids*

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
Non-salicylate NSAIDs: **INDOMETHACIN**, NAPROXEN	Anti-inflammatory	**DOC: ACUTE GOUT**	
COLCHICINE	Alkaloid: anti-inflammatory **MITOTIC POISON:** inhibits microtubule polymerization by binding to tubulin Inhibits leukocyte migration + phagocytosis	**2nd Line: Acute gout** **When NSAIDs or corticosteroids are contraindicated or ineffective* ***Contraindicated in pregnancy***	**LOW BENEFIT-TO-TOXICITY RATIO** **Diarrhea** Long term use: hematuria, alopecia, myelosuppression, gastritis, peripheral neuropathy
CORTICOSTEROIDS: PREDNISONE, TRIAMCINOLONE		**Acute gouty arthritis** **When NSAIDs & Colchicine are contraindicated or ineffective*	

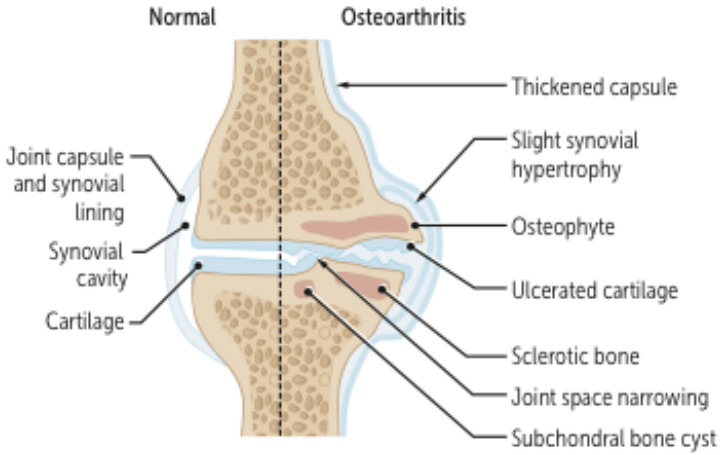
CHRONIC GOUT: Caused by genetic ↑purine synthesis, renal deficiency, ↑uric acid from chemotherapy, *Lesch-Nyhan*

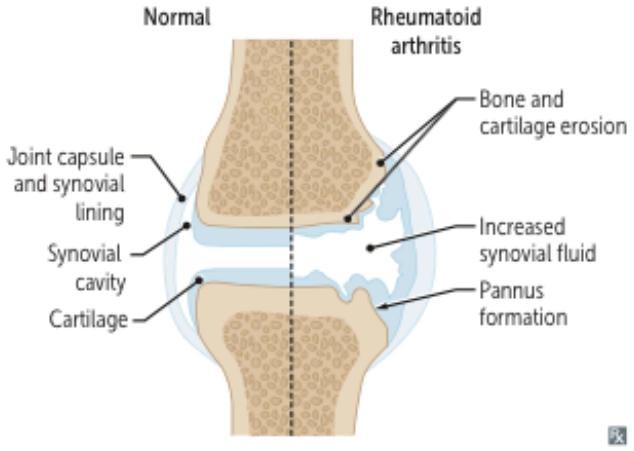
Uricosuric Drugs: **PROBENECID** **SULFINPYRAZONE**	**Promote renal excretion of uric acid** by inhibiting PCT reabsorption – *ineffective if GFR <50*	**DOC: GOUT w/ normal urinary uric acid excretion** ****Not used in high urate excretors***	
ALLOPURINOL	Purine analog **COMPETITIVE INHIBITOR OF XANTHINE OXIDASE** **PRODRUG** → alloxanthine by Xanthine Oxidase Prevents biosynthesis of uric acid	**DOC: GOUT in patients with** – **EXCESS uric acid excretion** – **Hx of uric acid STONES** – **RENAL FAILURE** **Combination Cochicine/NSAIDs* **Chronic tophaceous gout** ****Not used in acute gout attack*** *Use w/ caution: liver pts or myelosuppresion*	GI, Hypersensitivity Rash → Toxic Epidermal Necrolysis, Systemic Vasculitis **DRUG INTERACTIONS:** – Inhibits metabolism of **Azathioprine + Mercaptopurine**, *thus their doses must be **DECREASED** when given w/ Allopurinol*
FEBUXOSTAT	**X**anthine **O**xidase inhibitor – ↓uric acid levels	**Chronic mgmt. of hyperuricemia in gout patients who can't tolerate Allopurinol** **Combination Cochicine/NSAIDs*	**Few GI adverse effects**

****Hydrochlorothiazide & loop diuretics** decrease the clearance of uric acid & should be avoided in patients with Hx of gout*

Osteoarthritis and rheumatoid arthritis

	Osteoarthritis	Rheumatoid arthritis
ETIOLOGY	Mechanical—joint wear and tear destroys articular cartilage.	Autoimmune—inflammatory destruction of synovial joints. Mediated by cytokines and type III and type IV hypersensitivity reactions.
JOINT FINDINGS	Subchondral cysts, sclerosis A, osteophytes (bone spurs), eburnation (polished, ivory-like appearance of bone), synovitis, Heberden nodes (DIP), Bouchard nodes (PIP). No MCP involvement.	Pannus (inflammatory granulation tissue) formation in joints (MCP, PIP), subcutaneous rheumatoid nodules (fibrinoid necrosis), ulnar deviation of fingers, subluxation B. Rare swan neck and boutonnière deformities. Rare DIP involvement.
PREDISPOSING FACTORS	Age, obesity, joint trauma.	Females > males. 80% have ⊕ rheumatoid factor (anti-IgG antibody); anti–cyclic citrullinated peptide antibody is more specific. Strong association with HLA-DR4.
CLASSIC PRESENTATION	Pain in weight-bearing joints after use (e.g., at the end of the day), improving with rest. Knee cartilage loss begins medially ("bowlegged"). Noninflammatory. No systemic symptoms.	Morning stiffness lasting > 30 minutes and improving with use, symmetric joint involvement, systemic symptoms (fever, fatigue, weight loss, pleuritis, pericarditis).
TREATMENT	Acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine), biologics (TNF-α inhibitors).





RHEUMATOID ARTHRITIS

- **Interleukin 1b & TNFα**: pro-inflammatory cytokines involved in pathogenesis of RA
- Treatment is aimed at relieving pain & inflammation + maintaining & preserving joint function
  - *NSAIDs alleviate pain & joint inflammation, but they do not halt the loss of bone associated with RA* – ***used for initial management***
- **INITIAL THERAPY:** Methotrexate, sulfasalazine, hydroxochloroquine

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
DMARDs	Reduce & prevent joint damage – *Patients who have no responded to NSAIDs* No immediate analgesic effect		
METHOTREXATE	Folate anti-metabolite **Inhibits Folate Reductase** & ↓active form of folate Inhibits lymphocyte proliferation & production of cytokines Stimulates apoptosis in immune-inflammatory cells	**DMARD Of Choice: RA** **Effect usually seen in 4-6 weeks*	Hematotoxicity, Mucositis, Hepatotoxicity, Crystalluria
HYDROXYCHLOROQUINE	Stabilizes lysosomes & ↓chemotaxis	**Mild RA** **Used w/ Methotrexate or Sulfasalazine*	**Visual dysfunction (CINCHONISM)** **Hemolysis in G6PD deficient patients**
SULFASALAZINE	PRODRUG → sulfapyridine & 5-ASA ↓B cell functions & inhibits COX Inhibits effects of IL-1 & TNFα	**RA + Ulcerative Colitis** ***More effective than Hydroxychloroquine***	***More toxicity than Hydroxychloroquine*** GI, rash, hemolysis in G6PD deficiency, SLE-like syndrome
LEFLUNOMIDE	PRODRUG Inhibition of T cell proliferation via **Dihydroorotate DH** Deprives cell of UMP inhibiting RNA + DNA synthesis Arrests in G1 phase	**RA: Monotherapy or +Methotrexate**	Alopecia, rash, diarrhea, hepatotoxicity **METHOTREXATE + LEFLUNOMIDE = SEVERE HEPATOTOXICITY**
Biogenic Amines	When DMARDs are not enough		
ETANERCEPT	**Recombinant TNF-R** – ↓ its activity	**2nd Choice: RA** **Psoriatic arthritis** ***Standard Therapy: +Methotrexate**	**Injection site reactions** **Tuberculosis**
INFLIXIMAB	IgG Monoclonal Antibody to TNFα **Blocks TNF actions**	**RA** **Crohn's, Psoriasis, other Autoimmune**	
ADALIMUMAB	Recombinant mAb binds to TNFα	**Active RA**	
ANAKINRA	**Competitive IL-1 R Antagonist**	*Less effective than other biogenic amines*	
ABATACEPT	Genetically engineered fusion protein that interferes with T cell activation		
RITUXIMAB	Chimeric mAb against **CD20**	**Patients w/ inadequate responses to Methotrexate or anti-TNF**	
Corticosteroids	↓LTs, IL, & PAF	**Low Dose:** symptomatic relief when waiting for DMARDs effect	ACTH suppression, Cushingoid state, osteoporosis, GI, glaucoma, cataract, osteoporosis, hyperglycemia