Rheumatology in Primary Care

A Pharmacology Review

Trevor L. Shenk, DO
Family Physician
Family Medicine Residency Program
Penn Medicine Lancaster General Health

Pain and inflammation characterize the story of rheumatology. The Centers for Disease Control and Prevention (CDC) estimates that musculoskeletal and connective tissue diseases account for more than 8% of ambulatory office visits in the United States annually; most of these visits are associated with osteoarthritis.[1]

The use of prescription and over-the-counter (OTC) analgesics is ubiquitous, and non-steroidal anti-inflammatory drugs (NSAIDs) make up 5% to 10% of all medical prescriptions. Thus, medical providers must be familiar with their use.[2] In addition, the development of biologic drugs in addition to the disease-modifying antirheumatic drugs (DMARDs) for more autoimmune diseases requires increased familiarity with regard to indications and side effect profiles by all clinicians.

The following brief overview provides history, pharmacology, and guidelines for the most commonly used medications in the management of rheumatic disease.

PHARMACOLOGY REVIEW BY MEDICATION TYPE

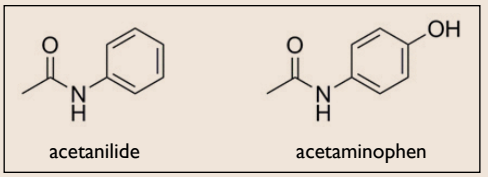
Acetaminophen

The mechanism of action of acetaminophen is not entirely clear but is thought to occur by blocking cyclooxygenase (COX) enzymes, decreasing prostaglandins, blocking serotonin neurotransmitters in the central nervous system, and modulating the endogenous cannabinoid system. In contrast to NSAIDs, acetaminophen does not have an anti-inflammatory effect. Acetaminophen toxicity is caused by the reactive metabolite *N*-acetyl-*p*-benzoquinone imine, which reacts with hepatocyte cellular proteins causing hepatic injury.

Of note, 50% of acetaminophen overdose events are unintentional and can be caused by chronic doses of only 4 g/day. The antidote for toxicity is *N*-acetyl cysteine, which must be given within eight hours of ingestion. While liver toxicity is the most serious adverse reaction, nausea, drowsiness, and hypersensitivity reactions may also occur. Unfortunately, inefficacy of acetaminophen for chronic musculoskeletal pain is a major drawback.

HISTORICAL SNAPSHOT
Acetaminophen

In the 1880s, two chemicals borrowed from the dye industry — acetanilide and phenacetin — were marketed as anesthetics for headaches. While useful, these chemicals caused methemoglobinemia. A compound discovered as a metabolite in the urine of people taking these drugs was concentrated and later synthesized for commercial use as acetaminophen.



NSAIDs

Understanding the mechanism of action of NSAIDs means understanding the concept of COX isoenzymes COX-1 and COX-2 and their varied physiologic functions. NSAIDs function by inhibiting COX enzyme activity to decrease the conversion of arachidonic acid into proinflammatory cytokines and thereby decreasing downstream pain signaling and other manifestations of inflammation including swelling and fever. COX-1 is constitutively expressed in most body tissues, whereas COX-2 is the inducible isoenzyme associated with pathologic states.[3]

The U.S. market offers many NSAIDs, but all the non-selective COX inhibitors carry the same basic risks. Gastrointestinal (GI) side effects of non-selective COX inhibitors most commonly include dyspepsia and heartburn but can also include gastric ulcers and perforation. COX-1 inhibition leads to reduction in prostaglandin levels and thus disruption in the gastric mucosal barrier, which makes surface cells of the stomach and esophagus vulnerable to gastric acid.

Additionally, factors that increase the risk of GI

complications include concomitant therapy with other medicines such as antiplatelet agents, anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors (SSRIs). Age greater than 65 years, severe illness, concomitant alcohol and tobacco use, history of peptic ulcers, and *H. pylori* infection also increase the risk.[4]

Several NSAIDs were formulated to selectively inhibit COX-2 in an effort to reduce the negative GI effects of non-selective COX inhibitors. Although rofecoxib and valdecoxib are no longer on the market due to increased risk of cardiovascular (CV) events, celecoxib remains on the market as the primary COX-2 selective agent. Celecoxib may serve a role in patients who require an NSAID and have high GI risk and relatively low cardiovascular risk.

The Food and Drug Administration (FDA) issued a black box warning regarding increased risk of heart attack or stroke associated with any non-aspirin NSAID use. For anyone with CV risk factors, when NSAIDs cannot be avoided, the lowest effective dose and shortest duration of therapy should always be prioritized.

The third major category of risk associated with NSAID use is universal to both selective and non-selective agents. Renal dysfunction, peripheral edema, and hypertension can all result from inhibition of PGI_2 and PGE_2 production by the kidneys. As potent vasodilators, these prostaglandins ensure adequate kidney perfusion unless COX inhibition limits their production. NSAID use can be especially dangerous in older adults, patients with chronic kidney disease or diabetes mellitus, or patients taking medications that might affect kidney perfusion.

Topical NSAIDs provide an alternative to oral NSAIDs and are approved for osteoarthritis of the knee and hand. Their efficacy in older patients is 30% to 40% of oral formulations. As an example, diclofenac gel is available in 1% concentration in the United States. Topical NSAID use is associated with 5% to 10% of the systemic exposure incurred by oral agents.[4] For hand osteoarthritis, topical NSAIDs rather than oral NSAIDs are preferred in persons older than 75 years.

Tramadol

Tramadol is a synthetically derived opioid with partial mu-opioid receptor binding. Tramadol provides additional pain management options for people with contraindications to NSAIDs, when other therapies are ineffective, or when no surgical options are available for patients with severe pain. Studies, however, suggest that tramadol use in a postoperative setting is more likely to result in chronic opioid use, thus providers should exercise caution if using this medication.[5]

HISTORICAL SNAPSHOT NSAIDs

- Hippocrates (400 BC) was known to make willow leaf tea as part of his medical practice. Research later showed that salicin in willow tree bark converts to salicylic acid *in vivo* to provide analgesia through COX enzyme inhibition.
- Acetylsalicylic acid (ASA) was synthesized and named aspirin in 1899.
- In 1961, Stewart Adams developed ibuprofen in hopes of curing rheumatoid arthritis.[4]
- Thirty billion OTC doses of NSAIDs and 70 million prescriptions are processed annually in the United States.[4]

Photo by peter-rabbit, via Flickr, CC BY-NC 2.0 DEED.

Duloxetine

Recent meta-analyses demonstrate some patients with osteoarthritis and fibromyalgia can benefit from the use of antidepressants such as duloxetine.[6,7] While the exact mechanism of action for duloxetine is unknown, it offers a wide array of indications through serotonin and norepinephrine reuptake inhibition, along with weak inhibition of dopamine reuptake.

Current FDA-approved indications include major depressive disorder, diabetic peripheral neuropathy, generalized anxiety disorder, fibromyalgia, chronic low back pain, and chronic musculoskeletal pain from osteoarthritis. Like other serotonin reuptake inhibitors, duloxetine may increase the risk of short-term suicidality and mania. The risk of suicidal thoughts and

behaviors is greatest in patients younger than 24 years old. Nevertheless, antidepressants like these decrease suicidal thoughts and behaviors in patients older than 65 years.[8]

Common side effects include nausea, dry mouth, headache, and fatigue. Providers should avoid rapid discontinuation of duloxetine due to potential for withdrawal symptoms. A gradual taper is advised when discontinuing this medication.

Disease-Modifying Antirheumatic Drugs

DMARDs are divided into several distinct categories by virtue of their synthesis and mechanisms of action (see Table 1). Conventional synthetic DMARDs (csDMARDs) include the traditional first-line therapies for disease-modifying activity: hydroxychloroquine, methotrexate, sulfasalazine, and leflunomide.

Hydroxychloroquine (HCQ) — used in anti-phospholipid syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) — works as an immunomodulator by inhibiting toll-like receptor signaling and inhibiting cyclic GMP-AMP synthase (cGAS) DNA binding to decrease pro-inflammatory cytokine expression. Of note, maculopathy may be seen in patients using HCQ and may lead to irreversible vision loss. This typically happens with HCQ dosing >5 mg/kg as is common for SLE patients. Other unique side effects include the development of blue-grey discoloration to skin, vivid dreams, and auditory hallucinations.

Table 1. Disease-Modifying Antirheumatic Drugs (DMARDs)

Class	Drug	Indication	Comments
Conventional synthetic (csDMARD)	hydroxychloroquine	Preferred initial therapy for DMARD-naïve patients with low disease activity.	Low cost and less bloodwork monitoring required; risk of retinal toxicity.
	methotrexate	Preferred initial therapy for moderate-to-severe disease and foundation of treatment for any DMARD combination.	Hold during acute hospitalization, infection, or antibiotic use; not recommended in the setting of liver or kidney disease.
	sulfasalazine	Alternate DMARD for initial rheumatoid arthritis (RA) management.	Excreted in bile and split into active metabolites by bacterial enzymes in large intestine.
	leflunomide	Recommended after trial of other csDMARDs.	Teratogenic; hepatotoxic, reverse toxicity by use of cholestyramine to disrupt enterohepatic recirculation.
Targeted synthetic (tsDMARD)	Janus Kinase inhibitors (baricitinib, tofacitinib, upadacitinib)	For moderate-to-severe RA after failure of tumor necrosis factor alpha (TNF-α) inhibitors.	Oral formulation, increased CV risk; avoid in patients with blood clotting disorder; increased risk of cancer; risk of infection.
Biologic (bDMARD)*	TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)	Generally, first-line biologic, in combination with methotrexate for moderate-to-severe disease (including RA, psoriatic arthritis, plaque psoriasis, inflammatory bowel disease) for corticosteroid sparing and reduced disease burden.	Avoid in patients with certain blood and solid tumor cancers; risk of infection.
	T-cell costimulatory inhibitor (abatacept)	For moderate-to-severe RA.	Possible lower infection risk compared to other biologics.
	IL-6 receptor inhibitors (sarilumab, tocilizumab)	For RA and temporal arteritis.	Avoid in patients with GI perforation.
	Anti-CD20 antibody (rituximab)	RA and antineutrophilic cytoplasmic antibody associated vasculitis, antiphospholipid syndrome, dermatomyositis, and lupus small vessel vasculitis.	Up to 25% incidence of reaction on initial transfusion, with decreased severity during subsequent transfusions.

** Considerations for Use of Biologics*

- *All options are expensive.*
- *Pretest for HIV, tuberculosis, and hepatitis B and C.*
- *Avoid live vaccines.*
- *Associated with increased risk of infection.*
- *Discontinue use during acute infection or hospitalization.*

As a dihydrofolate reductase inhibitor, methotrexate disrupts conversion of folic acid to tetrahydrofolic acid, depleting purines and nucleic acid synthesis, which results in immune cell apoptosis and decreased T-cell proliferation. Folic acid supplementation is important for patients taking methotrexate (MTX) as it reduces side effects during use. Long-term monitoring must be established for any patient taking MTX.

Both acute and chronic toxicities can cause liver function test abnormalities, bone marrow suppression, and increased risk of infection. Patients should not take MTX during any hospitalization, acute infection, antibiotic use, or when the glomerular filtration rate (GFR) is <30.

A first-line therapy in Europe, sulfasalazine can be used for both RA and inflammatory bowel disease, although the active metabolite is different depending on the target disease. After metabolism by gut bacteria, the active metabolites sulfapyridine and 5-aminosalicylic acid exhibit their effects.

Leflunomide produces an anti-inflammatory effect by disrupting T-cell progression into the S phase of the cell cycle and by blocking pyrimidine production. This medication is notable for a long half-life of 15 days and may remain detectable for two years after delivery. Because leflunomide is hepatotoxic, it should be avoided with any history of liver disease. Other side effects include nausea, vomiting, and fetal toxicity.

As with many aspects of rheumatology management, a systematic and stepwise approach with clearly defined goals is preferred (see Fig. 1). A treatment goal of low disease activity is realistic in chronic autoimmune disease such as rheumatoid arthritis. Every strategy must include consideration of side effects, costs, and patient preferences.

HISTORICAL SNAPSHOT DMARDs

- The natural precursor of hydroxychloroquine (HCQ), quinine has been reported to have been used by Incan descendants to cure a febrile illness in around 1630.[9]
- Chloroquine was introduced to rheumatology after soldiers given antimalaria prophylaxis in World War II were noted to have improvement in rashes and autoimmune arthritis.
- When Rex Hoffmeister began using methotrexate (MTX) to treat rheumatoid arthritis (RA) in the 1970s, the rheumatology community was hostile toward using an anti-cancer drug in a "benign disease." However, the original placebo-controlled trials of the 1980s pushed MTX to the forefront of pharmacotherapy for rheumatoid arthritis.[10]

Corticosteroids

Corticosteroid medications are among the most prescribed medications for treating pain in common rheumatic conditions. These powerful anti-inflammatory drugs inhibit pain by altering cytokine production; corticosteroids bind to intracellular receptors and change transcription at the DNA level. The change in cytokine expression leads to apoptosis of immune cells that would otherwise drive the inflammatory response.

In the short term, corticosteroids provide excellent relief. Early side effects include hyperglycemia, sleep disturbance, peripheral edema, weight gain, and

Fig. 1. Considerations for increasing tolerability and efficacy of methotrexate.

- Methotrexate is started at lower dose with titration toward full dose depending on laboratory and symptom monitoring side effects.
- Split weekly dosing over one 24-hour period results in higher absorption at the doses of 15 mg to 20 mg.
- Trial weekly injections if oral therapy is not tolerated or effective.
- Increase the dose of folic acid supplementation to mitigate methotrexate side effects.
- Alcohol use is discouraged in the setting of MTX use.

Fig. 2. Considerations for use of glucocorticoids in rheumatic disease.

- Consider a DMARD in place of glucocorticoids anytime more than three months of maintenance therapy is expected.
- Initiate a DMARD or switch to a separate class for anyone requiring a glucocorticoid to maintain their disease management target.
- Consider glucocorticoids, NSAIDs, or colchicine for treatment of acute gout flares as monotherapy for mild-to-moderate pain, or a combination of glucocorticoids with NSAIDs or colchicine for severe polyarticular disease.

increased appetite. Additionally, for locally injected corticosteroids, dermis atrophy and ligament weakness are concerns.

With long-term use, corticosteroids cause significant risk of multi-system degradation, including disruption of normal skin, hair, and bone structures; endocrine disruption causing adrenal insufficiency, Cushingoid features, or diabetes; and osteoporosis and increased risk of infections due to chronic immunosuppression. (See Fig. 2 on page 115 for considerations of glucocorticoid use in RA.)

Colchicine

Borrowed from cancer therapy, colchicine is an inhibitor of microtubule function in the cell, leading to impaired cellular trafficking which causes impaired neutrophil function and reduced pro-inflammatory cytokines. Colchicine deserves additional attention due to its versatile utility in the setting of multiple arthritic complaints. While often used in the setting of acute gouty arthritis, colchicine is also indicated for management of pain with familial Mediterranean fever or pericarditis.

Acute gout is an excruciatingly painful, yet common form of inflammatory arthritis. Management requires fast and effective pain control initiated within 24 hours of onset of an acute gout attack, and as soon as symptoms present if possible. Colchicine, along with other options such as NSAIDs and corticosteroids, offers a unique opportunity to treat gout effectively.

Patients with an established diagnosis of gout should have a treatment plan for acute gouty attack on hand, with written instructions and medication available at home.

Xanthine Oxidase Inhibitors

Initiation of urate-lowering therapy is considered in patients with two or more episodes of gout within one year, in patients with a severe initial episode, or in patients with polyarticular gout. Prevention of acute gouty arthritis is achieved through disruption of purine synthesis, which decreases serum uric acid levels.

The xanthine oxidase inhibitors, allopurinol and febuxostat, are first-line therapies. Since uric acid can precipitate into crystals at serum levels >6 mg/dL, maintenance therapy should be titrated to keep uric acid below this level. A lower level (<5 mg/dL) may be targeted.

HISTORICAL SNAPSHOT
Colchicine

- Derived from the corms of the *Colchicum autumnale* plant, colchicine has been used since ancient times, with the Egyptian *Ebers Papyrus* showing evidence of its use as far back as 1500 BC.[11]
- Although in the 1800s it became an "orphan drug" for many years, colchicine finally received FDA approval in 2009.[11]

Providers may consider initiating allopurinol at 100 mg and titrating to a maximum dose of 900 mg daily. The median dose of allopurinol necessary to keep uric acid levels <6 mg/dL is 450 mg daily. Allopurinol can be safely utilized when the creatinine clearance (CrCl) is as low as 10 mL/min.

An important consideration should be given to anyone whose family history suggests increased risk of developing hypersensitivity reaction to use of allopurinol. HLA-B*5801 allele testing should be performed in anyone considered at risk prior to initiating allopurinol therapy.

A more expensive alternative, febuxostat, was initially developed for use in chronic kidney disease; however, its cost and limited dosing options, along with a side effect profile similar to allopurinol, make febuxostat a less compelling alternative. Concerns regarding an increased

risk of cardiovascular events with this medication are still being investigated in post-marketing studies.

Second-Line Urate-Lowering Therapies

Probenecid lowers serum uric acid by blocking uric acid transporters in the renal tubules, resulting in uric acid excretion. This mechanism requires adequate kidney function (CrCl >30 mL/min) to be most effective. As a second-line therapy, probenecid is used in combination with an appropriately dosed xanthine oxidase inhibitor if serum urate levels are not at target. Patients should avoid probenecid use in acute gouty arthritis as it may exacerbate symptoms.

Pegloticase is reserved for severe gouty arthritis in patients refractory to appropriate dosing of other urate-lowering agents.

COLLABORATION MOVING FORWARD

Until now, many pharmacotherapies for rheumatologic disease have been non-specific in their use to attenuate inappropriate immune activity. Now targeted immune modulators — recently approved or in the process of development — for psoriatic arthritis, vasculitis, systemic lupus, and other less common autoimmune diseases require increased attention and continued study.

Newer infusions, for example, may not appear on standard medication lists in the electronic medical record, and a diagnosis of a rheumatologic condition should be a cue to all providers to review what therapies patients may have received.

Curiosity and clear communication among providers should remain standard practice. We should not hesitate to reach out to colleagues, to include rheumatology and pharmacy consultants, regarding questions about medications and their side effects.

CONCLUSION

Ancient remedies of chewing on *Colchicum* root or drinking willow leaf tea led to modern derivatives that remain in use today. Borrowed medications and broad strokes against autoimmune disease are being replaced by targeted immune modulators. Given the high prevalence of rheumatic disease, all clinicians should be familiar with available analgesic and anti-inflammatory pharmacotherapies.

ACKNOWLEDGEMENT

The author graciously acknowledges Rebecca M. Shepherd, MD, chief of rheumatology at LG Health, whose May 2022 Grand Rounds is the basis for this article.

REFERENCES

1. Santo L, Okeyode T. *National Ambulatory Medical Care Survey: 2018 National Summary Tables.* 2018. Accessed June 22, 2023. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-web-tables-508.pdf
2. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging Dis.* 2018;9(1):143-150.
3. Zidar N, Odar K, Glavac D, Jerse M, Zupanc T, Stajer D. Cyclooxygenase in normal human tissues — is COX-1 really a constitutive isoform and COX-2 an inducible isoform? *J Cell Mol Med.* 2009;13(9B):3753-3763.
4. Shepherd RM. Rheumatology medications: a brief history and pharmacological review. Grand rounds presented at: Penn Medicine Lancaster General Health; May 17, 2022; Lancaster, PA.
5. Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. *BMJ.* 2019; 365:l1849.
6. Chen B, Duan J, Wen S, et al. An updated systematic review and meta-analysis of duloxetine for knee osteoarthritis pain. *Clin J Pain.* 2021;37(11):852-862.
7. Lian YN, Wang Y, Zhang Y, Yang CX. Duloxetine for pain in fibromyalgia in adults: a systematic review and a meta-analysis. *Int J Neurosci.* 2020;130(1):71-82.
8. Eli Lilly and Company, ed. *Highlights of prescribing information: Cymbalta (duloxetine hydrochloride) delayed-release capsules for oral use.* Eli Lilly and Company; 2004.
9. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allergy Immunol.* 2012;42(2): 145-153.
10. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. *Trans Am Clin Climatol Assoc.* 2013;124:16-25.
11. Dasgeb B, Kornreich D, McGuinn K, Okon L, Brownell I, Sackett DL. Colchicine: an ancient drug with novel applications. *Br J Dermatol.* 2018;178(2):350-356.

Trevor L. Shenk, DO
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St.
Lancaster, PA 17602
717-544-4950
Trevor.Shenk2@pennmedicine.upenn.edu