A Review; Prevalence, Causes and Treatment of Gout and Hyperuricemia

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Abstract

The purpose of this paper is to conduct a critical analysis of the data regarding the various therapeutic approaches for the management of hyperuricemia. In affluent nations, the burden of gout has increased due to an increase in the prevalence of both hyperuricemia and gout in recent decades. Imaging methods have shown to be helpful in identifying urate deposition even before the onset of clinical symptoms. This allows for the assessment of the degree of deposition and the monitoring of crystal depletion objectively during urate-lowering therapy. Treating to target is becoming a more popular method for treating a variety of illnesses. Consequently, distinct goals have been suggested for various phases of the disease burden and therapy phases. The ultimate strategic goal, towards which all efforts should be directed, is the total dissolution of urate crystals in tissues, thereby preventing additional symptoms and structural harm to the musculoskeletal structures involved.
Keywords: Crystal deposition disease; Gout; Hyperuricemia; Uric acid

Introduction

Gout, and Hyperuricemia : The Silent Epidemic

In developed nations, there has been evidence of a rise in the occurrence of gout and hyperuricemia in recent decades. Recent research has demonstrated the link between hyperuricemia, but particularly gout, and cardiovascular outcomes as well as the potential for further advantages from early treatments. A novel strategy for treating hyperuricemia and gout may be provided by the observation that crystal deposition and subclinical inflammation occur prior to the clinical development of gout. Following a prolonged period of hyperuricemia, or serum urate (sUA) over the saturation threshold, gout is caused by the nucleation and development of monosodium urate (MSU) crystals in tissues in and around the joints. [1]The liver and gut are the primary sites of uric acid [UA] production, which is the end result of purine catabolism. With a few notable exceptions, including certain birds and Dalmatian dogs, this metabolic system has been extensively preserved throughout the evolutionary process in the majority of living species [2]. Serum levels of UA [SUA] are maintained below 7 mg/dL in men and 6 mg/dL in women during normal homeostasis [3], mostly because of a complicated regulatory mechanism involving the renal transport systems. Emerging pathogenic mechanisms highlight the role of ABCG2 expression in the colon and interactions with the gut microbiota.[5] Additionally, chronic hyperuricemia may result from an overproduction of uric acid or reduced renal excretion of uric acid.[4] Factors influencing serum uric acid levels include age (with an increase in hyperuricemia prevalence starting at age 60 and stabilizing after age 70), sex, cellular turnover, renal function, and external factors such as diet (including the intake of fructose, purines, and alcohol)[6].

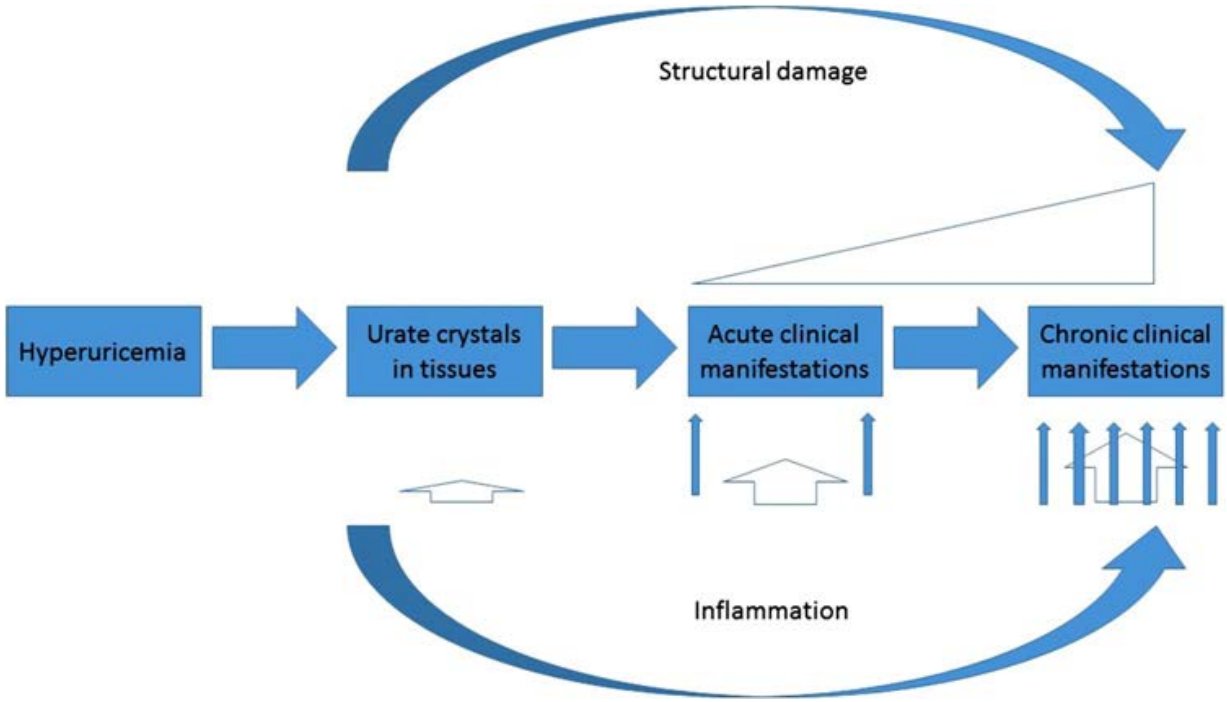

Figure1: Path from hyperuricemia to structural joint damage

Epidemiology

Gouty arthritis is the most common form of inflammatory joint disease in men older than 40 years.[7] According to the National Health Survey (1983–1985), there were 13.6 instances of self-reported gout for every 1,000 men and 6.4 cases for every 1,000 women. These figures show that the prevalence of gout has increased by about three times since 1969.[8]Conversely, gout cases determined by a physician indicate a consistently lower prevalence rate (1.0 to 3.0 cases per 1,000 women and 5.0 to 6.6 occurrences per 1,000 males).[9]

Prevalence of Hyperuricemia

The majority of research support the increasing trend of hyperuricemia, despite the fact that the frequency of the condition differed depending on the region and ethnicity [10–13]. There have been numerous studies on hyperuricemia conducted in Korea. According to a cohort research, male employees in one of Korea's biggest semiconductor manufacturing businesses who were between the ages of 30 and 59 had a cumulative incidence of hyperuricemia over a seven-year period of 23.1% [14]. Of the people who took part in the health check-up program in 2002, 9.3% had hyperuricemia [15]. 9.8% of patients in a single-center study with a sample size of 2,297 were found to have hyperuricemia between 2008 and 2010 [16]. Because both studies utilized the same definition of hyperuricemia as the patients at the tertiary hospital's health checkup center, they reported equal rates of hyperuricemia. The incidence of hyperuricemia in the Korean population was also reported by two epidemiological studies that made use of national surveillance data. According to statistics from the 2016 Korean National Health and Nutrition Examination survey (KNHANES), the age-standardized

prevalence of hyperuricemia is predicted to be 11.4% [17]. Based on data gathered from the Korean Genome and Epidemiology Study between 2004 and 2013, the overall frequency of hyperuricemia was 5.1% [18]. In Korea, the frequency of hyperuricemia varies, from 5.1% to 11.4%. The variations in the definition of hyperuricemia, length of data collection, estimation methodology, and study period could be the cause of the disparities between these studies. In general, Korea's prevalence of hyperuricemia has been rising over time, much like it has in other nations across the world; however, women's increases have been comparatively faster than men's. Global public health is becoming increasingly concerned about the rising incidence of hyperuricemia..

Prevalence of Gout

Reported estimates of gout prevalence range from 2.7% to 6.7% in countries (Figure 2) [Ahn, J. et al 2023]. The most recent estimate

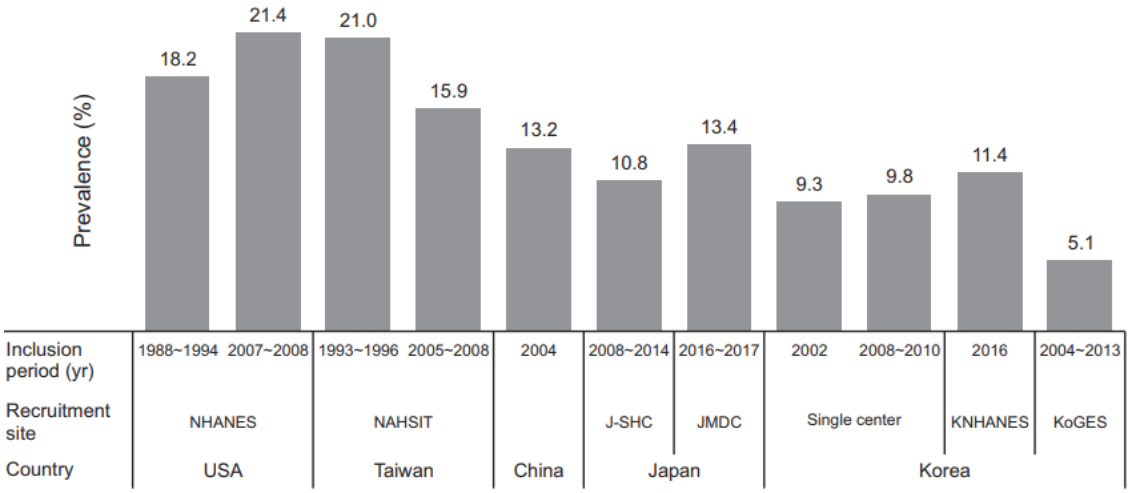

Figure 2. Worldwide prevalence rangesof hyperuricemia by country and time.

JMDC: Japan Medical Data Center, J-SHC:Japan Specific Health Checkups study, KNHANES: Korean National Health and Nutrition Examination Survey, KoGES: Korean Genome and Epidemiology Study, NAHSIT: Nutrition and Health Survey in Taiwan, NHANES: National Health and Nutrition Examination Survey.

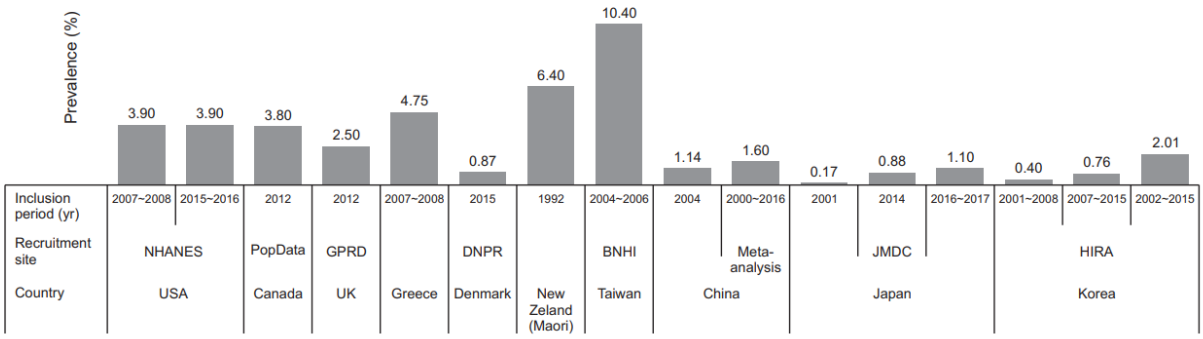

Figure 3. Worldwide prevalence ranges of gout by country and time.

BNHI: Bureau of National Health Insurance, DNPR: Danish National Patient Register, GPRD: General Practice Research Database, HIRA: Health Insurance Review & Assessment data, JMDC: Japan Medical Data Center, NHANES: National Health and Nutrition Examination Survey, PopData: PopulationData BC (British Columbia)

Pathophysiology

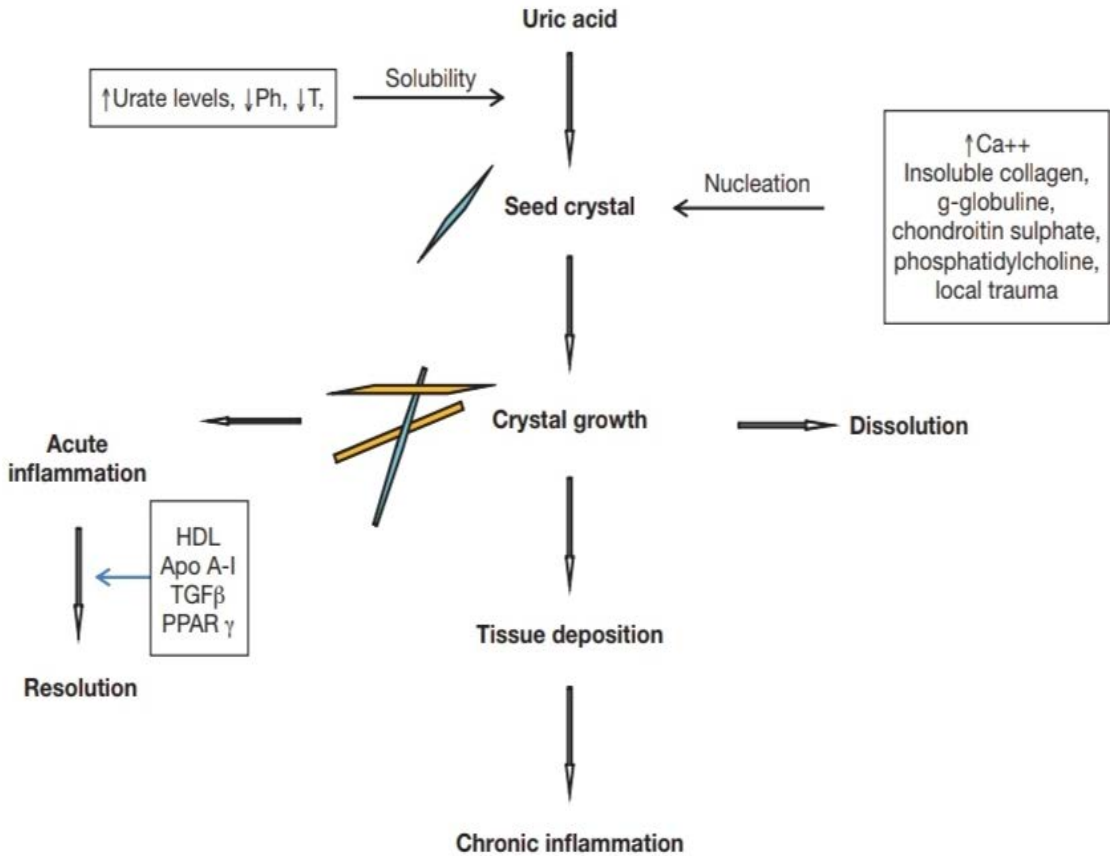

Figure 4. Pathphysiology of Gout

Clinical Features

Asymptomatic Hyperuricemia

An unusually high serum urate level without gouty arthritis or nephrolithiasis is called asymptomatic hyperuricemia. Serum urate concentrations above 7 mg/dL (416 μmol/L), or roughly the point at which plasma urate becomes supersaturated, are classified as hyperuricemia.[25]

While hyperuricemia is a common feature in gouty arthritis patients, hyperuricemia should not be confused with clinical gout. For 15 years, researchers from the Normative Aging Study measured serum urate levels serially on 2,046 men who were initially in good health. [26] The cumulative five-year incidence rates of gouty arthritis were as follows: 2.0 percent for serum urate levels of 8.0 mg/dL (475 μmol/L) or less, 19.8 percent for levels between 9.0 and 10.0 mg/dL (535 to 595 μmol/L), and 30 percent for levels above 10 mg/dL (595 μmol/L). Patients with hyperuricemia are at risk for developing nephrolithiasis and gout, but in the case of an asymptomatic patient, medication is typically not necessary. However, identifying hyperuricemia in an asymptomatic patient gives the doctor the chance to address or treat underlying acquired causes of hyperuricemia.

Acquired Causes of Hyperuricemia

Increased urate production

cause	
Nutritional	Excess purine, ethanol, fructose consumption
Hematologic:	Myeloproliferative and lymphoproliferative disorders
polycythemia Drugs	Ethanol, cytotoxic drugs, vitamin B (treatment of pernicious anemia)
Miscellaneous	Obesity, psoriasis, hypertriglyceridemia

Decreased renal excretion of urate

Drugs	Ethanol, cyclosporine (Sandimmune), thiazides, furosemide (Lasix) and other loop diuretics, ethambutol (Myambutol), pyrazinamide, aspirin (low-dose), levodopa (Larodopa), nicotinic acid (Nicolar)
Renal	Hypertension, polycystic kidney disease, chronic renal failure (any etiology)
Metabolic/endocrine	Dehydration, lactic acidosis, ketosis, hypothyroidism, hyperparathyroidism
Miscellaneous	Obesity, sarcoidosis, toxemia of pregnancy

Treatment

1.Drugs Reducing the Generation of Uric Acid: The Xanthine Oxidase Inhibitors

In the pathway of purine metabolism, the enzyme xanthine oxidase (XO), which is derived from xanthine dehydrogenase, converts hypoxanthine to uric acid (UA). During this conversion, reactive oxygen species (ROS) are generated.[27] An excess of ROS inhibits nitric oxide production, leading to endothelial dysfunction.[27] Xanthine oxidase inhibitors (XOIs) have been shown to reduce the risk of major and total cardiovascular events (Odds Ratio [OR] = 0.60, $p = 0.001$ and OR = 0.64, $p < 0.01$, respectively) as well as the onset or worsening of hypertension (OR = 0.54, $p = 0.002$), according to a meta-analysis of 81 randomized clinical trials (RCTs) involving 10,684 patients. Furthermore, XOIs are more effective in secondary prevention, significantly reducing the incidence of major cardiovascular events in high-risk individuals, as indicated by a sub-analysis of 9 studies with 616 hyperuricemic patients (Relative Risk [RR] = 0.42, $p < 0.01$).[28] In addition to lowering serum uric acid levels, XOIs may possess antioxidative properties due to their ability to limit ROS production.[29]

With an adequate tolerability profile, these medicines are the first choice in urate-lowering therapy for gout and are successful in the majority of hyperuricemic patients[30].

1.1 Allopurinol

Allopurinol and its metabolite oxypurinol, which are analogues of hypoxanthine and xanthine respectively, inhibit xanthine oxidase (XO) to reduce uric acid (UA) synthesis[31]. This medication can be administered orally or parenterally to treat gout and prevent the recurrence of kidney stones. Allopurinol is essential for preventing hyperuricemia in patients undergoing chemotherapy.[32] It has also been associated with slower progression of chronic kidney disease (CKD)[34,35] and improved flow-mediated dilation.[33] A clinical trial (ClinicalTrials.gov ID: NCT03865407) is currently investigating the effects of allopurinol on renal damage biomarkers and renal function in young CKD patients with high UA levels.

Allopurinol is rapidly absorbed in the upper gastrointestinal tract when taken orally, with a plasma half-life of 2-3 hours and peak plasma concentration reached in about 30 minutes.[36]Oxypurinol, the primary active metabolite of allopurinol, has a similar mode of action but a longer plasma half-life of 14-30 hours. It is filtered and partially reabsorbed in the kidneys.[36]

Allopurinol has a dosage-dependent effect on reducing serum uric acid (SUA) levels and is typically prescribed for chronic hyperuricemia at daily doses ranging from 100 mg to 600 mg[37], with a maximum daily dose of 800-900 mg[33] depending on the country and product label. However, a recent meta-analysis indicated that only lower doses of allopurinol (300 mg/day)[38] significantly reduce the risk of cardiovascular events. Allopurinol should generally be started at low doses and gradually increased to minimize the risk of acute gout attacks and hypersensitivity syndrome (AHS).[29] Co-administration of an anti-inflammatory drug or low-dose colchicine can further prevent acute gout attacks.[39]

The most commonly reported adverse effects of allopurinol include various degrees of skin rash and gastrointestinal issues. Treatment-emergent adverse effects can include eosinophilia, hepatitis, allopurinol hypersensitivity syndrome (AHS, which is rare but potentially fatal), and interstitial nephritis. Patients with renal impairment are advised to use lower dosages of allopurinol, as those with thiazide-treated CKD have an increased risk of developing AHS. The safety of allopurinol is also influenced by pharmacogenomics; patients with the HLA-B*5801 haplotype—disproportionately prevalent among Thai and Han Chinese individuals with at least stage 3 CKD—are at higher risk of severe side effects [40]. Additionally, individuals on didanosine should avoid allopurinol [41]. Those taking azathioprine or mercaptopurine concurrently with 300–600 mg/day of allopurinol need to reduce their immunosuppressant dosage to about one-third or one-fourth of the recommended amount. Monitoring treatment response and toxicity in these patients is essential [42]. It is important to recognize that these concerns may lead to underdosing allopurinol and inadequate treatment of hyperuricemia [43].

1.2.*Febuxostat*

Febuxostat, an oral non-purine selective XO inhibitor, effectively inhibits both reduced and oxidized forms of XO by targeting the active pterin-containing molybdenum center in the enzyme-substrate complex, thus reducing reactive oxygen species generation [44]. Administered orally, it is absorbed in the upper gastrointestinal system, reaching peak plasma concentration within an hour and maintaining a plasma half-life of 5 to 8 hours. Fruxostat undergoes hepatic conjugation for metabolism and excretion. Apart from exerting anti-inflammatory effects on endothelial cells, it demonstrates superior efficacy in lowering serum uric acid (SUA) levels compared to allopurinol.

The efficacy of fruxostat is attributed to its ability to suppress endothelial XO cell- and glycosaminoglycan-bound processes [47]. Clinical studies have shown that over a one-year period, febuxostat outperforms allopurinol in preventing arterial stiffness in gout patients [48]. However, in patients with stable cardiovascular artery disease, febuxostat lowers SUA levels without significant improvement in coronary endothelial dysfunction, as indicated by a recent phase 4 clinical trial [49].

The recommended daily dosage of febuxostat ranges from 80 to 120 mg, although smaller doses such as 40 mg/day have demonstrated significant reductions in SUA levels [45,46]. Notably, treatment with 40 mg/day of febuxostat appears to be more effective than 300 mg of allopurinol in achieving the target SUA value of <6 mg/dL.

1.3*Topiroxostat*

Topiroxostat, a selective XOI with favorable oral absorption, undergoes hepatic metabolism to produce its pharmacologically active metabolite, N-glucuronide topiroxostat (F11741) [50].

In vivo studies have shown that topiroxostat reduces urine albumin excretion (UAE) and XO plasma activity in a dose-dependent manner [51]. Specifically, a dosage of 160 mg/day of

Topiroxostat has been found to effectively lower serum uric acid (SUA) levels and UAE in hyperuricemic patients with stage III chronic kidney disease (CKD) [52].

Furthermore, in hyperuricemic patients undergoing hemodialysis, topiroxostat therapy has been demonstrated to safely reduce SUA levels at a significant rate, even at lower doses compared to allopurinol [53]. Additionally, the ETUDE trial has indicated that topiroxostat may improve renal function in patients with overt diabetic nephropathy [54].

However, there is currently limited clinical data available on the efficacy and safety of topiroxostat.

2.Drugs that Inhibit the Reabsorption of Uric Acid: The Uricosurics

Uricosuric drugs increase the renal clearance of uric acid (UA) primarily by inhibiting its reabsorption in the renal proximal tubule.Various transporters have been identified as playing a role in the secretion and reabsorption of UA across the apical and basolateral membranes of the proximal tubule [55]. Recent genetic analyses, such as genome-wide association studies (GWAS), have identified novel gene variants associated with human gout and SUA levels [56]. One hypothesis suggests the existence of a group of proteins termed the "urate (or UA) transportasome," which collaborate to transport substances through the epithelial cells of the proximal tubule [57]. Among these transporters, URAT1 (SLC22A12) is crucial for UA absorption from the lumen [58], while SLC17A1 (NPT1), SLC17A3 (NPT4), and ABCG2 (BCRP) encode additional transporters involved in UA renal filtration [59].

GLUT9 (SLC2A9) on the basolateral membrane primarily facilitates the movement of UA into the interstitium and blood [60]. GWAS meta-analyses have identified single nucleotide polymorphisms (SNPs) linked to SUA levels in loci harboring genes such as SLC2A9, SLC17A1, SLC17A3, SLC22A12, and ABCG2 among individuals of European descent [61]. Similar associations have been found in East Asian populations [62]. Additionally, a meta-analysis by the Global Urate Genetics Consortium (GUGC) discovered new SNPs associated with SUA concentrations, with loci like ABCG2 and SLC2A9 explaining a significant portion of the variance in SUA [63]. These loci are also associated with gout. Although allele frequencies differ among populations, many SNPs associated with SUA concentrations in European analyses have also been identified in Japanese, African-American, and Indian ancestry cohorts. While various genes are involved in UA transport in the human renal proximal tubule, only a subset has been linked to SUA concentrations and/or gout through GWAS, despite evidence of their involvement in vitro [64,65,66].

2.1*Probenecid*

Probenecid primarily inhibits the activity of the URAT1 (SLC22A12) transporter protein, hindering the reabsorption of organic anions from the renal proximal tubule. It may also affect OAT1 (SLC22A6), OAT4 (SLC22A11), and OAT10. Additionally, probenecid acts as a competitive inhibitor of pannexin 1, an ATP release channel implicated in inflammasome activation and the release of IL-1ß, a key component in atherosclerosis pathophysiology [67].

However, probenecid does not appear to affect GLUT9 (SLC2A9) in vitro at an effective pharmacological concentration of 1 mM [68].

Orally administered probenecid is almost completely absorbed, with a dose-dependent plasma half-life ranging from 4 to 12 hours. Its metabolism involves oxidation of the alkyl side chains and conjugation with glucuronic acid. Plasma proteins, particularly albumin, serve as the main binding sites for probenecid and its oxidized metabolites [69]. Renal excretion is the primary route of elimination for metabolites, while excretion of the parent drug is negligible and dependent on urine pH.

Probenecid enhances the uric acid-lowering effect of allopurinol, particularly in patients with an estimated glomerular filtration rate (eGFR) greater than 50 mL/min [28]. However, due to limited long-term safety and efficacy data, caution is advised when using probenecid in individuals with a creatinine clearance (CrCl) less than 50 mL/min, especially elderly patients [70]. Nonetheless, recent findings from a sizable observational trial involving 38,888 elderly gout patients suggest that probenecid therapy may be associated with a slightly lower incidence of cardiovascular events, including myocardial infarction, stroke, and worsening heart failure, compared to allopurinol [71]. Nevertheless, there is no evidence to suggest that probenecid therapy affects endothelial function in middle-aged, overweight, non-hypertensive individuals [72].

2.2.*Lesinurad*

Lesinurad received conditional approval in the US at the end of 2015 and obtained approval in the EU in 2016. It acts as a specific inhibitor of UA reabsorption by targeting the URAT1 transporter [73]. Additionally, Lesinurad inhibits the OAT4 transporter along with URAT1, which is significant in cases of diuretic-induced hyperuricemia. Unlike probenecid, Lesinurad does not inhibit OAT1 or OAT3, thereby reducing the likelihood of drug-drug interactions, particularly with medications like methotrexate and various antibiotics, antivirals, and antiretrovirals that interact with human OAT1-3 and whose concentrations may increase when combined with probenecid [74].

Due to its moderate induction of the CYP3A cytochrome, Lesinurad may lead to decreased exposure to medications metabolized by this cytochrome, such as colchicine, statins, sildenafil, amlodipine, and indomethacin [75,76]. Furthermore, it could diminish the effectiveness of hormonal contraceptives, necessitating individuals undergoing Lesinurad therapy to use alternative forms of contraception. Therefore, it is not recommended for patients to rely solely on Lesinurad while being treated with epoxide hydrolase inhibitors like valproic acid.

2.3Arhalofenate

Arhalofenate interacts with OAT4 and URAT2 to limit proximal tubular uric acid (UA) reabsorption. Additionally, it inhibits the release of IL-ß induced by urate crystals by modifying the gamma pathway of the peroxisome proliferator-activated receptor (PPAR) [77].

As the first urate-lowering antiflare medication, arhalofenate has demonstrated efficacy in reducing gout flares at a dosage of 800 mg compared to 300 mg of allopurinol without background colchicine. Therapy-emergent side events were equally common in the active therapy groups [78]. Arhalofenate may hold particular importance for the treatment of gout in elderly individuals, who often have contraindications to corticosteroids and non-steroidal anti-inflammatory medications and may struggle to tolerate long-term colchicine for flare prophylaxis [79]. However, the effectiveness and safety of arhalofenate have not only been studied in cases of renal impairment. Furthermore, while allopurinol ensures a greater decrease in serum uric acid (SUA) levels compared to arhalofenate, the latter's uricosuric and antiflare properties suggest promising prospects for combination therapy with a xanthine oxidase inhibitor (XOI) [66]. Indeed, a 12-week open-label phase 2 study has shown that 800 mg arhalofenate in combination with 40 mg or 80 mg febuxostat has a more pronounced effect on SUA levels. Moreover, there has been no clinically meaningful increase in blood creatinine, and no deaths or significant side effects have been reported [80].

Currently, phase III clinical trials are investigating the use of arhalofenate as a gout adjunct therapy in conjunction with febuxostat. However, it was withdrawn from type 2 diabetes treatment after advancing to phase II/III clinical trials.

2.4Verinurad

Verinurad, a highly specific and potent URAT1 inhibitor, is currently under development for the treatment of asymptomatic hyperuricemia and gout. With a potency over 100 times greater for URAT1 compared to other transporters, it stands as one of the most potent URAT1 inhibitors discovered to date and exhibits high selectivity for URAT1. In vivo studies have shown that Verinurad at doses of 40 mg can reduce serum uric acid (SUA) levels by up to 62%, while multiple doses of 10 mg have achieved a reduction of about 61%. Verinurad has demonstrated good tolerability across all doses, with no significant laboratory abnormalities, ECG abnormalities, or serious adverse events reported [81]. Additionally, when combined with 300 mg of allopurinol, Verinurad (at doses ranging from 2.5 to 20 mg) has been shown to produce a dose-dependent reduction in SUA levels without any instances of elevated serum creatinine [82].

The high potency of Verinurad has allowed for a more comprehensive understanding of the molecular relationship between URAT1 and its inhibitors. Competitive binding experiments with radiolabeled Verinurad have revealed that unique URAT1 inhibitors like benzbromarone, sulfinpyrazone, and probenecid all block Verinurad binding through a competitive mechanism [83].

Recent phase II placebo-controlled clinical trials have assessed the safety and effectiveness of Verinurad in individuals with asymptomatic hyperuricemia or gout. While Verinurad monotherapy has resulted in sustained decreases in UA levels, several adverse events related to the kidneys have been reported [84].

2.5*Pegloticase*

Pegloticase, a recombinant, pegylated mammalian uricase, has been evaluated for safety and effectiveness in several clinical trials. It has demonstrated the ability to resolve tophi, reduce the number of tender and swollen joints, alleviate pain, and improve overall assessments and quality of life for patients. Additionally, it significantly lowers serum urate levels. Even in patients with chronic refractory gout who do not achieve sustained urate-lowering, pegloticase treatment still provides significant clinical benefits, as indicated by post hoc assessments of clinical results [85].

Pegloticase does not appear to have a discernible effect on renal function, but it notably lowers blood pressure in patients with chronic refractory gout [86]. However, immunogenicity and the development of anti-drug antibodies pose significant challenges for pegloticase treatment. These antibodies can lead to higher drug clearance, loss of efficacy, and infusion responses. To mitigate these issues, concurrent administration of immunosuppressants such as methotrexate may be necessary [87].

3.Novel treatment approaches

Biologic drugs that target interleukin 1 (IL-1), such as anakinra, rilonacept, and canakinumab, have recently gained attention as potential treatments for acute gout. The NLR family, pyrin domain-containing 3 (NLRP3) inflammasome, an intracellular receptor found within monocytes, detects monosodium urate (MSU) crystals after they have been phagocytosed by synovial cells. Activation of the enzyme caspase 1 leads to the release of IL-1β and triggers a neutrophilic inflammatory response. Uric acid is a byproduct of purine metabolism in humans. During the Eocene era, higher mammals lost their ability to produce the enzyme uricase, which converts uric acid into the more soluble allantoin, rendering them susceptible to hyperuricemia. Pegloticase, a pegylated uricase, has been shown in recent studies to effectively reduce the size of tophi [88,89,90]. However, neither of these therapeutic approaches is currently widely used in clinical practice in the United Kingdom.

REFERENCE

1. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol. 2014 Mar;26(2):186-91. doi: 10.1097/BOR.0000000000000028. PMID: 24419750.
2. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol. 2002 May;19(5):640-53. doi: 10.1093/oxfordjournals.molbev.a004123. PMID: 11961098.
3. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, Yang XF. Uric acid, hyperuricemia and vascular diseases. Front Biosci (Landmark Ed). 2012 Jan 1;17(2):656-69. doi: 10.2741/3950. PMID: 22201767; PMCID: PMC3247913.
4. Cicero AF, Rosticci M, Fogacci F, Grandi E, D'Addato S, Borghi C; Brisighella Heart Study Group. High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects. Eur J Intern Med. 2017 Jan;37:38-42. doi: 10.1016/j.ejim.2016.07.026. Epub 2016 Aug 3. PMID: 27498274.
5. Pascart T, Lioté F. Gout: state of the art after a decade of developments. Rheumatology (Oxford). 2019 Jan 1;58(1):27-44. doi: 10.1093/rheumatology/key002. PMID: 29547895.
6. Katsiki N, Karagiannis A, Athyros VG, Mikhailidis DP. Hyperuricaemia: more than just a cause of gout? J Cardiovasc Med (Hagerstown). 2013 Jun;14(6):397-402. doi: 10.2459/JCM.0b013e3283595adc. PMID: 23032963.
7. Roubenoff R. Gout and hyperuricemia. Rheum Dis Clin North Am. 1990 Aug;16(3):539-50. PMID: 2217957.
8. Lawrence RC, Hochberg MC, Kelsey JL, McDuffie FC, Medsger TA Jr, Felts WR, Shulman LE. Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. J Rheumatol. 1989 Apr;16(4):427-41. PMID: 2746583.
9. Mikkelsen WM, Dodge HJ, Valkenburg H. The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia: tecumseh, michigan 1959-1960. Am J Med. 1965 Aug;39:242-51. doi: 10.1016/0002-9343(65)90048-3. PMID: 14320691.
10. O'Sullivan JB. Gout in a New England town. A prevalence study in Sudbury, Massachusetts. Ann Rheum Dis. 1972 May;31(3):166-9. doi: 10.1136/ard.31.3.166. PMID: 5032448; PMCID: PMC1005891.
11. 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 Oct;63(10):3136-41. doi: 10.1002/art.30520. PMID: 21800283.
12. Otaki Y, Konta T, Ichikawa K, Fujimoto S, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Narita I, Kondo M, Shibagaki Y, Kasahara M, Asahi K, Watanabe T. Possible burden of hyperuricaemia on mortality in a community-based population: a large-scale cohort study. Sci Rep. 2021 Apr 26;11(1):8999. doi: 10.1038/s41598-021-88631-8. PMID: 33903733; PMCID: PMC8076257.
13. Koto R, Nakajima A, Horiuchi H, Yamanaka H. Real-world treatment of gout and asymptomatic hyperuricemia: A cross-sectional study of Japanese health insurance claims data. Mod Rheumatol. 2021 Jan;31(1):261-269. doi: 10.1080/14397595.2020.1784556. Epub 2020 Jul 20. PMID: 32552370.
14. Chuang SY, Lee SC, Hsieh YT, Pan WH. Trends in hyperuricemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993-1996 to 2005-2008. Asia Pac J Clin

Nutr. 2011;20(2):301-8. PMID: 21669599.
15. Ryu S, Chang Y, Zhang Y, Kim SG, Cho J, Son HJ, Shin H, Guallar E. A cohort study of hyperuricemia in middle-aged South Korean men. Am J Epidemiol. 2012 Jan 15;175(2):133-43. doi: 10.1093/aje/kwr291. Epub 2011 Dec 12. PMID: 22156041.
16. Ahn JK. Epidemiology and treatment-related concerns of gout and hyperuricemia in Korean. J Rheum Dis. 2023 Apr 1;30(2):88-98. doi: 10.4078/jrd.2022.0001. Epub 2023 Mar 17. PMID: 37483480; PMCID: PMC10324937.
17. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol. 2018 Sep;37(9):2529-2538. doi: 10.1007/s10067-018-4130-2. Epub 2018 May 23. PMID: 29790110.
18. Koo BS, Jeong HJ, Son CN, Kim SH, Kim HJ, Kim GH, Jun JB. Distribution of serum uric acid levels and prevalence of hyper- and hypouricemia in a Korean general population of 172,970. Korean J Intern Med. 2021 Mar;36(Suppl 1). doi: 10.3904/kjim.2020.116. Epub 2020 Nov 24. PMID: 33227843; PMCID: PMC8009145.
19. Rai SK, Aviña-Zubieta JA, McCormick N, De Vera MA, Shojania K, Sayre EC, Choi HK. The rising prevalence and incidence of gout in British Columbia, Canada: Population-based trends from 2000 to 2012. Semin Arthritis Rheum. 2017 Feb;46(4):451-456. doi: 10.1016/j.semarthrit.2016.08.006. Epub 2016 Aug 17. PMID: 28040245; PMCID: PMC5315679.
20. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007-2016. Arthritis Rheumatol. 2019 Jun;71(6):991-999. doi: 10.1002/art.40807.
21. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: The National Health and Nutrition Examination Survey, 2007-2016. Arthritis Rheumatol. 2019 Jun;71(6):991-999. doi: 10.1002/art.40807. PMID: 30618180; PMCID: PMC6536335.
22. Anagnostopoulos I, Zinzaras E, Alexiou I, Papathanasiou AA, Davas E, Koutroumpas A, Barouta G, Sakkas LI. The prevalence of rheumatic diseases in central Greece: a population survey. BMC Musculoskelet Disord. 2010 May 26;11:98. doi: 10.1186/1471-2474-11-98. PMID: 20504294; PMCID: PMC2890601.
23. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2015 Apr;74(4):661-7. doi: 10.1136/annrheumdis-2013-204463. Epub 2014 Jan 15. PMID: 24431399; PMCID: PMC4392307.
24. Zobbe K, Prieto-Alhambra D, Cordtz R, Højgaard P, Hindrup JS, Kristensen LE, Dreyer L. Secular trends in the incidence and prevalence of gout in Denmark from 1995 to 2015: a nationwide register-based study. Rheumatology (Oxford). 2019 May 1;58(5):836-839. doi: 10.1093/rheumatology/key390. PMID: 30590724.
25. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med. 1987 Mar;82(3):421-6. doi: 10.1016/0002-9343(87)90441-4. PMID: 3826098.
26. Kelley W, Schumacher HR. Crystal-associated synovitis. Gout. In: Kelley WN, ed. Textbook of rheumatology. 4th ed. Philadelphia: Saunders, 1993:1291–336.

27. Cicero AFG, Fogacci F, Cincione RI, Tocci G, Borghi C. Clinical effects of xanthine oxidase inhibitors in hyperuricemic patients. Med Princ Pract. 2021 Apr 14;30(2):122-130. doi: 10.1159/000512178.
28. Bredemeier M, Lopes LM, Eisenreich MA, Hickmann S, Bongiorno GK, d'Avila R, Morsch ALB, da Silva Stein F, Campos GGD. Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2018 Feb 7;18(1):24. doi: 10.1186/s12872-018-0757-9. PMID: 29415653; PMCID: PMC5804046.
29. Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. Pharmacol Ther. 2017 Apr;172:139-150. doi: 10.1016/j.pharmthera.2016.12.004. Epub 2016 Dec 2. PMID: 27916655.
30. 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 Feb 8;13:23-28. doi: 10.2147/VHRM.S115080. PMID: 28223818; PMCID: PMC5308472.
31. Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46(8):623-44. doi: 10.2165/00003088-200746080-00001. PMID: 17655371.
32. Allopurinol Tablet. Accord Healthcare Inc. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=682dd8b8-fc6e-47c5-95b7-2d7ad96b750. Accessed 9 October 2019.
33. Cicero AFG, Pirro M, Watts GF, Mikhailidis DP, Banach M, Sahebkar A. Effects of allopurinol on endothelial function: a systematic review and meta-analysis of randomized placebo-controlled trials. Drugs. 2018 Jan;78(1):99-109. doi: 10.1007/s40265-017-0839-5. PMID: 29139092.
34. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006 Jan;47(1):51-9. doi: 10.1053/j.ajkd.2005.10.006. PMID: 16377385.
35. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010 Aug;5(8):1388-93. doi: 10.2215/CJN.01580210. Epub 2010 Jun 10. PMID: 20538833; PMCID: PMC2924417.
36. Pea F. Pharmacology of drugs for hyperuricemia. Mechanisms, kinetics and interactions. Contrib Nephrol. 2005;147:35-46. doi: 10.1159/000082540. PMID: 15604604.
37. Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. Curr Rheumatol Rep. 2009 Apr;11(2):135-40. doi: 10.1007/s11926-009-0019-z. PMID: 19296886.
38. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, Dalbeth N. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum. 2012 Aug;64(8):2529-36. doi: 10.1002/art.34488. PMID: 22488501.
39. Chung Y, Stocker SL, Graham GG, Day RO. Optimizing therapy with allopurinol: factors limiting hypouricemic efficacy. Am J Med Sci. 2008 Mar;335(3):219-26. doi: 10.1097/MAJ.0b013e31815acb10. PMID: 18344696.

40. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, Chen YT. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005 Mar 15;102(11):4134-9. doi: 10.1073/pnas.0409500102. Epub 2005 Mar 2. PMID: 15743917; PMCID: PMC554812.
41. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 14 April 2019.
42. Allopurinol Oral Tablets; Northstar Rx LLC: Memphis, TN, USA, 2015.
43. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, Chapman PT. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011 Feb;63(2):412-21. doi: 10.1002/art.30119. PMID: 21279998.
44. Pascual E, Sivera F, Yasothan U, Kirkpatrick P. Febuxostat. Nat Rev Drug Discov. 2009 Mar;8(3):191-2. doi: 10.1038/nrd2831. PMID: 19247302.
45. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005 Dec 8;353(23):2450-61. doi: 10.1056/NEJMoa050373. PMID: 16339094.
46. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher C, Joseph-Ridge N. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008 Nov 15;59(11):1540-8. doi: 10.1002/art.24209. PMID: 18975369.
47. Malik UZ, Hundley NJ, Romero G, Radi R, Freeman BA, Tarpey MM, Kelley EE. Febuxostat inhibition of endothelial-bound XO: implications for targeting vascular ROS production. Free Radic Biol Med. 2011 Jul 1;51(1):179-84. doi: 10.1016/j.freeradbiomed.2011.04.004. Epub 2011 Apr 15. PMID: 21554948; PMCID: PMC3130629.
48. Tausche AK, Christoph M, Forkmann M, Richter U, Kopprasch S, Bielitz C, Aringer M, Wunderlich C. As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout. Rheumatol Int. 2014 Jan;34(1):101-9. doi: 10.1007/s00296-013-2857-2. Epub 2013 Sep 12. PMID: 24026528.
49. Hays AG, Iantorno M, Schär M, Lai S, Czarny M, Breton E, Palmer RN, Whelton A, Weiss RG, Gerstenblith G. The influence of febuxostat on coronary artery endothelial dysfunction in patients with coronary artery disease: a phase 4 randomized, placebo-controlled, double-blind, crossover trial. Am Heart J. 2018 Mar;197:85-93. doi: 10.1016/j.ahj.2017.11.006. Epub 2017 Nov 23. PMID: 29447788.
50. Hosoya T, Sasaki T, Ohashi T. Clinical efficacy and safety of topiroxostat in Japanese hyperuricemic patients with or without gout: a randomized, double-blinded, controlled phase 2b study. Clin Rheumatol. 2017 Mar;36(3):649-656. doi: 10.1007/s10067-016-3474-8. Epub 2016 Nov 10. PMID: 27832384; PMCID: PMC5323498.

51. Nakamura T, Murase T, Nampei M, Morimoto N, Ashizawa N, Iwanaga T, Sakamoto R. Effects of topiroxostat and febuxostat on urinary albumin excretion and plasma xanthine oxidoreductase activity in db/db mice. Eur J Pharmacol. 2016 Jun 5;780:224-31. doi: 10.1016/j.ejphar.2016.03.055. Epub 2016 Mar 30. PMID: 27038523.
52. Hosoya T, Ohno I, Nomura S, Hisatome I, Uchida S, Fujimori S, Yamamoto T, Hara S. Effects of topiroxostat on the serum urate levels and urinary albumin excretion in hyperuricemic stage 3 chronic kidney disease patients with or without gout. Clin Exp Nephrol. 2014 Dec;18(6):876-84. doi: 10.1007/s10157-014-0935-8. Epub 2014 Jan 22. PMID: 24448692; PMCID: PMC4271138.
53. Nagaoka Y, Tanaka Y, Yoshimoto H, Suzuki R, Ryu K, Ueda M, Akiyama M, Nagai M, Miyaoka Y, Kanda E, Iwai S, Nagaoka M, Kanno Y. The effect of small dose of topiroxostat on serum uric acid in patients receiving hemodialysis. Hemodial Int. 2018 Jul;22(3):388-393. doi: 10.1111/hdi.12620. Epub 2017 Dec 11. PMID: 29227568.
54. Kato S, Ando M, Mizukoshi T, Nagata T, Katsuno T, Kosugi T, Tsuboi N, Maruyama S. Randomized control trial for the assessment of the anti-albuminuric effects of topiroxostat in hyperuricemic patients with diabetic nephropathy (the ETUDE study). Nagoya J Med Sci. 2016 May;78(2):135-42. PMID: 27303100; PMCID: PMC4885813.
55. Lipkowitz MS. Regulation of uric acid excretion by the kidney. Curr Rheumatol Rep. 2012 Apr;14(2):179-88. doi: 10.1007/s11926-012-0240-z. PMID: 22359229.
56. Wright AF, Rudan I, Hastie ND, Campbell H. A 'complexity' of urate transporters. Kidney Int. 2010 Sep;78(5):446-52. doi: 10.1038/ki.2010.206. Epub 2010 Jul 7. PMID: 20613716.
57. Reginato AM, Mount DB, Yang I, Choi HK. The genetics of hyperuricaemia and gout. Nat Rev Rheumatol. 2012 Oct;8(10):610-21. doi: 10.1038/nrrheum.2012.144. Epub 2012 Sep 4. PMID: 22945592; PMCID: PMC3645862.
58. Shin HJ, Takeda M, Enomoto A, Fujimura M, Miyazaki H, Anzai N, Endou H. Interactions of urate transporter URAT1 in human kidney with uricosuric drugs. Nephrology (Carlton). 2011 Feb;16(2):156-62. doi: 10.1111/j.1440-1797.2010.01368.x. PMID: 21272127.
59. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Hosoyamada M, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature. 2002 May 23;417(6887):447-52. doi: 10.1038/nature742. Epub 2002 Apr 14. PMID: 12024214.
60. Le MT, Shafiu M, Mu W, Johnson RJ. SLC2A9--a fructose transporter identified as a novel uric acid transporter. Nephrol Dial Transplant. 2008 Sep;23(9):2746-9. doi: 10.1093/ndt/gfn349. Epub 2008 Jul 7. PMID: 18606621; PMCID: PMC2734172.
61. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, Mangino M, Albrecht E, Wallace C, Farrall M, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet. 2009;5. doi: 10.1371/journal.pgen.1000504.
62. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, Takahashi A, Maeda S, Tsunoda T, Chen P, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet. 2012;44:904-909. doi: 10.1038/ng.2352.
63. Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, Pistis G,

Ruggiero D, O'Seaghdha CM, Haller T, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. 2013;45:145-154. doi: 10.1038/ng.2500.

64. Sato M, Iwanaga T, Mamada H, Ogihara T, Yabuuchi H, Maeda T, Tamai I. Involvement of uric acid transporters in alteration of serum uric acid level by angiotensin II receptor blockers. Pharm Res. 2008;25:639-646. doi: 10.1007/s11095-007-9475-y.
65. Burckhardt G, Burckhardt BC. In vitro and in vivo evidence of the importance of organic anion transporters (OATs) in drug therapy. In: Drug Transporters. Berlin/Heidelberg: Springer; 2011. pp. 29-104. doi: 10.1007/978-3-642-14541-4_2.
66. Pascart T, Richette P. Current and future therapies for gout. Expert Opin Pharmacother. 2017;18:1201-1211. doi: 10.1080/14656566.2017.1355547.
67. Silverman W, Locovei S, Dahl G. Probenecid, a gout remedy, inhibits pannexin 1 channels. Am J Physiol Cell Physiol. 2008;295. doi: 10.1152/ajpcell.00178.2008.
68. Bach MH, Simkin PA. Uricosuric drugs: The once and future therapy for hyperuricemia? Curr Opin Rheumatol. 2014;26:169-175. doi: 10.1097/BOR.0000000000000024.
69. Cunningham RF, Israili ZH, Dayton PG. Clinical pharmacokinetics of probenecid. Clin Pharmacokinet. 1981;6:135-151. doi: 10.2165/00003088-198106020-00004.
70. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63:2227-2246. doi: 10.1111/jgs.13702.
71. Kim SC, Neogi T, Kang EH, Liu J, Desai RJ, Zhang M, Solomon DH. Cardiovascular Risks of Probenecid Versus Allopurinol in Older Patients with Gout. J Am Coll Cardiol. 2018;71:994-1004. doi: 10.1016/j.jacc.2017.12.065.
72. Borgi L, McMullan C, Wohlhueter A, Curhan GC, Fisher ND, Forman JP. Effect of uric acid-lowering agents on endothelial function: A randomized, double-blind, placebo-controlled trial. Hypertension. 2017;69:243-248. doi: 10.1161/HYPERTENSIONAHA.116.08580.
73. Heel RC, Brogden RN, Speight TM, Avery GS. Benzbromarone: A review of its pharmacological properties and therapeutic use in gout and hyperuricaemia. Drugs. 1977;14:349-366. doi: 10.2165/00003495-197714060-00002.
74. Miner JN, Tan PK, Hyndman D, Liu S, Iverson C, Nanavati P, Hagerty DT, Manhard K, Shen Z, Girardet JL, et al. Lesinurad, a novel, oral compound for gout, acts to decrease serum uric acid through inhibition of urate transporters in the kidney. Arthritis Res. 2016;18:214-223. doi: 10.1186/s13075-016-1067-2.
75. Gillen M, Yang C, Wilson D, Valdez S, Lee C, Kerr B, Shen Z. Evaluation of pharmacokinetic interactions between lesinurad, a new selective urate reabsorption inhibitor, and CYP enzyme substrates sildenafil, amlodipine, tolbutamide, and repaglinide. Clin Pharm Drug Dev. 2017;6:363-376. doi: 10.1002/cpdd.314.
76. Shen Z, Tieu K, Wilson D, Bucci G, Gillen M, Lee C, Kerr B. Evaluation of pharmacokinetic interactions between lesinurad, a new selective urate reabsorption inhibitor, and commonly used drugs for gout treatment. Clin Pharm Drug Dev. 2017;6:377-387. doi: 10.1002/cpdd.316.
77. Sattui SE, Gaffo AL. Treatment of hyperuricemia in gout: Current therapeutic options, latest developments and clinical implications. Ther Adv Musculoskelet Dis. 2016;8:145-159. doi: 10.1177/1759720X16643673.
78. Poiley J, Steinberg AS, Choi YJ, Davis CS, Martin RL, McWherter CA, Boudes PF;

Arhalofenate Flare Study Investigators. A randomized, double-blind, active- and placebo-controlled efficacy and safety study of arhalofenate for reducing flare in patients with gout. Arthritis Rheumatol. 2016;68:2027-2034. doi: 10.1002/art.39611.
79. Abhishek A. Managing Gout Flares in the Elderly: Practical Considerations. Drugs Aging. 2017;34:873-880. doi: 10.1007/s40266-017-0496-3.
80. Steinberg AS, Vince BD, Choi YJ, Martin RL, McWherter CA, Boudes PF. The pharmacodynamics, pharmacokinetics, and safety of arhalofenate in combination with febuxostat when treating hyperuricemia associated with gout. J Rheumatol. 2017;44:374-379. doi: 10.3899/jrheum.161428.
81. Shen Z, Gillen M, Miner JN, Bucci G, Wilson DM, Hall JW. Pharmacokinetics, pharmacodynamics, and tolerability of verinurad, a selective uric acid reabsorption inhibitor, in healthy adult male subjects. Drug Des Devel Ther. 2017;11:2077-2086. doi: 10.2147/DDDT.S141803.
82. Fleischmann R, Winkle P, Miner JN, Yan X, Hicks L, Valdez S, Hall J, Liu S, Shen Z, Gillen M, et al. Pharmacodynamic and pharmacokinetic effects and safety of verinurad in combination with allopurinol in adults with gout: A phase IIa, open-label study. RMD Open. 2018;4. doi: 10.1136/rmdopen-2017-000584.
83. Tan PK, Liu S, Gunic E, Miner JN. Discovery and characterization of verinurad, a potent and specific inhibitor of URAT1 for the treatment of hyperuricemia and gout. Sci Rep. 2017;7:665. doi: 10.1038/s41598-017-00785-5.
84. Fitz-Patrick D, Roberson K, Niwa K, Fujimura T, Mori K, Hall J, Yan X, Shen Z, Liu S, Ito Y, et al. Safety and efficacy of verinurad, a selective URAT1 inhibitor, for the treatment of patients with gout and/or asymptomatic hyperuricemia in the United States and Japan: Findings from two phase II trials. Mod Rheumatol. 2019;29:1042-1052. doi: 10.1080/14397595.2018.1552895.
85. Schlesinger N, Lipsky PE. Pegloticase treatment of chronic refractory gout: Update on efficacy and safety. Semin Arthritis Rheum. 2020;S31-S38. doi: 10.1016/j.semarthrit.2020.06.001.
86. Johnson RJ, Choi HK, Yeo AE, Lipsky PE. Pegloticase Treatment Significantly Decreases Blood Pressure in Patients with Chronic Gout. Hypertension. 2019;74:95-101. doi: 10.1161/HYPERTENSIONAHA.118.12377.
87. Botson JK, Tesser J, Bennett R, Kenney HM, Peloso PM, Obermeyer K, LaMoreaux B, Weinblatt ME, Peterson J. Pegloticase in combination with methotrexate in patients with uncontrolled gout: A multicenter, open-label study (MIRROR). J Rheumatol. 2020. doi: 10.3899/jrheum.191267.
88. Martinon F, Pétrilli V, Mayor A et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440:237–241. doi: 10.1038/nature04516.
89. Sundy JS, Baraf HS, Yood RA et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306:711–720. doi: 10.1001/jama.2011.1169.
90. Roddy E, Doherty M. Treatment of hyperuricaemia and gout. Clin Med (Lond). 2013;13(4):400-403. doi: 10.7861/clinmedicine.13-4-400.