Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Hepatic Safety of Febuxostat and Allopurinol in Gout Patients: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

Christiyanti Dewi[1], Falerina Puspita[2], Widya Norma Insani[1,3], Rano Kurnia Sinuraya[1,3], Irma Melyani Puspitasari[1,3], Neily Zakiyah[1,3]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia; [2]Department of Pharmacy, RSUD Bandung Kiwari, Bandung, Indonesia; [3]Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia

Correspondence: Neily Zakiyah, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, 45363, Indonesia, Tel +62 84288888, Ext. 3510, Email neily.zakiyah@unpad.ac.id

Purpose: This study aimed to conduct an updated systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the hepatic safety of febuxostat and allopurinol in gout patients. Subgroup analyses were conducted based on age, dosage, and treatment duration.

Methods: This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Published studies were reviewed in PubMed, The Cochrane Library, and Scopus. The Cochrane Risk of Bias (RoB) 2 tool was used to assess the quality of the included studies. Risk ratios (RR) were estimated using binary outcomes of fixed effect model and were reported with corresponding 95% confidence intervals (CI). This study is registered on PROSPERO with number CRD42024611074.

Results: Out of 703 publications from the databases, a total of 15 studies met the inclusion criteria. The RR meta-analysis of the included studies was calculated using binary outcomes and a fixed effect model based on available hepatic safety events. We identified 5 RCTs with some concerns regarding the risk of bias, and 10 RCTs with a low risk of bias. Overall, hepatic safety outcomes were comparable between febuxostat and allopurinol, including across subgroups by age, dosage, and treatment duration. Febuxostat showed no significant difference in hepatic risk compared to allopurinol, with RRs of 1.03 (95% CI: 0.78–1.36) for overall liver function abnormalities, 1.03 (95% CI: 0.66–1.61) for investigator-defined liver abnormalities, and 1.21 (95% CI: 0.96–2.74) for hepatobiliary disorders.

Conclusion: This updated systematic review and meta-analysis found no difference in hepatic safety profiles between febuxostat and allopurinol in patients with gout across age categories, dosage levels, or treatment durations. Further research is warranted to address the limitations of sample sizes and the overall moderate quality of existing evidence.

Keywords: febuxostat, allopurinol, gout, hepatic safety, randomized controlled trial

Introduction

Gout is a chronic metabolic disease characterized by elevated serum uric acid levels and the deposition of monosodium urate crystals in joints and connective tissues. Clinically, it presents as recurrent episodes of acute arthritis, and if left untreated, may progress to chronic gouty arthritis, characterized by persistent joint inflammation, deformity, and tophus formation. Maintaining serum uric acid levels through appropriate treatment and lifestyle changes is essential for reducing both the clinical impact and financial burden associated with managing gout.[1–5]

Febuxostat and allopurinol have been extensively studied in clinical trials and are widely recommended as first-line medications to reduce serum uric acid in gout patients, and are included in treatment guidelines in several countries.[2,6–8] Both febuxostat and allopurinol are primarily metabolized in the liver, with different mechanisms. Allopurinol is metabolized to oxypurinol as an active metabolite, which is primarily cleared by the kidneys. Meanwhile, febuxostat

Received: 8 July 2025
Accepted: 24 November 2025
Published: 18 December 2025

is metabolized mainly by glucuronide formation and oxidation in the liver.[5,9–12] Due to its reliance on hepatic metabolism, it has raised concerns regarding potential hepatotoxicity.

Concerning long-term use of urate-lowering therapy, which is important for effective treatment of chronic gout, the incidence of abnormal liver function has been reported in clinical studies.[2,6–8] Numerous randomized controlled trials (RCTs) have demonstrated the efficacy of febuxostat in lowering serum uric acid levels, with some studies reporting superior outcomes compared to allopurinol.[6,7,13,14] However, the safety profile, particularly the hepatic safety of febuxostat relative to allopurinol, remains less clearly established.[6,7,9,13–17] A focused study on hepatic safety reported that febuxostat is safe compared to allopurinol in patients with fatty liver diseases. However, the number of patients enrolled in the study is limited.[9] Systematic analysis of hepatic safety data is essential to better understand the potential risks associated with long-term use of these medicines.

A previous systematic review summarized findings from RCTs evaluating hepatic adverse events, indicating that adult gout patients exhibited similar hepatic safety profiles for both febuxostat and allopurinol.[18] However, to date, no meta-analysis has synthesized these data to provide a comprehensive pooled estimate of hepatic risk between febuxostat and allopurinol. This gap is particularly important given the long-term use of urate-lowering therapy in gout and the need for a robust safety profile to support clinical decision-making. In addition, variations in patient age, dosage, and treatment duration across studies may contribute to heterogeneity in hepatic safety outcomes, highlighting the need for subgroup analyses.[2] These factors can influence drug metabolism capacity, potentially leading to drug accumulation in the liver and increasing the risk of hepatic injury.[9]

Therefore, this study aims to conduct a comprehensive systematic review and meta-analysis of RCTs to assess the hepatic safety of febuxostat compared to allopurinol in adult gout patients. By providing pooled-effect estimates of hepatic risk and examining potential modifiers, such as age and treatment duration, this analysis aims to generate evidence supporting safer and more informed gout management strategies to support clinical relevance of hepatic safety monitoring in long-term gout therapy.

Materials and Methods

Systematic Search Strategy

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] We systematically searched PubMed, The Cochrane Library, and Scopus for clinical trial articles reporting quantifiable hepatic safety data of febuxostat and allopurinol in adult gout patients, up to May 1, 2025. The detail of the electronic search terms in the databases is provided in Supplement 1. Citation references from identified articles were also manually reviewed to determine additional relevant publications. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) number CRD42024611074. The details of PRISMA checklist are provided in the Supplement 2.

Eligibility and Study Selection

This study assessed the hepatic safety profile of febuxostat and allopurinol in adults aged 18 years or older who had gout or hyperuricemia, using data from RCTs. Eligible studies were those that directly compared febuxostat and allopurinol and reported liver-related safety outcomes, including abnormalities in liver function tests, investigator-defined hepatic abnormalities, liver dysfunction leading to treatment discontinuation, or hepatobiliary disorders. We excluded studies that were non-English, non-RCT which includes observational studies (eg, case–control, cohort, cross-sectional), reviews, case reports, case series, systematic reviews and meta-analysis, conference abstracts or proceedings, economic evaluations, and non-peer-reviewed sources The research question and eligibility criteria followed the PICO framework: population adults with gout or hyperuricemia, intervention febuxostat, comparator allopurinol, and outcomes hepatic safety endpoints in RCT (ie, overall liver function abnormalities, hepatobiliary dysfunction, investigator-defined liver abnormalities).

To ensure accuracy and consistency of the selection process, two reviewers independently screened the articles from the databases during both initial title-and-abstract and full-text screening. Discrepencies were resolved through

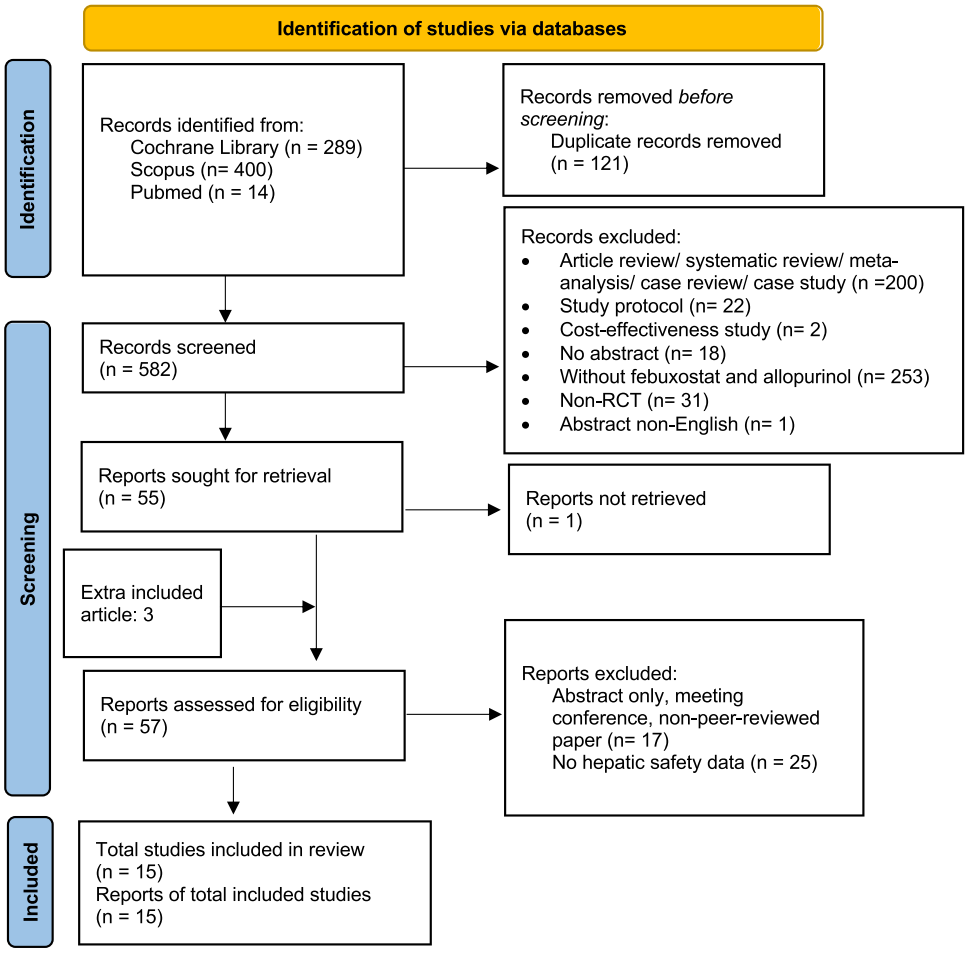


Figure 1 PRISMA 2020 flow diagram for systematic reviews. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71.

discussion. Duplicates and irrelevant studies were excluded. For all included studies, full-text data extraction and quality assessment were conducted using the Cochrane Risk of Bias (RoB) 2 tool.[20] Relevant information on study characteristics and hepatic safety outcomes was collected. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Data Collection and Quality Assessment

A predefined spreadsheet was used to organize data extracted from the included studies, which comprised information on the country, publication year, population, sample size, intervention dosage, and duration of therapy. Dichotomous hepatic safety events data were tabulated and estimated as risk ratio (RR).

The risk of bias was independently assessed by two reviewers and summarized in the meta-analysis. The Cochrane Risk of Bias (RoB) 2 tool was used to assess the methodological quality and potential biases of the included RCTs. RoB 2 evaluates five domains: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.[20–22] Two reviewers independently conducted the assessments, and any disagreements were resolved through discussion to reach consensus.

Data Analysis

Meta-analysis was conducted using R Studio. The total number of hepatic safety events and the number of participants who completed the study protocol were extracted from each included study. Risk ratios (RRs) with

95% confidence intervals (CIs) were calculated from the pooled data. Heterogeneity was assessed using the I^2 statistic. A random-effects model was applied when I^2 exceeded 30%; otherwise, a fixed-effects model was used. Subgroup analyses were undertaken to determine RR values in specific patient and treatment categories. Elderly patients were defined as those aged ≥65 years, consistent with the age categories reported in the included studies. Febuxostat dosage subgroups were categorized as 80 mg and 120 mg, as these were the most consistently reported therapeutic doses across the trials. Treatment duration subgroups were defined as short-term (<6 months) and long-term (≥6 months), based on the follow-up periods described in the included studies. These subgroup definitions and justifications were guided by the availability of data from the original publications.

Results

Study Characteristics

A total of 703 records were initially identified from PubMed, the Cochrane Library, and Scopus. After removing 121 duplicates, 582 records were screened based on title and abstract. We excluded 200 articles identified as reviews, systematic reviews, meta-analyses, case reviews, case studies; as well as 22 study protocols, 2 economic evaluation studies, 18 records without abstracts, 253 studies that did not involve febuxostat or allopurinol, 31 non-randomized controlled trials (non-RCTs), and 1 non-English abstract.

Following this, 55 full-text articles were assessed. One study could not be retrieved due to unavailability. An additional 3 eligible articles were identified through citation snowballing, resulting in a total of 57 studies for final eligibility review. Of these, 15 studies met the inclusion and exclusion criteria and were included in this meta-analysis.[13,14,23–35] The remaining 42 studies were excluded due to the following reasons: abstract-only publications, non-peer-reviewed records, or lacking hepatic safety outcomes.

Study Design

Of the 15 included studies, 10 were double-blind RCTs.[13,24–28,30] The remaining five were open-label or did not clearly report blinding.[23,29,32–34] Blinding might have been compromised in studies involving dose titration of allopurinol, especially among patients with renal impairment.[13,14,23,29,35]

Quality Assessment

Figure 2 summarized the RoB 2 assessment of the 15 included studies.[13,14,23–35] Ten studies have a low risk of bias, while five were rated as having "some concerns",[22,29–32] primarily due to lack of blinding,[23,30,32,33,36] where participants were aware of their assigned interventions during the trials. Measurement of outcome might not be objective and could be influenced by knowledge of the intervention received in an open-label study. In several studies, the randomization process is not clearly described, including the method used to generate a random allocation sequence.[23,25–27,30,31,34]

Participant Characteristics

Details of the 15 included studies are presented in Table 1.[13,14,23–35] A total of 14,186 gout patients from various countries, including the United States (US), Canada, Japan, China, European countries, Brazil, and the United Kingdom, were included. Some participants included in the study population had a predefined condition of hematologic malignancies (2%), chronic kidney disease (CKD) stage 2–5 (3%), end-stage disease with hemo-dialysis patients (1%), or elderly patients (43%).[27,30–32,34] Study publication years ranged from 2005–2024.[13,33]

The studies assessed a range of febuxostat doses: low dose of 10/20 mg22,16,23, 40 mg,[14,26,28,29] 80 mg,[13,14,23,26,28,29,33,35], 120 mg[13,23,27,34] and 240 mg[34] per day, compared to daily doses of allopurinol (50–600 mg).[13,14,23,28,29,31,33] Study durations varied from 7–9 days[27] to up to 3 years,[23] with one study not reporting duration.[32]

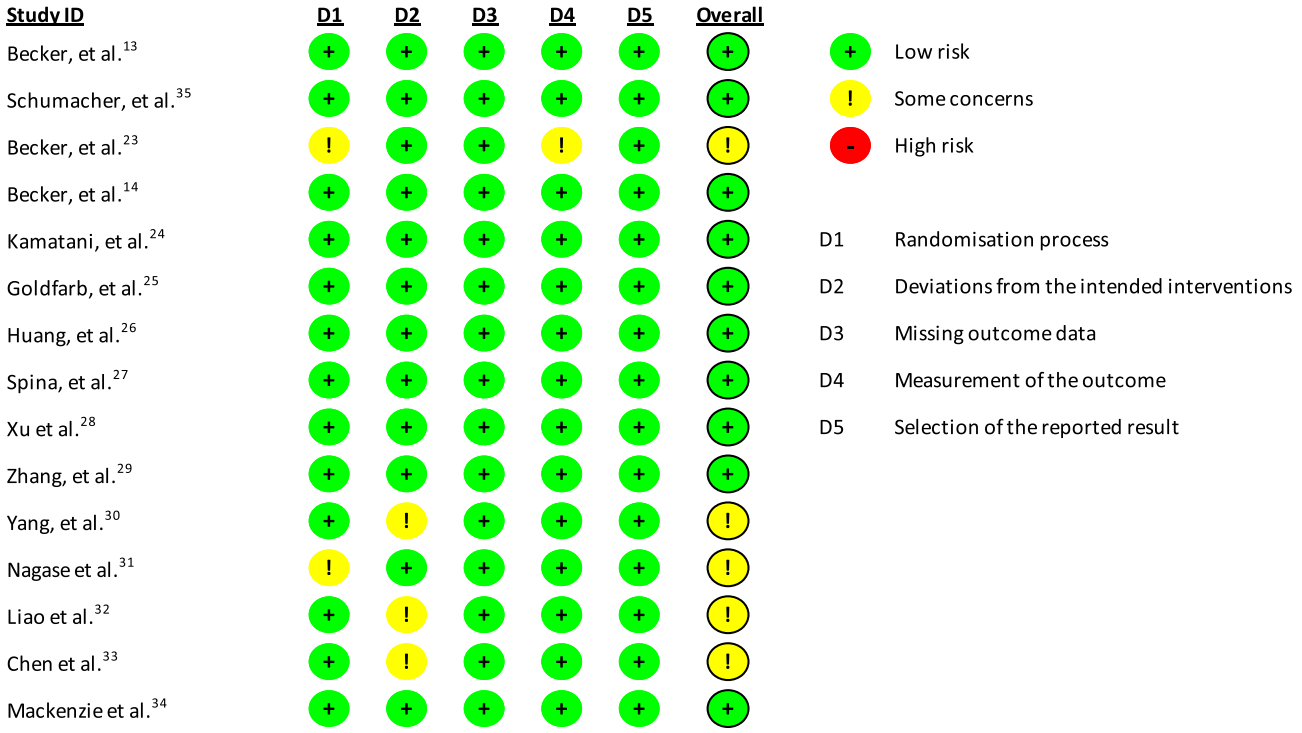


Figure 2 Assessment of quality of the included studies using the Cochrane Risk of Bias Tool (RoB 2.0).

Meta-Analysis Outcomes

Overall Liver Function Test

Figure 3 presents the overall liver function data from 7 studies.[13,14,26,28,29,32,33] Meta-analysis demonstrated no significant difference in overall liver function abnormalities between febuxostat and allopurinol (RR 1.03; 95% 0.78–1.36;I^2 = 1%,

Table 1 Characteristics of Included Studies

Study	Publication Year	Country	Study Design	Study Treatment Duration	Study Population (Indication)	Intervention (Dose per Day)	Number of Participants
Becker et al[13]	2005	United States and Canada	Randomized, double-blind controlled trial	52 weeks	Gout and with SUA concentration of at least 8.0 mg/dl, met the preliminary criteria of the American College of Rheumatology for acute arthritis of gout.	Febuxostat 80 mg, Febuxostat 120 mg, Allopurinol 300 mg	762
Schumacher et al[35]	2008	United States	Randomized, Double-blind, Parallel-Group Trial	28 weeks	Gout (defined by American College of Rheumatology), hyperuricemia (serum urate (SUA) level ≥ 8 mg/dl), normal or impaired renal function	Febuxostat 80 mg, Febuxostat 120 mg, Febuxostat 240 mg, Allopurinol 100/ 300 mg, Placebo	1072

(*Continued*)

https://doi.org/10.2147/TCRM.S552281

Table 1 (Continued).

Study	Publication Year	Country	Study Design	Study Treatment Duration	Study Population (Indication)	Intervention (Dose per Day)	Number of Participants
Becker et al[23]	2009	United States, Canada	Open label extension study	1-3 years	Gout (according to American Rheumatism Association, SUA ≥ 8.0 mg/dl)	Febuxostat 80 mg, Febuxostat 120 mg, Allopurinol 100/ 300 mg	1280
Becker et al[14]	2010	United States	Double-blind Randomized Controlled Trial	6 months	Gout (fulfilling American Rheumatology Association), SUA > 8.0 mg/dl)	Febuxostat 40 mg, Febuxostat 80 mg, Allopurinol 200/ 300 mg	2268
Kamatani et al[24]	2011	Japan	Allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study	8 weeks	SUA > 8.0 mg/dl	Febuxostat 10/ 20 mg, Allopurinol 100 mg	244
Goldfarb et al[25]	2013	United States	Phase II, double-blind randomized controlled trial	6 months	Higher Elevated urinary uric acid (uUA) excretion (> 700 mg/ 2g h)	Febuxostat 80 mg, Allopurinol 200/ 300 mg, Placebo	99
Huang et al[26]	2014	China	Allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study	8 weeks	SUA > 8.0 mg/dl	Febuxostat 40 mg, febuxostat 80 mg, Allopurinol 300 mg	516
Spina et al[27]	2015	European countries and Brazil	Double-blind, randomized, parallel-group, comparative pivotal study	7 - 9 days	Hematologic malignancies patient, SUA < 10 mg/dl	Allopurinol 200/ 300/ 600 mg, Febuxostat 120 mg	346
Xu et al[28]	2015	China	Randomized, allopurinol-controlled, double-blinded, triple-dummy, parallel study	24 weeks	Gout (defined by American Rheumatism Association (ARA) criteria), hyperuricemia (defined SUA 480 μmol/ L), normal renal function	Febuxostat 40 mg, febuxostat 80 mg, Allopurinol 100 mg	504

(*Continued*)

Table 1 (Continued).

Study	Publication Year	Country	Study Design	Study Treatment Duration	Study Population (Indication)	Intervention (Dose per Day)	Number of Participants
Zhang et al[29]	2019	China	Randomized, Double-blinded, Non-inferiority study	24 weeks	SUA > 7.0 mg/dl with a history of gout, SUA ≥ 8 mg/dl with complications or SUA ≥ 9.0 mg/dl without complication	Febuxostat 40 mg, Febuxostat 80 mg, Allopurinol 300 mg	599
Yang et al[30]	2022	China	Double-center, randomized, controlled study	6 months	Confirmed diagnosis of CKD stage 2 −3, complicated with SUA ≥ 7 mg/dl for male and SUA ≥ 6 mg/dl for female.	Febuxostat 20 mg, Allopurinol 50/ 100/ 200 mg	120
Nagase et al[31]	2019	Japan	Randomized controlled study	12 weeks	End-stage renal disease patients undergoing stable maintenance hemo- dialysis as an outpatient for more than six months	Febuxostat 20 mg, Allopurinol 100 mg	50
Liao et al[32]	2022	China	Randomized controlled study	Not defined in literature	Patient with Chronic Kidney Disease (CKD) Stage 3–5 combined with hyperuricemia	Febuxostat 40 mg, Allopurinol 100 mg	100
Chen et al[33]	2024	China	Prospective randomized controlled trial	24 weeks	Gout patient	Febuxostat 80 mg, Allopurinol 300 mg	98
Mackenzie et al[34]	2020	United Kingdom (Scotland and England)	Prospective, randomized, open-label, blinded-endpoint multicentre trial	7 years	Elderly gout patients (60 years or older)	Febuxostat 40 mg, Febuxostat 80 mg, Allopurinol 100 mg or 300mg	6128

Abbreviations: SUA, serum urate; uUA, urinary uric acid; ARA, American Rheumatism Association; CKD, Chronic Kidney Disease.

p = 0.41). Most liver function test abnormalities were mild to moderate. No cases of liver-related death were reported which is consistent with a previous systematic review.[18]

Investigator-Defined Liver Abnormalities

We sought consistent adverse events in liver function for both febuxostat and allopurinol.[23,26,27,29] These abnormalities, as identified through liver function tests, sometimes resulted in study withdrawal according to the investigator's assessment. A meta-analysis of three studies found no significant difference between febuxostat and allopurinol in investigator-defined liver abnormalities (RR 1.03; 95% 0.66–1.61; $I^2 = 0\%$, p = 0.51) (Figure 4). The cutoff for abnormal findings on liver function was not described in the literature; however, the investigator designated the abnormalities as AE based on the following parameters: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, abnormal findings on liver function tests, and transaminases increased.[14,27,35]

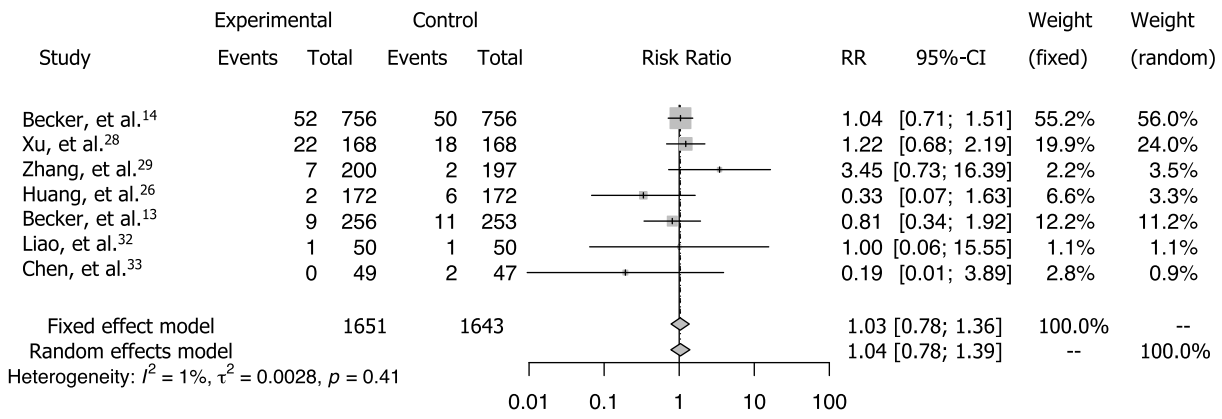


Figure 3 Forest plot of overall liver function test between the experimental group (febuxostat) and the control group (allopurinol).

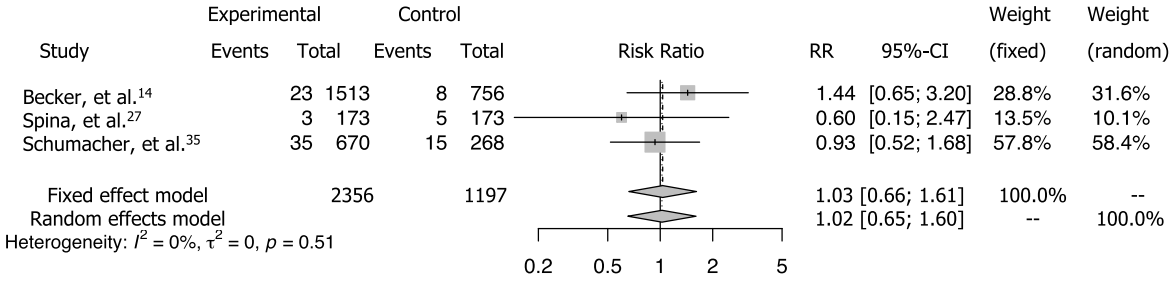


Figure 4 Forest plot of liver abnormal defined by investigator between the experimental group (febuxostat) and the control group (allopurinol).

Hepatobiliary Dysfunction

Four studies evaluated hepatobiliary dysfunction.[23,26–29] The pooled analysis showed no significant difference in risk between febuxostat and allopurinol (RR 0.96; 95% CI 0.33–2.74; I^2 = 39%, p = 0.19) (Figure 5).

Subgroup Analyses

We conducted subgroup meta-analysis based on febuxostat dosage, elderly age population, and treatment duration. We present a subgroup analysis for febuxostat doses of 80 mg (Figure 6a) and 120 mg (Figure 6b) per day. Analysis for the 40 mg dose was not possible due to the limited data available. No significant differences were found in liver function abnormalities requiring study withdrawal between these febuxostat doses and allopurinol.[13,23,35]

Five studies included data on elderly gout patients.[23,26,27,29,34] The hepatobiliary abnormalities showed comparable rates between febuxostat and allopurinol (Figure 7). Subgroup analysis by treatment duration (< 6 months vs ≥ 6 months)

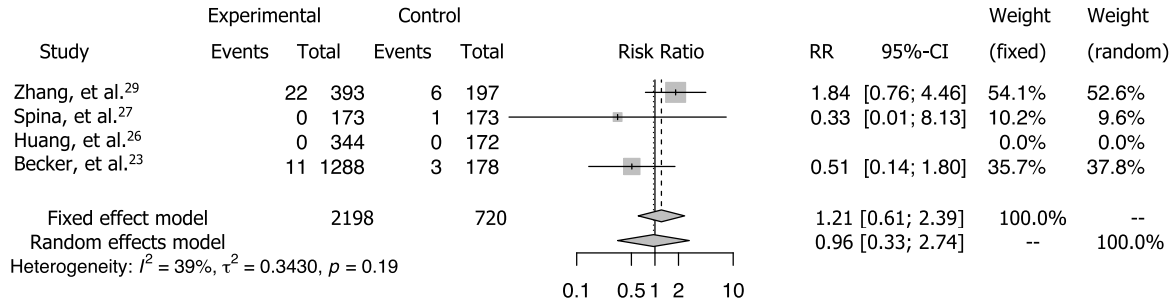
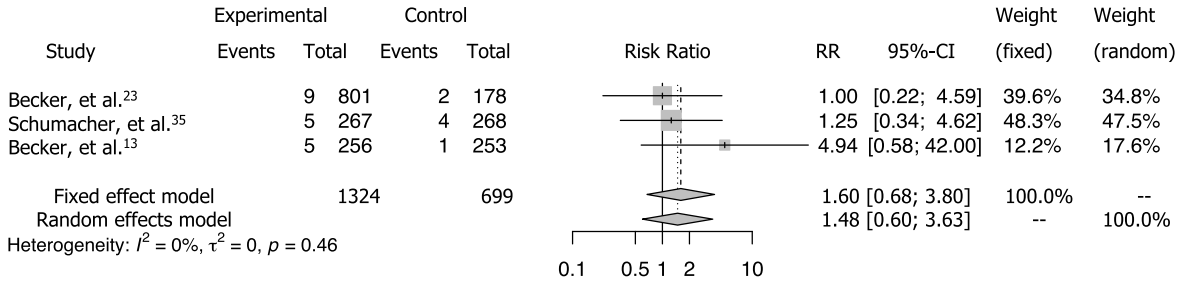


Figure 5 Forest plot of hepatobiliary dysfunction between the experimental group (febuxostat) and the control group (allopurinol).

a.



b.

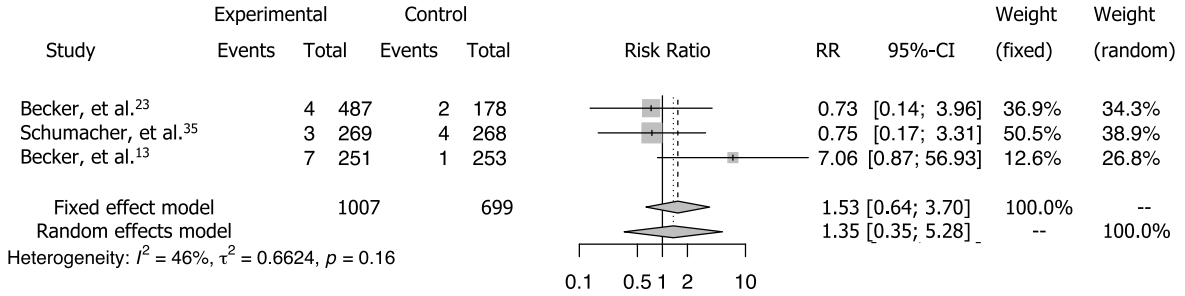


Figure 6 Forest plot of abnormal liver leading subject withdrawal between the experimental group (febuxostat) at dosage 80 mg and 120 mg.
Notes: 80 mg (**a**) and 120 mg (**b**).

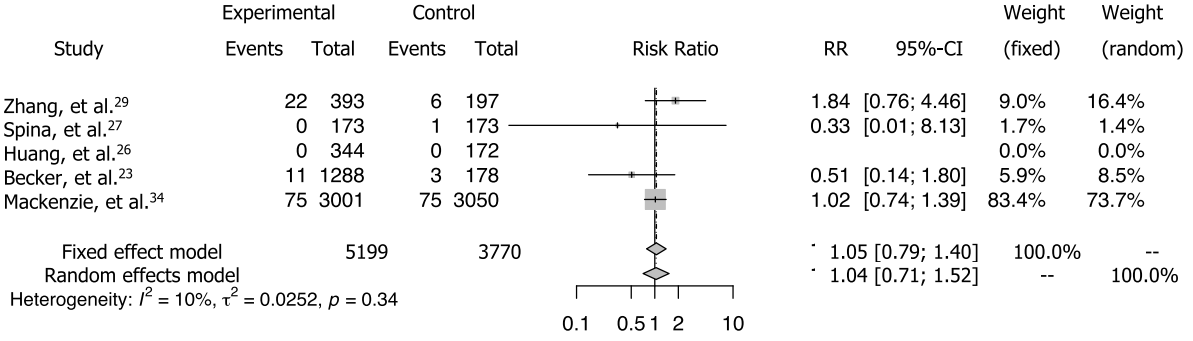


Figure 7 Forest plot of hepatobiliary abnormal between the experimental group (febuxostat) and the control group (allopurinol) that includes gout patient elderly population.

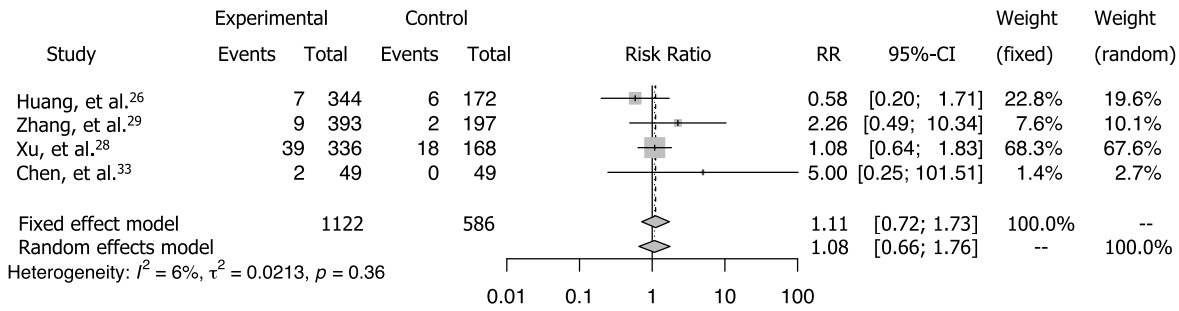
was conducted based on three studies.[13,14,30] The hepatic safety outcomes were comparable between febuxostat and allopurinol across both duration groups < 6 months (Figure 8a) and ≥ 6 months (Figure 8b).

Discussion

This meta-analysis demonstrates that febuxostat and allopurinol have comparable hepatic safety profiles in adult patients with gout or hyperuricemia. Across the included RCTs, no significant differences were observed in the incidence of liver function test abnormalities, investigator-defined hepatic adverse events, or hepatobiliary disorders.[13,14,23–35]

https://doi.org/10.2147/TCRM.S552281

a.



b.

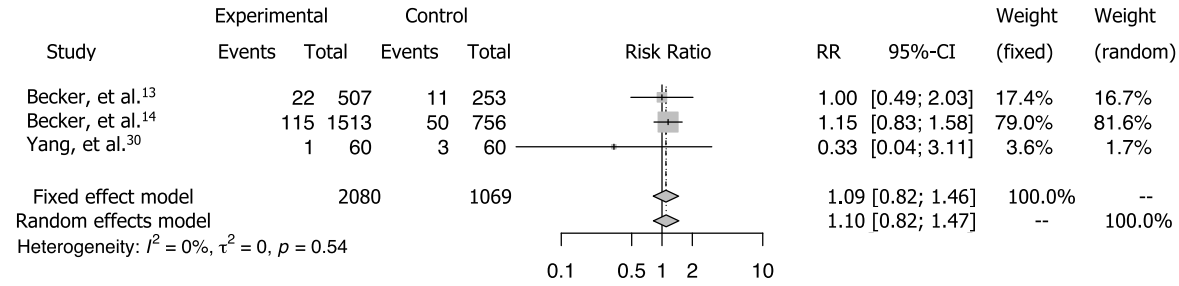


Figure 8 Forest plot of hepatobiliary abnormal between the experimental group (febuxostat) and the control group (allopurinol) based on treatment duration < 6 months and ≥ 6 months.
Notes: <6 months (**a**) and ≥6 months (**b**).

Subgroup analyses further confirmed these findings across different age groups (including elderly patients), febuxostat doses (80 mg and 120 mg daily), and treatment durations. These results offer important clinical reassurance regarding the hepatic safety of febuxostat, particularly as long-term urate-lowering therapy is often required in gout management.[18,36,37]

Our findings are consistent with a previous systematic review conducted in 2023, which reported that hepatic adverse events associated with febuxostat were not significantly different from those observed with allopurinol.[18] Although febuxostat is predominantly metabolized in the liver, emerging evidence also suggests it may exert hepatoprotective effects under certain conditions. For example, recent in vitro studies have demonstrated that febuxostat can inhibit lipid accumulation and inflammatory responses in HEp-G2 cells exposed to free fatty acids, thereby potentially mitigating hepatic injury.[38–40]

This study is the first meta-analysis to stratify hepatic safety outcomes by febuxostat dosage, patient age category, and treatment duration. In the geriatric subgroup, no statistically significant differences in hepatic safety were observed between febuxostat (RR: 1.47; 95% CI: 0.96–2.40) and allopurinol (RR: 1.42; 95% CI: 0.89–2.40). These results are in line with a previous network meta-analysis of six trials involving 1269 patients with asymptomatic hyperuricemia, which found no elevated risk of impaired liver function associated with urate-lowering therapy compared to placebo.[38]

In comparison with the previous systematic review, which included 11 studies,[18] the present analysis incorporates 15 studies, thereby expanding the evidence base and providing updated insights. As summarized in Table 1, the additional studies include randomized controlled trials that were not capture in the earlier review. The risk of bias assessment further strengthens the evaluation by systematically appraising study quality across larger set of trials. Importantly, the pooled quantitative results reflect this expanded dataset, offering more precise quantitative estimation of risk ratio and enabling subgroup analyses by age, dosage, and treatment duration. These additions contribute not only to a broader understanding of the hepatic safety profile of febuxostat versus allopurinol but also enhance the robustness and generalizability of the conclusions, thereby extending beyond the scope of the earlier review.

These results are also consistent with the Summary of Product Characteristics (SmPC), which indicates that there are no differences in hepatic safety concerns between febuxostat and allopurinol in elderly patients, who are considered a vulnerable population. The pharmacokinetics of these drugs in elderly patients are generally not expected to be significantly altered, except that special attention is advised for allopurinol use in patients with renal impairment. Since allopurinol and its metabolites are predominantly excreted via the kidneys, impaired renal function may result in drug and/or metabolite retention, leading to prolonged plasma half-lives.[38]

In this study, no dose-dependent trends in hepatic safety were observed with febuxostat at doses of 80 mg or 120 mg when compared with allopurinol.[13,23,35] This finding aligns with current SmPC data, which report that in patients with mild to moderate hepatic impairment receiving multiple doses of febuxostat 80 mg, the maximum concentration (Cmax) and area under the curve (AUC) of febuxostat and its metabolites did not differ significantly from those in patients with normal hepatic function.[41] However, the SmPC provides no further details regarding the administration of febuxostat 120 mg in patients with hepatic impairment.[42] Nevertheless, both the febuxostat and allopurinol SmPCs state that dose adjustment should be considered in patients with hepatic impairment, and that liver function tests are recommended prior to initiation and during the early stages of therapy.[41–43]

A major strength of this study is its focus on head-to-head RCTs comparing febuxostat and allopurinol, enhancing internal validity. We conducted a quantitative synthesis of hepatic safety outcomes across relevant subgroups and incorporated data from diverse populations across North America, Europe, Asia, and South America. Compared to previous reviews, which often focused on broader safety outcomes or indirect comparisons, our analysis provides more granular evidence specific to hepatic safety.[38,39] In addition, some included studies involved patients with complex clinical backgrounds, such as hematologic malignancies (2%), chronic kidney disease (3%), and end-stage renal disease requiring dialysis (1%), enhancing the applicability of findings to real-world clinical populations.[12,13,22–34]

Nevertheless, this study has several limitations. The number of eligible RCTs was relatively small, limiting the capacity to explore heterogeneity and detect small differences between treatment groups. Five trials were rated as having "some concerns" in the risk of bias assessment due to the lack of blinding, which may have introduced subjective bias.[22,29–32] In particular, studies involving dose titration of allopurinol in patients with renal impairment posed additional challenges for maintaining blinding. Moreover, long-term safety data for the liver remain limited. The longest follow-up among the included trials extended to seven years, and only one large-scale study involving elderly patients assessed long-term outcomes, reporting no significant difference in hepatobiliary disorders between febuxostat and allopurinol.[34] Another limitation is the underrepresentation of patients with significant comorbidities, such as advanced liver disease, malignancy, or renal failure. This limits the generalizability of our findings to high-risk populations.[27,30,32–34] Given that drug metabolism and hepatic susceptibility may vary with genetic background, comorbid conditions, diet, and lifestyle, continued pharmacovigilance using real-world data is essential to monitor long-term hepatic outcomes.[44]

Although no significant differences in hepatic safety were detected, liver function abnormalities were reported in all included studies, underscoring the importance of routine monitoring of liver function. In clinical practice, healthcare providers may consider febuxostat as a safe alternative to allopurinol in terms of hepatic risk, particularly when treatment individualization is needed due to intolerance, contraindications, or comorbidities. Both medications can be used with comparable confidence, provided that liver function is monitored according to current clinical guidelines. Given the inherent limitations of RCTs in detecting rare or long-term adverse events, additional evidence from continued monitoring through real-world safety databases is warranted. Future research should include long-term cohort studies and meta-analyses incorporating observational data to better capture hepatic safety signals across diverse patient populations.

Conclusion

This updated systematic review and meta-analysis of RCTs suggests that febuxostat and allopurinol exhibit comparable hepatic safety profiles in adult patients with gout. No significant differences were found in liver function test abnormalities, hepatobiliary disorders, or investigator-defined liver-related adverse events across age groups, febuxostat dosage levels, or treatment durations. While the overall risk of hepatic injury appears similar between the two agents, continued

hepatic monitoring remains essential in clinical practice. Clinicians are advised to tailor treatment decisions to individual patient characteristics, including comorbidities and potential risk factors, and to remain vigilant for liver-related adverse events, especially in long-term therapy, with liver function test monitoring and drug-dose adjustment. Lastly, for strengthening hepatic safety scientific information, we recommend further research using real-world data or future RCTs that integrate liver safety outcomes as primary endpoints.

Acknowledgments

The authors acknowledge the participating researchers who provided the raw data and published journals which was analysed in this study.

Funding

This study was supported by an Indonesia Endowment Fund for Education (Lembaga Pengelola Dana Pendidikan) scholarship (202406213204484), with open-access support from Universitas Padjadjaran.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hainer BL, Matheson E, Wilkes RT. Diagnosis, treatment, and prevention of gout. *Am Fam Physician*. 2014;90(12):831–836.
2. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012;2012(11). doi:10.1002/14651858.cd008653.pub2
3. Zhang WZ. Why does hyperuricemia not necessarily induce gout? *Biomolecules*. 2021;11(2):1–11. doi:10.3390/biom11020280
4. Singh JA, Gaffo A. Gout epidemiology and comorbidities. *Semin Arthritis Rheum*. 2020;50(3):S11–S16. doi:10.1016/j.semarthrit.2020.04.008
5. Gaffo AL, Saag KG. Core Evidence Febuxostat: the Evidence for Its Use in the Treatment of Hyperuricemia and Gout. *Core Evid*. 2009:25–36—.
6. Sapankaew T, Thadanipon K, Ruenroengbun N, et al. Efficacy and safety of urate-lowering agents in asymptomatic hyperuricemia: systematic review and network meta-analysis of randomized controlled trials. *BMC Nephrol*. 2022;23(1). doi:10.1186/s12882-022-02850-3
7. Suzuki S, Yoshihisa A, Yokokawa T, et al. Comparison between febuxostat and allopurinol uric acid-lowering therapy in patients with chronic heart failure and hyperuricemia: a multicenter randomized controlled trial. *J Int Med Res*. 2021;49(12). doi:10.1177/03000605211062770
8. Yu KH. Febuxostat: a novel non-purine selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in gout. *Recent Pat Inflamm Allergy Drug Discov*. 2007;1(1):69–75. doi:10.2174/187221307779815020
9. Lee JS, Won J, Kwon OC, et al. Hepatic safety of febuxostat compared with allopurinol in gout patients with fatty liver disease. *J Rheumatol*. 2019;46(5):527–531. doi:10.3899/jrheum.180761
10. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American college of rheumatology guideline for the management of gout. *Arthritis Care Res*. 2020;72(6):744–760. doi:10.1002/acr.24180
11. Flores NM, Nuevo J, Klein AB, Baumgartner S, Morlock R. The economic burden of uncontrolled gout: how controlling gout reduces cost. *J Med Econ*. 2019;22(1):1–6. doi:10.1080/13696998.2018.1532904
12. Kannangara DRW, Graham GG, Wright DFB, et al. Individualising the dose of allopurinol in patients with gout. *Br J Clin Pharmacol*. 2017;83(9):2015–2026. doi:10.1111/bcp.13307
13. Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *New Eng J Med*. 2005;353(23):2450–2461. doi:10.1056/NEJMoa050373
14. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2). doi:10.1186/ar2978
15. Tai V, Gow P, Stewart S, et al. An updated systematic review and meta-analysis of randomised controlled trials on the effects of urate-lowering therapy initiation during a gout flare. *Semin Arthritis Rheum*. 2024;65:152367. doi:10.1016/j.semarthrit.2024.152367
16. Jeong H, Choi E, Suh A, Yoo M, Kim B. `Risk of cardiovascular disease associated with febuxostat versus allopurinol use in patients with gout: a retrospective cohort study in Korea. *Rheumatol Int*. 2022;43(2):265–281. doi:10.1007/s00296-022-05222-0
17. Zhang S, Xu T, Shi Q, et al. Cardiovascular safety of febuxostat and allopurinol in hyperuricemic patients with or without gout: a network meta-analysis. *Front Med*. 2021:8. doi: 10.3389/fmed.2021.698437
18. Dewi C, Puspita F, Puspitasari IM, Zakiyah N. Hepatic safety of febuxostat and allopurinol for gout patients: a systematic review of randomized controlled trial. *Ther Clin Risk Manag*. 2023;19:731–743. doi:10.2147/TCRM.S424598
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021:372. doi: 10.1136/bmj.n71
20. Cochrane Methods. *Risk of Bias 2 Cochrane Review Group Stater Pack*. 2022 May.
21. Higgins J, Savovic J, Page MJ, Sterne JAC. Revised cochrane risk-of-bias tool for randomized trials (RoB 2). Rob2 development group. 2019.
22. Graña Possamai C, Cabanac G, Perrodeau E, Ghosn L, Ravaud P, Boutron I Inclusion of retracted studies in systematic reviews and meta-analyses of interventions: a systematic review and meta-analysis. *JAMA Intern Med*. 2025;185(6):702–709.
23. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol*. 2009;36(6):1273–1282. doi:10.3899/jrheum.080814

24. Kamatani N, Fujimori S, Hada T, et al. An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: Phase 3 clinical study. *J Clin Rheumatol*. 2011;17(4 Suppl 2). doi:10.1097/rhu.0b013e31821d36cc
25. Goldfarb DS, Macdonald PA, Gunawardhana L, Chefo S, McLean L. Randomized controlled trial of febuxostat versus allopurinol or placebo in individuals with higher urinary uric acid excretion and calcium stones. *Clin J Am Soc Nephrol*. 2013;8(11):1960–1967. doi:10.2215/cjn.01760213
26. Huang X, Du H, Gu J, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. *Int J Rheum Dis*. 2014;17(6):679–686. doi:10.1111/1756-185X.12266
27. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, Phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. *Ann Oncol*. 2015;26 (10):2155–2161. doi:10.1093/annonc/mdv317
28. Xu S, Liu X, Ming J, et al. A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia. *Int J Rheum Dis*. 2015;18(6):669–678. doi:10.1111/1756-185X.12648
29. Zhang F, Liu Z, Jiang L, et al. A randomized, double-blind, non-inferiority study of febuxostat versus allopurinol in hyperuricemic chinese subjects with or without gout. *Rheumatol Ther*. 2019;6:543–57. doi:10.6084/m9.figshare.9771893
30. Yang N, Cao B. Low-dose febuxostat exhibits a superior renal-protective effect and non-inferior safety profile compared to allopurinol in chronic kidney disease patients complicated with hyperuricemia: a double-centre, randomized, controlled study. *J Clin Pharm Ther*. 2022;47 (12):2214–2222. doi:10.1111/jcpt.13794
31. Nagase A, Ishimitsu T, Furuichi M, et al. Comparison of Therapeutic Effects of Allopurinol and Febuxostat in Chronic Hemodialysis Patients. *Dokkyo J Med Sci*. 2019;46(1):17–27.
32. Liao Z, Xu L, Wan B, et al. Comparison of febuxostat and allopurinol in the treatment of patients with chronic kidney disease stage 3~5 with hyperuricemia. *Emerg Med Int*. 2022;2022:1–4. doi:10.1155/2022/1177946
33. Chen X, Ye T, Dai Y, et al. Comparison of the therapeutic effects of febuxostat combined with a low-purine diet and allopurinol combined with a low-purine diet on the improvement of gout patients. *Int J Rheum Dis*. 2024;27(5). doi:10.1111/1756-185X.15165
34. Mackenzie IS, Ford I, Nuki G, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2020;396(10264):1745–1757. doi:10.1016/S0140-6736(20)32234-0
35. Schumacher HR, Becker MA, Wortmann RL, et al. 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 Care Res*. 2008;59(11):1540–1548. doi:10.1002/art.24209
36. Clinical practice guidelines for management of gout principal investigator: fernando Pérez Ruiz Coordinator: estíbaliz Loza Project Manager: maría Jesús García de Yébenes.
37. Gout: diagnosis and management NICE guideline. 2022. Available from: www.nice.org.uk/guidance/ng219. Accessed December 03, 2025.
38. Tien YY, Shih MC, Tien CP, Huang HK, Tu YK. To treat or not to treat? Effect of urate-lowering therapy on renal function, blood pressure and safety in patients with asymptomatic hyperuricemia: a systematic review and network meta-analysis. *J Am Board Fam Med*. 2022;35(1):140–151. doi:10.3122/jabfm.2022.01.210273
39. Zhang S, Xie Q, Xie S, et al. The association between urate-lowering therapies and treatment-related adverse events, liver damage, and major adverse cardiovascular events (MACE): a network meta-analysis of randomized trials. *Pharmacotherapy*. 2021;41(9):781–791. doi:10.1002/phar.2609
40. Tang W, Mu J, Chen QI, Li X, Liu H. The involvement and mechanism of febuxostat in non-alcoholic fatty liver disease cells. *J Biol Regul Homeost Agents*. 2018;32:545–551.
41. Electronic medicine compendium, Febuxostat (Adenuric) 80 mg film-coated tablets_SMPC_01AUG2023. Available from: https://www.medicines.org.uk/emc/product/487/smpc#gref. Accessed September 17, 2025.
42. Electronic medicine compendium, Febuxostat (Adenuric) 120 mg film-coated tablets_SMPC_01AUG2023. Available from: https://www.medicines.org.uk/emc/product/487/smpc#gref. Accessed September 17, 2025.
43. Electronic medicine compendium, Allopurinol 300mg Tablets_SMPC_23JUN2025. Available from: https://www.medicines.org.uk/emc/product/13159/smpc/print. Accessed September 17, 2025.
44. Jarvis JP, Peter AP, Keogh M, et al. Real-world impact of a pharmacogenomics-enriched comprehensive medication management program. *J Pers Med*. 2022;12(3):421. doi:10.3390/jpm12030421