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An Up-to-date Systematic Review on Real-world Evidence for the Management of Asymptomatic Hyperuricemia

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Abstract

The prevalence of hyperuricemia is increasing worldwide. The emergent concerns have provoked investigations into the management of AUH. While there are existing reviews discussing the pharmacological treatment of AUH based on randomized controlled trials, an updated review specifically focusing on the safety and effectiveness of pharmacological interventions in real-world settings for AUH is currently lacking. For that reason, the objective of this review was to provide a comprehensive summary of the existing evidence extracted from the available research studies that focused on the safety and effectiveness of the adopted medical treatment approaches for AUH in real-world settings. Based on the analysis verdicts, benzbromarone appeared to be the most effective urate-lowering therapy (ULT) in achieving the desired serum uric acid (sUA) levels and in lowering the incidence of initial gout flares. Febuxostat also demonstrated valuable effectiveness in our analysis. On the other hand, based on the safety of the popular allopurinol medication, one real-world study identified skin-related adverse effects associated with it. However, it is important to note that the studies included in the analysis were predominantly conducted in Japan and Taiwan, which limits the generalizability of these findings. To enhance the applicability of the review outcomes, future global studies should cover a wider assortment of populations from various countries and regions.

Keywords: Asymptomatic Hyperuricemia, Benzbromarone, Allopurinol, Febuxostat, Topiroxostat.

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INTRODUCTION

Hyperuricemia refers to the elevated levels of urate in the bloodstream, specifically 7 mg/dl in men and 6 mg/dl in women [1]. Asymptomatic hyperuricemia (AUH) is a term used when the serum urate concentration is elevated but no symptoms or signs of conditions like gout or uric acid renal disease are present. While these conditions can develop in hyperuricemic individuals, approximately two-thirds or more of them remain asymptomatic and never experience gout flares, tophaceous gout, hyperuricemic nephropathy, or uric acid nephrolithiasis [2].

The prevalence of hyperuricemia is on the rise worldwide, with estimates suggesting that nearly one-fifth of the general population and one-fourth of hospitalized patients have AUH [3]. In the United States, 20% of the general population is affected by asymptomatic hyperuricemia, and the rates may vary in other countries as well [4, 5]. Gout, the most common complication of hyperuricemia, is observed in nearly 4% of the U.S. population [3].

There are escalating concerns regarding the association between AUH and the metabolic syndrome variants and their consequences. Growing evidence from several medical investigations points out that AUH can be an indicator of hypertension, obesity, diabetes mellitus, and chronic kidney disease [4]. Recent research specifies that uric acid can have disadvantageous effects on vascular health and the integrity of the kidneys [6]. The possible mechanism of AUH contribution in these diseases is based on uric acid as a triggering factor in inflammation [4]. Since there are limited options available to slow down the deterioration of kidney function, it is worth considering the use of interventions based on lifestyle changes that can reduce uric acid production in hyperuricemic patients [6].

Treatment recommendations for AUH vary, ranging from no-treatment approaches to other protocols that include using urate-lowering therapies (ULT; Figure 1) to minimize the associated conditions. There is an enduring debate regarding a clearly outlined systematic guideline and a standard clinical approach to treating AUH. However, non-pharmacological approaches such as dietary restrictions, exercise, and weight loss are recommended for all patients [7, 8]. In addition to that, it is very important to keep in mind that

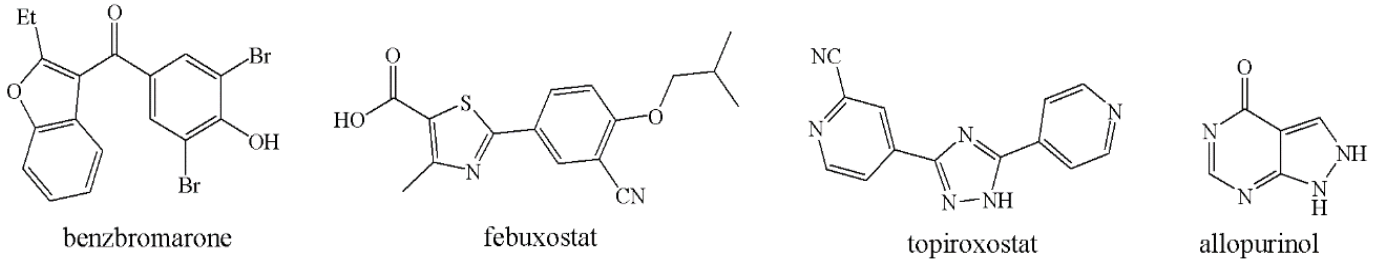


Figure 1: Popular urate-lowering therapies

known medications can elevate urate levels and in these cases such medications must be discontinued and replaced with other options, if possible, particularly those that have the opposite effect [7]. The divergences and sometimes the disagreements between observational studies and clinical trials make it difficult to provide specific recommendations for the potential benefits of ULT in individual patients with AUH [7, 9, 10]. Therefore, the risk of developing gout in this category of patients, estimated at 50%, needs to be carefully evaluated alongside the potential cutaneous and cardiovascular side effects of ULTs [7].

Despite the presence of reviews that discuss the pharmacological management of AUH based on randomized controlled trials [7, 9, 11], there is currently no updated review that specifically examines the safety and effectiveness of pharmacological interventions in real-world settings. Real-world evidence (RWE) refers to clinical evidence regarding the safety and effectiveness of medical products that are derived from real-world data (RWD) obtained through routine healthcare delivery. RWD can be sourced from various channels, such as electronic health records (EHRs), registries, claims and billing data, patient-generated data, as well as data collected from mobile health applications and wearable devices [12].

RWE proved to be a highly valuable and indispensable part of global medical services. It provides crucial insights that range from informing trial designs and supporting regulatory decisions to exploring additional applications for products already available on the market [13]. Studies utilizing RWE have yielded significant findings in various areas of health and disease, encompassing epidemiology, disease burden, treatment patterns, safety, treatment outcomes, long-term effects, and patient-reported outcomes such as satisfaction, quality of life, medication adherence, and patient overall experience [12, 14].

The objective of this review is to present a comprehensive summary of the existing evidence derived from primary research studies, focusing on the safety and effectiveness of various management approaches for AUH in real-world settings. The review intends to investigate a number of outcomes associated with the management of AUH, such as the reduction of urate levels, clinical symptoms, and any potential adverse events. Additionally, the study also considers inspecting secondary outcomes, including patient-reported experiences and the utilization of healthcare resources.

METHODS

The systematic review followed a predetermined protocol registered in PROSPERO (CRD42023441504) without any deviations throughout the study.

Search Strategy

In accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15], a comprehensive search was conducted across the various known databases, including PubMed, Google Scholar, British Medical Journals (BMJ), ScienceDirect, and the Cochrane Library, for peer-reviewed literature in full text from January 2018 to June 2023. Additionally, relevant articles were identified through the bibliographic examination of recent systematic reviews and meta-analyses. The search was limited to the five-year timeframe to focus on current evidences only, considering the emergent changes in treatment strategies for asymptomatic hyperuricemia [16].

To perform the searches, different combinations of terms such as "asymptomatic hyperuricemia," "current management strategies," and "real-world settings" were utilized. Each database was searched individually using Boolean operators (AND) and (OR), as well as Medical Subject Subheadings (MeSH) terms and keytext words.

Selection of Studies

Our inclusion criteria included prospective cohort studies, retrospective cohort studies, and comparative effectiveness studies that investigated pharmacological management strategies for individuals with asymptomatic hyperuricemia in real-world settings. We did not impose any specific restrictions on the type of real-world data and included various sources such as electronic health records (EHRs), claims and billing activity, product and disease registries, and patient-reported outcome (PRO) data.

We have structured the inclusion criteria according to the PICO (Population, Intervention, Comparator, and Outcome) framework:

The population: The population of interest comprised individuals diagnosed with asymptomatic hyperuricemia in real-world settings, with serum uric acid levels exceeding 6 mg/dL for females and 7 mg/dL for males [1]. The review encompassed studies that included diverse populations in terms of age, gender, ethnicity, and underlying comorbidities. Both primary care and specialized care settings were considered.

The intervention: The systematic review focused exclusively on pharmacological interventions aimed at reducing urate levels in the management of asymptomatic hyperuricemia in real-world settings. Studies examining symptom relief alone, such as non-steroidal anti-inflammatory drugs (NSAIDs), were excluded. Additionally, studies investigating non-pharmacological management strategies, such as lifestyle modifications or alternative therapies, were also excluded.

The comparator: The included studies compared either no treatment or different urate-lowering agents.

The outcomes: The review aimed to assess various outcomes related to the management of asymptomatic hyperuricemia, including urate reduction, clinical manifestations, and adverse events. Additional outcomes of patient-reported conclusions and healthcare resource utilization were also considered.

The study of evidence selection

After the search, all the recognized citations were brought into EndNote 20.0.1 (Clarivate Analytics, PA, USA), and all the repetitions were removed. The reviewing process was carried out in three steps:

Step 1: Titles and abstracts were filtered by the inclusion criteria.

Step 2: Relevant sources were retrieved, full texts were assessed against the criteria and the excluded sources were documented.

Step 3: Queries about study inclusion were resolved through discussions.

Quality appraisal and data extraction of included studies

For the quality assessment, we employed the Critical Appraisals Skills Program [17] (CASP) cohort study checklist, a widely used standardized tool endorsed by the Cochrane Qualitative and Implementation Methods Group [18]. The CASP checklist, designed for cohort studies, consisted of 12 questions that addressed three crucial aspects: the validity of study results, the study results themselves, and the local relevance of the results (Programme).

During the phase of data extraction, a standardized data extraction sheet was utilized that encompassed various categories of information. These categories included study details, study design and population, sample demographics, duration, type of intervention, intervention description, dosage/regimen, type of comparator, primary and secondary outcome measurement methods, main findings, conclusions, and limitations. In the event of any discrepancies or differences in data extraction among the authors, we engaged in discussions to reach a consensus.

Statistical Analysis

In order to formulate summary measures, descriptive statistics such as mean and median were employed. The nature of the included studies made it impractical to conduct a statistical meta-analysis. However, our descriptive analysis offers a comprehensive overview of management strategies for asymptomatic hyperuricemia in real-world settings. The findings of each study were summarized using both quantitative and qualitative approaches.

RESULTS

The literature search

The first search of the aforementioned databases resulted in a total of 1004 studies. After eliminating the duplicate studies from various databases, 883 studies remained. The categorization of the titles, abstracts, and full-text articles, identified 33 articles. However, 24 of them did not meet the inclusion standards due to various causes. Consequently, nine articles met the required criteria and those were considered for the next analysis. The search and selection process is visually presented in Scheme 1.

Quality assessment of the included studies

To assess the quality of the studies, we used the cohort study checklist from the CASP (Programme) [17]. Our findings revealed that two studies met all the relevant sub-questions outlined in the checklist [19, 20]. The remaining studies, though, fulfilled the domains concerning the validity and reporting of results. However, in the third domain, which pertained to the local relevance of the results, the response was either negative or inconclusive. The majority of studies provided this response due to a lack of generalizability in their reported findings. Table 1 presents the quality assessment of our included studies according to the CASP criteria [17].

Baseline Characteristics

Among the nine articles included in our review, eight had retrospective cohort designs, while one was a propensity score-matched cohort study. The majority of the studies (n= 6) were conducted in Japan, while the remaining three were carried out in Taiwan. The total population size included in the analysis was 2,904,014, with 65.2% men, and the average age was 56.9 years. The identified comorbid conditions among the participants were hyperlipidemia, hypertension, type 2 diabetes, renal diseases, cardiovascular diseases, metabolic syndrome, Down syndrome, and chronic obstructive pulmonary disease (COPD). In terms of data sources, six studies utilized health insurance claims data, while the remaining studies used adverse drug reaction reporting data, EHR, and a national database. To facilitate easy assessment, we have presented the summary of observational non-comparative studies in Table 2 and the observational comparative studies in Table 3.

The primary outcomes in the included studies

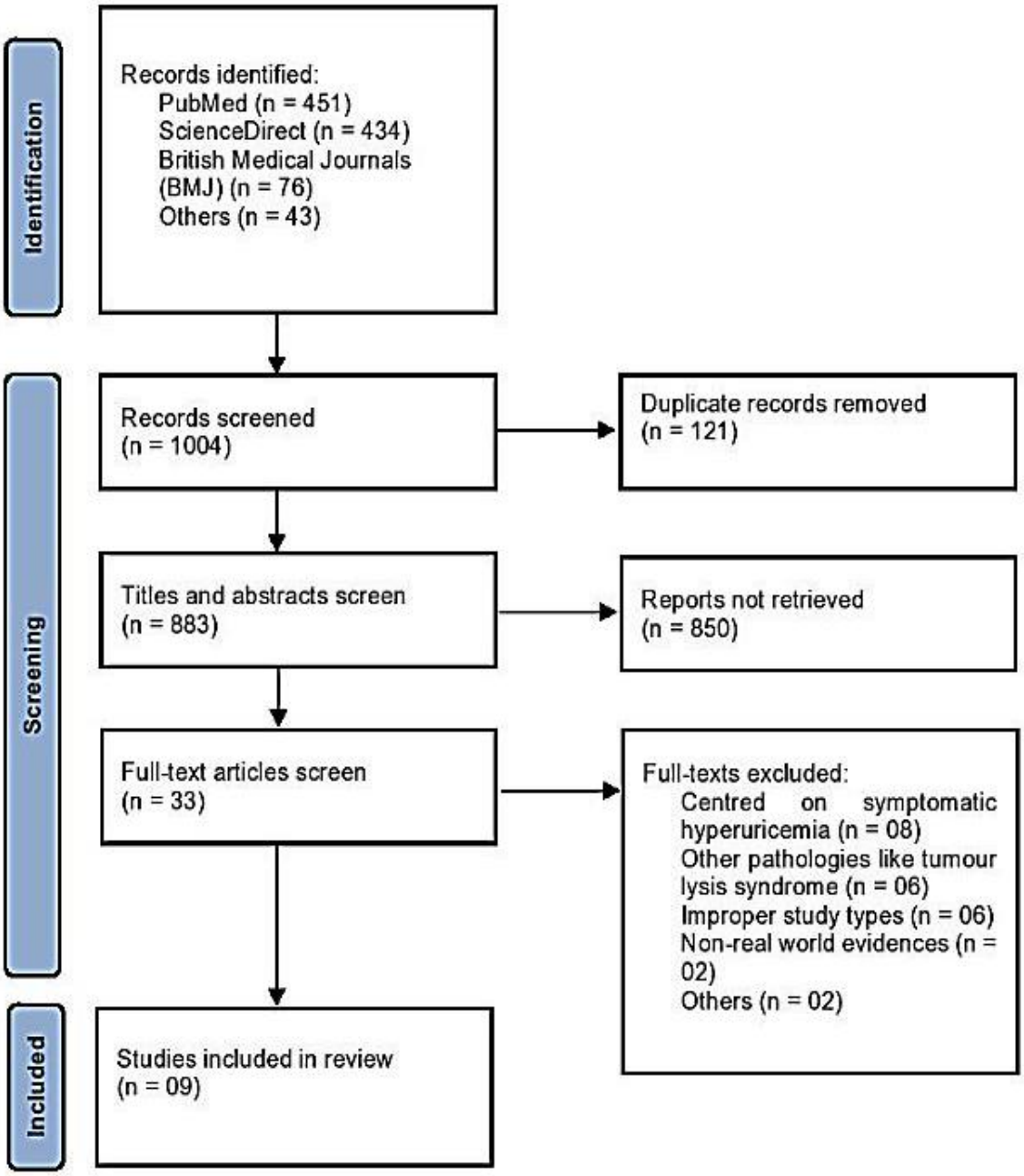
Different types of outcomes were investigated in the selected RWEs. Based on these, we identified two general main results of importance: the efficacy and safety of ULT therapy in AUH.

The effectiveness of urate-lowering therapeutics for asymptomatic hyperuricemia

There were seven RWEs in this review that analyzed the effectiveness of ULTs for AUH. The first study by Koto et al. [23] explored the treatment options for AUH in Japan. The findings of this study revealed that ULTs were prescribed to 72.4% of the patients diagnosed with AUH. Among the prescribed ULTs, febuxostat accounted for 48.6% of patients, allopurinol for 34.8%, benzbromarone for 12.3%, topiroxostat for 3.9%, and probenecid for 0.4%. The mean prescribed doses for these ULTs were 17.3 mg/day for febuxostat, 135.8 mg/day for allopurinol, 44.9 mg/day for benzbromarone, 51.1 mg/day for topiroxostat, and 503.2 mg/day for probenecid. The study found that 44.3% of all patients undergoing ULT treatment achieved the target, in comparison to 19.0% of patients who were not prescribed ULT. Specifically, the target was achieved by 46.8% of patients on febuxostat, 5.4% on allopurinol, 70.0% on benzbromarone, 36.7% on topiroxostat, and 44.0% on probenecid [23]. In a separate study by the same group [19], the incidence rate of gout flare was examined in different treatment subgroups. For the subgroup of subjects with AUH-prescribed ULT and having sUA (serum uric acid) levels ≤6.0 mg/dL, the incidence rate of gout flare was 0.033 flares per person-year. In the subgroup prescribed ULT and having sUA levels >6.0 mg/dL, the incidence rate was 0.083 flares per person-year. Subjects who were not on ULT had an incidence rate of 0.081 flares per person-year [19].

In the third study by Honda et al. [24], the use of ULTs in AUH in a Japanese pediatric population was assessed. A total of 97 patients were prescribed ULTs, with 44 receiving febuxostat, 31 receiving allopurinol, 15 receiving benzbromarone, 6 receiving topiroxostat, and 1 receiving probenecid. The median duration of febuxostat prescriptions was 256.0 days, while for allopurinol, it was 280.0 days. The mean prescribed dose ± SD in the study sample was 15.0 ± 10.2 mg for febuxostat and 126.0 ± 61.8 mg for allopurinol [24]. Similarly, Hakoda et al. described recent trends in the prevalence of AUH in relation to ULT in Japan. The prevalence of male patients with AUH who received ULT significantly increased from 1.77% to 2.14% during the period of 2010-2014. Among the study outcomes, the prevalence of asymptomatic hyperuricemia under ULT in women was less than one-tenth of that in men [26].

In addition to the four non-comparative studies, there were three comparative RWEs that assessed the effectiveness of different ULTs. The study by Peng et al. [24] focused on comparing the effectiveness of febuxostat and allopurinol in reducing uric acid levels and providing renal protection in patients with chronic kidney disease (CKD). The findings revealed that febuxostat usage resulted in a much better conservation of the targeted sUA level (80% of the sample patients) during the 2.5-year follow-up period, as compared to allopurinol. However, no significant differences were observed in the mean estimated glomerular filtration rate (eGFR) changes over time between the febuxostat and allopurinol groups. It was concluded that febuxostat is more effective for lowering the uric acid level but has the same effect on renal protection when compared to allopurinol [25].



Scheme 1: Flow diagram for searching and screening the related studies

Table 1: The quality assessment of the included studies [Reference number] based on the Critical Appraisals Skills Program (CASP) Cohort Study Checklist (Programme)

Study	Are the results of the study valid?	What are the results?	Will the results help locally?
(Lai et al., 2023) [21]	Yes	Yes	Can't tell
(Sawada et al., 2023) [20]	Yes	Yes	Yes
(Lai et al., 2022) [22]	Yes	Yes	Can't tell
(Koto et al., 2021) [23]	Yes	Yes	No
(Koto et al., 2021) [19]	Yes	Yes	Yes
(Honda et al., 2021) [24]	Yes	Yes	No
(Peng et al., 2020) [25]	Yes	Yes	Can't tell
(Hakoda & Kasagi, 2019) [26]	Yes	Yes	No
(Huang et al., 2019) [27]	Yes	Yes	No

The responses in CASP were determined by evaluating 12 sub-questions. A "yes" was assigned if all sub-questions were satisfied in a particular domain, a "no" if any sub-question received a negative response, and a "can't tell" was used when the study raised concerns in at least one sub-question in under-studied domain but didn't present a negative response for any sub-question.

Table 2: The observational studies [reference number] of real-world evidences for the management of asymptomatic hyperuricemia

Country/Study/ Design	RWE and Duration	Sample Demography	Comorbidities	Drugs Prescribed	Relevant Outcome(s)	Main Findings	Limitations
Japan (Koto et al., 2021) [23]/ Retrospective cross-sectional study	Health insurance claims; April 2016-March 2017	n = 1,820,838; ages 18-65 years, AUH was 2.6% (46,624)	Hyperlipidemia (59.7%), hypertension (53.7%), type 2 diabetes (28.9%), renal dysfunction (8.5%)	Febuxostat (48.6%), allopurinol (34.8%), benzbromarone (12.3%), topiroxostat (3.9%), probenecid (0.4%)	Prevalence of hyperuricemia and gout	Less than half of ULT patients reached the target SUA level (6.0 mg/dL). The percentages for achieving the target were 46.8% for febuxostat, 35.4% for allopurinol, 70.0% for benzbromar, 36.7% for topiroxostat, and 44.0% for probenecid.	Doubtful validity of definitions of pathological terms and not sure about actual usage of the drugs by the patients.
Japan (Koto et al., 2021) [19]/ Retrospective cohort study	Health insurance claims; April 2012-June 2019	n = 19,261; 98.3% men, with a mean age 43.2 and mean SUA 8.47mg/dL.	Hypertension (13.5%), Hyperlipidaemia (11.5%) and renal dysfunction (11.3%)	ULTs (not specified)	SUA control for prevention of gout flare in patients with AUH	Patients on ULT who achieved SUA ≤6.0mg/dL had lower rates of gout flare compared to those whose SUA remained >6.0mg/dL or were not receiving ULT.	Doubtful validity of definitions of pathological terms, non-generalizability of the findings, and the possibility that subjects did not take their ULT on the day of the check-up.
Japan (Honda et al., 2021) [24]/ Retrospective cross-sectional study	Health insurance claims; April 2016-March 2017	n = 696,277 children aged 0 to 18years; 276 patients identified as having gout or AUH	Kidney disease (34.8%), cardiovascular disease (22.8%), metabolic syndrome (42.8%), Down syndrome (5.4%)	ULTs (not specified)	Identify pediatric patients with gout or AUH, and patients prescribed ULTs, and analyze characteristic	ULT was prescribed for 34.6% of subjects with AUH and the proportion of ULT prescriptions increased with age, particularly in males.	Doubtful validity of definitions of pathological terms, non-generalizability of the findings.
Japan (Hakoda & Kasagi, 2019) [26]/ Retrospective cross-sectional study	Health insurance claims; 2010-2014.	n = 728,000-765,000	not reported	Allopurinol, febuxostat, benzbromaron, probenecid, topiroxostat	Prevalence of gout and AUH in relation to ULTs	Male patients in particular with AUH receiving ULT showed a significant increase from 1.77% to 2.14%.	Non-generalizability of the findings
Taiwan (Huang et al., 2019) [27]/ Retrospective cross-sectional study	Applications submitted; 1999-2016	Febuxostat	Cardiovascular disease/hypertension (86.2%), chronic kidney disease (58.6%), diabetes (46.6%)	Allopurinol	Use of allopurinol and related adverse reactions	The highest proportion of drug injury cases (44.6%) was observed in individuals with an eGFR ranging from 15 to 60 mL/min/1.73 m^2 who started allopurinol at a daily dose of 100 mg.	Small sample

AUH, Asymptomatic Hyperuricemia; eGFR, Estimated Glomerular Filtration Rate; RWE, Real World Evidence; SUA, Serum Uric Acid; ULT, Urate Lowering Therapeutics

Table 3: Comparative studies [reference number] of real-world evidences for the management of asymptomatic hyperuricemia

Country/Study/ Design	RWE and Duration	Sample Demography	Comorbidities	Intervention 01	Intervention 02	Relevant Outcome(s)	Main Findings	Limitations
Taiwan (Lai et al., 2023) [21]/ Retrospective cohort study	National database; 2003-2015	n = 9,107 (benzbromarone) and n = 4,554 (allopurinol); 71% men, mean age 56 years	CVD, CKD, COPD, CAD, DM, Hyperlipidemia, HTN	Benzbromarone	Allopurinol	Risk of CKD in people with AUH	The rate of CKD was lower in the benzbromarone group than in the allopurinol group (1.18 versus 1.99/per 100 person)	SUA data were unavailable, did not include data on febuxostat
Japan (Sawada et al., 2023) [20]/ Retrospective cohort study	Health Insurance claims; August 2010-March 2018	n = 1,357,671, follow-up 245 days (febuxostat); n = 1,273,211, follow-up 213 days (allopurinol); n = 258,786, follow-up 145 days (benzbromarone); n = 83,683, follow-up 167 days (topiroxostat)	not reported	Febuxostat or topiroxostat	Allopurinol and benzbromarone for the secondary control group	CV risk	CV risk was found to be 0.97% for the febuxostat group and 0.84% for the topiroxostat group. The benzbromarone group showed similar results. No elevated cardiovascular risk was observed when comparing febuxostat or topiroxostat with allopurinol	not reported
Taiwan (Lai et al., 2022) [22]/ Retrospective cohort study	National Health Insurance Program; 2001-2015	n = 6111 (benzbromarone), n = 6111 (allopurinol); 65% men, mean age 59 years	not reported	Benzbromarone	Allopurinol	First gout flare in AUH	Gout flare was lower in the benzbromarone group compared with an allopurinol group (3.29 versus 5.46 per 1000 person)	SUA data were unavailable, did not include data on febuxostat
Taiwan (Peng et al., 2020) [25]/ Propensity score-matched cohort study	HER; 2010-2015	n = 525, 76.76% men (febuxostat), n=525, 76% male (allopurinol) and treatment was observed for 2.5 years	not reported	Febuxostat	Allopurinol	Uric acid reduction and renal outcomes	Compared to allopurinol, febuxostat usage was associated with a higher rate of patients maintaining the target SUA levels for 80% of the follow-up time. However, there were no significant differences in mean eGFR changes over time between the two groups.	Residual confounders have biased the study results, more than one SUA reference range was applied

AUH, Asymptomatic Hyperuricemia; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; HER, Electronic Health Record, HTN, Hypertension; RWE, Real World Evidence; SUA, Serum Uric Acid

Lai et al. [21] compared the effects of benzbromarone and allopurinol on the risk of developing CKD in individuals with AUH. The study revealed that the benzbromarone group had a lower incidence rate of CKD compared to the allopurinol group (1.18 versus 1.99 per 100 person-years) [21]. Therefore, the combined results of both Peng et al. and Lai et al. support benzbromarone as a better agent for protection against renal injuries in comparison to febuxostat and allopurinol [21, 25]. Lastly, a comparative study conducted by Lai et al. [22] analyzed the effectiveness of benzbromarone versus allopurinol in reducing gout flares. The study indicated that the benzbromarone group exhibited a lower incidence rate of the first gout flare compared to the allopurinol group (3.29 versus 5.46 per 1000 person-months) [22].

In summary, the studies demonstrated that benzbromarone was the most effective in achieving the target sUA in AUH, followed by Febuxostat. Similarly, benzbromarone was also associated with a lower incidence rate of the first gout flare and CKD.

The safety assessment of urate-lowering therapeutics for asymptomatic hyperuricemia

The review encompassed two RWEs that assessed the safety of various ULTs for individuals with AUH. Huang et al. [27] conducted a study involving 174 allopurinol-related drug injury relief applications. The majority of cases (99.4%) involved skin-related injuries. The study identified common comorbidities among the cases, such as cardiovascular disease and hypertension (86.2%), chronic kidney disease (58.6%), and diabetes (46.6%). Similarly, the analysis revealed that the highest number of cases (44.6%) occurred in individuals with an estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min/1.73 m² who initiated allopurinol at a dosage of 100 mg/day [27]. On the other hand, Sawada et al. investigated the association between ULTs and cardiovascular events, specifically focusing on the risk of febuxostat and topiroxostat compared to allopurinol in Japan. The cardiovascular risks were lower when comparing febuxostat or topiroxostat with allopurinol. Similar results were observed in the benzbromarone group [20].

DISCUSSION

To the best of our knowledge, this systematic review represents the first attempt to evaluate the effectiveness and safety of pharmacological interventions specifically targeting AUH using the most current RWD. It is important to note that Sapankaew et al. [10] conducted an updated review on the effects of urate-lowering therapies (ULTs) in AUH; however, their study centred solely on randomized controlled trials (RCTs) that were particularly focused on febuxostat and allopurinol. The literature suggests that RWE holds significant value as it directly relates to clinical practice [28]. As a result, the findings from our review can be directly applied in clinical settings. Moreover, these findings can serve as a foundation for further exploration of potential pharmacological intervention strategies in AUH and other conditions where elevated serum uric acid levels play a prominent role [3].

Our systematic review conducted a thorough analysis of two important factors, efficacy and safety, pertaining to ULTs in the context of AUH. In terms of efficacy, our findings revealed that benzbromarone (among the ULTs studied) exhibited the highest effectiveness in achieving the desired sUA levels in AUH, resulting in a lower incidence rate of initial gout flares. Febuxostat followed closely as the next most effective option.

Inconsistent harmony with these findings is what had been revealed after we compared them with the results from primary research articles that explored the comparison of commonly used ULTs. In an earlier study published by Jackson et al. [29], febuxostat was reported to be more effective than fixed doses of allopurinol (200mg or 300mg) in geriatric participants aged 65 years or older. It was also concluded that febuxostat showed high effectiveness in patients with high renal impairment issues [24]. Similarly, Liao et al. found that febuxostat, in comparison to allopurinol, had a better ability to lower uric acid levels and reduce complications [30]. On the other hand, the studies comparing febuxostat and benzbromarone have produced conflicting outcomes. Liu et al. revealed that febuxostat could be used as an equivalent alternative to benzbromarone. The study did not distinguish any significant difference between these two drugs for their effect on serum uric acid in patients with hyperuricemia [31]. In comparison, Yan et al. demonstrated that benzbromarone exhibited superior efficacy in lowering uric acid levels compared to febuxostat, particularly in the treatment of relatively young and healthy patients [32].

However, ULT has not yet received international approval for the treatment of gout or hyperuricemia in children, as indicated by the treatment guidelines in Europe and the United States [33, 34]. However, we came across one piece of real-world evidence (RWE) that specifically concluded the effectiveness of ULTs in pediatric patients. The study highlights the necessity of developing appropriately tailored ULTs to meet the needs of this particular age group [24].

In our analysis of RWE results pertaining to the safety of ULTs, we identified two primary categories of adverse effects. Firstly, the results of one RWE identified allopurinol-induced skin-related adverse effects. Secondly, methodical research findings by Mockenhaupt and Yoshida et al. [35, 36] (, 2009;, 2023) pointed to the potential cardiovascular (CV) adverse effects in association with ULTs. Other scattered opinions from primary research studies aligned with these outcomes but remained speculative hypothetical notions without providing any substantial evidence to support a link between ULTs and CV events, which did not warrant any specific citation or deeper discussion.

CONCLUSION

The review systematically analyzed the efficacy and safety of common ULTs in AUH. The most important finding regarding efficacy is that benzbromarone emerged as the most effective ULT in achieving the sUA levels, resulting in a lower incidence of initial gout flares. Additionally, febuxostat demonstrated considerable effectiveness in our analysis. In terms of safety, we recognized an association between skin-related adverse effects and allopurinol.

Conflict of Interest

None declared.

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