FARMACIA, 2026, Vol. 74, 2
https://doi.org/10.31925/farmacia.2026.2.9 **ORIGINAL ARTICLE**

CO-PRESCRPTION OF ALLOPURINOL AND INDAPAMIDE IN CHRONIC PATIENTS

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Manuscript received: January 2026

Abstract

This study aims to examine the concomitant use of indapamide and allopurinol in 1840 electronic health records (EHRs) from the health insurance system for patients aged 30 to 100 with chronic conditions as of January 2024. 509/1840 EHRs had indapamide, and 72/1840 had allopurinol; of the 72 EHRs with allopurinol, 31 contained it associated with indapamide. The recommendation for allopurinol is strongly associated with indapamide use ($p = 0.004$) and with indapamide dose ($p = 0.018$), particularly with 1.5 mg ($p = 0.003$). Indapamide prescriptions are significantly associated with gender, age group, and allopurinol dose ($p < 0.05$). There was a significant association between gender and the daily allopurinol dose (chi^2, $p = 0.006$). The present findings highlight the need to establish the true frequency of hyperuricemia with indapamide (currently listed as unknown in the current SmPCs), which is determined, on the one hand, by the large number of patients treated and, on the other hand, by the long-term consequences (renal damage and gout).

Rezumat

Acest studiu își propune să examineze utilizarea concomitentă a indapamidei și alopurinolului în 1840 de prescripții electronice (EHRs) din sistemul de asigurări de sănătate pentru pacienți cu vârste cuprinse între 30 și 100 de ani cu afecțiuni cronice, începând cu ianuarie 2024. 509/1840 de prescripții conțineau indapamidă, iar 72/1840 conțineau alopurinol; dintre cele 72 de prescripții cu alopurinol, 31 îl conțineau asociat cu indapamidă. Recomandarea de alopurinol este puternic asociată cu utilizarea indapamidei ($p = 0,004$) și cu doza de indapamidă ($p = 0,018$), în special cu cea de 1,5 mg ($p = 0,003$). Prescripțiile de indapamidă sunt semnificativ asociate cu sexul, grupa de vârstă și doza de alopurinol ($p < 0,05$). Doza de indapamidă este puternic corelată cu vârsta pacienților și cu doza de alopurinol ($p < 0,05$), în timp ce doza zilnică de alopurinol prezintă o corelație notabilă cu sexul ($p = 0,006$). Constatările studiului de față evidențiază necesitatea stabilirii frecvenței reale a hiperuricemiei cu indapamidă (menționată ca necunoscută în rezumatul caracteristicilor produsului actual), care este determinată, pe de o parte, de numărul mare de pacienți tratați și, pe de altă parte, de consecințele pe termen lung (afectare renală și gută).

Keywords: alopurinol, indapamide, hyperuricemia, chronic diseases, EHR database

Introduction

Indapamide is a thiazide-like diuretic characterised by its unique indoline structure and additional vasodilatory properties. It effectively inhibits the Na^+/Cl^- co-transporter in the early distal convoluted tubule, promoting the excretion of sodium, chloride, and water. With a half-life of 14 to 16 hours, indapamide supports once-daily dosing at 0.625 to 2.5 mg, making it a convenient option for patients (1–4). The evidence strongly supports that indapamide should be widely prescribed in suitable patients, those with hypertension, congestive heart failure, left ventricular hypertrophy, renal impairment, and elderly or diabetic populations (2). Its use is growing, particularly in Europe and Asia (5). However, indapamide remains substantially underutilised in the USA primarily due to the dominance of other diuretics in clinical guidelines and prescribing habits (6) In the USA, hydrochlorothiazide dominates (7) because of the availability of combination products and entrenched prescribing patterns (8–10).

Romania presents one of the most compelling cases for widespread antihypertensive prescribing in Europe and therefore a strong theoretical demand for indapamide. The most recent SEPHAR IV survey (2020–2021), conducted on a representative sample of 1,477 Romanian adults, confirmed a hypertension prevalence of 46%, of which 81% were known

hypertensives and 19% were newly diagnosed. Awareness had improved substantially to 81%, treatment to 83.8%, but blood pressure control remained unsatisfactory at only 39.2% (11). In Romania, indapamide is commercially available under numerous trade names, including Tertensif (1.5 mg SR, Les Laboratoires Servier, France), Indapamid Labormed 1.5 mg SR, and Rawel 1.5 mg SR (KRKA, Slovenia) (12). The availability of dual and triple combinations (perindopril ± amlodipine) expands prescribing options. The Romanian national protocol for diagnosis and treatment of arterial hypertension (published by the Ministry of Health and adapted from the ESH/ESC Guidelines) classifies antihypertensive therapy by cardiovascular risk level. Pharmacological treatment is promptly initiated for grade 3 hypertension and for grade 1–2 hypertension with high or very high total cardiovascular risk (13). The protocol emphasises diuretics alongside angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and beta-blockers as one of the principal drug classes in hypertension management (14). Reimbursed policy, numerous commercial products (indapamide alone or in combinations), and high cardiovascular risk (15) are primary factors that ensure indapamide consumption.

While it is generally more lipid-neutral than traditional thiazides, it's important to remain vigilant for potential dose-dependent metabolic side effects, such as hypokalemia, hyperglycemia, and hyperuricemia. This awareness can guide effective management strategies and optimise patient outcomes (16). Evidence indicates that the increase in serum uric acid caused by indapamide can negate some of the cardiovascular benefits of blood pressure reduction, because even low doses can induce hyperuricemia (17). Indapamide producers mention in the Summary of Product Characteristics (SmPC) this effect, but with an unknown frequency (18,19)

Therefore, allopurinol is co-prescribed with indapamide in clinical practice in symptomatic gout or recurrent uric acid/calcium nephrolithiasis in patients who require continued diuretic therapy (20). This combination has direct randomised trial support and broad guideline endorsement (21). In all cases where allopurinol is co-prescribed with indapamide, low starting doses, gradual titration, and regular monitoring of renal function are mandatory (22). Allopurinol is the first-line urate-lowering therapy in a hypertensive patient with symptomatic gout on indapamide (23). The combination - indapamide + allopurinol - was directly studied in calcium nephrolithiasis + hypercalciuria + hyperuricosuria on indapamide (21). Allopurinol remains an appropriate therapeutic option, but it requires a low starting dose (≤ 50 mg), slow titration, and close monitoring in concurrent CKD stage ≥ 3 on indapamide (23). Allopurinol is not indicated in asymptomatic diuretic-induced hyperuricemia (23).

In this context, our retrospective study aimed to investigate the concomitant use of indapamide and allopurinol in 1840 electronic health records of 3 community-care pharmacies from Calarasi, Romania, in January 2024. Retrospective analysis of electronic databases containing medical records is a common practice (24). EHRs are valuable resources for pharmacovigilance and research. Still, the information is structured for the proper conduct of medical and pharmaceutical activities, not necessarily for research (25). The "Benefit, Risk, and Impact of Medication Monitor (BRIMM)" system was developed as an infrastructure for research that integrates EHRs with patient reporting (26). Other studies emphasise the importance and contribution of medical records to pharmacovigilance. From this perspective, the computer programs of the medical, pharmaceutical, and CJAS units (SIUI and EHR) represent valuable resources for pharmacovigilance and general research (27).

Materials and Methods

Study Design

This retrospective, cross-sectional, observational study was conducted in January 2024, and the data were extracted from the three pharmacy dispensing databases. The study was approved by the Institutional Ethics Committee (Approval Number 7462/14.03.2023). The patient data were anonymised prior to analysis; data analysis was limited to the baseline data and medication.

Study Setting and Data Source

The present study was conducted in three community care pharmacies located in Călărași County, Romania. Data were extracted from electronic pharmacy dispensing records maintained within the Romanian national health insurance system (SIUI/CJAS platform). The records comprised exclusively reimbursed prescriptions for chronic diseases issued under the national health insurance system.

Eligibility Criteria

This study included prescriptions originating from the Romanian national health insurance system, specifically those issued for chronic diseases with reimbursement status. Eligible patients were adults aged 18 years or older with documented chronic disease status as classified within the insurance system. Both male and female patients were included. The temporal scope was limited to prescriptions issued during January 2024.

On the other hand, the study excluded private (non-reimbursed) prescriptions, prescriptions for acute diseases, and those issued to pediatric patients (age < 18 years). Additionally, duplicate records and

incomplete or illegible records were excluded from the analysis.

Data Variables, Definitions and Outcomes

The following variables were extracted: sex, birth date, and age; allopurinol (Milurit) and indapamide (as categorical variables); and the strengths of each medicinal product.

The raw data were extracted at the pharmacy level using the filters in the Dirigent (Cegedim Healthcare Romania) software, and prescriptions issued in the CNAS social health insurance system were selected. The collection period was January 2024, and the data were exported to Excel. The database structure and the software's filtering allowed selection and ordering so that each patient was unique, and the 30-day criterion limited duplicate patients.

Confidential data were eliminated, and each patient was automatically assigned an ID number, which was handed over to the researchers. From the total prescriptions, the following were excluded according to the exclusion criteria: patients under 18 years of age; patients with acute (A), subacute (S), or vaccination (P) diagnoses; and TAB III prescriptions (primary processing). Prescriptions that met the eligibility criteria, namely age and a chronic diagnosis (C), were analysed. The data were structured as follows: ID, sex, date of birth, age at dispensing, and medications used (trade names).

Subsequently, a secondary processing was performed, during which medications containing indapamide alone or in combination were identified and allocated to the specific column based on the presence or absence of indapamide and the amount of active substance. The same procedure was performed for allopurinol.

The primary outcome of the study was the presence of concomitant allopurinol and indapamide prescriptions in the same dispensing record/patient during the study period.

Statistical analysis

All analyses were performed using XLSTAT v. 2023.1.4 by Lumivero (Denver, CO, USA). Descriptive statistics were used to summarise the characteristics of the EHR holders (age, indapamide/alopurinol recommendation, prescribed doses. Associations were assessed using the chi-square independence test or Fisher's exact test, where appropriate; post-hoc analysis was performed using the adjusted residual coefficient (rij), with values > |1.96| considered significant. Statistical significance was defined as $p < 0.05$ (28).

Results and Discussion

Baseline data

The median age of the EHR-identified patients was 68 years (60 years for females and 80 years for males); 57.83% belonged to the 61-80 age group (Table 2). Then, in decreasing order, follows the 51-60 age group (22.04% men and 17.77% women) and the 81-90 age group (12.63% men and 14.60% women). 509/1840 (27.66%) EHRs had indapamide, 72/1840 (3.91%) had allopurinol, and only 31/1840 EHRs had both drugs concomitantly (Table I).

Our findings show that 31/72 allopurinol prescriptions included this urate-lowering therapy (ULT) concomitant with indapamide. The common practice of prescribing allopurinol alongside indapamide is likely due to indapamide-induced hyperuricemia; however, the cross-sectional nature of our data prevents a definitive conclusion about causality. Over 70% (56/72) EHRs with allopurinol in our data set contained Allopurinol 100 mg, while 234/509 (45.97%) EHRs with indapamide recommended 1,5 mg SR Indapamide (Tertensif or Indapamid LPH 1.5 mg). 177/509 (34.77%) had Indapamide 1.25 mg. At this strength, indapamide is available only in dual combination with perindopril 5 mg (Noliprel forte 5/1.25, Les Laboratoires Servier, France) and in triple combination with perindopril 5 mg and amlodipine 5 or 10 mg (Triplixam 5/1.25/5 and 15/1.25/10, Les Laboratoires Servier, France). 58/509 (11.39%) indapamide users had indapamide 2.5 mg; it is combined with 10 mg perindopril (Noliterax 10/2.5, Les Laboratoires Servier, France) and in triple combination with perindopril 10 mg and amlodipine 5 or 10 mg (Triplixam 10/2.5/5 and 10/2.5/10, Les Laboratoires Servier, France). Finally, 40/509 (7.85%) contained indapamide 0.625; it is only available in combination with perindopril 2.5 mg (Noliprel 2.5/0.625, Les Laboratoires Servier, France).

Of 1840 prescriptions, 509 (27.66%) were for indapamide, and 72 (3.92%) were for allopurinol (Figure 1, A, B). The percentage of allopurinol prescriptions among 1331 prescriptions without indapamide was similar to the previous value, 3.08% (Figure 1C). Of 509 prescriptions for indapamide, 31 were concomitantly prescribed allopurinol (Figure 1D); the co-prescription rate was almost 2 times higher than in both greater groups (Figure 1, B, C, D).

Indapamide 1.5 mg was most commonly prescribed in patients aged 81-90 (57.35%), while combinations with 1.25 mg indapamide were most commonly used in patients aged 91-100 (66.67%) and 41-50 (52.38%, Figure 2A).

Table I

Baseline data of the EHR identified patients included in the present study

Aspect	Total		F		M	
	n	%	*n*	%	*n*	%
	1840	100	1096	59.57	744	40.43
Median age (years)	68		60		80	
Age group						
30-40	38	2.07	19	1.73	19	2.55
41-50	129	7.01	70	6.39	59	7.93
51-60	327	17.77	163	14.87	164	22.04
61-70	497	27.01	297	27.10	200	26.88
71-80	569	30.92	369	33.67	200	26.88
81-90	254	13.80	160	14.60	94	12.63
91-100	26	1.41	18	1.64	8	1.08
Allopurinol						
0	1768	96.09	1051	95.89	717	96.37
1	72	3.91	45	4.11	27	3.63
Indapamide						
0	1331	72.34	773	70.53	558	75.00
1	509	27.66	323	29.47	186	25.00
Allopurinol (mg/day)						
0	1768	96.09	1051	95.89	717	96.37
100	56	3.04	41	3.74	15	2.02
200	2	0.11	1	0.09	1	0.13
300	14	0.76	3	0.27	11	1.48
Indapamide (mg/day)						
0	1331	72.34	773	70.53	558	75.00
0.625	40	2.17	28	2.55	12	1.61
1.25	177	9.62	106	9.67	71	9.54
1.5	234	12.72	157	14.32	77	10.35
2.5	58	3.15	32	2.92	26	3.49

EHR with Indapamide or Allopurinol (1) or without (0).

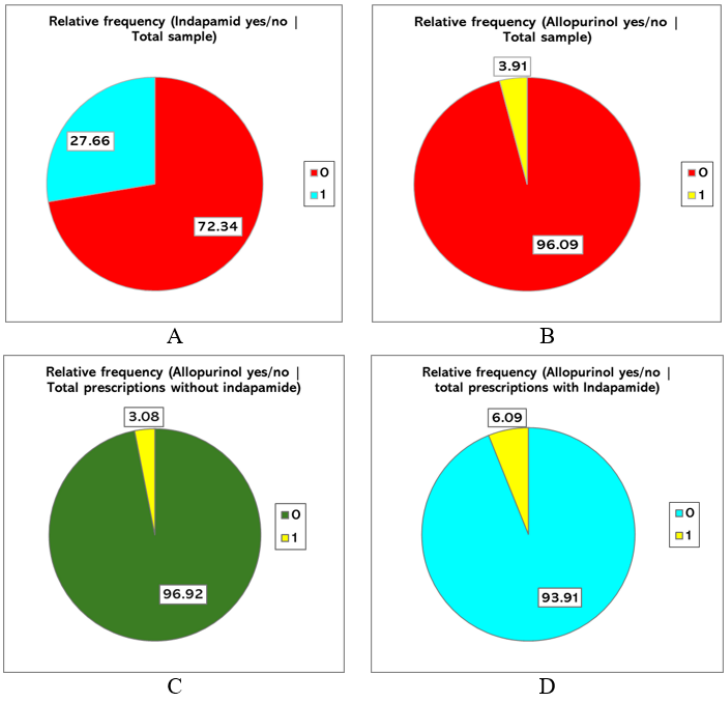

Figure 1.

A, B. Relative frequency of prescriptions with indapamide (A) and allopurinol (B) in all 1840. C, D. Relative frequency of prescriptions with allopurinol in all those 1331 without indapamide (C) and of co-prescriptions allopurinol-indapamide in all 509 ones (D).

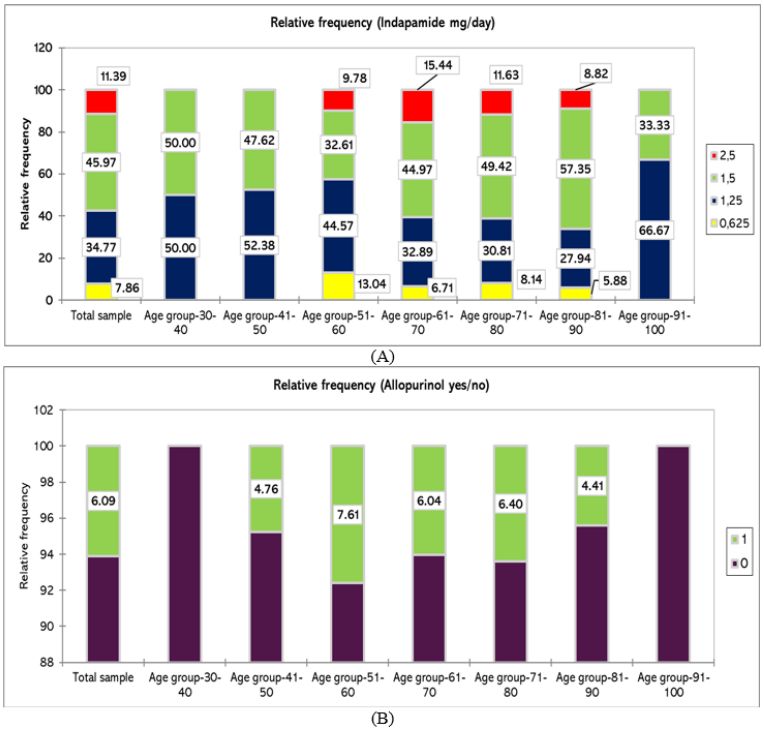

Figure 2.
Associations between age group and indapamide concentrations (A) and concomitant allopurinol prescription (B)

Allopurinol was prescribed in 6.09% of patients with indapamide. It was most often prescribed to patients aged 51-60 (7.61%), followed by those aged 71-80 (6.40%), while it was not used by patients aged 30-40 and 91-100 (Figure 2B). However, these cohorts were the least represented in the study, accounting for only 2.08% and 1.41% of the total population, respectively.

Associations between variables

Allopurinol recommendation is significantly associated with indapamide administration ($p = 0.003$) and indapamide daily dose ($p = 0.018$, Table II). Indapamide prescription is substantially associated with gender, age group, and allopurinol dose ($p < 0.05$, Table II). Significant associations were observed between indapamide dose, patient age, and allopurinol dosage ($p < 0.05$; Table II). Furthermore, the daily allopurinol dose was significantly associated with gender ($p < 0.05$; Table II).

Table II
Results of the chi-square independence test

Independence	DF (freedom degree)	Chi-square (observed value)	*p-value*
Allopurinol 0/1			
Indapamide 0/1	1	8.872	**0.003**
Indapamide dose	4	11.887	**0.018**
Gender	1	0.268	0.605
Age group	6	3.372	0.761
Indapamide 0/1			
Gender	2	4.427	**0.035**
Age group	6	20.651	**0.002**
Allopurinol dose	3	20.07	**0.000**
Indapamide dose (mg/day)			
Gender	4	9.012	0.061
Age group	24	42.41	**0.012**
Allopurinol dose	12	28.05	**0.005**
Allopurinol dose (mg/day)			
Gender	3	12.872	**0.006**

EHR with Indapamide or Allopurinol (1) or without (0); *p*-values in bold are statistically significant (<0.05).

Our findings show that 7.69% of prescriptions with indapamide 1.5 mg have allopurinol (100 mg - 7.26% and 200 mg – 0.43%, Figure 3). The literature indicates that even when indapamide modified-release tablets are used, the risk of hyperuricemia remains significant (29). Moreover, in an analysis of IQVIA Medical Research Data from the UK, Yan *et al*. reported that more than half of indapamide users discontinued or switched formulations during the first 2 years of follow-up (30). The poor compliance may be related to distinct side effects, such as hyponatremia, hyperuricemia, urinary frequency, and erectile dysfunction (31–39).

Almost 5.17% of prescriptions with indapamide 2.5 mg have allopurinol (100 mg – 3.45%, and 300 mg – 1.72%), while 5% of those with 0.625 mg indapamide have allopurinol 100 mg. The lowest per cent was observed in those receiving indapamide 1.25 mg with allopurinol 100 mg (4.52%, Figure 3).

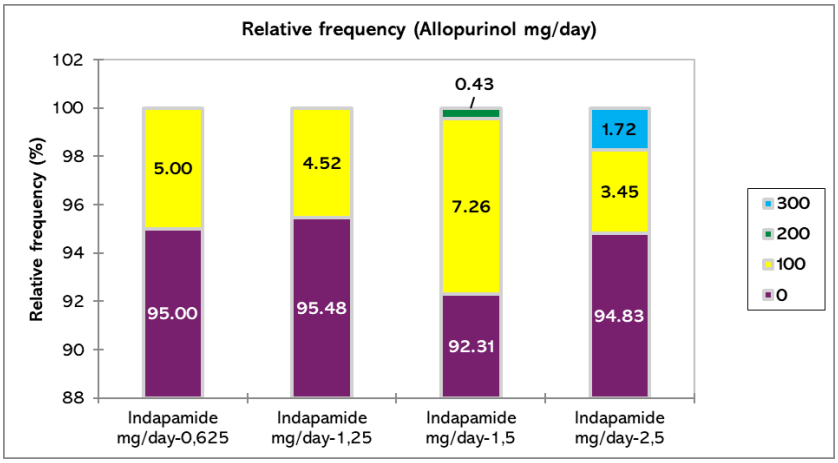

Figure 3.
Association between indapamide and allopurinol daily dose

Fisher's exact test revealed significant associations between variables (Table III). Allopurinol prescription was strongly associated with Indapamide administration and its daily dose of 1.5 mg ($r_{ij} > 2.900$, $p < 0.005$, Table III). Indapamide administration reveals a strong positive association with females and 100 mg allopurinol/day ($r_{ij} > 2.000$, $p < 0.05$, Table III). Indapamide at a daily dose of 1.5 mg was significantly associated with the female gender and 100 mg allopurinol prescriptions, whereas that of 2.5 mg was linked with the 61-70 age group ($p < 0.05$, Table III). Furthermore, 100 mg allopurinol is significantly associated with females, while the 300 mg dose is associated with males ($p < 0.05$, Table III).

All our findings suggest that concomitant prescribing of allopurinol and indapamide was requested to treat patients with hyperuricemia and characteristic clinical manifestations. Hyperuricemia is a risk factor for cardiovascular disease, and blood uric acid levels must be reduced (30). Hyperuricemia is also a well-known side effect of indapamide administration (40). To counteract uric acid elevation in the early 1970s, co-prescribing a xanthine oxidase inhibitor alongside a thiazide-type diuretic was a common practice (41,42). Their concomitant administration may increase serum oxypurinol concentrations and the risk of allopurinol toxicity, including hypersensitivity reactions, particularly in patients with decreased renal function (43). Thus, it is strongly contraindicated to prescribe allopurinol for asymptomatic indapamide-induced hyperuricemia (44). In this case, regular monitoring of uric acid levels and clinical symptoms is recommended before initiating urate-lowering treatment (45).

During therapy, it is very important to maintain normal uric acid levels, as highlighted by Nishino *et al*. (2022); their study found that maintaining uric acid levels within the normal range in patients who have suffered an acute myocardial infarction and have preserved ejection fraction improves prognosis (46). Blood glucose, uric acid, and potassium levels were investigated in a pharmacovigilance study conducted in Romania. The results of the study show increases in both individual and mean blood glucose and uric acid levels within 3 months of initiating treatment with indapamide 1.5 mg; the authors found a decrease in values after indapamide withdrawal, but these did not return to the initial levels (47).

However, according to IQVIA market data, indapamide is frequently used both alone and in combination. In January 2025, indapamide was released in 696940 boxes, perindopril indapamide in 895026 boxes, and perindopril indapamide amlodipine in 336619 boxes. This totals 1928585 boxes (38). During the same period, Allopurinol (Milurit, Egis Pharmaceuticals PLC, Hungary) in different concentrations was dispensed from pharmacies in Romania: 210247 boxes (48).

Table III
Results of Fisher's exact test

Independence	Fisher's exact test	r_{ij}	p
Allopurinol (1)			
Indapamide (1)		2.979	**0.004**
Indapamide 1.5 mg		3.191	**0.003**
Indapamide (1)			
Gender	F	2.104	**0.038**
Age group	31-40	–2.386	**0.016**
	41-50	–2.997	**0.002**
Allopurinol 100 mg		4.098	**0.000**
Indapamide dose			
1.5 mg			
Gender	F	2.512	**0.013**
0.625 mg			
Age group 51-60		2.045	0.057
1.25 mg			
Age group 51-60		1.974	0.062
2.5 mg			
Age group 61-70		2.204	**0.035**
1.5 mg			
Allopurinol 100 mg		4.024	**0.000**
Allopurinol dose			
100 mg			
Gender	F	2.114	**0.038**
300 mg			
Gender	M	2.919	**0.005**

EHR with Indapamide or Allopurinol (1); *p*-values in bold are statistically significant (<0.05).

The adverse reactions may not be recognised or diagnosed in time; therefore, the patients may be left indefinitely affected, with unpredictable consequences for their health. Indapamide increases uric acid levels by causing volume contraction and by directly inhibiting uric acid excretion in the proximal tubules of the kidneys. Chronic hyperuricemia, even when caused by medication, can cause renal dysfunction by triggering oxidative stress, renal ischemia, and inflammation within the kidney structure, which may lead to glomerulosclerosis and tubulointerstitial disease. In some instances, severe indapamide-induced electrolyte imbalances and hyperuricemia can directly contribute to the development or progression of chronic kidney disease (CKD) (49,50). Based on the figures provided, CKD resulted in significantly higher mortality than non-insulin-dependent diabetes mellitus during the specified period. In the National Institute of Statistics of Romania's 2023 annual report, 2553 deaths were attributed to CKD, corresponding to a rate of 11.6 *per* 100,000. For comparison, non-insulin-dependent diabetes mellitus in the same period generated 1546 deaths - 7.1 *per* 100,000 inhabitants (51). Therefore, CKD resulted in significantly higher mortality than non-insulin-dependent diabetes mellitus during the specified period.

In the present study, of 1840 EHRs with 509 prescriptions of indapamide, only 31 were associated with allopurinol. Indapamide 1.5 mg was prescribed to 45.97% of patients, but only 6.09% received allopurinol concomitantly (Figure 1). The remaining patients treated with indapamide had similar risks of increased blood levels of uric acid. The importance of recognising them in real time lies in reporting them on the dedicated regulatory authority page and in promptly addressing the dangers to the patient.

When combined with indapamide, perindopril can partially counteract the hyperuricemic effect of this thiazide-like diuretic by lowering the net reabsorption of uric acid in the proximal tubule (52). However, in high-risk patients, the combination of perindopril and indapamide can elevate serum creatinine, triglycerides, blood urea nitrogen, and uric acid levels compared with perindopril monotherapy (53). Our results reveal an association between 2.5 mg indapamide and 5.17% allopurinol administration, 1.72% requesting the highest dose of 300 mg (Figure 2). The dose of 0.625 mg indapamide is also associated with 5% allopurinol (Figure 2).

The following case study highlights the need to evaluate the hypothesis of iatrogenic hyperuricemia (as an adverse reaction to indapamide) in patients treated with indapamide and having high uric acid levels. Male, 50 years, chronic patient with hypertension and asthma, treated with: montelukast 10 mg, budesonide/formoterol 160/4.5 mg, ivabradine 5 mg, perindopril/indapamide 10/2.5 mg (Noliterax, Les Laboratoires Servier, France), and in July 2023 had a uric acid level of 9.4 mg/dL. The patient's history shows that the treatment with Noliterax began in June 2016. The evolution of uric acid levels is illustrated in Figure 4.

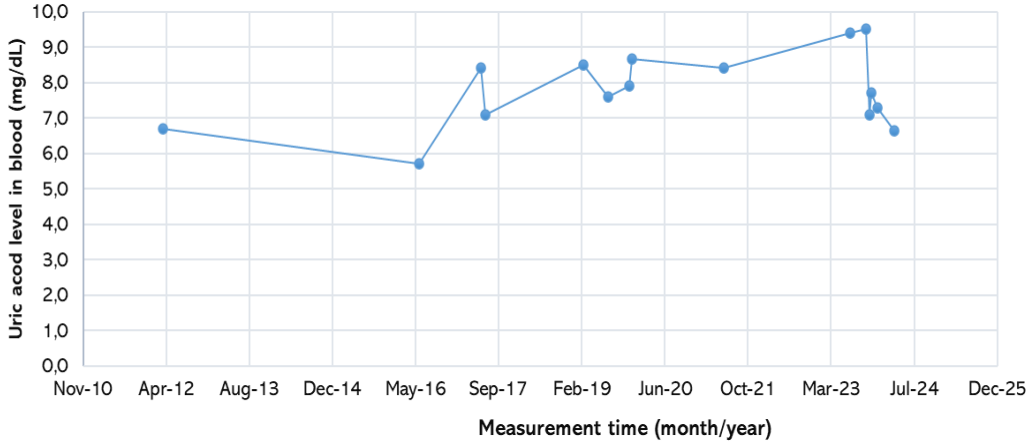

Figure 4.

Uric acid level evolution between 2012 and 2024 (normal range: 3.5 – 7.2 mg/dL). The green arrow marks the Noliterax® therapy beginning; the red arrow marks the highest level of uric acid in June 2023.

The patient was very cooperative, correctly administered the recommended medications, followed the doctor's instructions, kept his medical records, and periodically evaluated his health. He is evaluated by doctors from the following specialities: family medicine, cardiology, pulmonology, nephrology, and internal medicine. At the age of 48, in June 2021, his uric acid level was 8.4 mg/dL, and his family doctor referred him to nephrology for evaluation of elevated uric acid levels and glomerular filtration rate. Recommendations: a stricter regimen and return for evaluation, as he was suspected of gout and renal failure. At the age of 50, in 2023, he returned for a new evaluation, with an increased uric acid level 2 months (9.4 mg/dL in June and 9.5 mg/dL in October 2023). The specialist concludes that alopurinol is necessary in this case. Before introducing allopurinol into the therapy, the hypothesis of indapamide-induced hyperuricemia was evaluated by eliminating indapamide from the patient's antihypertensive medication. As a result, acid levels decreased from 9.5 to 7.2. mg/dL in two weeks and to 6.6. mg/dL by the end of February 2024. The indapamide-induced hyperuricemia is confirmed. Therefore, allopurinol was not included in the treatment.

In the triple combinations, the uricosuric properties of amlodipine, quantitatively the most powerful uric acid-lowering component in the trio, together with perindopril's mild uricosuria, are sufficient in most patients to offset indapamide's hyperuricemic tendency. This explains why perindopril/amlodipine/indapamide is associated with a more protective metabolic profile than any other considered combination antihypertensive medications in long-term comparative data (54).

ARBs can lower blood uric acid levels more than ACEs (55–58). Losartan and irbesartan are associated with a reduction in uric acid levels; valsartan, candesartan, or telmisartan have a neutral or slightly increasing effect (59-61) A recent study compared losartan with perindopril, beginning with a mean baseline uric acid level of 6.5 ± 1.1 mg/dL. After 12 weeks, uric acid levels declined significantly in the losartan group to 5.8 ± 0.9 mg/dL (mean reduction: 0.7 mg/dL). In contrast, the perindopril group showed a modest, non-significant reduction to 6.2 ± 1.0 mg/dL (mean reduction: 0.2 mg/dL). The study reported that the reduction in uric acid was significantly greater with losartan than with perindopril ($p < 0.01$) (62). Moreover, the recent FDA approval of the first indapamide-containing triple single-pill combination (telmisartan, amlodipine, and indapamide) may represent a turning point toward broader adoption (63–65).

In examining the link between indapamide and allopurinol, confounding by indication is an important challenge or limitation to consider. This is because the conditions that typically require the use of the diuretic, such as hypertension or CKD, are themselves major risk factors for hyperuricemia. Patients who are prescribed indapamide often have metabolic syndrome or impaired renal function, both of which are independently linked to higher serum uric acid levels and gout (66,67). In patients with hypertension, urate secretion is notably diminished, indicating that hypertension could induce the development of hyperuricemia. In its turn, uric acid can favour the development of blood hypertension, and several studies have shown that allopurinol has positive effects in hypertension, which may not be solely due to its ability to lower uric acid levels (68). Therefore, the frequent co-prescription of allopurinol may not only be a response to indapamide-induced uric acid increase but also a strategy to manage the patient's existing metabolic condition. To distinguish the drug's iatrogenic effects from the underlying disease, more sophisticated statistical techniques, such as

propensity score matching or multivariable regression, are needed to adjust for baseline comorbidities. Several limitations should be acknowledged. The geographic restriction to a single county, the one-month observation window, and the convenience-sampling approach limit the generalizability of the findings to broader populations or settings. Additionally, the study lacked access to serum uric acid measurements, clinical diagnoses, or data regarding the chronological order of medication initiation, which restricted the ability to establish temporal relationships and confirm hyperuricemia diagnoses. Finally, the case report describes a single male patient and serves an illustrative purpose; as such, it does not yield statistically generalizable conclusions beyond demonstrating the potential occurrence of the phenomenon under investigation.

However, despite the limitations noted above, the present study is clinically relevant, as it addresses an underreported pharmacovigilance issue. The data come from a real community pharmacy setting, and the case presentation is a useful addition that convincingly illustrates the clinical hypothesis.

Conclusions

The present findings highlight the need to establish the true frequency of hyperuricemia with indapamide, which is determined, on the one hand, by the large number of patients treated and, on the other hand, by the long-term consequences (renal damage and gout). At the same time, it would contribute to the prevention, identification, and correct treatment of adverse reactions. Health professionals would be more aware of the potential for side effects if the SmPCs mentioned them at the expected frequency. We consider that the diagnosis algorithm should always evaluate the hypothesis of iatrogenic hyperuricemia (as an adverse reaction to indapamide) in patients treated with indapamide who present with hyperuricemia.

Acknowledgement

Not applicable.

Funding

Not applicable.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

Institutional Ethics Committee Approval Number 7462/14.03.2023; A waiver of informed consent was included in the study approval.

AI use disclosure

Not applicable.

Conflict of interest

Velescu Bruno Ștefan is a Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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