Characterising Drug-Associated Nephrolithiasis: Insights from Global Adverse Drug Reaction Database

Editor's Pick

This insightful review examines drug-associated nephrolithiasis using the VigiBase pharmacovigilance database, identifying medications (some previously unrecognised) linked to kidney stone formation. Highlighting drugs such as indinavir, amoxicillin, and atazanavir, the authors provide valuable data on potential nephrotoxicity, offering important guidance for clinicians and future research.

Markus Peck-Radosavljevic
Klinikum Klagenfurt am Wörthersee, Austria

Authors: *Alexandre Baptista,[1,2] Ana Macedo,[1,2] Ana Marreiros,[1,2] André Coelho[3]

1. School of Medicine and Biomedical Sciences, Universidade do Algarve (UAlg), Faro, Portugal
2. Algarve Biomedical Centre (ABC), Faro, Portugal
3. Health & Technology Research Center (H&TRC) - Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisbon, Portugal

*Correspondence to ambaptista@ualg.pt

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Abstract

Purpose: Kidney stones are a common condition affecting the urinary system, with 8–12% of the global population experiencing them. Around 1–2% of all kidney stones are adverse drug reactions. VigiBase is a powerful tool to evaluate drug-associated events. However, to the authors knowledge, no study has yet analysed this database to identify the most common drugs associated with nephrolithiasis. The objective of this study was to analyse reports of nephrolithiasis and their associated medications in the VigiBase database.

Methods: The authors conducted a retrospective pharmacovigilance disproportionality analysis using data from VigiBase, covering 1968–2022. They employed the WHO's IC_{025} index to identify drugs with significant disproportion in notification frequency. Identified drugs were assessed using a bibliographic score (BS), ranging from 0–5, to determine their previous role as lithogenic agents.

Results: Of the 33,932,051 notifications extracted, 35,008 were related to drug-associated nephrolithiasis. Among all identified drugs, indinavir had the highest disproportionality index (IC_{025} 6.5), followed by amoxicillin (IC_{025} 5.9) and atazanavir (IC_{025} 5.3). The most frequently referenced drugs were adalimumab (n=2,193), infliximab (n=1,300), and etanarcept (n=1,287). Among these drugs, the authors observed a progressive increase in the BS associated with the IC_{025}, with a IC_{025} of 1.52 for those with a BS=0, and a IC_{025} of 6.5 for those with a BS=5. Notably, more than 40% of the retrieved and evaluated drugs were not considered lithogenic by the BS evaluation, thus an extensive literature review was conducted to confirm their new potential nephrotoxicity.

Conclusion: Although drug-associated kidney stones were infrequently reported in VigiBase, the authors' findings suggest potential new lithogenic associations with certain drugs, to be further analysed.

Key Points

1. Drug-induced kidney stones may account for up to 1–2% of all urolithiasis cases, yet are often under-recognised and preventable.

2. A narrative review based on pharmacovigilance data, structured by renal phenotype, focusing on drug-associated nephrolithiasis.

3. Recognising drug-induced stones enables better prevention, especially by reviewing drug histories in high-risk patients.

INTRODUCTION

Kidney stones are the most common condition affecting the urinary system, impacting approximately 8–12% of the global population,[1,2] predominantly individuals aged 20–49 years.[1] Drug-associated nephrolithiasis accounts for approximately 1–2% of all kidney stones.[3] These stones can develop through two pathways: 1) poor solubility of the drug, leading to crystal formation in the urine,[3] this model is seen with drugs like atazanavir,[4] or other protease inhibitors, and with sulfadiazine;[5] 2) urinary changes caused by these drugs, particularly modifications in pH and/or changes in the excretion of calcium, phosphate, oxalate, citrate, uric acid, or other purines. Prime examples of this mechanism include dietary supplements containing vitamin D/calcium, or treatment with carbonic anhydrase inhibitors[6] or topiramate.[7]

Pharmacovigilance is an essential tool for monitoring the safety and efficacy of medicines. Studies based on pharmacovigilance databases help identify the main medications associated with specific adverse reactions, providing insights into drugs strongly linked to these reactions. One such database is VigiBase, managed by the Uppsala Monitoring Centre on behalf of the WHO. It collects spontaneous and anonymous reports of adverse drug reactions (ADR) from more than 150 countries worldwide.

To the authors' knowledge, no study has yet evaluated which drugs are more frequently reported in VigiBase and associated with drug-associated nephrolithiasis.

MATERIALS AND METHODS

The authors performed a retrospective pharmacovigilance descriptive analysis

of the largest global database of ADRs notifications, following approval from the review board. Data for this study were obtained from VigiBase, an extensive database that compiles spontaneous ADR reports from a wide range of participating countries, ensuring full anonymity of the data. Covering the period from 1968–2022, stringent protocols were applied to eliminate duplicate notifications, with each report receiving a unique identification number for accurate referencing. The dataset offers up-to-date information and includes comprehensive details for each notification, such as anonymised patient data, notifier information, the severity of the ADR, the implicated drug, and a description of the identified adverse reaction. Although the data pool was already anonymised, the study underwent ethical review by the Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Algarve, which granted consent for data evaluation.

The compilation of notifications was carried out after filtering for relevant Medical Dictionary for Regulatory Activities (MedDRA) terms, such as 'nephrolithiasis', 'crystalluria', and related terms. Within these notifications, each drug was recognised by its active ingredient, in accordance with WHODrug nomenclature standards. Moreover, the drugs were classified into pharmacological categories following the WHO's anatomical Therapeutic Chemical (ATC) classification system. This method enabled a structured analysis of the data, focusing on distinct pharmacological groupings.

In this study, the authors employed disproportionality analysis utilising both the information component (IC_{025}) and the reporting odds ratio (ROR). The IC_{025} compares the observed frequency of a specific adverse reaction associated with a medication against its expected frequency in the general population. The ROR calculates an odds ratio to evaluate the association between a medication and an adverse event. An ROR >1 indicates a positive association, suggesting that the medication-induced adverse reaction occurs more frequently than expected. Therefore, while the IC adjusts observed and expected frequencies using a Bayesian approach, the ROR offers a straightforward measure of association based on odds ratios.

For the main medications evaluated using IC_{025} and ROR, a bibliographic score was developed to quantitatively determine the degree of nephrotoxicity evidenced in the literature. Each drug was evaluated in five different bibliographic sources regarding its role in the formation of kidney stones (two databases,[8,9] one website,[10] and two reference books[11,12]). A bibliographic score (BS) was developed and considered a surrogate for each drug lithogenic role (0: not lithogenic; 1–2: potentially lithogenic; 3–5: lithogenic). The score assigned to each medication corresponded to the total number of sources referencing the adverse event.

RESULTS

Between 1968–2022, VigiBase, the WHO's global database, accumulated a total of 33,932,051 notifications from numerous contributing countries. Out of these, we extracted 35,008 notifications associated with drug-induced nephrolithiasis, representing 0.1% of all reports during this period. These notifications implicated 3,283 active ingredients or combinations suspected of causing drug-associated nephrolithiasis.

Most notifications of drug-associated nephrolithiasis were reported by consumers (44.1%), followed by physicians (23.9%) and other health professionals (15.6%). The majority of reported cases originated from the USA (72.8%), Canada (7.4%), and the UK (2.8%). Female consumers accounted for the highest proportion of notifications (51.8%), with the most affected age group being 45–64 years old (29%), followed by those aged 18–44 years (16.2%), and the 65–74 years bracket (11.4%).

The MedDRA term 'nephrolithiasis' was the most frequently reported, constituting 94.2% of the notifications. 'Urinary tract infection' was the most common concurrent condition, noted in 8.3% of the cases (Table 1).

Table 1: Frequencies of either main or concomitant Medical Dictionary for Regulatory Activities terms most frequently reported.

Main MedDRA Terms reported		Concomitant MedDRA Terms reported	
Nephrolithiasis	94.2%	Urinary tract infection	8.3%
Ureterolithiasis	4.2%	Pain	7.9%
Crystalluria	1.6%	Fatigue	6.4%
Crystal urine present	1.1%	Nausea	6.0%
Medication crystals in urine present	0.1%	Back pain	6.0%
Urinary stone analysis	0.0%	Urinary tract infection	4.8%

MedDRA: Medical Dictionary for Regulatory Activities

Table 2: Drugs most associated with nephrolithiasis or having a higher disproportionality index and their relationship with the bibliographic score.

Active Ingredient	Notifications	ATC Class	Phenotype	IC_{025}	ROR	BS
Indinavir	820 (2.3%)	J	Nephrolithiasis	6.5	111.98	5
Sulfadiazin	95 (0.3%)	J	Nephrolithiasis	3.4	22.73	4
Topiramate	734 (2.1%)	N	Nephrolithiasis	4.2	21.16	4
Amoxicillin	227 (0.6%)	J	Crystalluria	5.9	1.48	3
Amoxicillin-ClavulanicAcid	60 (0.4%)	J	Crystalluria	2.7	10.76	3
Atazanavir	447 (1.3%)	J	Nephrolithiasis	5.2	47.34	3
Ritonavir	202 (0.6%)	J	Nephrolithiasis	3.2	10.54	3
Tocilizumab	238 (0.7%)	L	Nephrolithiasis	1.6	3.58	3
Adalimumab	2,193 (6.3%)	L	Nephrolithiasis	1.7	3.44	2
Lansoprazole	607 (1.7%)	A	-	-	8.95	2
Mesalazine	102 (0.2%)	A	Nephrolithiasis	1.8	4.48	2
Teriparatide	901 (2.6%)	H	Nephrolithiasis	2.4	5.65	2
Etanercept	1,287 (3.7%)	L	Nephrolithiasis	1.1	2.26	1

Table 2: Drugs most associated with nephrolithiasis or having a higher disproportionality index and their relationship with the bibliographic score. Continued.

Infliximab	1,300 (3.7%)	L	Nephrolithiasis	2.7	6.96	1
Lenalidomide	492 (1.4%)	L	-	-	1.57	1
AlendronicAcid-Cholecalciferol	106 (0.3%)	M	Nephrolithiasis	3.7	18.98	0
FumaricAcid	394 (1.1%)	D	Nephrolithiasis	1.3	2.61	0
IbandronicAcid	89 (0.1%)	M	Nephrolithiasis	1.6	3.12	0
ZolendronicAcid	255 (0.5%)	M	Nephrolithiasis	1.8	4.21	0
Cholecalciferol	46 (0.1%)	M	Nephrolithiasis	2.3	6.2	0

ATC: anatomical Therapeutic Chemical; ATC A: alimentary tract and metabolism; ATC H: systemic hormonal preparations (excluding sex hormones and insulins); ATC J: antiinfectives for systemic use; ATC L: antineoplastic and immunomodulating agents; ATC ATC M: musculo-skeletal system, ATC N: nervous system; BS: bibliographical score; IC_{025}: information component; ROR: reporting odds ratio.

Among the pharmacological classes associated with drug-related nephrolithiasis, the ATC Class L: antineoplastic and immunomodulating agents was most prevalent, accounting for 39.3% of the notifications; followed by almost as half of the notifications by ATC Class A: alimentary tract and metabolism (14.8%); and by ATC Class J: antiinfectives of systemic use (14.6%).

In terms of specific drugs, those with the highest disproportionality index, medications reported more frequently in this reaction than expected, included indinavir (IC_{025}: 6.5), amoxicillin (IC_{025}: 5.9), atazanavir (IC_{025}: 5.3), and topiramate (IC_{025}: 4.2). These drugs also had a high average bibliographic score of 3.75, within an interval of 3–5, demonstrating their known nephrotoxicity. Conversely, those most frequently reported (absolute numbers) as adalimumab (n=2,193), infliximab (n=1,300), etanercept (n=1,287), and the COVID-19 vaccine (n=1,140) (tozinameran accounted for 56.8% and elasomeran for 27.0% of the cases), showed a low average bibliographic score of 0.75, with scores ranging from 0–2. These scores suggest the possibility of new nephrotoxins.

Of the medications most frequently reported or with the highest disproportionality, 50% had no bibliographic references indicating a lithogenic role (BS 0), while 23.3% were considered potential nephrotoxins (BS 1–2), with another 36.7% of those drugs evaluated being considered known nephrotoxins (BS 3–5), as detailed in Table 2.

In 77.3% of the notifications for drug-associated nephrolithiasis, the cases were classified as serious, primarily due to the development of medically important conditions, which accounted for 67.4% of these cases and followed by caused or prolonged hospitalisation (42.2%). Within the serious outcomes, the ATC Class A: alimentary tract and metabolism, was most frequently implicated in fatal outcomes, reported in 31.9% of such cases. Sitagliptin emerged as the most frequently reported active ingredient in these notifications, accounting for 10.8%.

DISCUSSION

To the best of the authors' knowledge, this study is one of the first to compile results from VigiBase, one of the world's largest databases of spontaneous ADR notifications. It highlights drugs frequently implicated in these notifications, both by reporting frequency and disproportionality index.

Surprisingly, over 70% of the primary drugs reported, or with a high disproportionality index, were found to be non-lithogenic or only potentially lithogenic. Drug-associated nephrolithiasis appears to be a rare condition (or underdiagnosed), which is corroborated by the minimal spontaneous notifications during the study period.

Globally, men are more predisposed to developing kidney stones,[13] although recent data suggest a shifting epidemiology, with an increasing incidence among women.[14] The authors' findings reflect this trend, showing a higher reporting frequency among female consumers (51.8%) compared to males (43.6%), although specific epidemiological data on drug-associated nephrolithiasis remain scarce. While differences in reporting patterns between consumers and healthcare professionals may exist, the authors' dataset did not provide sufficient information to allow for definitive conclusions regarding the source of the reports.

In the authors' analysis and considering the main medications evaluated, half were regarded as potential new nephrotoxins or lithogenic drugs, considering their BS of 0. Overall, the medications evaluated showed moderate to low disproportionality values, except for some medications with BS 3–5. This suggests that the association of these medications with the phenotype in question is not strong.

In these potential new nephrotoxins or lithogenic agents, some stand out. One of these medications is the combination alendronic acid + cholecalciferol (IC_{025} 3.7 and ROR 18.98), which did not reveal bibliographic references obtained through the authors' BS. However, the absence of this association is curious since deeper research shows associations between cholecalciferol (IC_{025} 2.3 and ROR 6.29) and nephrolithiasis.[15] This raises the question of why the combination alendronic acid + cholecalciferol does not have such literature references. One possible reason is that this combination actually represents the association of two medications that are antagonistic to the formation of renal stones. Alendronic acid not only reduces urinary calcium excretion,[16] but also inhibits the crystallization of the calcium-phosphate complex,[17] thereby preventing kidney stone formation.

Another medication considered a potential new nephrotoxin is the antiviral combination of emtricitabine + tenofovir disoproxil (IC_{025} 2.8 and ROR 8.07), to which no literature references associating this dual combination with the development of nephrolithiasis could be found, even after extensive research, including exploration within HIV medication literature. IFN-β1a is another potential new lithogenic drug (IC_{025} 2.1 and ROR 4.7), in which thorough literature evaluation failed to uncover any references that even remotely support this association. The same with natalizumab (ROR 3.57), nor was there in the evaluation of biosimilars.[18]

Ibandronic acid has been reported as a therapeutic solution for reducing kidney stone formation, noted as one of the most potent inhibitors of crystallisation.[19] However, the authors found 83 notifications associating this medication with this phenotype. Upon further evaluation of these notifications, only five of them co-reported other lithogenic drugs as a concomitant medication, suggesting a potential bias in attributing the association between nephrolithiasis and ibandronic acid. Similar reasoning can be applied when evaluating the association between zoledronic acid and nephrolithiasis. However, among those medications for which the authors' BS was null, there are some in which they were able, in a deeper literature search, to find associations with nephrolithiasis. One of those examples was omeprazole and pantoprazol, both known for their association with nephrolithiasis in a dose-dependent manner.[20] Tofacitinib, despite having a BS of 0, is already known for its association with nephrolithiasis,[21] albeit showing a low association with an IC_{025} of 1.49 and an ROR of 2.85. The same occurred with sodium oxybate, which has also seen nephrolithiasis reported as an ADR in other references.[22]

In the description of the results of drug-associated nephrolithiasis, the authors found that certain medications were reported much more significantly than

others. Among these, adalimumab (IC_{025} 1.7 e ROR 3.44) stands out (6.3% of the notifications), which showed an BS of 2, indicating that it is already a medication with some evidence of nephrotoxicity. This medication is a monoclonal antibody that blocks TNF-α,[23] used in the treatment of diseases such as Crohn's disease and ankylosing spondylitis, with literature references associating it with this phenotype.[24] However, as nephrolithiasis is an apparent extra-articular manifestation of the disease[25] and adalimumab is used to treat these conditions, it is plausible that there may be biases associated with the incidence of nephrolithiasis associated with the use of adalimumab. In fact, recently, in a study evaluating the odds ratio of biological treatments and nephrolithiasis, adalimumab showed an odds ratio of 1.1 without statistical significance ($p<0.05$).[26]

Similarly to adalimumab, infliximab (IC_{025} 2.7 and ROR 6.96) is a monoclonal anti-TNF-alpha antibody,[27] which was also described in the reported spontaneous notifications (3.7%). Indeed, prevalence studies of renal stone disease in patients treated with anti-TNF have demonstrated a significant association between this class of drugs and increased risk of nephrolithiasis, and recently this association was widely described in a Danish population-based study, which reported an increased risk of nephrolithiasis in patients under this type of medication.[28]

Finally, etanercept, a fusion protein of the p75FC receptor of human tumour necrosis factor obtained by DNA recombinant technology, used in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, etc.,[29] was the third most reported medication in notifications of renal stone disease associated with medication use, being involved in 3.7% of the notifications obtained. Its association with the nephrolithiasis phenotype, according to our results, was considered very weak, with an IC_{025} of 1.1 and ROR of 2.26. However, there may be some pathophysiological substrate for this association since etanercept has been associated with the development of hypercalcemia,[30] which is a strong risk factor for the development of kidney stones.

Among the medications showing a stronger association with nephrolithiasis (due to their high disproportionality index), indinavir stands out. This medication exhibited the highest IC_{025} among the highlighted drugs, with an IC_{025} of 6.5 and ROR 111.98, indicating a significantly higher disproportionality index concerning nephrolithiasis. In other words, it is involved in nephrolithiasis notifications much more frequently than expected in the general population. This aligns with extensive literature documenting the association between indinavir and nephrolithiasis. In fact, it is estimated that approximately 20% of patients taking this medication present some type of urinary crystallisation or even the presence of kidney stones,[31] with isolated kidney stone formation estimated to have an incidence between 4–13%.[32] The formation of kidney stones results from the excretion of indinavir in the urine, which has low urinary solubility, leading to crystal formation,[33] causing up to 67% of patients treated with Indinavir to present with asymptomatic crystalluria, with symptoms in 8% and nephrolithiasis in 3%.[34]

Another medication strongly linked to this phenotype is amoxicillin (IC_{025} 5.9). In fact, the association of amoxicillin with kidney stones is well known, especially when used in high intravenous doses.[35] Despite this lithogenic effect, it also appears that this association is a characteristic of its pharmacological class, largely associated with the elimination of colonisation by Oxalobacter formigenes,[36] leading to reduced fecal degradation of oxalate. Oxalobacter formigenes, by degrading oxalate in the intestine, results in lower urinary oxalate concentration, thus providing protection against calcium oxalate stone formation.

Similarly, atazanavir, another medication for HIV infection treatment, showed a strong link to nephrolithiasis (IC_{025} 5.3 and ROR 47.34), often used in conjunction with other antivirals, notably ritonavir.[37] Although its label states that nephrolithiasis

associated with atazanavir is "rare",[37] this association has been reported in post-marketing contexts.[37] Specifically, atazanavir significantly increases the risk of nephrolithiasis more than other regimens involving other protease inhibitors.[38] Atazanavir, by reaching high urinary concentrations, triggers the formation of atazanavir crystals,[4] but only after long periods of exposure to the medication,[39] which is the mechanism of its association with nephrolithiasis. Indeed, switching from atazanavir to other antivirals is recommended in patients who have developed kidney stones.[40]

Finally, topiramate, a medication indicated for migraine prophylaxis, was another medication that showed a strong association with this phenotype (IC_{025} 4.2 and ROR 21.16). One of the earliest references to the association between topiramate and nephrolithiasis was in the year 2000,[41] and since then, publications have been made about the various changes caused by topiramate, both in paediatric ages and in the underlying urinary pathophysiological mechanisms of kidney stone formation,[42] where kidney stone formation results from the development of hypocitraturia and elevated urinary pH, leading to high formation of calcium phosphate stones. It is estimated that patients taking an average dose of 300 mg/day and with an average treatment duration of 48 months have a prevalence of symptomatic nephrolithiasis of 10.7%,[43] although this association is disputed by some authors.[44]

Although pharmacovigilance studies do not provide definitive conclusions, they offer insights for further discussion and confirmation in dedicated studies. Identifying medications with high IC_{025} values should lead to several implications, particularly in terms of surveillance.[45] A medication with a high IC_{025} value should undergo more rigorous and frequent monitoring by healthcare professionals and regulatory agencies (EMA, FDA, Brazilian Health Regulatory Agency [Anvisa]), which may conduct a more detailed safety review. This could involve additional data analysis, epidemiological studies, or even clinical trials to confirm the association between the medication and the adverse reaction.[46] In essence, a high IC_{025} serves as a potential alert signal that can trigger a series of actions aimed at ensuring patient safety and maintaining the medication's continued effectiveness, while balancing the benefits and risks of treatment.[47]

Population-based or cohort studies published about drug-associated nephrolithiasis are scarce. One study that utilised a pharmacovigilance database specifically evaluated acute kidney injury in the context of nephrolithiasis but exclusively in patients using SGLT2 inhibitors.[48] Other studies that also assessed pharmacovigilance databases for the adverse reaction 'nephrolithiasis' did so exclusively for specific medications or classes such as proton pump inhibitors[49] and SGLT2 inhibitors.[50] Another population-based study only reflects a significant increase in the annual incidence of nephrolithiasis, at an average rate of 1%, in both children and adults, to which medications available on the market may have also contributed.[51] Delving into the existing literature, the authors' data support medications such as topiramate, sulfadiazine, indinavir, atazanavir, and antibiotics, among other frequently implicated medications,[52,53] while also putting into perspective the possibility of new lithogenic agents.

Research on nephrolithiasis associated with medication use also involves advancing our understanding of the mechanisms associated with the development of nephrolithiasis, whether they are metabolic risk factors related to receptors, promoters, and inhibitors, or through the evaluation of the roles of the immune system, microbiome, or sex hormones.[54] In addition to this pathway, the discovery of new medications, or new treatment or prevention pathways for nephrolithiasis,[55] may also help identify new solutions to reduce or prevent the development of nephrolithiasis associated with medication use. The exploration of new biomarkers and the use of AI will certainly provide more answers to the countless questions currently being asked. Pharmacovigilance-based

studies, in the future, whether through the development of connectable networks between various databases or through the introduction of deep learning, will improve the identification of signals and enhance the post-marketing knowledge of newly introduced medications.[56]

This study boasts several strengths, beginning with the generalisability of its results. Drawing from VigiBase, a database aggregating data from over a hundred countries, ensures the findings can be generalised across diverse populations. Another significant advantage is the standardised approach to data collection mandated by VigiBase, employing both the MedDRA dictionary and WHODrug. This standardisation minimises biases in data manipulation, enhancing the reliability of the study. Additionally, the study's ability to identify signals is noteworthy. Leveraging such a comprehensive data source facilitates the detection of drugs associated with specific adverse reactions, potentially uncovering new signals. Furthermore, the integration of the IC_{025} disproportionality index into VigiBase facilitates the analysis process, reducing the likelihood of calculation errors or biases that may occur with other disproportionality methods. However, the detection of signals through disproportionality analysis does not establish a causal relationship, nor does it confirm that the clinical event is more frequently associated with the drug in question. It merely suggests that this adverse drug reaction is reported more frequently for this drug compared to others.

However, this study is subject to certain limitations. Firstly, as this study relies on spontaneous reports of ADRs, the available data lack both clinical narratives and information on the temporal relationship between drug administration and the adverse reaction. Moreover, causality assessment may be biased due to inherent limitations of spontaneous reporting systems. Secondly, the authors' classification of lithogenic roles based on five bibliographic references may not be as precise as direct evidence linking drugs to kidney lithiasis. Moreover, the results of our study may also be influenced by several biases inherent in pharmacovigilance studies. Among these biases, they highlight underreporting bias, which can lead to an underestimation of the frequency of adverse events, making a medication appear safer than it actually is. Additionally, there is the bias of selective reporting, where there is a tendency to report newer adverse reactions (Weber effect), more severe reactions, or those associated with well-known medications, creating a false perception of higher risk for these drugs. Furthermore, since the majority of notifications assessed involve more than one medication, we must also consider recall or information bias, where clinical information obtained may inadvertently be distorted (incorrect information regarding occurrence, severity, or medications involved) or significant parts of information may be missing, leading to conclusions that are not based on all actual facts. This could even lead to wrongly attributing causality to a different medication.[57]

Despite these caveats, the study provides valuable insights into medications most commonly associated with nephrolithiasis, highlighting several drugs with potential new lithogenic roles. However, further studies are required to confirm these findings.

CONCLUSION

Pharmacovigilance studies enable direct data collection from clinical settings, and their analysis can pinpoint medications most frequently associated with specific phenotypes. This underscores the need for heightened scrutiny of these drugs and emphasises the importance of enhanced surveillance to improve patient safety.

Reports of drug-associated kidney stones in VigiBase are infrequent. The authors' data highlights some of the medications most linked to nephrolithiasis, identifying those with a strong association through disproportionality indices (IC_{025} and ROR). Additionally, this study employed a BS developed by the authors to identify potential new nephrotoxins. These findings necessitate targeted studies to evaluate the lithogenic potential of these medications.

Nevertheless, clinicians should remain vigilant when prescribing these drugs, monitoring patients for the development of kidney stones, and minimising potential iatrogenic effects. The authors urge every clinic to actively report any adverse drug reactions encountered in clinical practice.

DATA AVAILABILITY STATEMENT

The data will be available for consultation if deemed necessary.

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