



Review Article

An evidence-based approach for providing cautionary recommendations to sulfonamide-allergic patients and determining cross-reactivity among sulfonamide-containing medications

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SUMMARY

What is known and Objective: Prescribing sulfonamide-containing medications for patients with sulfonamide allergy continues to complicate medical decisions. We examined the cautionary recommendations in the approved drug monographs and primary literature, and formulated an evidence-based grading of cautionary recommendations for sulfonamide allergy and cross-reactivity among sulfonamide-containing medications.

Methods: Drug monographs were collected from six countries and three drug compendia. Two reviewers independently extracted the data from the contraindication, warning and/or precaution sections of drug monographs. Evidence for cross-reactivity was examined in the primary literature and compared with drug monograph recommendations. Consequently, medications were categorized based on the strength of recommendation and level of evidence by consensus.

Results and Discussion: We identified wide variability in cautionary recommendations ranging from no warning or precaution to contraindication among the sources reviewed. The recommendations were located mainly in the contraindication section of monographs for France (65.2%), United Kingdom (51.9%), Italy (50.0%), South Korea (43.5%), United States (38.2%) and Canada (37.0%), whereas in drug compendia, the recommendations were found in the precaution section for Martindale (51.4%) and Micromedex-Drugdex (33.3%), and contraindication and precaution section for the American Hospital Formulary Service Drug Information 2010 (30.8%). Evidence from the primary literature varied with recommendation included in drug monographs. Evidence-based categorization was carried out for 16 medications. Two sulfonamide-moiety-containing drugs were considered safe, six non-sulfonylarylamines required precaution, and eight medications from all three sulfonamide chemical classes were considered mostly unsafe.

What is new and Conclusion: There are significant discrepancies in cautionary recommendations included in drug-labels and drug compendia. Statements concerning cross-reactive hypersensitivity with other sulfonamides generally suggest theoretical possibilities. The consensus evidence-based grading instrument developed may be useful for deriving cautionary recommendations for sulfonamide-allergic patients.

WHAT IS KNOWN AND OBJECTIVE

Sulfonamides were among the first synthetic antimicrobial medications to be used clinically.¹ From a modern perspective, the term refers to a diverse group of drugs, all of which contain the sulfonamide functional group ($-SO_2NH_2$). Based on the chemical structure, sulfonamides can be divided into three types: sulfonylarylamines, non-sulfonylarylamines and sulfonamide moiety-containing drugs.² Antimicrobial sulfonamides (sulfonylarylamines) rank second to beta-lactams as the most common cause of drug allergy.^{1,3} Hypersensitivity reactions to sulfonamides have been documented since shortly after the introduction of sulfanilamide,⁴ and they occur in about 3% of patients in the general population and 60% of patients with HIV infection.^{5,6} The most common manifestation of sulfonamide allergy is a generalized maculopapular rash accompanied by fever and urticaria, and the most serious reactions are called hypersensitivity or idiosyncratic adverse drug reactions.^{5,7} Rarely, one case per million person-years, antimicrobial sulfonamides may be associated with life-threatening conditions like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^{1,8,9} Based on the sulfonamide functional group, two known types of allergic reactions may occur. The first is the immunoglobulin (Ig) E mediated type-1 reaction that requires the presence of a heterocyclic ring at the sulfonamide-N1 position; it presents usually within 1–3 days after therapy begins and is associated with maculopapular or urticarial rash.² The second type is the more common hypersensitivity reaction that develops 7–14 days after beginning therapy, requires the presence of an unsubstituted amine group at the N4 position (Fig. 1), and is associated with the formation of cytotoxic or immunogenic hydroxylamine and nitrosoamine metabolites from Cytochrome P450 oxidation of the N4 arylamine.^{2,10}

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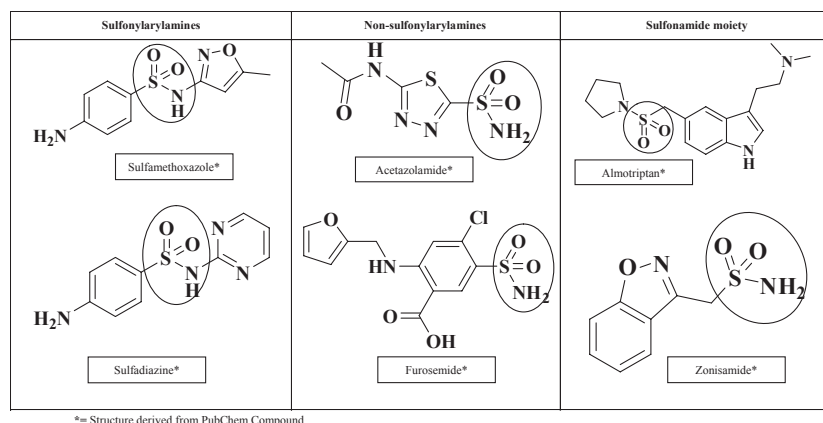


Fig. 1. Structural difference between classes of sulfonamide drugs. *Sulfonylarylamines*: sulfonamide moiety is attached directly to a benzene ring with an unsubstituted amine ($-\text{NH}_2$) moiety at the N4 position. *Non-Sulfonylarylamines*: sulfonamide moiety is attached to a benzene ring or other cyclic structure, but does not have an amine group at the N4 position. *Sulfonamide Moiety*: sulfonamide moiety is not connected to a benzene ring or other cyclic structure. *Structure derived from PubChem Compound.

Patients with a history of sulfonamide allergy are thought to be at increased risk for another reaction; thus, taking other sulfonamide drugs is contraindicated despite scarce data supporting it.^{11–13} Clinicians often have no relevant scientific evidence that supports their decision making.^{14,15} Hence, concern about potential cross-allergenicity between sulfonamide-containing medications remains a persistent issue that continues to complicate medical decision making.¹⁶

One potential source of cautionary recommendations about sulfonamide allergy is the approved drug monograph or manufacturer's package inserts (MPIs) available in the online drug product database in each country. The MPIs aim to provide information essential for the safe and effective use of medicines.^{17,18} However, a previous study has revealed inconsistent product labelling information regarding use in patients with a history of sulfonamide hypersensitivity ranging from no warning or precaution to a contraindication.⁵ In a study where pharmacists were surveyed, 78.2% reported using dispensing software among a variety of resources to assess drug allergy problems, and their attitudes and knowledge surrounding the issue of cross-reactivity between non-antimicrobial sulfonamides and their antimicrobial counterparts varied significantly.¹⁹ Cautionary statements in a drug monograph may be based on individual case reports or extrapolated from previous encounters with similar agents, causing disparate and confusing implications.¹² We examined cautionary recommendations in the approved drug monographs, compared how this information is reflected in the primary literature, and formulated an evidence-based grading of cautionary recommendations for sulfonamide allergy and cross-reactivity among sulfonamide-containing medications.

METHODS

Definition

Considering the international scope of the resources reviewed, we used the term 'monograph' when referring to the approved drug label or MPI.

Data sources

A list of sulfonamide-containing medications was created by literature search^{2,11,12,20} and they were classified into three distinct groups: sulfonylarylamines, non-sulfonylarylamines and sulfonamide moiety-containing drugs, based on their chemical structure validated from the PubMed/PubChem compound database (Fig. 2). Each sulfonamide-containing medication was searched for the up to date drug monograph available in the online drug product databases from six countries: Canada (<http://www.hc-sc.gc.ca/>), France (<http://sante-az.aufeminin.com/>), Italy (<http://www.torinomedica.it/>), South Korea (<http://ezdrug.kfda.go.kr/kfda2>), United Kingdom (UK) (<http://www.medicines.org.uk/emc/>) and United States of America (USA) (<http://www.access-data.fda.gov/scripts/cder/drugsatfda/>), as well as (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>) for unlocated labels, and three drug compendia: Micromedex 2.0 (Drugdex, Truven Health Analytics Inc., Rightanswer, Midland, MI, USA) (<http://www.thomsonhc.com/home/dispatch>), Martindale (<http://www.medicinescomplete.com/>) and the American Hospital Formulary Service Drug Information 2010 (AHFS DI).²¹ These compendia were selected for wider acceptability in acquiring reliable and evidence-based drug information internationally.

Data extraction

Data extraction was conducted by two independent reviewers and any discrepancy was settled by discussion with a third reviewer. The cautionary statements were extracted from each drug monograph as identified in the contraindication, warning or precaution section. Cautionary statements associated with terms like *hypersensitivity to sulfonamides*, *sulfonamide allergy*, *sulfa allergy*, *cross-sensitivity*, *cross-reactivity* or *cross-allergy with sulfonamides* were considered for analysis. We also searched for any evidence-based literature referred to in the drug monograph in support of their recommendation. In addition, we carried out a thorough search in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and ClinAlert (<http://cla.sagepub.com/>) databases to examine how the information about cross-reactivity among sulfonamide-containing

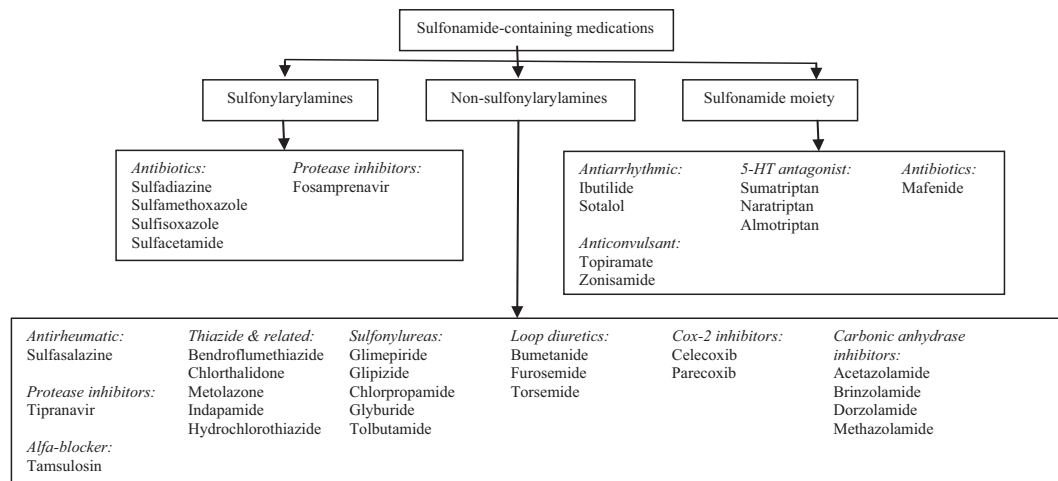


Fig. 2. Classification of sulfonamides based on chemical structure.

medications is reflected in the primary literature. We used the search terms 'Drug name + allergy', 'Drug name + hypersensitivity' and 'Drug name + cross-reactivity' for each sulfonamide-containing medication to search both databases.

Grading cautionary recommendations

To advise caution of an appropriate degree among sulfonamide-containing medications, a grading system based on systematic weighing of the strength of recommendation and the level of evidence was formulated with consensus. With the goal of improving the generalizability and acceptance of the recommendation into clinical practice, we formed a consensus panel

composed of a multidisciplinary group of Allergy and Immunology expert, Clinical Pharmacologist and Pharmacist. The panel met in person on three occasions to discuss questions to be addressed, prepare the draft and finalize the grading recommendation. An external peer review from a practicing clinician was obtained for feedback. The panel made a grading of the strength of recommendation from unsafe to safe considering two factors: recommendations from the drug monograph and actual findings from the primary literature, and they considered the level of evidence²² as obtained from higher quality research like meta-analyses or randomized controlled trials (RCTs) to lesser quality studies like case reports or expert consensus (Box 1).

Box 1. Grading cautionary recommendations for sulfonamide allergy and cross-reactivity

Category/class	Definition
Strength of recommendation	
I Unsafe (Contraindication)	Contraindicated in drug monographs, and strong agreement exists between studies and/or expert opinion in concluding cross-reactivity with other sulfonamides
II a Mostly unsafe (Warning)	Contraindicated in drug monographs, but disparity may exist between studies in concluding cross-reactivity with other sulfonamides, and the weight of evidence and/or expert opinion argues against use
II b Unsafe, in some cases (Precaution)	1. Caution advised ^a in drug monographs, but disparity may exist between studies in concluding cross-reactivity with other sulfonamides or within same drug class, and the weight of evidence and/or expert opinion favours use 2. No caution advised in drug monographs, but evidence for cross-reactivity exists
III Safe	No caution advised in drug monographs, and evidence shows no cross-reactivity exists
IV Indeterminate	Recommendation may change when evidence becomes available
Level of evidence^b	
A	Evidence from meta-analysis (quantitative systematic review), and high-quality randomized controlled trials (RCTs)
B	Evidence from non-quantitative systematic review, non-randomized clinical trials, lower quality RCTs, clinical cohort and case-control studies
C	Consensus/ expert opinion, case reports or case series

^aContraindication, warning and/or precaution.

^bAdapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician*, 2002;65:251–258.

Table 1. Location of cautionary statements for sulfonamide allergy

S. No.	Section	Countries, n (%)						Compendia, n (%)		
		Canada (n = 27)	France (n = 23)	Italy (n = 22)	S. Korea (n = 23)	UK (n = 27)	USA ^a (n = 34)	AHFS DI (n = 26)	Martindale (n = 35)	Micromedex (n = 33)
1.	Contraindication	10 (37.0)	15 (65.2)	11 (50.0)	10 (43.5)	14 (51.9)	13 (38.2)	–	–	9 (27.2)
2.	Warning	6 (22.2)	–	–	2 (8.7)	–	12 (35.2)	3 (11.5)	–	–
3.	Precaution	1 (3.7)	8 (34.8)	–	8 (34.8)	–	5 (14.7)	4 (15.4)	18 (51.4)	11 (33.3)
4.	Warning & precaution	5 (18.5)	–	8 (36.4)	–	13 (48.1)	7 (20.6)	1 (3.8)	–	–
5.	Contraindication & precaution	–	–	–	–	–	8 (30.8)	–	–	5 (15.2)
6.	Contraindication & warning	–	–	–	–	–	1 (3.8)	–	–	–

^aLabel could have information in more than one section.

RESULTS AND DISCUSSION

Overall, 35 drugs were identified in three different sulfonamide chemical classes. The cautionary statements were located in different sections like contraindication, warning and/or precaution (Table 1). The majority of cautionary statements were found in the contraindication section for approved drug labels in the following countries: France 65.2% (15/23), United Kingdom 51.9% (14/27), Italy 50.0% (11/22), South Korea 43.5% (10/23), United States 38.2% (13/34) and Canada 37.0% (10/27). This corresponds with the findings from a previous study conducted using US MPIs.² In contrast, for drug compendia, the majority of cautionary statements were located in the precaution section: Martindale 51.4% (18/35) and Micromedex (Drugdex) 33.3% (11/33), and contraindication and precaution section for AHFS DI 30.8% (8/26). The locations of recommendations varied among the three compendia, reflecting more of the in-house categorization formats; Martindale provided all cautionary advice in the precaution section, whereas AHFS DI provided it in the caution section, which was often subdivided into combined subsections like contraindication and precaution.^{21,23}

Discrepancies among cautionary recommendations

Table 2 shows the discrepancies in recommendations found in the sources reviewed. Wide variability was observed between countries and compendia in providing cautionary recommendations for sulfonamide allergy. For example, acetazolamide was contraindicated in United Kingdom, France and South Korea for use in patients with known hypersensitivity to any sulfonamides, whereas the drug was contraindicated in United States for possible cross-sensitivity. In contrast, the drug was advised for caution in known hypersensitivity to any sulfonamides in Italy and the Martindale drug compendium, but Micromedex and AHFS DI cautioned the drug as adverse reactions attributable to sulfonamides might occur. Five drugs (chlorpropamide, ibutilide, sotalol, tolbutamide and topiramate) were identified as having no recommendations for sulfonamide allergy by most of the sources examined.

Statements concerning cross-reactive hypersensitivity

Among the 35 sulfonamide-containing medications, only 10 were identified as having a statement concerning cross-reactive hypersensitivity in their drug monograph. Two drugs (mafenide and

acetazolamide) in United States and one drug (furosemide) in Italy were contraindicated, stating the possibility of cross-sensitivity with other sulfonamides. However, sulfadiazine in United States was only provided with a warning. The remaining drugs (sulfacetamide, fosamprenavir, tipranavir, metolazone, sumatriptan and almotriptan) were identified as having the theoretical possibility of cross-allergy or hypersensitivity between different sulfonamides.

Citation of evidence in drug monographs

References to the primary literature were not identified in drug monographs in various countries and drug compendia, with the exceptions of Canadian drug monographs, amounting to 92.6% (25/27), and all of the Micromedex (Drugdex) drug monographs. Among the Micromedex (Drugdex) drug monographs, 61.8% (21/34) cited the United States Food and Drug Administration (US FDA) approved MPIs as their source of evidence for providing cautionary recommendations for sulfonamide allergy. Drug compendia are often bulky volumes of information and they provide reference material separately, as done by AHFS DI by explaining in their user guide how they can be accessed.^{21,24} Nevertheless, it is not surprising that, in the absence of primary literature, these drug compendia considered US FDA approved MPIs as their principal resource, as it is often the only readily accessible source. Furthermore, it is unlikely that drug compendia would issue their own recommendations, tending, rather, to reflect the published literature.²⁵

While examining the primary literature, most of the medications lacked evidence for cross-reactivity, and the drug monograph cautionary recommendations differed (Table 3). To advise caution of an appropriate degree among sulfonamide-containing medications, we formulated an evidence-based grading system whereby the strength of recommendation was determined through consideration of drug monograph recommendations supported by primary evidence (Box 1). Evidence-based categorization was possible for 16 medications, among which sulfonamide moiety-containing drugs like ibutilide and sotalol were considered safe with respect to cross-reactivity. Six non-sulfonylarylamines required precaution, whereas the remaining eight medications from all three sulfonamide chemical classes were considered to be mostly unsafe (Box 2).

This study has some limitations. We lacked adequate literature evidence while we attempted to formulate evidence-based grading

Table 2. Variability in cautionary recommendations in approved drug labels across countries and compendia

Drugs	Recommendations
Non-sulfonylarylamines	
Acetazolamide	1A, ^{b, d, e} 1B, ^a 2A, ^{f, h} 2E, ^{g, i}
Bendroflumethiazide	1A, ^{a, d, g} 3A, ^{b, h}
Brinzolamide	1A, ^{b-d, f} 2A, ^g 2E, ^{a, e, i} 3A, ^h
Bumetanide	1A, ^{c, d} 2A, ^{a, g, i} 3A, ^{b, e}
Celecoxib	1A, ^{a-g} 2A, ^{h, i}
Chlorpropamide	3A, ^{a, c, g-i} NA, ^{b, d-f}
Chlorthalidone	1A, ^{a-c, e-g} 2E, ⁱ 3A, ^h
Dorzolamide	2C, ^{a-g} 3A, ^h
Furosemide	1A, ^{b, d, e} 1B, ^f 2A, ⁱ 2B, ^h 2E, ^{a, g}
Glimepiride	1A, ^{b-f} 2E, ^{a, g} 3A, ^h
Glipizide	1A, ^{b, d-e} 3A, ^{a, f-i}
Glyburide	2E, ^{a, g} 3A, ^{c, h-i}
Hydrochlorothiazide	1A, ^{a-g} 2E, ⁱ 3A, ^h
Indapamide	1A, ^{a-g} 2E, ⁱ 3A, ^h
Methazolamide	1A, ^g 2E, ^{a, h} 3A, ^c
Metolazone	1A, ^g 2B, ^{a, e, f} 2E, ⁱ 3A, ^{b-c, h}
Parecoxib	1A, ^{b, d, f} 2A, ^h
Sulfasalazine	1A, ^{a-g} 2A, ^h 2E, ⁱ
Tamsulosin	2E, ^{a, g, i} 3A, ^{b-e}
Tolbutamide	3A, ^{a-c, g-i} NA, ^{d-f}
Tipranavir	1B, ⁱ 2B, ^{a, c, h} 3A, ^{b, d}
Torsemide	1A, ^{a, g} NA, ^{b-f, h-i}
Sulfonylarylamines	
Fosamprenavir	1B, ⁱ 2A, ^{b, d, g, h} 2B, ^{a, c}
Sulfacetamide	1A, ^g 2A, ^h 2B, ^a 3A, ^f
Sulfadiazine	1A, ^{b, d, g} 2A, ^{c, h} 2B, ^a 2E, ^{e, i} 3A, ^f
Sulfamethoxazole	1A, ^{a-d, f-g, i} 2E, ^{e, h}
Sulfisoxazole	1A, ^{a, c, g} 2A, ^h
Sulfonamide moiety	
Almotriptan	2A, ^{b-f, h} 2B, ^{a, g} 3A, ⁱ
Ibutilide	3A, ^{a, c, f-h}
Mafenide	1B, ^{a, i} 2E, ^h 3A, ^e
Naratriptan	2D, ^{b-e, h} 3A, ^{a, g, i}
Sotalol	3A, ^{a-e, g, i}
Sumatriptan	2A, ^{c-d, f, h} 2B, ^e 2D, ^b 3A, ^{a, g, i}
Topiramate	1A, ^d 3A, ^{a-c, e-i}
Zonisamide	1A, ^{g, i} 1C, ^{a, b, f} 2A, ^h 3A, ^e

Drug monographs from countries and compendia:

a = USA, b = UK, c = Canada, d = France, e = South Korea, f = Italy, g = Micromedex, h = Martindale, i = AHFS DI.

Drug monograph cautionary recommendations:

¹Contraindication: ^{1A}Drugs contraindicated in known hypersensitivity to any sulfonamides;

^{1B}Drugs contraindicated for possible cross-sensitivity with other sulfonamides;

^{1C}Drugs contraindicated for serious immune-based reactions associated with sulfonamides.

²Warning and/or precautions: ^{2A}Caution advised in patients having known hypersensitivity to any sulfonamides;

^{2B}Caution advised for cross-sensitivity between different sulfonamides, which may occur or is theoretically possible;

^{2C}Caution advised to discontinue treatment if rash occurs as adverse effect attributable to sulfonamides;

^{2D}Caution advised for theoretical risk of hypersensitivity in patients with known hypersensitivity reaction;

^{2E}Caution advised as adverse reactions attributable to sulfonamides may occur or have been rarely reported;

³No caution advised: ^{3A}Label reviewed but contained no information on sulfonamide allergy; NA, Label not located.

of cautionary recommendations. As a consequence, more than half of the sulfonamide-containing medications fell into the indeterminate class. Also, most of our recommendations have limited strength of evidence (evidence level C). Nevertheless, we incorporated a consensus approach, which is considered valuable in clarifying lack of evidence and contradictory findings²⁶ and also improve the generalizability and acceptability of the recommendation. We did not attempt to assess the reason behind the widely assorted information among drug-monograph sources. This may be due to the fact that information included in a drug monograph could differ significantly in format and content due to variation in the related local guidelines, legislation, drug-safety data, unpublished reports released by drug manufacturers or spontaneous reports collected through national post-marketing surveillance systems, resulting in distinct labelling. Moreover, in many cases the original and complete evidence supporting drug information is not published and the clinical relevance remains unknown.²⁷ The drug monographs or MPis were collected as a cross-sectional data source, hence the cautionary recommendation appearing on the more recent and revised version may vary with the study drugs. Sulfonamide allergy and cross-reactivity issues due to sulfonamide-containing medications were assessed in general, not for specific populations like HIV-infected individuals.

WHAT IS NEW AND CONCLUSION

The drug monographs in six countries and three drug compendia show wide variability in their recommendations, ranging from no warning or precaution to contraindication; they also contained variously worded statements concerning use in patients with sulfonamide allergy and cross-reactivity. Agreement among drug monographs was poor when more than two sources were compared. Statements concerning cross-reactive hypersensitivity with other sulfonamides reflected only theoretical possibilities. Also, the drug monographs cited little or no evidence for the recommendations made. Health care professionals should examine the evidence carefully and make a careful risk-assessment of the individual patient, paying particular attention to the patient's prior history of sulphonamide hypersensitivity rather than merely relying on drug-monograph information. A potentially useful drug should not be denied to any patient unless there is good supporting evidence.²⁵ Thus, providing evidence-based cautionary recommendations is essential for safe prescribing. The evidence-based grading instrument developed can be a useful tool for deriving cautionary recommendations for sulfonamide-allergic patients. Nevertheless, higher quality evidence should be generated particularly for drugs categorized into the indeterminate class.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Box 2. Categorizing sulfonamide-containing medications for use in sulfonamide allergy and cross-reactivity based on grading recommendations

Category		Sulfonamide-containing medications
I	Unsafe (Contraindicated for cross-reactivity)	–
IIa	Mostly unsafe (Warning for cross-reactivity)	Acetazolamide, Furosemide, Hydrochlorothiazide, Indapamide, Mafenide, Sulfadiazine, Sulfamethoxazole, Zonisamide
IIb	Unsafe, in some cases (Use with precaution)	Celecoxib, Glimepiride, Glyburide, Metolazone, Chlorpropamide, Tolbutamide
III	Safe (No cross-reactivity)	Ibutilide, Sotalol
IV	Indeterminate	Bendroflumethiazide, Brinzolamide, Chlorthalidone, Glipizide, Parecoxib, Sulfasalazine, Sulfisoxazole, Torsemide, Almotriptan, Bumetanide, Dorzolamide, Fosamprenavir, Methazolamide, Naratriptan, Sulfacetamide, Sumatriptan, Tamsulosin, Tipranavir, Topiramate

Table 3. Comparison of cautionary recommendations in approved drug labels with findings from primary literature

Drugs	Evidence from primary literature		Grade of evidence ^a
	Findings	Study type	
Mostly contraindicated			
Acetazolamide	Possible cross-reactivity with sulfonamides ^{28–30}	Case report	CIIa
Celecoxib	1. No increased risk of hypersensitivity with sulfonamides ⁵ 2. Possible cross-reactivity with Glyburide ³¹	Meta-analysis, Case report	AIIb
Furosemide	Possible cross-reactivity with Hydrochlorothiazide ³²	Case report	CIIa
Glimepiride	Cross-reactions between same drug class like Chlorpropamide and Tolbutamide exist ^{33–35}	Case report	CIIb
Hydrochlorothiazide	Possible cross-reactivity with Furosemide ³²	Case report	CIIa
Indapamide	1. Risk of hypersensitivity not confirmed with Hydrochlorothiazide, Chlorthalidone, and Furosemide ^{2,36} 2. Possible cross-reactivity with Sulfamethoxazole and Sulfadiazine ³⁷	Review, Case report	CIIa
Mafenide	Sulfadiazine should be avoided ³⁸	Case report	CIIa
Sulfadiazine	Avoid use of Sulfamethoxazole and Mafenide ^{38,39}	Case report	CIIa
Sulfamethoxazole	1. Strong cross-reactivity exist with Sulfasalazine ⁸ 2. Possible cross-reactivity with Zonisamide, Furosemide, Bumetanide, and Torsemide ^{40,41} 3. No cross-reactivity found with Celecoxib, Furosemide, and Glipizide ^{42–45}	<i>In vitro</i> study, Clinical study, Case report	CIIa
Zonisamide	Possible cross-reactivity with Sulfamethoxazole ⁴⁰	<i>In vitro</i> study	CIIa
Warning and/or precautions provided			
Glyburide	Possible cross-reactivity with Celecoxib ³¹	Case report	CIIb
Metolazone	No increased risk for hypersensitivity reaction with Celecoxib ⁵	Meta-analysis	AIIb
No caution advised (label reviewed but contained no information on sulfonamide allergy)			
Chlorpropamide	Cross-reactions between same drug class exist ^{33–35}	Case report	CIIb
Tolbutamide	Cross-reactions between same drug class exist ^{33–35}	Case report	CIIb

^aSee Box 1 for strength of recommendation and level of evidence codes.

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