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COMMENTARY

# "Doctor, I have a Sulfa Allergy": Clarifying the Myths of Cross-Reactivity

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## ABSTRACT

Our purpose is to present an evidence-based approach, directed primarily towards eye-care specialists, clarifying whether certain drugs should or should not be used in patients with sulfonamide allergy. We conducted a literature search using PubMed to identify the risk of ophthalmic-specific drugs in patients with a self-reported sulfonamide allergy. MeSH key words included "sulfonamide" and "hypersensitivity". Articles specifically geared towards ophthalmic diseases were sought. The evidence illustrates that individuals with sulfonamide allergy are intrinsically predisposed to higher rates of allergic reaction that is not specific towards sulfonamide non-antimicrobials or sulfur-based medications. We provide a simplified algorithm using the 2017 Clinical Guide to Ophthalmic Drugs to help busy eye care clinicians determine whether a certain common ophthalmic medication is safe or unsafe to prescribe in a patient with a "sulfa allergy".

**Keywords:** Acetazolamide (Diamox); Blephamide; Brinzolamide (Azopt); Carbonic anhydrase inhibitors; Cross-reaction; Dorzolamide; Hypersensitivity; Methazolamide (Neptazane); Polytrim; Sulfa allergy; Sulfonamide (Trusopt)

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As eye care clinicians, it is quite common to have our patients tell us they have a "sulfa allergy". Given that we have heard of rare accounts of fatality from presumably cross-reacting properties, it makes sense why we may be afraid to use certain medications. Food and Drug Administration (FDA) warnings for these medications have further ignited this fear of prescribing. Since there is a paucity of literature specifically for ophthalmologists clarifying the use of certain medications in patients with a history of sulfa allergy, our aim is to help our colleagues understand what drugs we can and cannot use in such circumstances.

The discovery of sulfonamide antimicrobials in the early 1930s was heralded as a major

advancement in the management of severe infectious diseases [1]. Since then, sulfonamides have remained one of the most commonly prescribed antimicrobials [1, 2]. Given this high usage, it is not uncommon for patients to report an allergy to the medication. Although around 3% of the population report a "sulfa allergy", studies show that only 3% of these patients have true hypersensitivity [3, 4]. Sulfonamide antibiotic reactions encompass the entire spectrum of hypersensitivity reactions (types 1–4). Type 1 hypersensitivity is IgE-mediated and may include an anaphylactic sequelae. Type 2 reactions involve antibody-mediated cytotoxic cellular injury that may result in various cytopenias. Lastly, type 3 and type 4 hypersensitivity results in the formation of antigen–antibody immune complexes or a delayed T cell-mediated reaction, respectively, either of which may progress to the life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis [4, 5].

There are important chemical differences between sulfonamide antibiotics and sulfonamide non-antibiotics. The chemical structure of a sulfonamide antibiotic uniquely contains an arylamine (NH2) side chain at the N4 position and a 5- or 6-member aromatic heterocyclic ring and one or more nitrogen groups at the N1-sulfonamide position [5]. In contrast, although non-antimicrobial sulfonamides are sulfur-based, these medications have a different chemical structure [5]. Thus, theoretically these two groups of medications should not cross-react. The majority of retrospective analyses also support this concept. The largest and strongest evidence comes from Strom et al. [6], a study that showed that although patients with a history of a sulfonamide antimicrobial allergy were more likely to react to sulfonamide non-antimicrobials (9.9% vs. 1.1%), they also found that the group given penicillin, a biochemically distinct group, were even more likely to react (14.2%). The authors concluded that patients allergic to sulfonamide antibiotics are likely predisposed to further allergic reactions with other drugs, rather than specifically to sulfa-based medications. Most subsequent authors have agreed with this statement [7, 8].

In ophthalmology practice, many of our medications are derived from some form of sulfur element. Drugs that end with "sulfate" or "sulfite" are structurally different from sulfonamides. For instance, common ophthalmic medications such as atropine sulfate, polymyxin B sulfate/trimethoprim (Polytrim®), gentamicin sulfate, and neomycin sulfate are by definition not considered sulfonamides, as they lack the characteristic $SO_2NH$ moiety linked directly to a benzene ring that defines such a group [9]. Supporting our understanding, there has been no case report dating back to 1965 documenting any allergic reaction of any related sulfate- or sulfite-related drug to patients with a history of a sulfa allergy.

In the realm of neuro-ophthalmology and glaucoma, there are sometimes overlapping sulfonamide non-antimicrobial medications that can be used to treat specific conditions in both fields. While acetazolamide (Diamox®) can be used as an oral agent to decrease intraocular pressure, both acetazolamide and furosemide are the mainstay treatments for idiopathic intracranial hypertension. Notably, these medications lack the characteristic arylamine that defines sulfonamide antibiotics. Despite this structural difference, many past authors have suggested that patients with a history of self-reported sulfa allergy should not take any sulfonamide derivatives, including acetazolamide and furosemide [10–14]. A retrospective chart review by Lee et al. [15] that included patients with intracranial hypertension and a self-reported sulfa allergy found that 37% of patients on acetazolamide and/or furosemide had no cross-reactivity, 56% had predictable adverse reactions specific for the medication, and 7% of the cases had urticaria. Thus, although there is a low risk of cross-reactivity as exhibited by the urticarial reaction, there was no significant evidence to suggest that a self-reported sulfa allergy is likely to produce a life-threatening cross-reaction with either medication. The same warnings appear for the orally administered methazolamide (Neptazane™), used for glaucoma management. However, an exhaustive literature search shows no documented evidence of cross-reactivity of this medication with those who have a self-reported

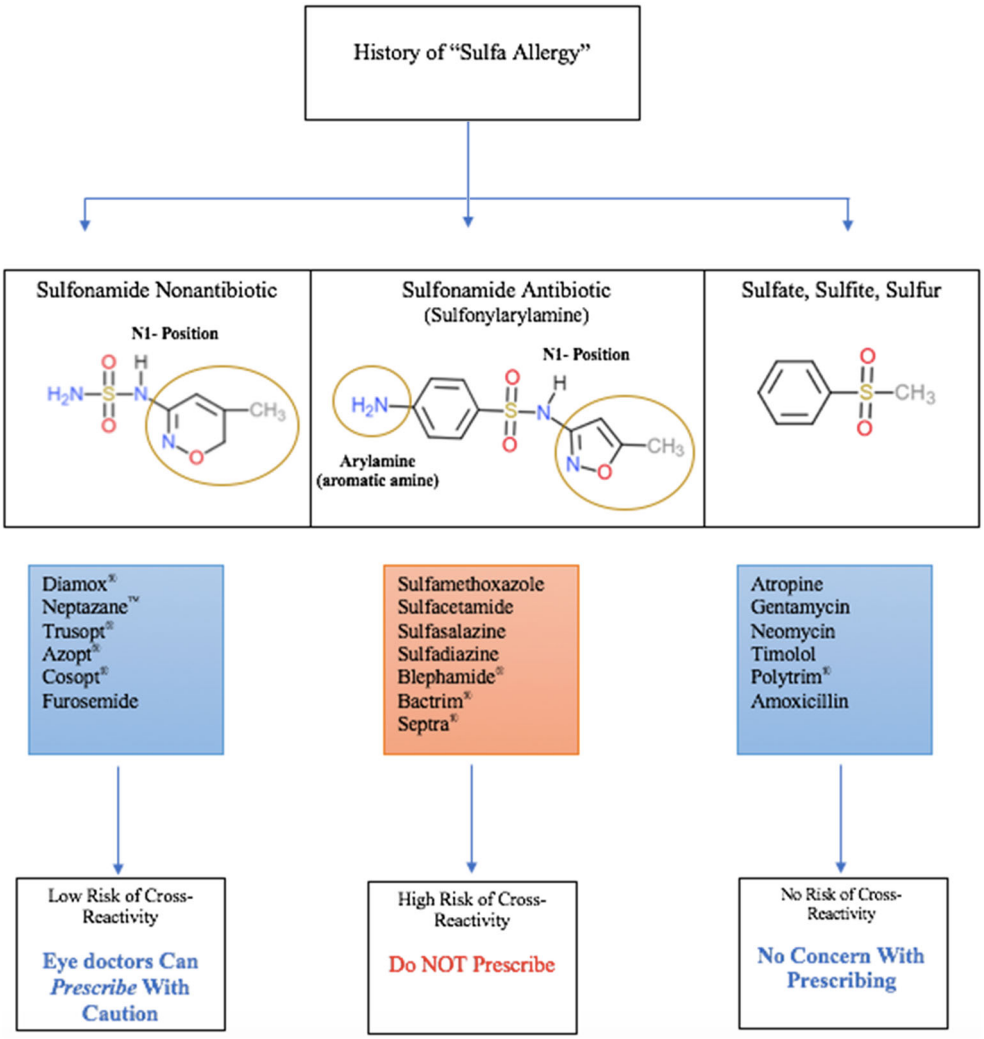


**Fig. 1** An eye care specialist's simple guide to self-reported "sulfa allergy". Informs ophthalmologists of safe prescribing practices of common sulfur-based ophthalmic medications from the 2017 Clinical Guide to Ophthalmic Drugs [17] using evidence-based medicine. Patients with a past allergic reactions are more likely to have future allergic reactions regardless of specific medication type [9]. Use clinical judgment, weighing both benefits and risks, and document specific allergic reaction (i.e., anaphylaxis, urticaria, etc.) before giving these medications

history of sulfa allergy. The same conclusion ascertained in the Lee et al. [15] study can likely be extrapolated to this medication—an unlikely chance that this medication cross-reacts in those with true sulfonamide antibiotic allergy to cause a life-threatening reaction. A retrospective study by Guedes et al. [16] in 2013 demonstrated that the use of topical carbonic anhydrase inhibitors (CAI), such as dorzolamide (Trusopt®) and brinzolamide (Azopt®), may be safe in patients who report a history of sulfa allergy. Although the rates of allergic reaction in patients on topical CAI were higher in those with a prior sulfa allergy than in those without, there were no significant differences in rates among patients with other prior non-sulfa-based allergic reactions. Patients on prostaglandin analogues, which are biochemically distinct, also experienced a higher rate of allergic reactions, with no significant difference from those taking topical CAIs. This indicates that the rate of allergic reaction is likely not

dependent on the medication, but rather an intrinsic predisposing factor to hypersensitivity reactions.

Overall, the fear of prescribing certain medications in patients with self-reported sulfa allergy seems unjustified given the collection of evidence reported in past literature. From the evidence, there should be no concern in prescribing medications such as gentamicin, Polytrim®, neomycin, and similar drugs that are sulfur-based. Some eye clinicians even fear prescribing timolol in these patients, since the beta-blocker contains a sulfur ring. However, it should be emphasized that these drugs are not sulfonamides and do not cross-react in individuals with sulfonamide allergies. Similarly, the evidence suggests that medications like Diamox® and other oral or topical carbonic anhydrase inhibitors should also be prescribed as needed, so long as the patient does not have a history of a life-threatening allergic reaction to sulfonamide drugs. Patients with glaucoma who are at significant risk for visual impairment or blindness have significant potential benefit from these medications. We have constructed a table that informs ophthalmologists and all other eye care specialists of safe prescribing practices of common sulfur-based ophthalmic medications using evidence-based medicine (Fig. 1). We hope that this table guides you in making an appropriate clinical decision the next time a patient presents with a history of sulfonamide allergy, and that this alleviates the fear of providing efficacious medications just because the patient has a "sulfa allergy".

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