

The move away from 1st generation antihistamines

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First generation antihistamines are widely available over-the-counter in Canada and have been for decades. Diphenhydramine (Benadryl®), a 1st generation antihistamine, was first approved for use in 1946. Concerns have been raised over the side effects of these antihistamines and their place in therapy.

The Canadian Society of Allergy and Clinical Immunology (CSACI) has recently released a position statement recommending against

the use of 1st generation antihistamines and published their key points.¹ (Figure 1) Similarly, the Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines do not recommend 1st generation antihistamines for the treatment of allergic rhinitis in adults.²

We spoke with Dr. Nina Jindal, allergist and clinical immunologist at St Michael's Hospital in Toronto, ON for her perspective on the use of 1st generation antihistamines (AH) in therapy.

Figure 1. CSACI Position Statement on 1st Generation AHs: Key Points¹

1. First-generation AHs are associated with significant and, at times, serious adverse effects including fatal outcomes, and they should not be used as first-line treatment in allergic disease.
2. Despite package warnings, the level of CNS impairment caused by 1st generation AHs is not fully appreciated both by health care professionals and the public, which has resulted in preventable fatal injuries.
3. Newer generation AHs are proven to be much safer than 1st generation AHs, have a faster onset of action, and have superior potency, selectivity and efficacy.
4. Despite the widespread availability of newer generation AHs, older AHs remain over-utilized.
5. To encourage the cessation of the routine use of older AHs including diphenhydramine (Benadryl®), this class of medications should have eventual consideration for availability on a behind-the-counter basis only.
6. Further efforts are needed to disseminate this information to healthcare providers and patients to help change practice and improve patient health and safety.

“ Newer generation H₁-antihistamines are safer than 1st generation H₁-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria.”

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– CSACI Position Statement¹

Q. Do you see a place in therapy for 1st generation AHs and do you use them in your practice?

In adults, truthfully, I do not. There are so many 2nd generation AH alternatives out there that are better medications – safer and effective, that I don't need to use 1st generation AHs.

Situations where parenteral administration is needed would be the exception (eg. laryngeal edema in the ER), as there are no 2nd generation antihistamines available in IV or IM forms and diphenhydramine is the only option for these situations.

Q. What are the risks of 1st generation AHs?

Sedation is a common side effect of 1st generation AHs. There are good studies on the impairment caused by 1st generation AHs due to their ability to cross the blood brain barrier. Patients have been found, for example, to have impaired REM sleep and have a harder time driving in a straight line after using 1st generation AHs for several days in a row. These studies really highlight the real-world situations where patients will be getting in their cars, going to work or picking up their kids, and we

have to be cognizant of the impact of these side effects on peoples' lives.

In particular, the elderly is a population where it is really important to think twice before using a 1st generation AH. I have seen several elderly patients suffer adverse outcomes due to 1st generation sedating AHs including hip fractures from falling, and prolonged hospitalizations as a result.

Cardiac toxicity, specifically the risk of QT prolongation and torsade de pointes must also be considered, especially in the elderly with comorbidities and polypharmacy. Unlike 2nd generation AHs, where the risk was recognized and studied, this risk was not known when 1st generation AHs were approved and was therefore not studied. Health Canada did add a black box warning in 2016 for hydroxyzine's risk of QT prolongation and torsade de pointes.

1. Fein M et al., CSACI Position Statement: Newer Generation H₁-antihistamines Are Safer Than First-Generation H₁-antihistamines and Should Be the First-Line Antihistamines for the Treatment of Allergic Rhinitis and Urticaria, *Allergy Asthma Clin Immunol*, 2019 Oct 1;15:61.
2. Brozek JL et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines: 2010 Revision, *J Allergy Clin Immunol*, 2010 Sep;126(3):466-76.