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PRACTICAL CONSIDERATIONS IN ANTIHISTAMINE SELECTION

Antihistamines are medications that are used by dermatologists for the labelled indications of urticaria and IgE mediated allergies. They may also be used off-label for conditions including, but not limited to, mast cell-mediated diseases and pruritus of any type.

With so many antihistamines available in Canada, it can be hard to choose which one to recommend or prescribe. With a focus on oral H1 antihistamines, the ones primarily used in dermatology, this review will explore and provide a practical overview to help physicians select ideal antihistamines for each patient based on their similar and unique characteristics.

The History of Antihistamines:

The realization that histamine played a role in allergic disease led to the search for compounds that could counteract its physiologic effects. The first antihistamines were identified in the 1930's by a group led by Daniel Bovet, a Swiss-Italian pharmacist at the Pasteur institute in Paris. For this work with antihistamines, as well as other discoveries, he was awarded the Nobel Prize for physiology or medicine in 1957.[1] The first antihistamine to be used in humans, phenbenzamine, in 1942, was quickly replaced and followed by many other antihistamines including diphenhydramine, tripelennamine, chlorpheniramine, and promethazine. After 1945 antihistamines became widely used for allergic diseases such as allergic rhinitis, urticaria and hay fever.[1]

Mechanism of Action:

There are 4 identified histamines receptors, H1, H2, H3 and H4 all of which have different sites of expression and activities (**Table 1**). Based on this, the H1 and H2 receptors have been targeted for therapeutic use in allergic disease.

Histamine Receptor	Roles
H1	Pruritus Vasodilation Vascular permeability
H2	Vasodilation Vascular permeability Regulation of T lymphocytes
H3	Negative feedback histamine synthesis and release
H4	Pruritic responses (atopic dermatitis)

Table 1. *Types of histamine receptors and their roles; courtesy of Jennifer Lipson, MD*

H1 and H2 antihistamines are inverse agonists. They act by down regulation of the constitutively active state of their respective receptors. This is achieved by stabilization of the receptor into the inactive conformation which results in shifting the equilibrium to the inactive state. Many of the symptoms of urticaria and allergic diseases are mediated by histamine activating H1-receptors on endothelial cells and sensory nerves. Of note, allergic disease is unlikely to be due to histamine alone, as evidenced by the incomplete suppression of physical findings with oral H1-antihistamines, despite their profound effect on pruritus, and the fact that the duration of effect is hours and not just minutes. Other mast cell meditators such as platelet activating factor (PAF), leukotrienes, cytokines, as well as other cellular infiltrates have also been shown to be involved in allergic disease, which may explain the clinical response shown in allergic disease with a short course of systemic steroids.[2] Some of these mediators are targets of newer therapeutics such as rupatadine, a new antihistamine which also inhibits PAF.

H2 antihistamines such as cimetidine and ranitidine have not shown robust clinical effect in the treatment of allergic disease and are no longer part of the treatment algorithm for the management of chronic urticaria. They are effective in treating histamine-evoked gastric acid secretion.

H1 antihistamines are divided into two major groups: First generation and second generation H1-antihistamines. (**Table 2**)

First Generation Antihistamines	Second Generation Antihistamines
Diphenhydramine	Cetirizine
Ketotifen	Loratadine
Promethazine	Desloratidine
Chlorpheniramine	Fexofenadine
Hydroxyzine	Rupatadine
Doxepin (is a tricyclic antihistamine)	Bilastine

Table 2. *First and second generation H1- antihistamines; courtesy of Jennifer Lipson, MD*

The limitations of first generation "sedating" antihistamines:

First generation antihistamines have a limited role in the treatment of most patients and have been largely replaced by second generation H1 antihistamines due to a plethora of side effects including sedation, paradoxical agitation, impaired cognitive function (i.e., working memory , attention, psychomotor speed, etc.), anticholinergic effects (i.e., dry mouth, blurred vision, constipation, urinary retention, etc.), weight gain, interactions with alcohol, interactions with medications (cytochrome p450 metabolism), QT prolongation, erectile dysfunction, and dysuria.[3,4]

The most concerning of these side effects are the sedation, psychomotor impairment, and the potential impact of a long-term effect on cognition. First generation antihistamines are prohibited for transportation workers (i.e., pilots, bus drivers, etc.) in many jurisdictions and have been implicated in fatal motor vehicle accidents due to their effect impairing driving performance.[5] Sedating antihistamines are also problematic in children. In school aged children these medications have been associated with poor school performance and in very young children with paradoxical agitation.[4]

In elderly patients there are also unique considerations, as they are more susceptible to anti-cholinergic side effects such as confusion, urinary hesitation and dry mouth and eyes.[6] As well, it has been shown in a prospective cohort study that higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and patients about this serious potential anticholinergic medication-related risk are important in order to minimize the use of these medications.[7]

The push to limit the use of first generation antihistamines:

Given significant concerns regarding side effects of first generation H1-antihistamines, it is strongly recommended NOT to use first generation antihistamines in children or adults with allergic disease. First generation H1-antihistamines are excluded from the American and International Urticaria Guidelines (as are H2 antihistamines), and only the second generation H1 antihistamines are recommended.[8]

The Global Allergy and Asthma European Network (GA^{2}LEN) has suggested that first generation antihistamines should no longer be made available over the counter. Second generation antihistamines are 'non' or 'minimally' sedating and not anti-cholinergic. As a group, the second generation H1-antihistmaines have minimal capacity to cross blood brain barrier and cause sedation or altered cognitive function; have minimal affinity for muscarinic receptors resulting in minimal anti-cholinergic side effects; and lastly, they have minimal risk for cardiac toxicity.[4,9]

"Later generation" antihistamines

All remaining antihistamines will be referred to as 'later generation antihistamines' as they all share the important features of being more effective and less sedating due to their polarity and inability to cross the blood brain barrier, lower cardiotoxicity and minimal anti-cholinergic effect. These later generation agents include:

Factors to consider in selecting an antihistamine

Efficacy:

Later generation antihistamines
Classic second generation antihistamines: loratadine, fexofenadine and cetirizine
Newer second generation antihistamines: rupatadine and bilastine
Third generation antihistamines which are derived from the second generation antihistamines. They are more potent and have fewer side effects
Desloratadine (metabolite of loratadine), fexofenadine (metabolite of terfenadine) and levocetirizine (the active enantiomer of cetirizine, not available in Canada)

Even after limiting the therapeutic option to later generation antihistamines, clinicians may still find it difficult to select an antihistamine as all are generally considered safe and effective. The lack of head-to-head studies make it difficult to compare efficacy across these molecules and indirect treatment comparisons are complicated by differing definitions of efficacy and efficacy endpoints.

A systematic review of RCTs of H1 antihistamines in 2014 concluded that there was insufficient evidence to make specific recommendations of one antihistamine over another at approved doses. This review looked at cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine, and did NOT include bilastine and rupatadine.[10]

One double-blinded placebo controlled randomized parallel group multinational study in 525 chronic spontaneous urticaria (CSU) patients looked at changes in reflective and instantaneous symptoms scores, Dermatology Life Quality Index (DLQI), and CSU-associated discomfort and sleep disturbance which were assessed as secondary outcomes. Results showed that bilastine and levocetirizine have a similar statistically significant reduction in urticaria scores (pruritus, and wheal number and size) compared to placebo.[11,12]

In a randomized, double-blind six-week trial involving 70 patients with CSU, researchers sought to examine the effectiveness of cetirizine versus rupatadine. Both drugs demonstrated statistically significant improvements in mean total symptom score, mean pruritis score and mean wheal scores at 3 and 6 weeks. At 6 weeks there was statistically significant greater improvement with rupatadine as compared with the cetirizine group.[13]

In a double-blind, randomized, parallel-group, multicentre, placebo-controlled study comparing rupatadine to desloratadine in children aged 2-11 years with CSU , rupatadine demonstrated a statistically superior reduction in mean pruritus score (57%) compared to placebo; desloratadine did not. The absolute change in the modified cumulative 7-day Urticaria Activity Score (UAS7) at 42 days showed statistically significant differences between active treatments vs. placebo (-5.5 ± 7.5 placebo, -11.8 ± 8.7 rupatadine and -10.6 ± 9.6 desloratadine; $p < 0.001$) and without differences between antihistamines compounds. There was a 55.8% decrease for rupatadine followed by desloratadine (-48.4%) and placebo (-30.3%).[14]

There have also been other head-to-head comparative studies examining suppression of histamine-induced wheal and flare responses in humans. While good predictors of potency, these histamine-induced wheal flare models may not accurately predict the clinical efficacy of antihistamines in patients

Bilastine 20 and 50 mg compared with cetirizine 10 mg showed no major differences in magnitude or duration of wheal/flare suppression but bilastine had a more rapid onset of effect.[15] In another study comparing bilastine, desloratadine and rupatadine, bilastine was shown to have greater maximum wheal inhibition at 6 hours and maximum reduction in flare area as compared with both desloratadine and rupatadine (which were both similar) and compared to placebo. Bilastine was also significantly better at reducing itching sensation compared with desloratadine and rupatadine (neither significantly reduced itch compared to placebo).[16]

Antihistamine	Tradename	Standard Adult dose	Standard Pediatric Dose	Dosing Considerations
Loratadine Onset: within 2 hours Duration: lasts 24 hours Take on empty stomach Sedation in up to 4-8% of patients (3-6% in placebo)	Claritin	10 mg daily	2-5 yo: 5 mg daily >5 yo: 10 mg daily	• Dose adjust for severe hepatic impairment, avoid in severe renal impairment • No clinically relevant P450 interactions
Desloratadine (5x more potent than loratadine) No reported sedation Onset within 1 hour Duration: lasts 24 hours	Aerius	12 yo: 5 mg daily	N/A	• Use with caution in severe renal /hepatic impairment • Avoid if personal or family history of seizures • No clinically relevant P450 interactions
Cetirizine	Reactine (Rx for 20 mg tab)	10 mg daily	12+ yo: 5-10 mg daily 6-11 yo: 5-10 mg daily 2-10 yo 2.5-5 mg daily	• Dose adjust for chronic renal or liver impairment (5 mg daily) • CI if CrCl <10 mg/mL • No P450 interactions • Most sedating 2nd Gen
Fexofenadine Onset within 1-2 hours Duration: lasts minimum of 12 hours Do not take with fruit juice	Allegra	12 years old: 120 mg daily or 60 mg BID	Approved 12 yo: 60 mg BID (off-label UPTODATE: 6 mos-2 years: 15 mg BID 2-11 yo 30 mg BID)	• No dose adjustment for elderly, hepatic impairment • Start half dose if renal impairment • No P450 interactions
Rupatadine	Rupall (Rx)	10 mg daily	2-11 yo: 10-25 kg: 2.5 mg OD >25 kg: 5 mg OD	• With or without food • Avoid in patients with renal or hepatic impairment • P450 interactions
Bilastine	Blexten (Rx)	20 mg daily	4-11yo: 10 mg OD 12-18yo: 20mg OD	• 1 hr before or 2 hours after food • No P450 Interactions • P Glycoprotein interactions

Table 3. *Second generation antihistamines available in Canada (Over the counter and by prescription); courtesy of Jennifer Lipson, MD*

Distinguishing features of the later generation H1 antihistamines:

There are only 3 later generation H1 antihistamines available in Canada exclusively by prescription: loratadine, desloratadine and fexofenadine. Their profile, including important considerations, can be found in **Table 4**.

Cetirizine has been available for use since 1987 and is the only second generation H1 antihistamine available both over the counter and by prescription in Canada. It is approved for children ages 2 and up, has demonstrated no significant drug interactions, no effect on QT prolongation in plasma levels three times the maximal recommended dosage and is well tolerated with minimal sedation. It can be taken with or without food and is contraindicated in patients who may be allergic to cetirizine or hydroxyzine (it's parent compound) or who have a creatinine clearance < 10 mg/mL. It does require dose adjustments for patients with renal and hepatic impairment.[17]

Bilastine has been approved for use by prescription in Canada since 2016. Since 2022, it has been approved specifically for pediatric patients aged 4 and older as both an oral solution and a orodispersible tablet (quick melt). For patients aged 18 and over, the regular tablet format is available. It is well tolerated with very low rates of sedation. There is no dose adjustment required for patients with hepatic or renal impairment. It is a substrate of p-glycoprotein, so it is recommended to avoid use of bilastine with erythromycin, ketoconazole, cyclosporine, ritonavir, diltiazem and other p glycoprotein inhibitors (increase levels), QT prolonging drugs and grapefruit juice. Interestingly, it can be dosed up to 100 mg without affecting the QT interval, however it is still contraindicated in patients with history of QT prolongation or torsades de pointes.[18] It has been studied in cold urticaria, with safety and efficacy of doses up to 80 mg daily for 7 days confirmed in a cold contact urticaria controlled trial.[19] While the product monograph suggests taking bilastine on an empty stomach, data has since demonstrated a lack of significant clinical relevance and pharmacodynamic interaction between bilastine and food.[19]

Rupatadine is the only H1 antihistamine that is active against histamine and also inhibits the potent pro-inflammatory mediator PAF. PAF is an important mediator in allergic disease. Platelets have important functions including inducing and maintain allergic inflammation. PAF is released by several cell types (i.e., eosinophils, macrophages, endothelial cells, mast cells, and platelets) which have no direct action on platelet aggregation. It increases vascular permeability and plays a role in allergic rhinitis, urticaria, asthma and anaphylaxis.[20-22]

Rupatadine is approved for use in children aged 2 years and older in Canada since 2016 and is available in suspension format for pediatric patients and in tablet format for adults. Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the drug, maintaining activity for up to 24 hours.[23] It can be taken with or without food and has the lowest somnolence rates of all the antihistamines currently available in Canada. No somnolence was seen in pediatric studies. Clinicians should note P450 drug interactions which can be found in the product monograph. Rupatadine should be avoided in patients taking statins and other P450 substrates and in patients with renal or hepatic dysfunction as it has not been studied in these special populations. Rupatadine is contraindicated in patients with QT prolongation/torsades de pointes. It has been shown that there is no effect on QT interval at 10 times the standard dose of rupatadine. All the later generation H1 antihistamines, including rupatadine, are felt to have a safe cardiotoxic profile at up to four times the standard licensed dose in patients who lack other risk factors for cardiotoxicity.[9,24,25]

Pregnancy and lactation:

Among first generation H1 antihistamines, no teratogenic effects have been reported when used at any time during pregnancy. There are fewer later generation antihistamines that have data to support their use in pregnancy. Cetirizine, desloratadine and loratadine have the most data supporting safety in pregnancy from several retrospective series and registry data. Fexofenadine animal studies failed to show teratogenicity however decreases in pup weight and survival were observed. There are no human data on fexofenadine; however, limited data from terfenadine did not find an increased risk of major malformations.

There is limited data for the use of first generation antihistamines during breastfeeding. Studies have shown that only minimal amounts of these drugs are secreted in breast milk. In a telephone follow-up study, 10% of mothers reported irritability and colicky symptoms in their infants exposed to various antihistamines, and drowsiness was reported in 1.6% of infants. None of the reactions

required medical attention. Therefore, short-term, or occasional use of first generation H1 antihistamines would not be expected to be a concern during breastfeeding. Cetirizine, fexofenadine, loratadine, and desloratadine are minimally excreted in the breastmilk and should not cause sedation/adverse effects to the breastfeeding infant. The use of rupatadine and bilastine in pregnancy and lactation are not recommended due to lack of data. Cetirizine, desloratadine or loratadine are the antihistamines of choice in pregnancy. Cetirizine, loratadine, desloratadine or fexofenadine are the antihistamines of choice in lactation.[26]

Key Features	Cetirizine	Bilastine	Rupatadine
Indication	Allergic Rhinitis Ages 2+ CSU ages 2+	Allergic Rhinitis ages 4+ CSU ages 4+	Allergic Rhinitis ages 2+ CSU ages 2+
Administration	OTC 5 mg, 10 mg Rx: 20 mg Tablets, quickmelts, suspension	Rx: 20 mg tablet for adult Rx: 10 mg quickmelt pediatric Rx: suspension 2.5mg/mL	Rx: 10 mg tablet for adult Rx: 1mg/mL solution pediatric
Onset of action	20-60 min	1 hour	1 -2 hours
Duration of action	24 hours	At least 26 hours	Up to 24 hours
Somnolence rate	9.6% (24% at 20 mg) Lower in pediatric patients (1%/4% for 5/10 mg)	4.1%	2.7% Not seen in pediatric study
Drug interactions	N	P glycoprotein QT prolonging drugs Grapefruit juice (increase levels)	P 450 Grapefruit juice (decreases levels)
Renal dosing	Y	N	Avoid
Hepatic Dosing	Y	N	Avoid
Approval in children for urticaria	Y	Y (new)	Y
Safety in pregnancy/nursing	Y	N	N

Table 4. *Summary of prescription second generation antihistamines; courtesy of Jennifer Lipson, MD*

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