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Multidisciplinary Real-World Experience With Bilastine, a Second Generation Antihistamine

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ABSTRACT

Introduction: Allergic conditions frequently require treatment with antihistamines. First-generation antihistamines can potentially interfere with restful sleep, cause "morning after" effects, impair learning and memory, and reduce work efficiency. Second-generation antihistamines, such as bilastine, have been demonstrated to decrease allergy symptoms effectively without causing night-time sleep disturbances and related adverse events.

Method: A real-world case project was developed to help optimize patient care by recognizing the role bilastine can play for allergic conditions where antihistamine treatment is needed. The presented real-world patient cases conducted by the panel members are supported with evidence from the literature, where available. Any discussion concerning off-label use should be considered an expert opinion only.

Results: The real-world cases presented here used bilastine in conditions such as perennial and seasonal allergic rhinitis, chronic urticaria, as well as urticarial vasculitis and pruritus associated with inflammatory skin conditions. The treated patients were between 9 and 76-years old providing information on a full spectrum of patients that require treatment with antihistamines.

Conclusions: The presented real-world cases using the second-generation antihistamine, bilastine, demonstrated favorable outcomes for the treated patients. While effectively relieving symptoms, the antihistamine was reported to be safe and well-tolerated.

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INTRODUCTION

Allergic conditions, such as seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and urticaria (both acute and chronic) are frequently treated with antihistamines (AHs).[1,2] Most first-generation AHs have a long history and were introduced decades before clinical pharmacology studies, and randomized controlled trials were required by regulatory agencies.[2] Consequently, first-generation AHs that were previously approved for use are assumed to be safe and effective.[2] However, physicians have become aware these first-generation AHs cause impairment and potentially interfere with restful sleep, cause hangovers or "morning after" effects, impair learning and memory, and reduce work efficiency.[3] Additionally, various second-generation AHs have been developed that decrease allergy symptoms effectively, while potentially increasing quality of life and reducing night-time sleep disturbances.[4] One of these new second-generation AHs approved for the treatment of various allergic conditions such as SAR and chronic spontaneous urticaria (CSU) is bilastine (Blexten, Aralez Pharmaceuticals Canada Inc.).[5-7] Bilastine is available by prescription; it is not derived from nor is it a metabolite of another AH, has a rapid one-hour onset of action and provides sustained efficacy.[5-9] This AH does not penetrate the brain, is scarcely metabolized and does not interact with cytochrome P450.[6,7] For the treatment of allergic conditions in adults and adolescents over 12 years of age, a daily oral dose of bilastine 20 mg is recommended.[7]

This current real-world case project serves as a mechanism to help optimize patient care by recognizing the role bilastine can play in the treatment of a broad range of conditions such as SAR, PAR, urticarial vasculitis as well as both chronic and inducible urticarias. Additionally, the project explores where bilastine can manage pruritus due to skin conditions, such as in atopic dermatitis (AD), which may require adjunctive AH use to skincare and AD treatment.

METHODS

A real-world case-based approach was used to explore the role bilastine can play in the treatment of conditions that require AH use. These real-life patient cases are coupled with evidence from the literature. Recommendations given by the panel reflect the use of bilastine for these conditions and demonstrate how patients can benefit from its use. Any discussion concerning off-label use should be considered an expert opinion only.

The target audience for this publication are physicians, such as allergists and dermatologists, who treat patients with conditions requiring AHs.

LITERATURE REVIEW

A literature review was conducted to explore the role of second-generation AHs, and to assess their value for patients with conditions requiring AHs. Databases searched were: EMBASE, MEDLINE, CINAHL, PubMed, The Cochrane Library, RCP Guidelines Database, and DARE. The searches were conducted February 24–25, 2019, and included guidelines and other publications in the English language, which were dated from 2000 to 2019. References selected further included evidence on bilastine and its use in the presented cases. Medical subject heading terms were used in various combinations in the literature searches and included: 1st and 2nd generation AHs use, specifically bilastine; efficacy for conditions requiring AHs; allergic rhinoconjunctivitis, chronic urticaria, safety of AHs; elimination; tolerance; anticholinergic effects; cardiotoxicity; metabolism; AHs interaction with other drugs; drowsiness using AHs and use of AHs during various activities (such as driving and flying a plane); adverse events; effects of its use in populations of various age groups and impact on quality of life.

ROLE OF THE PANEL

An expert panel (authors) of allergists and dermatologists who commonly treat patients with bilastine was established to present real-life case studies covering conditions including SAR, PAR, urticarial vasculitis, urticaria and pruritus due to various causes, such as AD. The panel members used a template for their case studies, which asked the following questions: What are the case and the impact of the condition? What are the treatment options, and what treatment(s) were previously used? Why might bilastine work in this case, where does it fit and what were the results of bilastine use? Did any adverse events occur? If yes, describe. What (if any) are the special circumstances related to this particular case and what lessons are learned?

During a one-day authorship meeting, the panel presented their cases, followed by a group discussion, after which the authors decided which of the real-world cases using bilastine were included in the manuscript. The publication was developed, reviewed by the panel members, and prepared for publication.

Antihistamines for Treatment of Allergic Conditions

First-generation AHs

AHs have been in use since 1940 for various allergic conditions.[1] The first generation AHs were discovered by Bovet and Staub in 1937 and have anticholinergic and sedative activity.[1,10,11] AHs act as inverse agonists rather than antagonists of histamine H1-receptors, which are members of the superfamily of G-protein-coupled receptors (GPCRs).[10] The older first-generation AHs penetrate readily into the brain to cause sedation, drowsiness, fatigue, impaired concentration, and memory, possibly by negatively impacting rapid-eye-movement (REM) sleep.[10,12,13] These first-generation AHs may cause detrimental effects on learning and examination performance in children, may impair the ability of adults to work and drive, and their use should be discouraged.[10,12] Both the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines[14] and the European Academy of Allergy and Clinical Immunology (EAACI) / Global Allergy and Asthma European Network (GA² LEN)/ European Dermatology Forum (EDF)/ World Allergy Organization (WAO) guidelines for the management of urticaria[13] recommend (strong recommendation, high quality evidence) the use of second-generation, non-sedating AHs and discourage the use of first-generation AHs.

Many physicians still combine a second-generation AH in the morning with a sedating first-generation AH at night to enhance sleep. Staevska et al. compared levocetirizine with or without nightly hydroxyzine, and noted the two treatments were equally effective in decreasing symptoms, quality of life improvement, and lack of nighttime disturbance; however, hydroxyzine increased daytime somnolence.[4]

A media audit of US coverage of transport accidents from 1996 to 2008 in which first-generation AHs were implicated, revealed 54 fatalities.[12] The authors suggested this was likely a gross underestimation of the true figure because these were only media reported events.[12] A similar audit performed on second-generation AHs found no articles that associated these AHs as a cause of transport accidents.[12]

Second-generation AHs

Second generation AHs cause less sedation because of their limited penetration of the blood-brain barrier.[10] They are highly selective for the histamine H1-receptor and have minimal anticholinergic effects.[10] The second-generation AHs commonly

used in Canada for treatment of symptoms in allergic rhinitis and urticaria are desloratadine, cetirizine, fexofenadine, loratadine, rupatadine and bilastine. Even though these are all 2nd generation antihistamines they have different attributes. For example, cetirizine can cause somnolence in some individuals, fexofenadine has a relatively short duration of action and may be required to be taken twice daily for all-round daily protection and loratadine, desloratadine, as well as rupatadine, are extensively metabolized within the liver by the group of enzymes belonging to the P450 cytochrome system[10,15]

Bilastine is a newer second-generation AH that is rapidly absorbed without being metabolized and has a bioavailability of 60%.[16] I*n vitro*, this AH has a high selectivity for the H1-receptor and no antagonism against other receptors such as serotonin, muscarinic M3-receptors, adrenoceptors and H2- and H3-receptors.[16] Since bilastine is not metabolized, no dose adjustment is required in patients with hepatic impairment.[17] Bilastine has a rapid onset of action, within one hour, and a long duration of action, greater than twenty-six hours.[17,18] With regards to bilastine and safety, at the recommended dose of 20 mg daily, treatment-emergent adverse reactions with bilastine, including somnolence, are equal to placebo.[17] Bilastine does not cross the blood-brain barrier, and therefore at the 20 mg dose, it does not affect functional performance, the ability to drive, potentiate the effects of alcohol and lorazepam or cause the impaired performance of tasks related to flying.[5,6,17,19] In clinical trials where bilastine was administered at doses of up to 40 mg once daily, it did not affect psychomotor performance and did not affect the subjects' driving performance in a standard car driving test.[6,20]

Bilastine fits many of the properties for an ideal AH, described by the ARIA guidelines: Potent and selective activity at H1 receptors, rapid onset and long duration of action, and efficacy in PAR and SAR. Other beneficial properties include a lack of interactions with cytochrome P450, lack of sedation, cognitive or psychomotor impairment, no anticholinergic activity, no cardiac safety concerns, and no potential for tachyphylaxis.[21]

Seasonal and Perennial Allergic Rhinitis

Allergic rhinitis

Allergic rhinitis is a chronic condition mostly occurring in children, adolescents, and young adults.[22] Prevalence of 10%–25% has been shown in a cross-sectional study among four world geographic regions: Asia, Europe, the Americas, and Africa.[22] Symptoms are more intense during spring and autumn;[22] allergens provoke symptoms such as nasal itching, sneezing, rhinorrhea, and nasal obstruction frequently leading to reduced quality of life.[22-24] Histamine, released by mast cells and basophils, is responsible for the symptoms.[7,22-24]

TABLE 1.

Seasonal Allergic Rhinitis, Perennial Allergic Rhinitis Studies			
Author/Year	**No and Type of Patients**	**Type and Length of Treatment**	**Results**
Kuna P, 2009[15]	N = 681 - SAR	Placebo, bilastine 20 mg, cetirizine 10 mg. Oral, QD for 14 days	Significantly superior to placebo and comparable to cetirizine in relieving symptoms of SAR. Lower incidence of total AEs, somnolence, fatigue and drug-related AEs compared to cetirizine.
Bachert C, 2009[25]	N = 721 - SAR	Placebo, Bilastine 20 mg, Desloratadine 5 mg, Oral, QD for 14 days	Significantly fewer symptoms compared to placebo and comparable to desloratadine both for efficacy and safety.
Sastre J, 2012[28]	N = 650 - PAR	Placebo, Bilastine 20 mg, Cetirizine 10 mg. Oral, QD for 4 weeks. An open-label extension phase evaluated the safety of bilastine 20 mg administered to patients (n=513) for one year.	A post-hoc analysis indicated that bilastine and cetirizine were similarly effective and more effective than placebo. Bilastine was safe and well-tolerated over a 1-year treatment period.
Okubo K, 2017[26]	N = 765 - PAR	Placebo – oral QD, Bilastine 20mg – oral QD, Fexofenadine 60 mg – oral BID for 14 days.	Significantly superior to placebo and comparable to fexofenadine in relieving symptoms of PAR. Bilastine showed a rapid onset of action, and total nasal symptom score was significantly greater than fexofenadine on day 1.
Okubo K, 2017[27]	N = 58 SAR/ N = 64 PAR	Bilastine 20mg – oral for 12 weeks (SAR and PAR) and 1 year (PAR only).	Bilastine was safe, well-tolerated, and effective for patients with SAR and PAR. The observed improvement was maintained for 1 year in PAR patients, with no loss of drug efficacy.
Novak Z, 2016[37]	N = 509 children (aged 2 to >12) – AR or chronic urticaria	Placebo, Bilastine 10mg – oral for 12 weeks	Bilastine had a safety and tolerability profile similar to that of a placebo.

Bilastine was safe and well-tolerated over a 1-year treatment period.

TABLE 2.

Chronic Spontaneous and Inducible Urticaria			
Author/Year	**No and Type of Patients**	**Type and Length of Treatment**	**Results**
Zuberbier, 2010[35]	N = 516 with CSU	Placebo,bilastine 20 mg, levocetrizine 5 mg. Oral, QD for 4 weeks.	Bilastine significantly reduced the total symptom scores from day 2 onwards compared to placebo. Bilastine was safe and well-tolerated as compared with placebo. Comparison with levocetirizine indicated both treatments to be equally efficacious.
Yagami, 2017[34]	N = 197 with CSU or pruritus associated with skin diseases.	Bilastine 20 mg, Oral, QD for 52 weeks.	All efficacy variables improved during treatment, and long-term treatment for 52 weeks was safe and well-tolerated. Bilastine improved symptoms of both conditions early in treatment, and the efficacy was maintained throughout the 52 weeks.
Serra, 2019[32]	N = 115 with CSU, eczema/dermatitis, prurigo or cutaneous pruritus	Bilastine 20 mg, Oral, QD for 8 weeks. Non-responder patients (<30% improvement in pruritus score at week 2) were up-dosed to 40mg, QD from week 2.	Bilastine demonstrated efficacy for the relief of pruritus associated with urticaria and other skin diseases in adults, with a good safety profile. Up-dosing to 40mg in non-responding patients after 2 weeks of treatment was efficacious without any safety concerns.
Weller, 2018[33]	N = 29 with CSU who had not responded sufficiently to licensed doses of other AHs	Bilastine 20, 40 and 80 mg, Oral, QD for 6 weeks. At 2 weeks patients without a complete response (UAS7 ≤ 3) were up-dosed by an additional 20 mg QD	Bilastine 20 mg was effective in relieving the symptoms of CSU. Up-dosing to double the licensed dose of bilastine appeared to be sufficient for the majority of CSU patients. A proportion of the severely affected patients benefited from 80 mg.
Krause, 2013[31]	N = 20 with cold contact urticaria (CCU)	Bilastine 20 mg up-dosed to 40 and 80 mg daily each for 7 days with 14-day washout periods compared to placebo in a 12-week study.	Bilastine 20 mg was effective (P<0.0001) in reducing CTT. Up-dosing to 80 mg significantly (P<0.04) increased its effectiveness without sedation.

Antihistamine (AH); Critical Temperature Thresholds (CTT); Urticaria Activity Score (UAS)

The efficacy of bilastine in SAR and PAR has been confirmed in several studies comparing bilastine to either placebo alone or to placebo and other AHs (Table 1).[15,25-28]

The Kuna et al. trial was a double-blind, randomized, controlled study performed in patients suffering from SAR to determine the efficacy and safety of bilastine 20 mg compared to cetirizine 10 mg, and placebo.[15] The mean total symptom scores were reduced in the bilastine and cetirizine treated groups to a similar, and significantly greater extent, compared with placebo. Bilastine demonstrated a significantly lower incidence of somnolence and fatigue compared to cetirizine.[15] An additional multicenter study evaluated bilastine (20 mg), desloratadine (5 mg) or placebo treatment in 721 patients with SAR.[25] After 14 days of treatment, both nasal and non-nasal symptoms had significantly decreased in those patients who received the drugs compared to placebo.[25]

Chronic urticaria

Chronic spontaneous urticaria and other chronic forms of urticaria are disabling, impair quality of life and affect performance at work and school.[29] CSU is characterized by the appearance of spontaneously occurring pruritic erythematous wheals that generally resolve in less than 24 hours.[30] These wheals may appear daily for more than 6 weeks; in 50% of cases, associated angioedema or severe associated swelling occurs.[30] CSU has a prevalence of 0.5-1% of the general population, occurring mostly in women; the peak age of onset is 20-40 years, and 10-50% may have the disease longer than 5 years.[3]

International urticaria guidelines recommend second-generation AHs as first-line treatment.[13,29] As a second-step in therapy, before resorting to other treatments, these second-generation AHs have been recommended at high doses (up to 4x therapeutic dose) based on studies showing the benefit of a higher dosage of 2nd generation antihistamines and expert opinion.[29]

Bilastine has been assessed in multiple clinical trials involving patients with chronic urticaria (Table 2).[31-35] In a double-blind, controlled clinical trial with placebo and levocetirizine in patients with CSU, the total symptom score was reduced from the second day of treatment with bilastine, bilastine showed better

results than placebo, and bilastine had a safety profile similar to placebo.[35]

Long-term treatment with bilastine has also been investigated in an open-label, single-arm, one-year safety study.[34] This study demonstrated that bilastine significantly reduced all rash and itch symptoms at the first time point (2 weeks), and this response was maintained throughout the 52 weeks showing that bilastine does not cause tachyphylaxis. Throughout the treatment period bilastine was well tolerated with only 2.5% of patients reporting mild or moderate bilastine-related adverse events and only two reports of somnolence similar to placebo-treated patients.[34]

Bilastine was also investigated in three up-dosing studies in patients with CSU and cold contact urticaria.[31-33] At doses of 40 and 80 mg, bilastine further improved upon the symptom score outcomes for urticaria patients. Since bilastine is a non-brain penetrating antihistamine it is an ideal AH for up dosing the daily dose four-fold in difficult-to-treat urticaria.[8]

Pruritus associated with dermatological conditions

The involvement of histamine in pruritus associated with various skin conditions varies. For example, histamine H1-receptor-induced pruritus in AD is lower than that in patients with CSU.[34,36] Two studies that included patients with CSU or pruritus associated with skin diseases showed that bilastine is effective in reducing itch scores for skin conditions such as AD, prurigo and cutaneous pruritus (Table 2).[34,32] One of these studies allowed for 52 weeks of treatment, and no loss of drug sensitivity at 20 mg once daily was seen.[34]

This second-generation AH is effective for chronic pruritus related to skin diseases such as AD and demonstrates that second-generation AHs may be an effective adjunct to AD treatment, in addition to patient education, a primary skincare plan, the use of moisturizers, and topical anti-inflammatory therapy.

Real-Life Cases

The cases presented here by the authors focused on the use of bilastine in conditions such as SAR, PAR, and chronic urticaria, as well as less common but challenging conditions such as urticarial vasculitis and pruritus in skin conditions.

Advisors discussed the use of AHs, then presented, reviewed, and critiqued the various cases. A final consensus vote (75% consensus needed) on the cases revealed a unanimous consensus on ten different cases for inclusion in the publication.

SAR and PAR

Table 3 discusses a 21-year-old female with PAR (Case 1) and a 9-year-old boy with a pet allergy and a history of seasonal allergies (Case 2). Both patients tolerated bilastine very well and had a rapid response to treatment with no adverse events reported. The panel members noted that in cases 2 and 5 bilastine is presently off-label in the pediatric population; however, phase 3 clinical data demonstrates that bilastine is safe for use in children as young as 2 years of age.[37] As well, bilastine was recently approved in Europe for children age 6 – <12 years of age and in Mexico for children 2 – <12 years of age. The panel members proposed a liquid pediatric formulation of the AH is needed, especially for use in children down to 2 years of age.

CSU and dermatographism or angioedema

Table 4 shows three cases: A 19-year-old female with CSU and dermatographism (Case 3), a 24-year-old female with CSU and angioedema (Case 4), and a 12-year-old male with an 8-month history of daily urticaria and intermittent angioedema (Case 5).

The patient described in case 4 had previously used oral diphenhydramine 25 mg, sometimes up to 3 times/day (TID), which only controlled pruritus and swelling for a few hours. After one month of bilastine use, her condition had cleared after which the AH was used PRN. Her quality of life dramatically improved, positively impacting her study, quality of sleep, social life, and self-image. According to the panel members, the sedation caused by using first-generation AHs is not helpful in treating pruritus and should be discouraged because of potentially serious side effects.[1-6,12]

Inducible urticaria: cold urticaria and cholinergic urticaria

Table 5 presents two cases with inducible urticaria: A 29-year-old female with cold contact urticaria (Case 6) and a 22-year-old male with cholinergic urticaria (Case 7). The patient in Case 6 received previous treatment with cyproheptadine 16 mg, cetirizine 40 mg, and at bedtime doxepin 75 mg, which caused sedation and systemic side effects. After changing her medication to bilastine 40 mg twice daily, the patient had fewer and less severe outbreaks and no systemic symptoms.

The correct diagnosis for the 22-year-old male with cholinergic urticaria took a long time; in fact, before proper diagnosis, the patient was even treated (unsuccessfully) for conditions such as scabies and AD. However, with the combination of proper education on his condition, and bilastine 20 mg daily used as needed, this patient has recovered the confidence to exercise again, thereby improving his QoL significantly. The panel agreed that education on cholinergic urticaria and its differential diagnoses is crucial for successful treatment.

Urticarial vasculitis

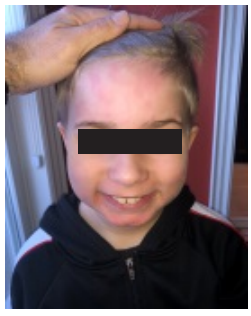
Table 6 presents case 8 about a 43-year-old female with urticarial vasculitis, which is difficult to diagnose from a biopsy. Consequently, for over 8 years after the first symptoms occurred, numerous biopsies showed negative results. Eventually, however, confirmation of the condition from a biopsy was obtained; the patient's condition improved significantly after she was prescribed bilastine.

TABLE 3.

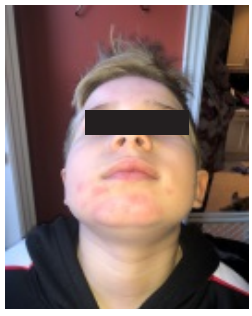
Case Studies of Patients with Allergic Rhinitis					
No	**Case and Issues**	**Previous Treatment**	**Why Bilastine Was Chosen**	**Disease Management**	**Follow up/ Learning Points**
1	21-year-old female with PAR has rhinorrhea, sneezing and nasal obstruction, ocular symptoms, SOB on exercise, fatigue, lack of energy and difficulty to concentrate. Her daily symptoms occur mostly in the morning and at home. Previous allergy workup = allergy to dust mites. Review of systems = unremarkable; family history positive for allergies. She reduced dust in her home and had no pets. Physical examination showed large and pale turbinates, no polyps; conjunctival redness; no wheezing on forced expiration.	OTC antihistamines, taken on a PRN basis – were sedating; but she did like the effect. Nasal steroids were tried but dropped due to local irritation (burning and bleeding).	Because of published efficacy data and innocuous profile (no cardiovascular nor CNS effects and minimal potential for interaction with other drugs).	Bilastine 20 mg QD. Patient significantly improved; reduction of nasal symptoms, no ocular or pulmonary symptoms; medication well tolerated.	Consider treating with bilastine 20 mg until all symptoms are gone – usually 1 or 2 months up to 6 months
2	9-year-old boy (58.5 inches/87 pounds and blood work normal) has a pet allergy and reacts when exposed to the family's dog. He has had SAR since age 5 and has symptoms yearly from May-Sept, skin prick test conducted March, 2017 (age 7) and tested positive for tree mix, ragweed and weed mix. When closely interacting with the family dog he develops hives on the face, neck and eyes (Figures Case 2-1, Case 2-2): - 1st breakout 2 days after puppy came home: red itchy swollen eye with raised red hives below the eye. - 2nd breakout 5 days later: red blotchy patches on neck and face. - 3rd breakout 5 days later: red blotchy patches on neck and face. - 4th breakout 8 days later: red blotches on face. The condition has been present for 1 month and impacts on his daily activities, social life and quality of sleep (due to itching).	None	it is effective for the treatment of urticaria and allergic rhinitis, bilastine also has robust pediatric safety data in this same population.	Bilastine 10 mg (half a tablet), upon breakout (approx every 5 days, which fits with the pharmacokinetics of bilastine), used for all breakouts during the month of the condition. Hives and itch completely resolve within twenty minutes of treatment each time. No longer has an impact on daily activities, social life and sleep disturbance. After each treatment he returns to normal within 20 minutes and is extremely happy with the outcome (Figure Case 2-3).	Continue to take bilastine 10 mg as needed

Antihistamine (AH); Central nervous system (CNS); Over-the-counter (OTC); Perennial allergic rhinitis (PAR); Seasonal allergic rhinitis (SAR); Shortness of breath (SOB); Once a day (QD); Twice a day (BID); Three times a day (TID); Four times a day (QID); Oral (PO); As needed (PRN)

CASE 2 PATIENT DETAILS: Photo is from third breakout – hives on face and neck.



Before treatment



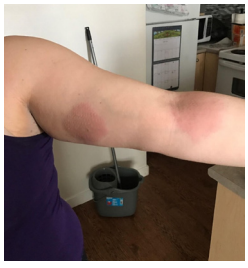
20 minutes after treatment

TABLE 4.

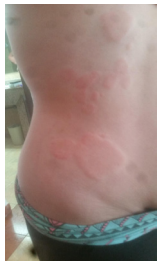
Case Studies of Chronic Spontaneous Urticaria and Angioedema					
No	**Case and Issues**	**Previous Treatment**	**Why Bilastine Was Chosen**	**Disease Management**	**Follow up/ Learning Points**
3	19-year-old female with CSU and dermatographism, sometimes accompanied by swollen lips and face, symptoms started 2 months ago. She studies long hours and has frequent viral infections. School and sleep are affected by pruritus and medication related fatigue. She is embarrassed to be out when there is a rash and swelling. When rash is gone her skin still welts upon rubbing.	Cetirizine 20 mg am and diphenhydramine 50 mg at bedtime. Prednisone on two occasions.	Because of its efficacy, and minimal sedation.	Bilastine 20 mg BID started 2 weeks ago. She was instructed to stop medication when symptoms resolve.	Fewer hives, less swelling and pruritus. She sleeps better, is less tired and better able to study. She still has some dermatographism, which is improving.
4	24-year-old female university student with CSU and angioedema. More than 12-week history of hives on the trunk and extremities, with substantial swelling of the lips on a daily basis (Figures: Photo Case 4-1, Case 4-2, Case 4-3). Very itchy, adversely affecting daily activities, social life, self-image and sleep.	Diphenhydramine 25 mg PO, sometimes up to TID. Controls pruritus and swelling for a few hours then lesions and swelling recur. Medication takes hours to work; patient feels sedated with decreased daytime productivity.	Good prior experience with similar cases. Effective, safe, tolerable and reliable. It is a prescription medication (drug coverage).	Replaced diphenhydramine with bilastine 20 mg BID x 7 days. Upon follow-up bilastine was increased to 40 mg BID x 30 days, after which the condition cleared (Figure: Photo Case 4-4), then bilastine 20 mg QD x 30 days followed by PRN. Referral for allergy testing and care by family physician.	Fast onset and clearance, less hives, swelling and intensity of pruritus. Improved study productivity, sleep, social life and self-image.
5	12-year-old male (54.3 inches/89 pounds) with an 8-month history of daily urticaria, intermittent angioedema (lips, eyes), significantly impacting his daily activities.	Desloratadine, minimal improvement. Bilastine 20mg QD was started by primary care physician 3 months prior to presentation in this clinic.	Previous treatment with desloratadine unsuccessful.	Bilastine, 20 mg QD x 3 months resulted in marked improvement, symptoms are less intense, resolve more quickly, now breakouts are 1-3 times per week. Dose increased to 20 mg QD or BID. Condition and quality of life improved.	Almost symptom free for up to 2 months (mild swelling ~2x/mo). Bilastine restarted to prevent these symptoms (20 mg QD or BID). Bilastine was well tolerated with no adverse effects.

Chronic spontaneous urticaria (*Case 3:* CSU and dermatographism (Susan Waserman) *Case 4:* CSU with angioedema (Jaggi Rao) *Case 5:* CSU and angioedema (Tim Vander Leek). Once a day (QD);Twice a day (BID);Three times a day (TID); Four times a day (QID); Oral (PO); As needed (PRN)

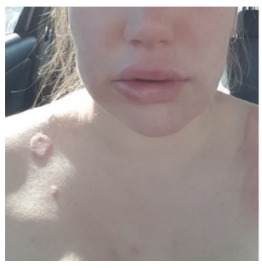
CASE 4 BEFORE



Case 4-1

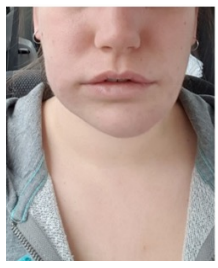


Case 4-2



Case 4-3

CASE 4 AFTER



Case 4-4

TABLE 5.

Case Studies of Patients With Inducible Urticaria					
No	**Case and Issues**	**Previous Treatment**	**Why Bilastine Was Chosen**	**Disease Management**	**Follow up/ Learning Points**
6	29-year-old female with cold contact urticaria symptoms which started to occur ~5 years ago and are getting worse with time. On several occasions, patient experienced a generalized urticarial rash, which was accompanied, on two events, with dyspnea and dizziness. According to Wanderer's classification based on severity: Type III (one or more episodes associated with symptoms and signs indicative of respiratory or cardiovascular compromise). The condition negatively impacted her QoL. Ice cube test– clearly positive.	Cyproheptadine 16 mg caused such sedation that she had to stop medication. Cetirizine 40 mg gave a clinical response; however, she reduced the dose because of serious side effects. At bed time doxepine 75 mg.	Effective and less sedation.	Cetirizine replaced by bilastine 40 mg BID. Clinical response – very good in terms of: - Significant reduction of number of attacks and their severity - No more systemic symptoms	Follow-up ice cube test gave minimal response.
7	22-year-old male with cholinergic urticaria presented with recurrent itchy, small, urticarial wheals post-exercise and stress, which go away after 2-3 hours. Bothers him at the gym, makes him self-conscious. Clinically cholinergic urticaria (not painful). He has seen several physicians (walk-in clinics) and no one is certain what he has.	Previously treated as scabies (ineffective) and also treated as AD with topical steroids (no help).	Controls the condition well, no sedation or mood disturbance.	Educated re: disease Bilastine 20 mg PO BID, as needed controlled the disease effectively.	Bilastine 20 mg PO BID, episodically when he feels he needs it.

Case 6: Cold urticaria (Jacques Hebert) *Case 7:* Cholinergic urticaria (Charles Lynde). Quality of life (QoL); atopic dermatitis (AD); Twice daily (BID); Oral (PO)

TABLE 6.

Case Study of a Patient With Urticarial Vasculitis					
No	**Case and Issues**	**Previous Treatment**	**Why Bilastine Was Chosen**	**Disease Management**	**Follow up/ Learning Points**
8	43-year-old female presented with urticarial vasculitis. She has a history of ulcerative colitis and sclerosing cholangitis. Colectomy for high-grade dysplasia followed in 2011. In 2010, started to have urticarial plaques on face/trunk/limbs. Lesions present but little pruritus. Many previous biopsies were negative for urticarial vasculitis (finally positive in 2018). Low C3-C4. Impact of skin condition: Daily activities (yes); professional life (yes), social life (yes), self-image (ves), sleep disturbance (no).	Cetirizine, desloratadine (for years), dapsone added in 2011 to improve control. Was well controlled on that combination (except when under psychological stress she developed a few lesions). She complained of drowsiness.	Cetirizine/desloratadine were replaced by bilastine 80 mg QD to improve drowsiness and maintain efficacy.	Condition has improved (however, patient was reluctant to reduce dapsone). Good control with bilastine + dapsone (except for a few outbreaks each year when under psychological stress). Impact of skin condition: daily activities (no); professional life (no), social life (no), self-image (no), sleep disturbance (no); No adverse events.	Continue bilastine as needed + dapsone is continued for 14 days.

Case 8: Urticarial vasculitis (Pierre-Luc Dion) (Table 6).

TABLE 7.

Case Studies of Patients With Pruritus					
No	**Case and Issues**	**Previous Treatment**	**Why Bilastine Was Chosen**	**Disease Management**	**Follow up/ Learning Points**
9	76-year-old retired male presented with constant itching without a skin eruption (pruritus of unknown origin) except for occasional dry skin in the winter for 4.5 years. Itching was worse in the winter even if his skin was adequately moisturized. Skin biopsy: Superficial perivascular dermatitis. QOL: Hard to concentrate due to itch.	Protopic, nerisone, system steroids, doxepin, loratadine, rupatadine, refrigerated lotion. Tried BB UVB reduced pruritus, but worsened when decreased to once a week. He became dependant on phototherapy for 2 years.	Refractory pruritus unresponsive to other AHs; dependant on UVB 2x/ week. In Japan, bilastine is indicated for pruritus and it has several studies showing efficacy in pruritus.	Bilastine (20 mg OD) in addition to bb-UVB/twice a week. UVB was discontinued and pruritus controlled with bilastine 20mg OD for a month; no adverse events.	Refractory pruritus of unknown etiology, which is dependent on UVB may respond to bilastine monotherapy, allowing for UVB to be discontinued
10	63-year-old female with AD, asthma, allergic rhinosinusitis, pruritic and heat/sun sensitivity. AD exacerbated with heat/sun exposure; blistering type of reaction. Patient avoided light exposure, wore gloves, used bandages, felt "poisoned" by the condition, which has a severe impact on daily activities, sleep, mood and self-image. Location of lesions and erythema: Arms, legs, neck.	Desloratadine, diphenhydramine, clobetasol propionate.	Other antihistamines have not been significantly effective in controlling skin eruptions.	Bilastine, 20 mg/day (on medication for 2 months); fluticasone nasal spray. Improvements started 1 day after taking bilastine – itchiness and facial puffiness reduced, improvement in QoL leading to improvement in mood and self- image; less drowsy.	Primary skin care plan in AD is important. The AH may be an effective adjunct to AD treatment to control pruritus.

Pruritus: *Case 9:* Pruritus of unknown origin (Lyn Guenther), Dermatitis/eczema *Case 10:* Atopic dermatitis (Gordon Sussman)
Quality of life (QOL); Broad band (BB); atopic dermatitis (AD)

Pruritus of unknown cause and pruritus associated with AD

Table 7 discusses two patients with pruritus: In case 9, the patient presents with pruritic symptoms due to an unknown cause, while case 10 involves a patient with AD-related pruritus. For these patients, education on their conditions, avoidance of pruritic triggers, and the implementation of a primary skincare plan using a moisturizer were essential to improving their condition. Second-generation AHs can sometimes help to treat pruritus related to AD, but not the AD itself. In case 10, bilastine is shown as an effective adjunct to AD treatment to control pruritus. However, adherence to therapy is important for success. Again, panel members emphasized that the sedation caused by using first-generation AH is not helpful in treating pruritus and can also cause serious side effects.[1-6,12]

Suggestions for bilastine use

Second generation AHs such as bilastine may work, even when other AHs do not. The effective clinical response in many of the presented patient cases was achieved not because treatment with first-generation AHs are ineffective but because the patient **could not tolerate** the first generation AH. It must be recognized that first-generation AHs have serious side effects significantly and negatively impacting QoL.

The panel members recommended that for pruritic conditions, bilastine is continued until all symptoms subside, usually, 1 to 2 months duration, up to 6 months, or longer if necessary. The panel suggested a minimum of 2–3 months with no condition activity or symptoms before discontinuing bilastine, after which the AH is taken as needed. In SAR an AH is to be taken for the duration of the pollen season, and those with PAR can take it indefinitely. In those patients with CSU the time they need to take AH varies considerably. Generally we treat until the disease is gone.

The panel members concluded that their task is not only to teach about the risks of first-generation sedating AHs but also to educate healthcare providers (including primary care physicians) and their patients on how and why they should use second-generation AHs.

The authors stated: "Bilastine is not available in the US, but it is in Canada, and we find it effective." Although guidelines from the US recommend second-generation AHs, due to lack of availability, the choices are more limited.[38]

CONCLUSIONS

Second-generation AHs are thoroughly investigated in clinical pharmacology studies and randomized controlled trials. Every day clinical practice can pose challenges when selecting an effective and safe AH for the treatment of allergic conditions. The real-world cases presented here applied bilastine in conditions such as SAR, PAR, chronic urticaria, and less common but challenging conditions such as urticarial vasculitis and pruritus in

inflammatory skin conditions. This second-generation AH, bilastine, was shown to be effective in relieving symptoms, was safe and well tolerated even when used over a prolonged period.

DISCLOSURES

The authors have no conflicts of interest to declare.

Some of the settings for bilastine use in this article are considered 'off-label'. Use of bilastine in off-label settings is left up to the discretion of the treating health care professional after careful clinical evaluation.

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