Expert Opinion

Fexofenadine: biochemical, pharmacokinetic and pharmacodynamic properties and its unique role in allergic disorders

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Background: Fexofenadine is one of several second-generation H_1-antihistamines approved for the treatment of various allergic disorders; however, it shows numerous unique properties that make it an optimal choice for many patients. *Objective*: To review the pharmacology, efficacy and safety of fexofenadine and the attributes differentiating it from other H_1-antihistamines. *Methods*: We performed a literature search in PubMed/MEDLINE (1966 – March 2009) using the keywords fexofenadine, antihistamine, allergic rhinitis and chronic urticaria. We also reviewed data provided by the manufacturer in addition to reports from various governmental agencies. *Results/conclusions*: Fexofenadine is devoid of sedative and anticholinergic effects and may offer equivalent or greater efficacy in treating allergic disorders compared with other currently available second-generation H_1-antihistamines. In addition, fexofenadine may offer cost savings over other selected H_1-antihistamines owing to its recent availability in generic form in the US.

Keywords: allergic rhinitis, antihistamine, fexofenadine, H_1-antihistamine, nonsedating

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1. Introduction

1.1 Allergic rhinitis

Allergic rhinitis (AR) is the most common atopic disease and the sixth most common chronic illness in the US, affecting 10 – 30% of adults and ≤ 40% of children [1,2]. In England, an estimated 3.3 million people have been diagnosed with AR [3], whereas epidemiologic data from other parts of the world are scarce and generally rely on self-reporting of AR. Prevalence rates throughout Western Europe and China approximate those observed in the US [4,5]. Most concerning is the continued rise in the prevalence of AR. In the past 30 years, the prevalence of AR in England, Sweden and Australia has doubled [6]. Although AR is not associated with significant mortality risk, it can result in significant morbidity, reductions in quality-of-life measurements, loss of productivity and significant healthcare costs. Consequently, medications that prevent and/or attenuate these negative outcomes are important.

1.2 Mechanisms of inflammation

On initial exposure to an allergen, sensitization begins with presentation of the allergen to $CD4^+$ T lymphocytes by antigen-presenting cells. In turn, $CD4^+$ T lymphocytes produce and release various interleukins and cytokines that promote the production of

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IgE sensitized to the specific allergen. Although the initial sensitization process elicits no outward symptoms of an allergic reaction, re-exposure to the allergen triggers a cascade of events culminating in the characteristic symptoms of AR.

The inflammatory process in AR entails early- and late-phase reactions responsible for varying symptomatology. Early-phase inflammation begins within minutes of allergen re-exposure when IgE-sensitized molecules traversing the epithelium come into contact with tissue-bound mast cells. IgE subsequently binds to the high-affinity FcεRI receptor on the mast cell surface and in the presence of multivalent antigens (e.g., an allergen), cross-linking of FcεRI receptors initiates mast-cell degranulation [7]. On degranulation, the mast cell disseminates newly and pre-formed inflammatory mediators including histamine, proteases, prostaglandins, cytokines and leukotrienes, among others. Sneezing, rhinorrhea, nasal pruritis and, to a lesser extent, congestion, are the predominant early-phase symptoms. Ocular symptoms, including pruritis, edema and excess lacrimation, are also commonly found in patients suffering from AR and may be of similar severity to nasal symptoms [8]. Altogether > 19 different mediators have been identified, but histamine accounts for ≥ 50% of these symptoms and nearly all can be explained by histamine via its interaction with the H_1 receptor resulting in vascular leakage and through stimulation of nerve endings [9,10].

The late-phase response typically occurs between 3 and 5 h after allergen re-exposure. In contrast to the early-phase reaction where histamine plays a major role, late-phase reactions are mediated primarily by chemotactic recruitment of neutrophils, eosinophils, basophils, mast cells, mononuclear cells and other inflammatory cells. These cells promote and sustain the inflammatory reaction in concert with mucosal gland secretion of mucoglycoconjugates and antimicrobial compounds that dilate the vasculature and result in sinusoidal filling [11]. Consequently, the late-phase reaction is characterized primarily by congestion.

1.3 H_1-antihistamines

Histamine is produced and released primarily by mast cells and basophils. Although four histamine receptors have been identified (H_{1-4}), only H_1 is believed to be the primary receptor implicated in allergic responses. However, H_2, H_3 and H_4 may also play minor roles by promoting proinflammatory cytokine production and increasing the expression of adhesion molecules [12,13]. Because of the vital role that histamine and the H_1 receptor play in eliciting AR symptoms, H_1-antihistamines have long been a mainstay of AR treatment.

Originally developed in the late 1930s, first-generation oral antihistamines are effective for the treatment of AR-associated rhinorrhea, sneezing and pruritis. However, their lipophilicity owing to aromatic rings and alkyl side chains permit crossing of the BBB and interaction with CNS H_1 receptors, thus limiting their use [14]. Further complicating their adverse event profile is the poor selectivity for the H_1 receptor and corresponding ability to bind muscarinic receptors resulting in significant anticholinergic effects [15-17]. They are often referred to as sedating antihistamines and have been associated with impaired performance at school, work and home [15,18].

In contrast to first-generation antihistamines, second-generation antihistamines are generally more selective for H_1 receptors and can be dosed once daily owing to their longer duration of action compared with the former. Structurally, the core moiety of first- and second-generation antihistamines is similar; however, the substitution of charged side chains found in second-generation antihistamines promotes lipophobicity and results in a diminished ability to traverse the BBB resulting in reduced or absent sedative and anticholinergic effects [14]. Numerous second-generation antihistamines are currently available in both over-the-counter (OTC) and prescription-only preparations, each with unique attributes. The discussion herein will focus on the second-generation antihistamine fexofenadine.

2. Fexofenadine

2.1 Biochemical properties

Fexofenadine is a member of the piperidine class of second-generation antihistamines, similar to loratadine, desloratadine and FDA-unapproved ebastine. It is an inverse agonist at the H_1 receptor and exerts its antihistaminic effect by binding the inactive form of the receptor that exists in equilibrium with the active form. Stabilization of the inactive form of the receptor ensues and shifts the equilibrium towards the inactive state, subsequently reducing the number of active receptors to which endogenous histamine may bind [19]. Fexofenadine also down-regulates constitutive receptor activity, even in the absence of histamine [20]. Although it is commonly classified as such [21], fexofenadine is not a neutral antagonist (i.e., competitive antagonist of both active and inactive H_1 receptors) and is more appropriately termed an H_1-antihistamine rather than an H_1 receptor antagonist.

As is the case with all H_1-antihistamines, most of the clinical benefits associated with fexofenadine are believed to be owing to its antihistaminic properties. However, *in vitro* data suggest that fexofenadine also shows anti-inflammatory effects [22]. In particular, fexofenadine inhibits the expression of intracellular adhesion molecule 1 (ICAM-1), which is displayed promptly on epithelial cells after allergen exposure and is believed to play a prominent role in allergic inflammation [23]. However, this only occurs at concentrations ≥ 50 μg/mL, whereas the C_{max} of fexofenadine at approved doses generally does not surpass 0.5 μg/mL [23,24]. Fexofenadine also inhibits macrophage-mediated release of IL-6, an important mediator of the acute-phase response, in a concentration-dependent manner [25]. At concentrations ≥ 0.25 μg/mL, fexofenadine inhibits CC chemokine ligand-5 (CCL5) and eotaxin, chemotactic factors responsible for recruiting various

Table 1. Pharmacokinetic properties of fexofenadine according to dose.

Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng*h/mL)	$t_{1/2}$ (h)	Ref.
60	77	2.1	333	3.2	[35]
	114	2.3	446	3.1	[36]
	163	2.5	779	3.5	[34]
	199	1.5	1,041	–	[61]
	201	3.2	1,142	–	[62]
	201	2.3	1,130	11.0	[63]
	209	1.4	1,348	13.1	[37]
	295	2.0	2,076	4.5	[33]
80	180*,‡	3.9	1,254	14.0	[64]
	210*	2.9	1,584	14.4	[64]
	502	1.1	2,400	11.2	[65]
120	179§	2.5	1,121	5.4	[66]
	267*	2.6	1,843	17.6	[64]
	288	2.4	1,616	2.6	[67]
	382	2.6	2,524	15.5	[64]
	436	2.0	1,685	3.0	[39]
	611	1.5	3,637	11.0	[8]
	699§	1.0	4,133	10.1	[6]
180	330	2.0	1,525	4.8	[86]
	735	1.5	4,108	10.3	[87]

*Dose administered using several 40 mg capsules; ‡Administered while fasting; §Dose administered using several 60 mg tablets.

inflammatory cells (e.g., eosinophils and basophils) implicated in the late-phase response [26]. Additionally, at this concentration, fexofenadine suppresses peripheral blood leukocyte production of thymus and activation regulated chemokine (TARC), a CC chemokine produced by various cells that may be responsible for sustaining allergic immune responses [27,28]. In contrast to some other second-generation antihistamines, fexofenadine seems to inhibit COX activity. At lower concentrations, inhibition of COX-2 activity predominates and is inversely correlated with concentration such that at higher concentrations (above those achieved with approved doses), COX-1 inhibition occurs [29]. Finally, animal studies have suggested that fexofenadine inhibits fibroblast NO production at concentrations ≥ 50 µg/mL and suppresses plasma NO levels after ≥ 2 weeks of oral administration [30].

2.2 Pharmacokinetic profile

The pharmacokinetic properties of fexofenadine at varying doses are summarized in **Table 1**. Fexofenadine is rapidly absorbed reaching peak plasma concentrations in ~ 1 – 3 h. Because fexofenadine is a substrate for numerous active transporter systems in the intestinal tract, absorption may be altered by transport across the intestinal membrane. Specifically, P-glycoprotein (P-gp) and members of the organic anion transport polypeptide (OATP) family have been implicated in fexofenadine uptake. P-glycoprotein, an efflux transporter encoded in humans by the MDR1 gene, has been of particular interest in association with H_1-antihistamines. Theoretically, reduced P-gp activity in the intestinal membranes may result in increased systemic absorption owing to a reduction in the amount of drug that is actively pumped back into the intestinal tract. Fexofenadine is a well-identified substrate of P-gp; however, data regarding the clinical effects of concomitant administration of fexofenadine with P-gp inhibitors and inducers are conflicting. Available data suggest that fexofenadine administration with known P-gp inhibitors, including ketoconazole [21], itraconazole [31], verapamil [32], azithromycin [32], erythromycin [21], quercetin [33] and single doses of St John's wort [34] significantly increases the AUC and/or C_{max} of fexofenadine by ≥ 20%. Similarly, administration of fexofenadine with P-gp inducers such as rifampin and long-term administration of St. John's wort may reduce the AUC and/or C_{max} [35,32]. However, in many cases these pharmacokinetic parameters are no different after repeated concomitant administration with inhibitors/inducers than when fexofenadine is given alone [36,31]. Interestingly, fexofenadine is a racemic mixture of isomers with approximately equipotent antihistaminic activity [21]; yet, R(+)-fexofenadine achieves significantly higher peak plasma concentrations (~ 2:1 ratio) than S(-)-fexofenadine, which may be related to the greater affinity of P-gp for the S-isomer [37,31,38]. Substances that inhibit or induce OATP, an influx transporter implicated in the absorption of some drugs, may also significantly affect fexofenadine levels. Animal studies administering fexofenadine with grape fruit juice, orange juice and apple juice (known P-gp and OATP inhibitors) have observed reductions in the AUC of fexofenadine by 58, 31 and 22%, respectively [39,40]. Although inhibition of P-gp would be expected to increase concentrations, these observations suggest that inhibition of OATP-mediated influx of fexofenadine predominates.

The volume of distribution (V_d) of fexofenadine is estimated at 5 – 6 L/kg [41] although the true V_d may be considerably lower (~ 1.5 L/kg) [24], in part because of its relatively poor bioavailability (estimated at ~ 30%) in humans [42]. Animal studies have revealed significantly lower oral bioavailability, ranging from 1.4 to 6.6% in various species [24]; however, a true estimation of oral bioavailability in humans is difficult because virtually all human fexofenadine studies have been performed using oral formulations only.

Fexofenadine undergoes minimal hepatic metabolism (≤ 5%) and is excreted unchanged in the urine (10%) and feces (80%) [21]. Thus, the potential for hepatic CYP-mediated drug–drug and drug–food interactions with fexofenadine is virtually nonexistent, making it an attractive option in patients experiencing polypharmacy. Coadministration of

Table 2. Relative sedative and anticholinergic effects of select first- and second-generation antihistamines.

Antihistamine	Sedative effects		Anticholinergic effects
	Approved doses	Supratherapeutic doses	
First-generation			
Diphenhydramine	+++	+++	++
Hydroxyzine	+++	+++	++
Chlorpheniramine	++	++	++
Promethazine	+++	+++	+++
Second-generation			
Cetirizine	+	++	0
Levocetirizine	0	0/+	N/a
Loratadine	0/+	++	+/++
Desloratadine	0	0/+	+/++
Fexofenadine	0	0	0

0: No demonstrated potential; +: Minimal potential; ++: Moderate potential; +++: High potential.
Data extracted from various studies examining sedative [45,70-75] and anticholinergic [76-78,58] activity.

fexofenadine with known CYP 3A4 inhibitors such as erythromycin and ketoconazole has resulted in increased fexofenadine concentrations without differences in adverse events rates [23]. However, these pharmacokinetic changes are more likely owing to P-gp inhibition rather than a CYP-mediated interaction as discussed previously. It should also be noted that minimal hepatic metabolism is a distinction held by several second-generation antihistamines.

2.3 Pharmacodynamic profile

Fexofenadine shows a relatively rapid onset of action, ~ 2 h after allergen exposure. However, it is more effective when taken daily, before the onset of symptoms, rather than on an as needed basis. Because symptoms peak in the early morning owing to the circadian rhythm of AR, second-generation antihistamines dosed at night offer better control than morning administration [43]. Fexofenadine, as with other second-generation antihistamines, anchors to the H_1 receptor in several locations resulting in elongation of dissociation times and a longer duration of action than would be anticipated by its $t_{1/2}$ [41].

Fexofenadine is relatively unique among the antihistamine class in that it is a zwitterionic compound and thus contains both a positive and negative charge (a trait shared by cetirizine and levocetirizine). It is particularly hydrophilic as compared with first- and, to a lesser extent, other second-generation antihistamines and strongly resists crossing the BBB. Positron-emission tomography studies using ^{11}C-doxepin to assess CNS H_1 receptor displacement have observed high occupancy rates by first-generation antihistamines such as chlorpheniramine and ketotifen (≥ 70%), corresponding to their known sedative effects [44]. Conversely, second-generation, or nonsedating, antihistamines tend to occupy only a small proportion of CNS H_1 receptors, with significant variations between agents. Cetirizine occupies ~ 25% of cortical H_1 receptors compared to 0% with fexofenadine [45]. These findings are consistent with higher rates of sedation for cetirizine and first-generation antihistamines than for fexofenadine (**Table 2**). The lack of sedation seen with fexofenadine may be attributable to P-gp-mediated efflux given that fexofenadine is a well-known substrate of P-gp and that P-gp is found in ample supply on the epithelial lining of the BBB. One study coadministering cyclosporin A (a P-gp inhibitor) with various first- and second-generation antihistamines revealed that fexofenadine did not appreciably cross the BBB regardless of cyclosporin administration [46]. Thus, it seems unlikely that the mechanism responsible for low sedation with fexofenadine is highly correlated with P-gp efflux.

Although receptor occupancy (RO) and binding affinity have been suggested as surrogate markers for efficacy, the clinical correlation between the two is unclear. For example, RO for fexofenadine 6 h after a single dose is ~ 95% whereas it drops to 12% by 24 h [47]; however, no consistent lack of efficacy has been demonstrated at the end of the 24-h dosing interval [48-50]. In comparison with other second-generation antihistamines, fexofenadine shows a considerably reduced binding affinity [51], yet there is no consistent data suggesting that this observation translates into reduced efficacy. Thus, the use of these parameters alone is insufficient to predict clinical efficacy.

2.4 Clinical efficacy

In the US, fexofenadine is approved for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU), but not perennial AR (PAR). The literature is replete with placebo-controlled trials showing the efficacy of fexofenadine in SAR [41]; however, trial data in subjects suffering from PAR and CIU is less commonly encountered. Comparisons of fexofenadine with other second-generation antihistamines have revealed small but significant differences among agents (**Table 3**). Of the currently available agents, cetirizine/levocetirizine, desloratadine and fexofenadine seem to have roughly equivalent efficacy, exceeding that of loratadine.

Of particular interest, fexofenadine seems to have moderate efficacy at reducing nasal congestion symptoms, a somewhat surprising observation given that antihistamines are believed to be relatively ineffective in attenuating late-phase allergic responses. As discussed previously, histamine plays only a minor role in the induction of nasal congestion as compared with other inflammatory cells (e.g., eosinophils and basophils). However, an analysis of six placebo-controlled trials observed significant improvements in 12-h reflective symptom assessments of nasal congestion for all fexofenadine doses as compared with placebo [52]. Moreover, because nasal congestion severity was not used as inclusion criteria, these trials may have included subjects with absent or minimal nasal congestion and, consequently, these results may be conservative. Several individual trials have observed similar results including one study that observed significant reductions in nasal congestion with fexofenadine 120 mg/day compared with loratadine 10 mg/day [53].

2.5 Safety and tolerability

The most common adverse effects associated with fexofenadine are summarized in **Table 4** and stratified by age group. Although fexofenadine is currently approved in the US for the treatment of SAR only in persons aged ≥ 6 years, safety data exists for its use in children as young as 6 months [54]. Overall, fexofenadine is well-tolerated and discontinuation owing to side effects generally occurs in < 5% of patients. Many of the significant adverse effects associated with first-generation and early second-generation antihistamines have not been observed in pre- or post-marketing safety evaluations of fexofenadine.

Fexofenadine is the active metabolite of the second-generation antihistamine terfenadine, which has been withdrawn from the US market over concerns of cardiotoxicity, including prolongation of the QTc interval and, rarely, ventricular dysrhythmias [55]. Fexofenadine, in single doses ≤ 800 mg/day and multiple doses of 690 mg twice daily, has not been associated with any of the cardiovascular complications of its parent drug [56,57]. Additionally, fexofenadine shows no anticholinergic potential and does not bind muscarinic receptors on the heart as is the case with first-generation antihistamines and desloratadine [58]. Although most of the antihistamines are associated with some level of sedation (**Table 2**), fexofenadine (at doses ≤ 360 mg/day or 240 mg twice daily) has been consistently devoid of this adverse effect [48-50,56,59].

3. Conclusion

Fexofenadine is an effective and well-tolerated agent for patients experiencing SAR and CIU. It is unique among other H_1-antihistamines in that its potential for sedation and cognitive impairment is essentially nonexistent owing to its poor BBB penetration and lack of anticholinergic effects. Furthermore, it undergoes minimal biotransformation in the body and has few clinically significant drug–drug interactions. However, because administration with substances that inhibit or induce P-gp and/or OATP transport may significantly alter fexofenadine concentrations, patients should be appropriately monitored for safety and efficacy when combining these agents. Although numerous comparisons with other second-generation antihistamines have shown variable differences in efficacy, fexofenadine seems to have similar or greater efficacy compared to other members of the class. In addition, fexofenadine has consistently shown efficacy in reducing nasal congestion, a finding that is absent in some other second-generation antihistamines.

4. Expert opinion

Fexofenadine occupies a unique place in the current arsenal of antihistamines available in the US in that it is the only generically available second-generation agent that requires a prescription. The most recently approved agents desloratadine and levocetirizine are available as brand products only, whereas loratadine and cetirizine are available generically and without prescription. Thus, for many patients and healthcare providers alike, cost becomes a prominent factor in selecting between initial agents, particularly when no clearly efficacious benefit has been explained for any single agent. In 2007, OTC sales of Claritin® (loratadine; Schering-Plough, Kenilworth, NJ) exceeded $400 million, making it one of the most successful OTC products in the US and it is reasonable to expect that the OTC drug Zyrtec® (cetirizine; Sanofi-aventis, Bridgewater, NJ) will follow suit [60].

Although the OTC availability of these agents may reduce individual patient costs as well as healthcare system costs overall, physicians and pharmacists should continue to select initial agents based on individualized patient factors. Loratadine is an appropriate first-line agent in patients with low-to-moderate symptoms of AR but may be partially or completely ineffective in patients with more severe disease. Furthermore, loratadine may cause unwanted sedative and anticholinergic effects, albeit significantly less than other OTC first-generation antihistamines such as diphenhydramine. Cetirizine may be more effective in patients with moderate-to-severe AR, but has a greater potential for sedative effects than loratadine. Desloratadine is touted as more

Table 3. Overview of active-comparator clinical trial data for fexofenadine.

Study (indication)	Design	Dose (sample size)	Results
Van Cauwenberge *et al.* [53] (SAR)	DB, R, PC (14 days)	FEX 120 mg/day (n = 232) LOR 10 mg/day (n = 228) PCB daily (n = 225)	FEX ≈ LOR > PCB in reducing mean 24-h reflective TSS score ($p \leq 0.001$) and individual symptom scores for sneezing, rhinorrhea, itchy nose, palate or throat ($p \leq 0.05$) FEX > LOR > PCB in reducing itchy, watery or red eyes ($p \leq 0.05$) FEX > LOR ≈ PCB in reducing nasal congestion ($p \leq 0.05$)
Howarth *et al.* [48] (SAR)	DB, R, PC (14 days)	FEX 120 mg/day (n = 211) FEX 180 mg/day (n = 202) CET 10 mg/day (n = 207) PCB daily (n = 201)	FEX 120 mg ≈ FEX 180 mg ≈ CET > PCB in reducing mean 24-h reflective TSS score ($p \leq 0.0001$), instantaneous TSS at trough ($p < 0.003$) and all individual scores ($p < 0.05$)
Berger *et al.* [79] (SAR)	DB, R, PC (15 days)	FEX 180 mg/day (n = 288) DES 5 mg/day (n = 290) PCB daily (n = 144)	FEX ≈ DES > PCB in reducing instantaneous morning TSS score ($p = 0.006$ for DES, $p = 0.024$ for FEX, both versus PCB; $p = 0.491$ for comparison of FEX versus DES)
Prenner *et al.* [80] (SAR)	DB, R, X* (14 days)	FEX 60 mg twice daily (n = 328) LOR 10 mg/day (n = 331)	LOR > FEX for entire cohort in reducing mean 24-h reflective TSS score ($p = 0.019$) LOR > FEX for initial responders in reducing mean 24-h reflective TSS score ($p = 0.0037$) More nonresponders improved after crossover to LOR than to FEX ($p = 0.005$)
Horak *et al.* [49] (SAR)	DB, R, X‡ (2 days)§	FEX 120 mg daily (n=39 total) CET 10 mg daily PCB daily	FEX ≈ CET > PCB in reducing major symptom complex (sum of symptom scores for runny or itchy nose, sneezing, watery eyes) on day 1 (2 – 6 h post-dose) and day 2 (0 – 6 h post-dose) ($p < 0.05$)
Hampel *et al.* [75] (SAR)	DB, R (14 days)	FEX 180 mg/day (n = 248) CET 10 mg/day (n = 247)	FEX ≈ CET in reducing mean 24-h reflective TSS
Wilson *et al.* [81] (SAR)	DB, R, PC, X§ (14 days)	FEX 180 mg/day (n = 49 total) DES 5 mg/day PCB daily	FEX ≈ DES > PCB in reducing peak nasal inspiratory flow, nasal blockage, nasal irritation and total nasal symptoms ($p < 0.05$) FEX ≈ DES ≈ PCB in controlling nasal discharge or eye symptoms
Lee *et al.* [82] (PAR)	DB, R, PC, X§ (single-dose study)	FEX 180 mg/day (n = 16 total) DES 5 mg/day LEV 5 mg/day PCB daily	FEX ≈ DES ≈ LEV > PCB in reducing peak nasal inspiratory flow ($p < 0.05$ for all comparisons to PCB)
Handa *et al.* [83] (CIU)	DB, R (28 days)	FEX 180 mg (n = 45) CET 10 mg (n = 52)	CET > FEX for complete symptom resolution (experienced in 51.9 versus 4.4%, respectively; $p = 0.00001$)

*Crossover treatment in nonresponders to initial study drug only; ‡Three-way crossover in which patients received all study medications; §Each drug study period followed by ≥ 7-day washout period.

CET: Cetirizine; CIU: Chronic idiopathic urticaria; DB: Double-blind; DES: Desloratadine; FEX: Fexofenadine; LEV: Levocetirizine; LOR: Loratadine; PAR: Perennial allergic rhinitis; PC: Placebo-controlled; PCB: Placebo; R: Randomized; SAR: Seasonal allergic rhinitis; TSS: Total symptom score; X: Crossover.

Table 4. Most common adverse effects of fexofenadine stratified by age group.

Adverse effect	Percentage of patients experiencing adverse effects		
	Fexofenadine		**Placebo**
Adolescents and adults (≥ 12 years) [21]	60 mg twice daily (n = 679)		Twice daily (n = 671)
Viral infection	2.5		1.5
Nausea	1.6		1.5
Dysmenorrhea	1.5		0.3
Older children (6 – 11 years) [84]	30 mg twice daily (n = 673)		Twice daily (n = 700)
Headache	5.8		4.3
Upper respiratory infection	2.1		1.3
Worsening cough	1.6		0.9
Young children (2 – 5 years) [85]	30 mg twice daily (n = 222)		Twice daily (n = 231)
Pyrexia	5.9		5.6
Vomiting	5.0		4.8
Worsening cough	4.5		3.0
Very young children (6 months to 2 years) [54]	15 mg twice daily (n = 85)	30 mg twice daily (n = 108)	Twice daily (n = 199)
Vomiting	14.1	5.6	13.6
Diarrhea	4.7	5.6	2.0
Worsening cough	2.4	3.7	4.0

effective than loratadine owing to its increased binding affinity for the H_1 receptor, but there are no significant clinical trial data to substantiate this claim. Moreover, there are no clinical data to suggest that it is any more efficacious than fexofenadine, cetirizine or levocetirizine. Although it seems to have a lower potential than loratadine, desloratadine may cause sedation at supratherapeutic doses as well as anticholinergic effects at approved doses. It is not available generically and many patients and insurance providers will prefer less expensive alternatives. Levocetirizine offers similar efficacy to cetirizine with a reduced sedative potential; however, similar to desloratadine, it is not currently available in generic form. Thus, fexofenadine may offer the greatest balance of efficacy, safety and cost, particularly in patients with moderate-to-severe allergic disorders with or without nasal congestion and in those with contraindications to other antihistamines or alternative drug classes used to treat allergic disorders.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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