DOI: 10.1111/j.1468-3083.2011.04185.x JEADV

REVIEW ARTICLE

Pharmacological rationale for the treatment of chronic urticaria with second-generation non-sedating antihistamines at higher-than-standard doses

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Abstract

Chronic urticaria (CU) is a long-lasting and distressing condition that impairs patient quality of life (QoL) by disrupting sleep and diminishing work/school productivity. Thus treatment should not only be safe and effective but also not add to this impairment or increase risks to health or safety. Non-sedating second-generation antihistamines, with their long duration of action, pharmacodynamic properties that allow once-daily dosing and lack of drug–drug interactions and sedative effects, are the first-line symptomatic treatment option, but some patients have no adequate response to standard doses of these medications. Other therapeutic approaches to refractory urticaria have been suggested but have been limited by sparse clinical data and/or significant adverse effect profiles. Although discouraged by treatment guidelines, sedating antihistamines are frequently prescribed for nighttime use when urticaria symptoms are severe as add-on therapy to a non-sedating antihistamine. However, their pronounced effects on rapid eye movement sleep and hangover negatively impact QoL, learning and performance, and limit their use for patients in occupations that require alertness. For patients who do not respond adequately to standard doses of non-sedating second-generation antihistamines, increasing the dose of non-sedating antihistamines thus may represent the safest therapeutic approach. Given the fact that only few controlled studies have assessed the efficacy and safety of high-dose non-sedating antihistamines in CU, patient safety should be a key consideration when choosing a specific antihistamine.

Received: 8 November 2010; Accepted: 29 June 2011

Conflict of interest

The author has received industry consulting and research grants from the following companies: Ansell Healthcare, Bayer Schering Pharma, DST, Fujisawa Pharmaceuticals, Hal Allergenen Laboratorium BV, Henkel, Kryolan GmbH, Leti Pharma GmbH, Merck, Sharp & Dohme Corp, Novartis, Procter & Gamble, Sanofi-Aventis, Schering-Plough Corp, Stallergenes, and UCB Pharma.

Funding sources

Medical writing and editorial assistance was provided by Sandra Westra, PharmD, Karl Torbey, MD, and Patricia C. Abramo of AdelphiEden Health Communications, New York, New York. This assistance was funded by Merck Sharp & Dohme Corp. The author received no honorarium or payment for authorship of this review.

Introduction

Chronic urticaria (CU) is characterized by the recurrence of transitory cutaneous weals accompanied by redness, itching and, frequently, angio-oedema, with each episode lasting ≥6 weeks.[1] The debilitating, uncomfortable symptoms of CU cause marked impairment of quality of life (QoL). Patients with CU attribute sleep disturbances, social isolation, altered emotions and difficulties with activities of daily living to their disease.[2] Moreover, significantly ($P \leq 0.05$) greater impairment on QoL has been reported on measures of physical functioning, bodily pain, general health and emotional well-being in patients with CU than in healthy controls or individuals with respiratory allergies.[3]

Current treatment for CU is directed at reducing intensity of itching and decreasing number and extent of weals. CU management guidelines recommend non-sedating second-generation antihistamines as first-line treatment.[4,5] However, CU remains a difficult condition to treat and alternative approaches are required for those patients who do not respond adequately to standard doses of non-sedating second-generation antihistamines.[4,5] Patient safety is a key consideration in evaluating alternative treatment

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options. Care must be taken to avoid therapies that inadvertently worsen patient QoL or increase health or safety risks.

This review examines the pharmacological rationale for the treatment of CU with higher-than-indicated doses of second-generation antihistamines in patients who do not respond to indicated doses, with an emphasis on safety considerations of increased dosing.

Methodology

A comprehensive Medline literature search was conducted for the following terms, alone or in combination: *urticaria, CU, antihistamines, histamine, histamine receptors, second-generation antihistamines* (including *cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine* or *rupatadine*), *updosing, uptitrating, safety* and *tolerability*. The search found articles reporting results from placebo-controlled clinical trials and observational studies from 1980 to current in patients who had treatable or refractory CU treated with antihistamines. The reference lists of the resulting articles and from urticaria treatment guidelines were also consulted. Studies of refractory urticaria treated with higher-than-standard second-generation antihistamines were included in this review.

Pathogenesis of CU

The primary trigger in the pathogenesis of urticaria is dermal mast cell degranulation with release of histamine and other preformed inflammatory mediators from cytoplasmic granules.[6] The resulting chronic urticarial weal involves oedema of the upper and mid dermis, with associated pruritus, upregulation of endothelial adhesion molecules and an inflammatory perivascular infiltrate consisting of neutrophils and/or eosinophils, macrophages and T cells in the affected skin.[1] The role of histamine in CU is well established, exerting its effects via activation of H_1-receptors on endothelial cells and sensory nerves, resulting in weal formation, neurogenic flare and pruritus.[5] Some patients develop CU symptoms in response to physical factors such as cold, sun or pressure (i.e. physical urticarias). Evidence suggests an autoimmune aetiology in approximately 45% of patients with spontaneous CU, whereas the aetiology remains unknown in the remaining 55%.[6–8]

First-line treatment options

Non-sedating second-generation antihistamines are recommended for first-line treatment of CU.[4,5] These agents have a long duration of action, pharmacodynamic properties that allow for once-daily dosing and mostly lack the drug–drug interactions and sedative effects associated with first-generation antihistamines.[5] The efficacy of standard doses of second-generation antihistamines in CU has been well documented in randomized, placebo-controlled clinical trials of 4–6 weeks' duration (Table 1).[9–16]

Limited comparator data are available that suggest variations in response to therapeutic effects among second-generation antihistamines in CU. A randomized, double-blind study of 116 CU patients comparing cetirizine (10 mg) with fexofenadine (180 mg) showed that a significantly ($P = 0.00001$) higher proportion of patients responded with clearance of symptoms with cetirizine (52%) than with fexofenadine (4%) after 1 month of treatment.[17] In a placebo-controlled study of 116 patients, loratadine (10 mg) showed a more rapid effect ($P < 0.01$ at Day 3) in improving CU symptoms compared with cetirizine (10 mg) and placebo.[9] In addition, a higher proportion of patients was symptom-free (63%) with loratadine compared with cetirizine (45%) and placebo (13%) ($P < 0.05$). In a 4-week placebo-controlled study of 247 CIU patients, mizolastine (10 mg) and loratadine (10 mg) showed superior efficacy vs. placebo ($P = 0.0061$ and 0.0221, respectively) and comparable tolerability vs. placebo.[10]

Alternative approaches for the unresponsive patient

Despite proven efficacy of second-generation antihistamines in CU, some patients do not achieve adequate response with indicated doses. Across a number of clinical trials of antihistamines at standard doses, 4–56% of patients showed complete response to treatment.[11,13,16] An Internet survey conducted in Europe revealed that itching and physical discomfort remained inadequately addressed in 68% of respondents and sleep disturbances from CU remained inadequately addressed in 48%.[18] Among all respondents, 78% were taking prescription or over-the-counter medications.

Treatment for patients with refractory disease remains a challenge in the management of CU. Evidence-based recommendations are lacking owing to inconclusive data for treatment of this patient population. A number of approaches to treat CU unresponsive to standard doses of second-generation antihistamines have been adopted.[5]

Sedating antihistamines

Sedating, first-generation antihistamines have been used as adjunctive therapy for patients whose symptoms have not been completely controlled with non-sedating second-generation antihistamines, particularly when symptoms interfere with sleep at night.[19] However, these agents have pronounced anticholinergic effects and central nervous system (CNS) sedative actions, and can impair QoL, learning and performance.[5] Functional impairment occurs even at the lowest recommended doses of first-generation antihistamines and is similar to that produced by alcohol or other CNS depressants.[20] Moreover, when taken at night, the first-generation antihistamines chlorphenamine, diphenhydramine and promethazine were found to alter rapid eye movement sleep, delaying its onset and reducing its duration.[20] Residual effects such as impairment in divided attention, vigilance, working memory and sensory-motor performance and reduced latency to daytime sleep have also been reported the following morning, creating a potentially dangerous hangover effect.

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Table 1 Randomized, placebo-controlled trials of standard doses of second-generation antihistamines for chronic urticaria*

Study (*N*)	Duration (week)	Daily dosage	Efficacy variables (at study end)						
			Reduction in pruritus severity	Reduction in number of weals	Investigator-rated global assessment	Reduction in urticarial episodes	Reduction in size of weals	Reduction in total symptom score	Improvement in DLQI score
Guerra 1994[9] (116)	4	LOR 10 mg CET 10 mg PBO	— —	— —	$P < 0.01$ — 63%, 45%, and 13% of LOR, CET, and PBO patients, respectively, had complete resolution of symptoms	— —	— —	— —	— —
Dubertret 1999[10] (247)	4	LOR 10 mg MIZ 10 mg PBO	$P = 0.0265$ $P = 0.0065$	— —	— —	$P = 0.0221$ $P = 0.0061$†	— —	$P = 0.0064$ $P = 0.0096$	— —
Breneman 1996[11] (188)	4	CET 10 mg HYD 25 mg t.d.s. PBO	$P < 0.04$ $P < 0.04$	$P < 0.04$ $P < 0.04$	$P < 0.001$ $P < 0.001$	$P = 0.002$‡ $P = 0.001$	$P < 0.04$ $P < 0.04$	— —	— —
Ortonne 2007[12] (137)	6	DL 5 mg PBO	$P < 0.001$ (at day 14)	$P \leq 0.016$	$P < 0.001$ (at day 42)	—	$P \leq 0.009$	—	—
Kaplan 2005[13] (255)	4	FEX 180 mg PBO	$P < 0.001$	$P < 0.001$	$P < 0.001$ 13% and 8.8% of FEX and PBO patients, respectively, had complete resolution of symptoms	—	—	$P < 0.001$	—
Nettis 2006[14] (106)	6	LEV 5 mg PBO	$P < 0.05$	$P < 0.05$	—	$P < 0.05$	$P < 0.05$	53% of LEV patients had total disappearance of symptoms vs. 0% of placebo patients	—
Brostoff 1996[15] (56)	4	MIZ 10 mg PBO	$P = 0.004$	—	$P < 0.001$	—	—	$P = 0.002$	—
Gimenez-Arnau 2007[16] (333)	4	RUP 10 mg RUP 20 mg PBO	$P < 0.005$ $P < 0.0001$	$P < 0.05$ —	— —	— —	— —	$P < 0.005$ $P < 0.0001$	— 26.6% vs. 18.4%

*P values are vs. placebo, except where indicated.

†After 2 weeks; end-of-study P values not available for this measure.

‡vs. placebo and hydroxyzine.

CET, cetirizine; DL, desloratadine; DLQI, Dermatology Life Quality Index; FEX, fexofenadine; HYD, hydroxyzine; LEV, levocetirizine; LOR, loratadine; MIZ, mizolastine; PBO, placebo; RUP, rupatadine; t.d.s., three times daily.

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Patients do not necessarily develop tolerance to the somnolence and psychomotor impairment induced by first-generation antihistamines.[21] The negative consequences of not developing tolerance can still be serious because patients may also misjudge the effects of these agents, just as patients report not feeling impaired after alcohol intake although objective measurements show that they are.[21] A perhaps underappreciated consequence of this is the association of sedating antihistamines with aviation and motor vehicle accidents.[20] When taken in large doses, brompheniramine, diphenhydramine and promethazine may be associated with a prolonged QTc and cardiac arrhythmias.[20]

Combination therapy with antihistamines

Clinical studies have demonstrated additional benefits by combining an H_1-antihistamine with an H_2-antihistamine compared with H_1-antihistamine monotherapy.[22,23] Activated H_2-receptors in cutaneous blood vessels cause vasodilation that manifests in the skin as flushing and erythema.[24]

Analysis of the effects of H_1- and H_2-antihistamines shows that combinations of agents with common liver metabolism exhibit greater efficacy than those with distinct metabolic pathways.[22] In one study, cimetidine 300 mg/4 × day significantly ($P < 0.05$) increased mean plasma concentrations of loratadine 10 mg/day taken over 10 days.[25] Cimetidine inhibits cytochrome P450 enzymes, which are responsible for loratadine metabolism.[26] However, mean plasma concentrations of a 10-mg dose of cetirizine, which is excreted through the kidneys, were not altered when administered with cimetidine 600 mg.[27] These findings suggest that the potential benefit of combination therapy is likely pharmacokinetic in nature, because of an increase in the area under the plasma drug concentration-time curve and subsequent increased effects at the H_1-receptor, rather than being a genuine synergistic effect.[28]

Alternative combinations, such as combining sedating and non-sedating H_1-antihistamines or combining two different non-sedating H_1-antihistamines, may also result in increased plasma concentrations of the H_1-antagonist. Consideration must be given to the possibility of increased side-effects with all such combinations, because of unique side-effect profiles of the different agents.

Antileucotrienes

Although their role in CU is not well defined, findings from clinical studies have suggested that the combination of antihistamines with antileucotrienes may offer benefits in a subgroup of patients with CU.[29,30] However, little evidence exists to demonstrate that antileucotrienes are efficacious as monotherapy for CU.[4,31]

Immunosuppressive agents

Unlicensed oral drug treatments include immunosuppressive drugs such as cyclosporin A and corticosteroids. Two small studies showed that cyclosporine at daily dosages of 4 or 5 mg/kg is effective for CIU non-responsive to standard doses of non-sedating antihistamines.[32,33] A randomized, double-blind study in 99 patients with refractory CIU also demonstrated efficacy of cyclosporine added to cetirizine.[34] As a result of a high incidence of adverse effects, current guidelines recommend cyclosporine only for patients with severe disease refractory to any dose of antihistamine.[5]

A short course of corticosteroids may be appropriate for acute exacerbations of antihistamine-resistant CU.[4] However, corticosteroids are not recommended for long-term treatment because of risk for severe adverse effects (e.g. peptic ulcer, infection, diabetes, cataracts, hypertension and osteoporosis).[19]

Other treatment options

Limited clinical data exist on additional treatments for CU uncontrolled by first- and second-line therapies. Published reports consist of small open-label studies or case reports. Thus, large, well-designed, controlled trials are needed to determine where these third- or fourth-line treatments fit in the armamentarium of refractory CU therapy.

Dapsone, a sulfone derivative with antibacterial and anti-inflammatory properties, improved refractory CU symptoms in three small, 12-week, open-label studies.[35–37] Most patients in these studies reported complete/partial resolution of CU symptoms after treatment with oral dapsone 25–100 mg/day ≤3 months. Dapsone was well tolerated[35–37] but has been associated with dose-related anaemia, peripheral neuropathy, rash and gastrointestinal complaints.[38] In rare instances, methemoglobinemia, blood dyscrasias and dapsone hypersensitivity syndrome have been reported.

The immunosuppressive agent mycophenolate, investigated in a small, open-label, uncontrolled trial of nine CU patients with poor response to antihistamines and/or corticosteroids, found significant reduction in pruritus and weal scores after 6 weeks of mycophenolate 1000 mg three times daily ($P < 0.002$ and 0.004, respectively).[39] Mycophenolate use is associated with gastrointestinal complaints and, rarely, leucopenia, anaemia and dose-dependent immune suppression-related infections.[38]

Anticoagulants and antifibrinolytics may also provide symptom relief in patients with CU unresponsive to antihistamines.[40,41] Clinical investigation indicates that CU patients often present with elevation of coagulation and fibrinolysis markers and that these markers may correlate with disease severity.[42] However, caution must be used when prescribing these agents because haemorrhagic complications and osteoporosis (with heparin) may occur. Rare instances of skin necrosis, cholesterol embolization, hepatotoxicity and heparin-induced thrombocytopenia have also been reported with anticoagulants.[43]

The mechanism by which the antimetabolite methotrexate improves CU symptoms remains speculative, although it may contribute by inhibiting or altering cytokine and chemokine activity.[44] Methotrexate may provide a steroid-sparing regimen for patients with antihistamine-resistant CU responsive to corticosteroids.[44]

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Methotrexate has been associated with gastrointestinal complaints, stomatitis, marrow suppression, rash, hepatotoxicity, alopecia and infections.[38]

Small, open-label studies suggest that the monoclonal antibody omalizumab, used to treat allergic asthma, may also be effective in the treatment of refractory CU.[45,46] Commonly reported adverse events include arthralgia, general pain, arm pain, leg pain, fatigue, dizziness, fracture, pruritus, dermatitis and earache. Malignancies have also been observed in clinical studies.[47]

Second-generation antihistamines at higher-than-standard doses

The European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA^{2}LEN/EDF/WAO) guidelines state that before considering alternative treatment, a trial of second-generation antihistamines at doses up to four times indicated is warranted.[5] Similarly, the British Association of Dermatologists guidelines highlight that it has become common practice to increase the dose of second-generation antihistamines above the standard dose range for patients who do not respond to standard doses, when the potential benefits outweigh any risks.[4] Given the low toxicity of the newer, non-sedating second-generation antihistamines, this approach represents a logical next treatment step in CU management vs. switching to or adding an alternative medication.

Data from several dose-ranging studies in patients with CIU suggest that the effects of non-sedating second-generation antihistamines are dose dependent.[48,49] Two 4-week, double-blind, placebo-controlled trials have assessed a range of doses of fexofenadine (20, 60, 120 and 240 mg three times daily) for treatment of CIU symptoms in patients (N = 418 and 439) with moderate to severe pruritus.[48,49] Both studies demonstrated a significant linear trend for improvement in pruritus score and number of weals (Fig. 1a,b) as the dose of fexofenadine increased. Fexofenadine-treated patients also experienced less interference with sleep and daily activities because of urticaria compared with those receiving placebo, with a significant linear trend for improvement in these end points with increasing fexofenadine dose (Fig. 1c).

In an analysis of pooled data (N = 538) from two randomized, double-blind, placebo-controlled, multicentre studies of CU patients treated with rupatadine 10 or 20 mg daily, responder rates were defined as the percentage of patients who exhibited symptom reduction of at least 50% or 75% compared with baseline after 4 weeks of treatment.[50] Treatment with rupatadine at both dosages was significantly more efficacious than placebo and the 20-mg dose resulted in higher percentages of patients with ≥75% symptom reduction compared with the 10-mg dose for all three variables assessed (Fig. 2a–c).

To date, there are limited controlled studies examining the efficacy of updosing with non-sedating antihistamines in CU. One double-blind study was conducted in 80 patients with difficult-to-treat CU randomized to receive levocetirizine or desloratadine 5 mg/day for 1 week; patients who did not achieve symptom relief received 10 mg then 20 mg of the drug daily during the second and third weeks, respectively.[51] Approximately 75% of patients receiving either drug showed increased benefit with the 10- or 20-mg doses. The proportions of high-dose responders reporting

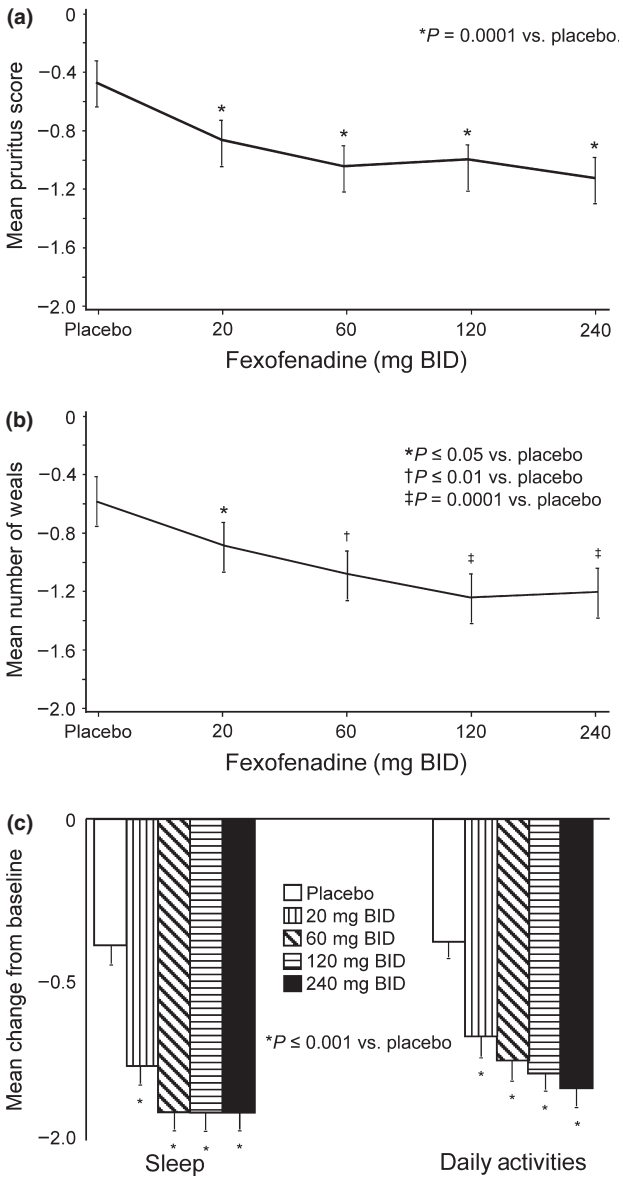

Figure 1 Linear trend for improvement in (a) mean pruritus score, (b) mean number of weals and (c) sleep and daily activity interference with increasing fexofenadine dosages for chronic urticaria. Reprinted from *J Clin Allergy Immunol*, 104/5, Finn AF Jr, Kalpan AP, Fretwell R, *et al.*, A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria, 1071–1078. Copyright 1999, with permission from Elsevier.[48]

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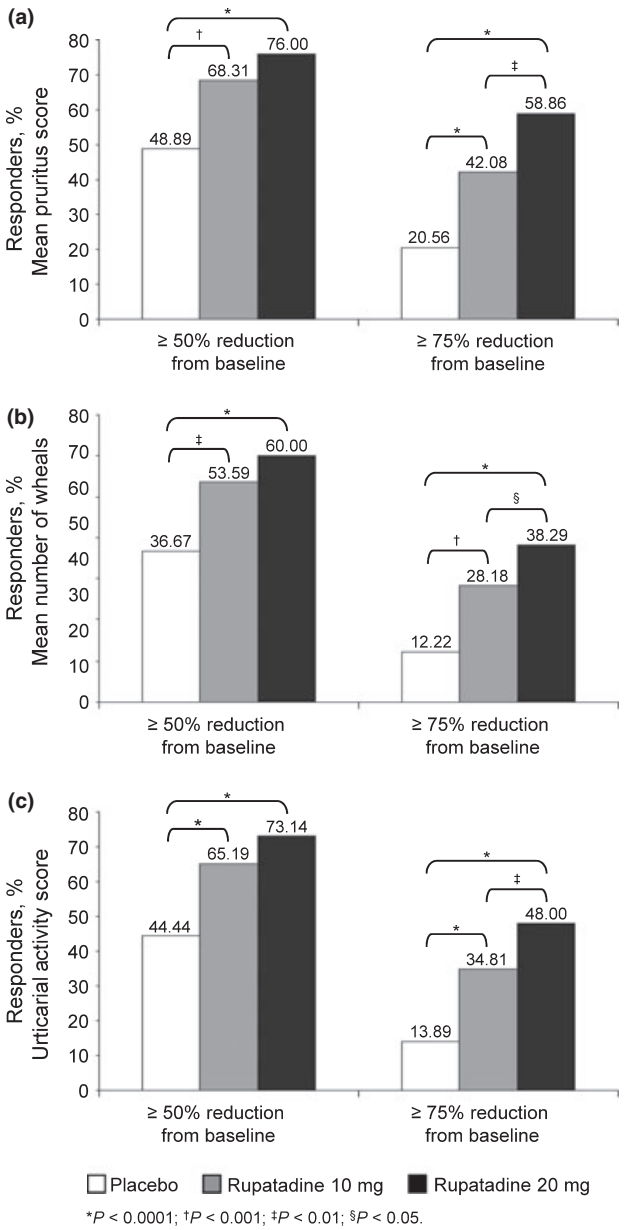

Figure 2 Percentage of patients obtaining a ≥50% and 75% improvement in (a) MPS, (b) MNW and (c) mean UAS after 4 weeks' treatment with rupatadine 10 or 20 mg vs. placebo. MNW, mean number of weals; MPS, mean pruritus score; UAS, urticaria activity score. Reprinted with permission from Gimenez-Arnau.[50]

>50% improvement in discomfort were 41%, 56% and 63% with 5, 10 and 20 mg desloratadine, respectively, and 52%, 65% and 74%, respectively, with similar doses of levocetirizine. The proportions of high-dose responders reporting >50% improvement in QoL were 24%, 45% and 55% with 5, 10 and 20 mg desloratadine, respectively, and 59%, 74% and 81%, respectively, with similar doses of levocetirizine. The differences between the two agents were statistically significant ($P < 0.003$ for discomfort improvement; $P < 0.013$ for QoL). The investigators concluded that increasing second-generation antihistamine doses up to 4-fold relieves CU symptoms without compromising safety in approximately 75% of patients with CU.

These results are supported by an open-label study in 21 patients with CIU who responded poorly to cetirizine 10 mg/day during a 1- to 2-week screening period and then were randomized to group A (cetirizine 20 mg/day for 2–4 weeks) or group B (cetirizine 20 mg/day for 1–2 weeks followed by cetirizine 10 mg/day for 1–2 weeks).[52] Urticarial activity scores improved in both groups during the first 1- to 2-week period compared with screening period scores ($P < 0.01$). During the second period, scores worsened among group B patients, for whom the cetirizine dose was titrated down to 10 mg, while scores improved further among group A patients who continued the higher dosage of 20 mg.

In contrast to these observations, a small, prospective case series suggested that cetirizine did not provide any further benefits at high doses. Asero *et al.*[53] examined 22 adult patients with moderate/severe CU treated with cetirizine at the licensed dose (10 mg/day) during the first week of the study, followed by a 3-fold increased dose (10 mg × 3/day) during week 2. Only one patient showed a satisfactory response to the increased dose of cetirizine, with the remaining subjects requiring alternative treatments (steroids, cyclosporine or immunosuppressants) to control their disease.

The effects of high-dose desloratadine have also been examined in patients with acquired cold urticaria. A total of 30 patients were treated with desloratadine 5 mg/day, 20 mg/day or placebo for 7 days in a double-blind, three-way crossover trial.[54] Both desloratadine doses were well tolerated, reduced cold-induced weal volume and resulted in significant improvements in critical temperature thresholds (CTTs) and critical stimulation time thresholds compared with placebo (Table 2); desloratadine 20 mg/day, however, performed significantly better than the standard dosage of 5 mg/day.

Potential anti-inflammatory effects of second-generation antihistamines demonstrated by *in vitro* findings may provide an explanation for the effects of antihistamines at high doses.[55,56] Preclinical studies have shown that antihistamines can inhibit a number of mediators besides histamine, including leucotrienes, prostaglandins, thromboxanes, platelet-activation factor, bradykinin, tachykinins, cytokines, chemokines and adhesion molecules involved in systemic allergic inflammation important in the pathogenesis of urticaria.[55,56] Some of the antiallergic effects may be explained by mast-cell stabilizing properties.[55,56] These non-histamine-mediated effects express a different dose-response curve than the antihistamine response for which these drugs were originally developed and on which the regular dose was defined. Clinical findings in urticaria underline this hypothesis and

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Table 2 Weal volume and cold provocation thresholds after treatment with desloratadine standard dose (5 mg/day) or high dose (20 mg/day) for acquired cold urticaria.[63]

	Weal volume (mm^3)*	CTT (°C)	CSTT (min)
Placebo (SD)	1064.55 (1200.72)	20.47 (5.30)	1.20 (1.18)
Desloratadine 5 mg (SD)	461.91 (787.21)	15.17 (7.74)*	2.38 (2.19)‡
Desloratadine 20 mg (SD)	158.16 (376.41) $P < 0.001$ vs. 5 mg	10.83 (9.03)*,† $P \leq 0.01$ vs. 5 mg	3.87 (2.33)†,§ $P < 0.001$ vs. 5 mg

*Mean weal volume area under curve over 90 min after cold provocation after treatment.

†$P < 0.001$ vs. placebo.

‡$P \leq 0.01$ vs. desloratadine 5 mg.

§$P < 0.001$ vs. desloratadine 5 mg.

CSTT, critical stimulation time; CTT, critical temperature threshold; SD, standard deviation.

updosing may also be an interesting possibility for treating other allergic conditions where inflammatory mechanisms apart from mast-cell histamine release are involved. However, more research is needed in this area.

Safety of high-dose second-generation antihistamines

In the absence of extensive data on dose escalation of second-generation antihistamines in CU, it is important that physicians are familiar with dosing and adverse effects of treatments. The potential for increased adverse effects, therefore, is a key consideration in antihistamine choice. Of particular concern are somnolence and impairment of CNS and psychomotor function. As a result of their histamine blockade at H_1-receptors in the CNS, first-generation sedating antihistamines frequently cause somnolence or other CNS adverse effects. Non-sedating second-generation antihistamines are favoured over first-generation agents because of their reduced propensity to cross the blood-brain barrier and to cause CNS side-effects.[5] One potential mechanism for the limited CNS exposure with non-sedating second-generation antihistamines is the P-glycoprotein (P-gp)–mediated efflux system.[57] P-gp, which is coded by human *MDR1* (multidrug resistance) gene, is an energy-dependent efflux pump that exports its substrates out of the cell. P-gp is expressed in tumour cells and in a broad variety of normal tissues with excretory function (small intestine, liver and kidney) and at blood-tissue barriers (blood-brain barrier, blood-testes barrier and placenta).[57]

Results from knockout animal studies have shown that second-generation antihistamines with little or no sedative effect—desloratadine, loratadine and cetirizine—are P-gp substrates, whereas the sedating antihistamines—diphenhydramine, hydroxyzine and triprolidine—are not. The affinity of non-sedating antihistamines for P-gp at the blood-brain barrier may explain the lack of CNS side-effects of second-generation H_1-antihistamines.[58]

Although second-generation antihistamines as a class are often considered to be comparable in terms of safety, they are a heterogeneous group of compounds with safety characteristics that differ from one molecule to another. Studies have evaluated the differing extent of sedative effects across the second-generation antihistamines. These studies have used a variety of assessment parameters, including central H_1-receptor occupancy analysis, on-the-road driving tests, psychomotor tests and subjective sedation assessments.[59–62] Findings from additional studies have been summarized in Table 3.[63]

Table 3 Central nervous system effects of desloratadine, fexofenadine and levocetirizine. Reprinted with permission from Devillier 2008[63]

Effect	Desloratadine	Fexofenadine	Levocetirizine
Somnolence (%)	0.7	0	2.1–6.8
Drowsiness/sedation (%)	0.1	ND	0.4
Cognitive or psychomotor impairment	No impairment of driving performance No sedative or performance-impairing effects No difference from placebo in somnolence, wakefulness and psychomotor performance No potentiation of alcohol-induced performance impairment	No sedation or impairment of psychomotor performance No impairment of driving performance or aspects of psychomotor and cognitive function, even when combined with a dose of alcohol equivalent to 0.3 g/kg of bodyweight	Both the US and the EU labels recommend that patients who wish to operate machinery, drive or engage in possibly hazardous activities take their response to levocetirizine into account before taking the drug, as some people experience fatigue, asthenia or somnolence Some studies report a lack of significant impairment of driving performance, psychomotor and cognitive function or memory and psychomotor performance

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Clinicians often ask, 'Is updosing single non-sedating second-generation antihistamines safer than combining multiple non-sedating antihistamines?' This cannot be clearly answered because studies are lacking. However, as a general principle, it is safer to increase one drug of a class, as is done in hypertension, because there is clearly a single pharmacological profile. Moreover, safety studies have only looked at the updosing of monotherapies.

Demonstration of the correlation between cognitive decline and brain H_1-receptor occupancy has led to the use of positron emission tomography (PET) studies with [11C]doxepin as a tool to measure histamine H_1-receptor occupancy in the brain. Using this parameter, Tashiro *et al.*[59] have shown that histamine H_1-receptor occupancy in the brain is negligible with fexofenadine 120 mg (−0.1%) but moderately high with cetirizine 20 mg (26.0%).

A study in healthy volunteers found greater impairment in objective cognitive and psychomotor performance tests with hydroxyzine 25 mg, cetirizine 10 mg or rupatadine 20 mg with alcohol compared with alcohol alone. At a lower dose of 10 mg, rupatadine in combination with alcohol did not increase objective impairment compared with alcohol alone.[60] These findings suggest a dose-response effect on impairment with the combination of rupatadine and alcohol.

In an animal study, Gupta *et al.*[61] analysed the time course of H_1-receptor occupancy of levocetirizine in the periphery and the brain using two dose levels of levocetirizine—one comparable with the human therapeutic dose of cetirizine (0.1 mg kg^{-1}) and the other at a 10-fold higher dose. At the low dose of levocetirizine, H_1-receptor occupancy in the brain was <20%, whereas with the higher dose, brain H_1-receptor occupancy ranged from 50% to 70% during 8 h post-dosing, indicating the potential for central side-effects. Although this concentration is higher than the 4-fold increase recommended for treatment of CU in patients non-responsive at standard doses, these findings suggest a dose response for adverse effects.

Several studies have examined the sedative effects of fexofenadine and desloratadine at high doses. In a double-blind, placebo-controlled study in healthy volunteers, Hindmarch *et al.*[62] examined the effects of high-dose fexofenadine (360 mg) on the CNS. Fexofenadine was found to be indistinguishable from placebo in disruptive effects on aspects of psychomotor and cognitive function. Fexofenadine did not significantly affect brake reaction time at doses of 120 mg vs. hydroxyzine 30 mg or placebo in healthy volunteers while driving or who were driving while completing simple or complex calculations or while operating cellular phones.[64] In a 6-way crossover, double-blind study of fexofenadine, loratadine and promethazine, fexofenadine 80–180 mg was not significantly different from placebo in cognitive function or psychomotor function at 1.5, 3, 6, 9, 12 and 24 h post-dose.[65] Loratadine 10 mg did not significantly impair cognitive function; by contrast, promethazine caused significant impairment.

In a randomized, two-way crossover, placebo-controlled trial, treatment with desloratadine 45 mg once daily (nine times the standard dose) for 10 days in 24 healthy adults (age range, 20–48 years) was not associated with prolonged QTc interval or other cardiovascular effects.[66] There were no changes in QTc interval >6.5% from baseline at Day 10; maximum QTc intervals observed were similar between desloratadine and placebo (433 vs. 429 ms, respectively). The difference from baseline in ventricular heart rate (9.4 bpm) was significantly higher with desloratadine vs. placebo (no *P* value reported); however, this difference was not clinically concerning. No pathological changes in electrocardiograms were observed in an active-comparator–controlled study of levocetirizine or desloratadine at conventional doses or at doses of 10 or 20 mg increased weekly in 80 patients aged 19–67 years with CU.[51]

Conclusions

Modern non-sedating antihistamines are the first-line symptomatic treatment option; however, some patients do not have an adequate response to standard doses of these medications. Current data provide convincing evidence to support a dose escalation approach up to 4-fold as suggested by the guidelines with a single non-sedating H_1-antihistamine.

For patients who do not respond adequately to standard doses of non-sedating second-generation antihistamines, increasing the dose of these agents is likely to represent the safest therapeutic approach. There is a need for clear guidance on which antihistamines to use, appropriate dosing regimens, and the likely response. Given the lack of controlled studies assessing the efficacy and safety of high-dose non-sedating antihistamines in CU, patient safety should be a key consideration when choosing a specific antihistamine. Additional well-controlled, well-designed clinical trials in CU are required to clarify which non-sedating antihistamines should be used, in what dose, and for how long, when CU does not respond to standard therapy.

Clinical recommendations regarding the use of first-generation antihistamines, increased dosages of second-generation antihistamines, and third- and fourth-line alternatives for CU are based on incomplete and inconsistent data. Ideally, conclusions about their use should be restricted to those agents for which there is specific evidence. Where data are limited or do not exist, the prescribing clinician should make thoughtful and responsible prescribing selections.

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