

EXPERT OPINION

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Pharmacotherapy of chronic spontaneous urticaria

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Introduction: Urticaria, by definition, is a disease presenting with wheals, angioedema or both. In patients with recurrent angioedema without wheals, urticaria needs to be distinguished from bradykinin-mediated angioedema, for example, hereditary angioedema or ACE inhibitor-induced angioedema.

Areas covered: Urticaria is comprised of acute and chronic forms. The latter group of chronic urticaria has many different subtypes needing partly different therapeutic approaches. However, all therapeutic approaches for symptomatic treatment center on reducing mast cell-mediator-release and preventing its effect.

Expert opinion: The current guidelines recommend non-sedating, second generation H1-antihistamines (nsAHs) as the first-line treatment. If needed, nsAHs are to be used at higher doses (up to fourfold the standard dose), and Omalizumab, Montelukast or Cyclosporin A (not in preferred order) are recommended as third-line options. Many alternative treatments have been reported but not tested in randomized controlled trials. These include among others dapsone, H2-antihistamines, anticoagulants and methotrexate. Some therapies should no longer be used according to current guidelines, since studies have shown their inefficacy or because new safety concerns have emerged. This mainly refers to the formally propagated use of sedating antihistamines at night, which change REM-sleeping-patterns and learning curves and have been shown in head-to-head trials to not be superior in efficacy to non-sedating antihistamines.

Keywords: antihistamines, anti-IgE, omalizumab, urticaria

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1. Definition and classification of urticaria

Urticaria is defined by the appearance of wheals, angioedema or both. Urticaria symptoms are brought about by the release of histamine and other mediators from activated mast cells of the skin. However, wheals or angioedema can also occur due to non-mast-cell-derived mediators such as bradykinin (hereditary angioedema) or IL-1 (Muckle-Wells Syndrome or Schnitzler Syndrome). These conditions need to be considered in patients with recurrent angioedema without wheals and in patients with wheals but without angioedema, respectively.

As per the definition given above, urticaria is a disease or group of diseases must not be seen synonymously with 'occurrence of wheals', is histamine-mediated wheals can co-occur with other conditions such as anaphylaxis that are not urticaria.

Urticaria is classified according to its course: acute urticaria is defined as the appearance of wheals and/or angioedema for < 6 weeks, whereas chronic urticaria subtypes show persistence of symptoms for longer than 6 weeks. Urticaria is further subclassified as spontaneous and inducible, depending on whether symptoms occur unprompted or only in response to specific triggers.

Table 1 shows the current classification of chronic urticaria according to the consensus conference 'Urticaria2012' held on 28 and 29 November 2012 in Berlin.

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Article highlights.

- Second-generation antihistamines are first-line treatment.
- First-generation antihistamines should be avoided.
- Long-term steroid treatment should be avoided.
- Updosing second-generation antihistamine is established as second-line treatment.
- Omalizumab is a novel approach in the refractory patient.

This box summarizes key points contained in the article.

Chronic spontaneous urticaria as well as chronic inducible urticaria subtypes can be severely debilitating and tend to markedly impair quality of life and work place productivity [1-3].

2. Pathogenesis of urticaria and non-pharmacological treatment approach

The treatment of urticaria, according to current guidelines, should aim to achieve complete symptom control. Symptomatic therapies are built on preventing the release and/or effects of mast cell-mediators with histamine being the most prominent one.

As in all diseases, the best treatment of urticaria is to identify and eradicate the underlying cause of the disease. The clinical signs and urticaria symptoms are based on the degranulation of dermal mast cells releasing histamine and other pre-formed and newly generated inflammatory mediators [4]. This results in the formation of itchy wheals (activation of skin sensory nerves and swelling of the upper layers of the dermis) or angioedema (more prominent swelling of the deeper layer of the dermis and subcutis). In addition, inflammatory perivascular infiltrates can be seen consisting variably of neutrophils and/or macrophages, as well as T-cells and eosinophils, while an activation of endothelial adhesion molecules can be observed also in uninvolved skin [5,6]. In patients with chronic inducible urticaria, this mast cell degranulation is dependent on and directly related to an identifiable external trigger, for example, a contact allergen in contact urticaria or UV irradiation in solar urticaria, and some patients benefit from avoiding relevant triggers. This is not the case in chronic spontaneous urticaria, where symptoms develop unprompted and independent of specific triggers. In some, but not all patients, with chronic spontaneous urticaria, underlying causes can be identified, eradicated and patients cured, for example, helicobacter infection or non-IgE-mediated adverse reactions to drugs or food. In other patients, etiological factors, for example, antibodies against the high-affinity IgE-receptor [7] can be identified, but their elimination (and cure) is not possible. Furthermore, the receptor has no pathophysiological relevant role in all patients, in some it is apparently an epiphenomenon as patients with the antibodies

became free of symptoms, for example, under pseudoallergen-free diet (ZITAT ZUBERBIER High affinity IgE receptor/Wien). Treatment for physical urticaria and most patients with chronic spontaneous urticaria, therefore, relies largely on symptomatic therapy.

3. Pharmacological treatment

3.1 First-line pharmacological treatment

Non-sedating second-generation antihistamines (nsAHs) are recommended as first-line treatment of urticaria in all international guidelines [8-10]. These agents have been developed from their sedating predecessors, and they have several advantages in safety as well as their duration of effects (once-daily dosing). Many nsAHs are metabolites and most of them show no drug interactions, which are frequently seen with first-generation, sedating antihistamines. The efficacy of nsAHs in chronic urticaria and other urticaria subtypes has been clearly demonstrated in randomized, placebo-controlled clinical trials of the highest quality [11-18] as summarized in Table 2 [19]. As majority of the trials have been placebo-controlled, only limited data are available for comparing treatment effects of individual nsAHs in urticaria patients.

In recent studies, bilastine, the newest licensed nsAH has been compared in urticaria and in allergic rhinitis with levocetirizine [20] and fexofenadine [21]. These studies showed comparable results. Currently, it is impossible to make a list in which nsAH is possibly stronger but in individual patients different response rates are observed (not ruling out a placebo effect in this observation).

Currently, all international and national guidelines recommend nsAH as first-line treatment [9,22]. Up to 50% of chronic urticaria patients, however, are not sufficiently treated with standard doses of nsAHs, and second-line, third-line as well as in rare cases alternative treatment approaches are required. In preparation for the international consensus conference 'URTICARIA2012' to revise the international guidelines on urticaria, we have analyzed the risk-benefit ratios according to published evidence for standard urticaria treatment options.

The guidelines recommend clearly against the first-line use of first-generation sedating antihistamines due to the bad benefit-risk ratio. The major concern here is that their sedating effects, which are often advertised to help patients sleep despite their itch, are, in fact, comparable to those of narcotics. Sedating antihistamines result in alterations of sleep patterns and phases, for example, REM-sleep is reduced and delayed, they impair cognitive functions and performance leading to learning disabilities and loss of productivity at work and school, and they increase the rates of accidents during the following 24 h. Their unfavorable risk-benefit ratio has been extensively reviewed in a GA²LEN position paper [23]. Unfortunately, first-generation sedating antihistamines are still frequently used ('old habits die hard'),

Table 1. Classification of chronic urticaria subtypes (presenting with wheals, angioedema or both) [62].

Chronic urticaria subtypes	
Chronic spontaneous urticaria (CSU)*	Inducible urticaria
Spontaneous appearance of wheals, angioedema or both ≥ 6 weeks due to known or unknown causes	Physical urticarias Symptomatic dermographism [‡] Cold urticaria [§] Delayed pressure urticaria [¶] Solar urticaria Heat urticaria [#] Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

*For example, autoreactivity, that is, the presence of mast cell-activating autoantibodies.

[‡]Also called *urticaria factitia*, dermographic urticaria.

[§]Also called cold contact urticaria.

[¶]Also called pressure urticaria.

[#]Also called heat contact urticaria.

although head-to-head trials show that these drugs are not more effective and are less safe than nsAHs.

4. Second-line pharmacological treatment

The treatment with antihistamines is the only licensed therapy of urticaria, and several studies have shown that an nsAH up dosing (up to fourfold of the licensed dose of a single tablet; thus 2×2 tablets) in urticaria is useful. Based on this evidence, the international guidelines recommend up dosing of nsAH as the second step in those patients who do not respond satisfactorily to standard doses. Up dosing of nsAHs is now universally accepted as second-line treatment for all forms of chronic urticaria, and the efficacy and safety of nsAH up dosing has been shown in clinical trials with bilastine [24], cetirizine [25], desloratadine [26,27], levocetirizine [28], fexofenadine [29,30] and rupatadine [31]. For a recommended treatment algorithm see Figure 1.

5. Third-line pharmacological treatment

The previous international guidelines had suggested using montelukast, omalizumab, cyclosporin A, dapsone or H₂-antihistamines to treat urticaria patients refractory to second-generation antihistamines. A recent Cochrane review has shown that the data available for the efficacy of using H₂-antihistamines is insufficient to back a recommendation to use this drug [32]. The effect of dapsone is not very clear as well [33,34] and the drug is no longer recommended to be used as routine third-line therapy in urticaria. More and better evidence is available for add on montelukast [35,36], and cyclosporine A (3.5 mg/kg) [37,38]. Omalizumab (anti-IgE),

the newest drug included in the guidelines recommended treatment algorithm has now been shown in four of four randomized controlled trials to be very effective and safe in chronic spontaneous urticaria, independent of the background of autoreactivity and IgE levels [39-42].

6. Alternative approaches in drug treatment

The vast majority of patients will respond to the treatment [43] recommended in the guideline. However, in individual cases contraindications or lack of effect may require alternative approaches. The level of evidence for all alternative approaches is very low. New evidence coming up that change in the coagulation system may be relevant in some people with chronic urticaria [44,45], older trials using warfarin [46,47] or heparin [48] become more interesting again. Other suggestions mostly published as case reports include the use of hydroxychloroquin [49], sulfasalazin [50], methotrexate [50], oxatamide [51-53], nifedipin [54], as well as Interferon [55,56].

Corticosteroids are also a possibility to consider in the treatment of urticaria, but guidelines clearly recommend against their long-term use since usually high levels of up to 40 mg prednisolone is needed, far above the Cushing level with obligatory adverse events. For a short-term course in acute exacerbations of chronic urticaria as well as in acute urticaria, however, corticosteroids remain to play a role.

7. Expert opinion

Urticaria represents a common disorder in clinical practice that causes confusion to treating physicians and has major detrimental effects on quality of life, with sleep deprivation and psychiatric co-morbidity being frequent [43]. Nowadays, different subtypes of urticaria have been clearly described. Moreover, important findings of the last two decades about the underlying pathogenic mechanisms that are involved in chronic urticaria and especially the autoreactive form of the disease with the identification of functional autoantibodies against the high-affinity IgE-receptor (FcεR1) or IgE and the documentation of complement activation have broadened our knowledge about this fascinating entity. Besides, as our knowledge on the field of neuroendocrinology is expanded, the role of stress in urticaria regains more interest. Although recent studies have documented the bidirectional crosstalk between both the nervous system and the skin [57-60], the relationship between stress and chronic spontaneous urticaria is not clear at the clinical level.

Every physician treating urticaria patients is familiar with the fact that the natural course of the disease is unpredictable and varies remarkably among different subtypes. Unfortunately, no one really knows which cases of acute urticaria will become chronic. Besides, even after the remission of the disease little is known about the proportion and the specific characteristics of patients who will experience a relapse.

Table 2. Supporting evidence/adapted sources for first-line treatment of urticaria with modern second-generation H1-antihistamines [62].

Drug	Daily dose	Duration	N active drug	Study design	p < 0.05 vs PL	Compared drug, daily dosage (n)	p < 0.05 vs drug	Remarks	Limitations	Quality	Importance	Year	Citation
Azelastine	4 mg	2 weeks	73/Azel, 23/Cet	DB PC COMP	Yes	Cetirizine 10 mg	No	Pruritus: Azel > CET; Whealing: CET > Azel	Patients with urticaria were studied together with patients with other allergic diseases, for example, allergic rhinitis			1998	[63]
Azelastine	4 mg	3 weeks	Azel 17, Eb 17	DB PC MC COMP	Yes	Ebastine 10 mg	No		0	High	High	2001	[64]
Bilastine	20 mg vs 5 mmg levo	4 weeks	173 (bila) 165 (levo)	DB PC COMP	Yes	Levocetirizine 5 mg	No		0	High	High	2010	[19]
Cetirizine	10 mg	15 days	30	DB CRO	Yes	-	-	Patients with Aoe were excluded	0	High	High	1988	[65]
Cetirizine	10 mg	4 weeks	62 Cet, 62 Astem, 63 Placebo	DB COMP	-	Astemizole 10 mg	Yes	Wheal: CET > Astem	0	High	High	1990	[66]
Cetirizine	10 mg	4 weeks	28	DB PC CRO	Yes	-	-		0	High	High	1991	[67]
Cet, Astem	10 mg	4 weeks	62, 62	DB PC CRO	Yes	-	n.s.		0	High	High	1991	[68]
Cetirizine	10 mg	20 days	15	DB COMP	-	Terfenadine 2 x 60 mg	Yes	CET > TERF	0	High	Low	1993	[69]
Cetirizine	10 mg	2 weeks	64	DB PC COMP	Yes	Terfenadine 2 x 60 mg	No (efficacy), yes (side effects)	TERF caused fewer side effects	0	High	High	1993	[70]
Cetirizine	5 mg	4 weeks	28	DB MC COMP (children 2 - 6 years)	-	Oxatomide 25 mg	No	Children with angioedema were excluded	0	High	High	2001	[71]
Cetirizine	10 mg	4 weeks	52	DB COMP	-	Fexofenadine 180 mg	Yes					2004	[72]
Desloratadine	5 mg	6 weeks	95	DB PC MC	Yes	-	-		0	High	High	2001	[73]
Ebastine	10 mg	2 weeks	100	DB PC MC	Yes	-	-		0	High	High	1991	[74]
Ebastine	10 mg	12 weeks	69	DB PC MC COMP	Yes	Terfenadine 2 x 60 mg	No		0	High	High	1996	[75]
Fexofenadine	20, 60, 120, or 240 mg	4 weeks	PL: 79, Fexo 20 mg: 90, 60 mg: 90, 120 mg: 77, 240 mg: 82 - all 2 x daily	DB PC MC	Yes	-	-	Fexo 60 = 120 = 240 > 20 mg - Fexo improved performance/work productivity - BID trend to 240 superior 120				2000	[76]
Fexofenadine	2 x 60 mg	4 weeks	169		Yes	-	-		0	High	High	2000	[77]

Aoe: Angioedema; Astem: Astemizole; Azel: Azelastine; BID: twice daily; Bila: Bilastine; Cet: Cetirizine; COMP: comparison; CRO: crossover; DB: double blind; Eb: Ebastine; Fexo: Fexofenadine; Levo: Levocetirizine; MC: multicenter; PC: placebo controlled; PL: placebo; SB: single blind; TERF: Terfenadine.

Table 2. Supporting evidence/adapted sources for first-line treatment of urticaria with modern second-generation H1-antihistamines [62] (continued).

Drug	Daily dose	Duration	N active drug	Study design	$p < 0.05$ vs PL	Compared drug, daily dosage (n)	$p < 0.05$ vs compared drug	Remarks	Limitations	Quality	Importance	Year Citation
DB PC MC (two identical studies)												
Fexofenadine	2 × 10 mg or 2 × 60 mg or 2 × 120 mg	1 week	226 – 2 × 10 mg, 2 × 60 mg, 2 × 120 mg	DB dose-finding	–	–	Yes (compared to fexo 2 × 10 mg)	Fexo 2 × 60 (n = 75) and 2 × 120 (n = 76) > 2 × 10 mg (n = 75), efficiency proven in Japanese patients similar to American patients	0	High	High	2001 [78]
Fexofenadine	180 mg	3 weeks	11	DB PC	Yes	–	–		0	High	High	2002 [79]
Mizolastine	10 mg	4 weeks	28	DB PC MC (two centres)	Yes	–	–		0	High	High	1996 [17]
Mizolastine	10 mg	4 weeks	88	DB PC MC COMP	Yes	Loratadine 10 mg, n = 79	No	No difference with respect to Aoe	0	High	High	1999 [12]
Mizolastine	10 mg	4 weeks	39	DB PC MC	Yes	–	–		No primary report – cannot be included in this evaluation	Low	Low	1999 [80]
Mizolastine	10 mg	4 weeks	26	DB COMP	–	Loratadine 10 mg – 35	No	Miz had a better reduction of Aoe and of the mean total duration of episodes	0	High	High	2000 [81]
Rupatadine	10 or 20 mg	4 weeks	10 mg – 112; 20 mg – 109	DB PC MC	Yes				0	High	High	2007 [18]
Rupatadine	5 mg, 10 mg or 20 mg	4 weeks	5 mg – 68; 10 mg – 73; 20 mg – 67	DB PC	Yes			Trend analysis showed dose dependent improvement	0	High	High	2007 [82]
Levocetirizine	5 mg	4 weeks	81	DB PC MC	Yes				0	High	High	2006 [83]

Aoe: Angioedema; Astem: Astemizole; Azel: Azelastine; BID: twice daily; Bila: Bilastine; Cet: Cetirizine; COMP: comparison; CRO: crossover; DB: double blind; Eb: Ebastine; Fexo: Fexofenadine; Levo: Levocetirizine; MC: multicenter; PC: placebo controlled; PL: placebo; SB: single blind; TERF: Terfenadine.

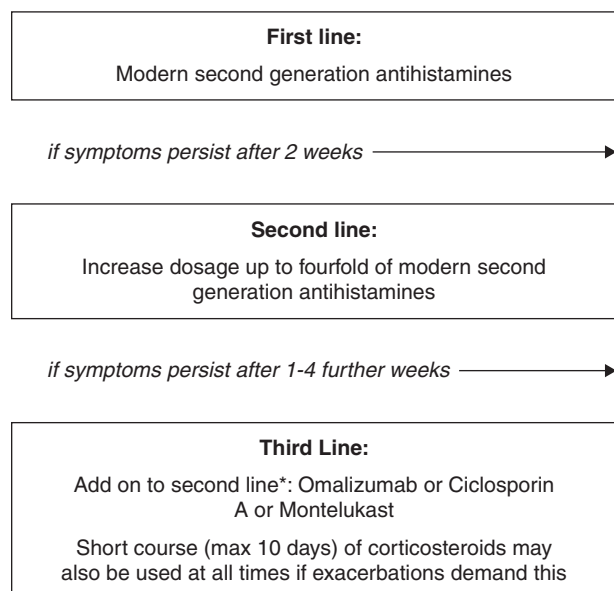


Figure 1. Recommended treatment algorithm for urticaria [62].

First-line = high-quality evidence: low-cost and worldwide availability (e.g., modern second-generation antihistamines exist also in developing countries mostly cheaper than old sedating Antihistamines), per daily dose as the half-life time is much longer, very good safety profile, good efficacy. *Second-line = high-quality evidence:* low-cost, good safety profile, good efficacy. *Third-line as add on to AH: Ciclosporin A = high-quality evidence:* medium to high cost, moderate safety profile, good efficacy. *Omalizumab = high quality evidence:* high cost, very good safety profile, very good efficacy. *Montelukast = low-quality evidence:* low-cost, good safety, low efficacy. *Short course of corticosteroids = low quality evidence:* low-cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but very low for lasting efficacy.

Figure is based on the Consensus discussion held during the 4th International Consensus Meeting on Urticaria 2012. 'The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of Urticaria. The 2013 revision and update' submitted to Allergy.

*The order of third-line treatments does not reflect preference.

Despite the progress on pathogenesis, the reasonable goal to identify predictive factors for the course of the disease remains unfulfilled. Except Autologous Serum Skin Test that represents a reliable clinical diagnostic tool for autoreactive urticaria [61] which seems to be more severe and resistant to treatment, no other clinical or laboratory markers have documented evidence of their value in distinguishing severe forms of the disease. This fact is clearly reflected in all therapeutic algorithms of chronic urticaria; even the recent guidelines propose a three-step treatment option and this stepwise approach (Figure 1) is based solely on the patient's response to the previous treatment. There are no different therapeutic options, at least evidence-based, according to different

urticaria subtypes or the possible underlying pathogenic mechanisms.

In majority of the patients suffering from chronic urticaria the causes and/or the triggers are not identified. Therefore, the optimal approach of a causal and curative treatment is not feasible for a large number of sufferers. Nevertheless, nsAHs are the mainstay of symptomatic therapy, effective in most cases of chronic urticaria even up to fourfold increase in daily dose is needed. While good quality evidence is available for ciclosporin, the growing evidence of the effectiveness of omalizumab in resistant to nsAHs chronic urticaria creates the prospect of a credible and effective treatment for next years. The mode of action for this anti-IgE-treatment is, however, not clear at present, since unlike in asthma, the treatment does not need to be adjusted according to total IgE-levels. Consequently, omalizumab in chronic urticaria provides a model for further research on pathogenesis and the elucidation of possible unidentified mechanisms.

All the urticaria treating physicians must be aware of constantly monitoring disease activity while a step-down procedure should be evaluated at regular intervals. Three months of complete response are considered a reasonable time period for reducing treatment intensity.

Conclusively, urticaria represents a fascinating clinical challenge for any physician while chronic spontaneous urticaria. The research on the natural course of chronic spontaneous urticaria and for the identification of underlying causes of the disease, as well as in inducible forms of urticaria and their treatment, should be intensified. Besides, more effective and safe therapies should be investigated focusing on the subpopulation of the non-responders to H1-antihistamines. Finally, studies on compliance and reason for non-compliance should be carried out for guideline-recommended treatments.

Declaration of interest

T Zuberbier: Consulting with the following companies: Ansell, Bayer Schering, DST, FAES, Fujisawa, HAL, Henkel, Kryolan, Leti, Menarini, Merck, MSD, Novartis, Procter and Gamble, Sanofi-Aventis, Schering Plough, Stallergenes, UCB. Organizational Affiliations: Scientific Advisory Board, German Society for Allergy and Clinical Immunology, Expert Commission 'Novel Food' of the German Federal Ministry of Consumer Protection, Head, European Centre for Allergy Research Foundation (ECARF), Committee member, WHO Initiative Allergic Rhinitis and its Impact on Asthma (ARIA), Member, World Allergy Organisation Communications Council, Secretary General, Global Allergy and Asthma European Network (GA²LEN). M Makris has received honoraria for consulting and/or lectures, and/or was/is a study physician for Astra Zeneca, MSD, GSK and Novartis. M Maurer has received research funding, honoraria for consulting and/or lectures, and/or was/is a study physician for FAES, Genentech, GSK, Moxie, MSD, Novartis, UCB, Sanofi and Uriach.

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