

High-dose antihistamines for chronic spontaneous urticaria in adults

Chronic spontaneous urticaria (CSU) is a common skin disease characterised by intermittent wheals (hives), angioedema or both lasting for at least 6 weeks.^{1,3} Second-generation antihistamines are widely used to manage symptoms but are not completely effective in many patients at licensed doses.⁴ Some guidelines recommend off-label use of high-dose antihistamines as the next therapeutic step.^{2,3} Here, we review the evidence supporting this recommendation.

About chronic spontaneous urticaria

CSU affects around 0.5–1% of the population at any time and occurs more commonly in women.⁵ Although any age group can be affected, the peak incidence is in those aged 20–40 years. Remission is common but around 10% are still affected after 5 years. The natural course of CSU is unpredictable, with spontaneous remissions and relapses.⁶ Co-existent angioedema and more severe symptoms may indicate a more prolonged time-course.^{1,5} Although rarely life-threatening, chronic urticaria reduces an individual's well-being and quality of life, affects sleep and is associated with anxiety and depression.^{3,5}

Causes and triggers of urticaria

CSU is a complex mast cell-driven disease and the exact trigger may remain unknown, although autoimmune mechanisms have been implicated.^{1,7} Some patients have functional IgG autoantibodies against the high affinity IgE receptor or IgE bound to mast cells.^{1,8} A number of causative and aggravating factors have been identified, including alcohol and drugs (e.g. NSAIDs, opiates and ACE inhibitors).¹

Urticaria may also be induced by physical factors such as heat, cold, pressure and vibration, or associated with syndromes (e.g. urticarial vasculitis or auto-inflammatory syndromes), which are not considered further here.³

Symptoms

Wheals are red, raised itchy skin eruptions caused by vasodilation and increased vascular permeability, resulting from mast cell

activation and the release of histamine and other inflammatory mediators such as platelet-activating factor (PAF), leukotrienes and cytokines.^{2,3} Many symptoms of urticaria are mediated primarily by histamine on H₁-receptors on endothelial cells (the wheal) and sensory nerves (neurogenic flare and pruritus).³ The wheals can vary in size from a few millimetres to several centimetres.¹ In contrast to urticaria, which involves the superficial skin layers, angioedema can affect the deeper dermis and subcutaneous tissues of the face, oro-pharynx, genitalia and occasionally the gastro-intestinal tract.^{1,3} Angioedema may persist for days and can be painful rather than itchy.¹ Urticaria and angioedema can co-exist or occur separately.

Diagnosis

The diagnosis of CSU is based primarily on an accurate history of the clinical presentation, including the frequency, onset, triggers, timing, pattern of recurrence and duration of attacks.¹ The need for investigation should be guided by the clinical history, examination and response to antihistamines. Only very limited investigations are recommended in CSU and these include a full blood count (eosinophils may be raised in parasitic infections and in some drug-induced reactions; neutrophils may be raised in urticarial vasculitis), erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Elevated ESR and/or CRP suggest an underlying systemic condition (e.g. chronic infection).^{1,2} However, the results of investigations in cases of CSU are often negative.

Assessment of disease activity

The validated Urticaria Activity Score (UAS) is recommended by some guidelines for assessing disease activity in CSU.^{3,9} The number

of weals and the intensity of pruritus are scored individually for the past 24 hours using a scale from 0 (no disease activity) to 3 (intense activity) and summed to obtain disease severity (range 0–6) for 1 day.⁶ The UAS7 is the sum of the UAS scores over 7 days (range 0–42).⁶ A UAS7 score of less than 7 indicates control of disease, whereas a score of more than 28 indicates severe disease.¹⁰ Estimates for minimally important difference for the UAS7 range from 9.5 to 10.5 (4.5 to 5.0 for the itch and 5.0 to 5.5 for weals).^{9,11}

The Chronic Urticaria Quality of Life questionnaire (CU-Q₂oL) is a self-administered questionnaire in which the patient indicates how much they have been troubled by each of 23 items (e.g. urticaria interfering with work, sleep or physical activities) on a scale of 1 (not at all) to 5 (very much), with higher scores indicating worse quality of life.^{3,10,12}

Treatment

Nonpharmacologic approaches include avoiding exacerbating factors such as heat, tight clothing, alcohol or NSAIDs (e.g. a trial of at least several weeks without NSAIDs).^{1,2,10}

For people with mild urticaria with an identifiable and avoidable trigger, urticaria is likely to be self-limiting without pharmacological treatment.¹⁰

Antihistamines

For people with symptoms requiring treatment, second-generation antihistamines targeting the H₁-receptor are usually used.³

Older first-generation antihistamines (e.g. chlorphenamine, promethazine) have pronounced anticholinergic and sedative effects that last more than 12 hours, whereas their antipruritic effects last only 4–6 hours.³ Also, interactions occur between sedating antihistamines and alcohol or drugs affecting the CNS (e.g. analgesics, hypnotics, sedatives and mood-elevating drugs). First-generation antihistamines can also interfere with sleep, learning and performance, especially in older people. Sedating antihistamines are not recommended as first-line agents for the routine management of chronic urticaria.

Two of the early second-generation antihistamines, astemizole and terfenadine, prolonged the QT interval and were withdrawn from the market.^{3,13}

Newer second-generation antihistamines are generally well tolerated; they are long-acting and relatively non-sedating (see Table 1).^{1–3}

Table 1: Once-daily antihistamines¹⁴

Drug	Maximum licensed daily dose for urticaria	Available over the counter?	NHS cost for 28 days
Bilastine	20mg	No	£14.08
Cetirizine	10mg	Yes	£0.68
Desloratadine	5mg	No	£0.93
Fexofenadine	180mg	No	£2.01
Levocetirizine	5mg	No	£4.08
Loratadine	10mg	Yes	£0.61
Mizolastine	10mg	No	£6.46
Rupatadine	10mg	No	£28.00

Costs based on prices in *Chemist and Druggist* and the *Drug Tariff*.

A *Cochrane* review that included 73 randomised controlled trials (RCTs) involving 9,759 participants (none in primary care), assessed short-term (<2 weeks) or intermediate-term (2 weeks to 3 months) use of antihistamines for CSU.⁴ The authors concluded that at standard doses, some antihistamines suppressed urticaria more effectively than placebo (e.g. cetirizine 10mg: 36% vs. 13%; relative risk [RR] 2.7, 95% CI 1.5 to 4.9; p<0.01; one short-term study and one intermediate-term study). However, results for each drug comparison were from a few studies or only a single study, and some studies involved less than 25 people. It was not possible to identify the most effective drug, as head-to-head studies were not available for all comparisons. Overall, standard doses were only effective in some patients. Adverse events, such as headache or dry mouth, were tolerable with most antihistamines and sedation was mainly minor, but many studies did not address quality of life.

A more recent systematic review that assessed the effect of increased doses of non-sedating antihistamines in patients with CSU included 15 studies, of which only five were graded as high quality.¹⁵ For high-dose versus standard-dose regimens, there were no significant differences in response rates or number of weals. Increasing the dose increased the chance of improvement in pruritus (RR 2.3, 95% CI 1.7 to 3.1) and around 60% of patients not responding to standard doses did respond to the higher dose. However, there was significant heterogeneity between the studies making firm conclusions difficult.

High-dose second-generation antihistamines

A limited number of studies have assessed the benefit of higher doses of various antihistamines.^{16–23}

Cetirizine

Two small open-label RCTs^{16,17} and two double-blind crossover studies^{18,19} evaluated a total of 76 patients treated for 1–3 weeks, and suggested that cetirizine 20mg daily may improve weals and itching in adults with severe CSU refractory to standard doses of cetirizine.²⁴ However, symptoms remained in some participants on the higher dose, and the studies had many limitations (e.g. small size, short duration, lack of blinding or active comparator treatments). No data are available from high-quality studies on cetirizine at doses greater than 20mg. There were few adverse effects in the studies, although some patients noted drowsiness.

Levocetirizine and desloratadine

In a double-blind trial, 80 patients with CSU were randomised to receive levocetirizine or desloratadine, at the standard dose (5mg) for week 1; 10mg for week 2; 20mg for week 3; then switched to 20mg of the other drug for week 4 if symptoms were not completely relieved.²⁰ At the end of week 3, more patients on levocetirizine were symptom-free than with desloratadine (22 vs.12; p<0.04). Also, seven patients who did not respond to 20mg desloratadine became symptom-free with 20mg levocetirizine; none of the 18 levocetirizine non-responders benefited with 20mg desloratadine. Increasing antihistamine doses improved quality of life (cumulative proportion of patients with an improvement in quality of life score of >50% at week 3 was 62% with levocetirizine vs. 46% with desloratadine) but did not increase somnolence. No patients discontinued due to adverse events.

Rupatadine

In a double-blind RCT, 334 patients with CSU were randomised to receive rupatadine 10mg, rupatadine 20mg or placebo once daily.²¹ The mean pruritus score (MPS; on a scale of 0 [none] to 4 [very severe warranting doctor visit]) at baseline was 2.5. At 4 weeks, rupatadine 10mg and 20mg produced statistically significant reductions in the MPS from baseline of 1.4 (58%; $p < 0.05$ vs. placebo) and 1.6 (63%; $p < 0.05$ vs. placebo), respectively, compared with a reduction of 1.1 (45%) with placebo. The difference between 10mg and 20mg was not statistically significant. The higher dose caused more somnolence (2.7% vs. 8.3%; p value not reported).

Fexofenadine

In an open-label case series, 37 patients with CSU and mean baseline UAS score 3.6 received fexofenadine 180mg for 1 week.²² The 26 patients who remained symptomatic increased the dose to 360mg for the second week and then the 14 patients who were still symptomatic increased the dose again to 540mg. At the end of 4 weeks, only one patient remained symptomatic and the mean UAS was 0.2. One patient taking 540mg complained of mild sedation and two patients reported headache with the higher doses.

Loratadine

In a retrospective study involving patients with CSU in a tertiary dermatology and allergology clinic, nine were treated with loratadine 10mg, of whom none achieved a sufficient effect at the standard dose and 1 (11%) did at double the dose.²³

What do guidelines say?

A number of guidelines on the management of CSU support using second-generation long-acting non-sedating antihistamines at up to four times the licensed dose to manage symptoms that are not sufficiently controlled with standard doses, based on limited evidence.^{1–3,10,24}

The 2015 British Society for Allergy and Clinical Immunology guideline recommends starting with a standard dose of a non-sedating H_1 -antihistamine.¹ Higher doses may be used at step 2 (up to four times the standard dose).

The 2007 British Association of Dermatologists guideline suggests that all patients should be offered the choice of at least two non-sedating H_1 -antihistamines because responses

and tolerance vary between individuals.²⁴ The guideline also notes that it has become common practice to increase the dose above the manufacturer's licensed recommendation for patients who do not respond when the potential benefits are considered to outweigh any risks. The guideline is in the process of being updated.²⁶

The 2013 European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization joint guideline recommends standard dose second-generation antihistamines at step one.³ A trial using up to a fourfold dose of modern second-generation antihistamines can be considered if symptoms of urticaria persist after 2 weeks at a standard dose.

The 2014 American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology guideline states that second-generation antihistamines are safe and effective therapies in patients with CSU and are considered first-line agents.² For patients not responding to monotherapy at standard doses, treatment options include using higher doses of second-generation antihistamines (2–4 times the standard dose).

The National Institute for Health and Care Excellence (NICE) states that referral to a dermatologist or immunologist is advised for people whose symptoms are not well controlled on antihistamine treatment.¹⁰ In a review of the evidence on high dose cetirizine for chronic urticaria, NICE concluded that a dose of 20mg appears to be well tolerated and the benefits may outweigh the risks for some people whose quality of life is significantly impaired by the condition.²⁵

Guidance on off-label prescribing

The General Medical Council in the UK advises that medicines should usually be prescribed in accordance with their licence.²⁶ It may be necessary to prescribe a medicine outside its market authorisation where there is no suitably licensed product that will meet the patient's need. When prescribing a medicine off-label, a doctor should be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy. In addition, decisions should be made in collaboration with the patient by discussing the options with them and ensuring that they have sufficient information about the medicine to allow them to make an informed decision.

Conclusion

Chronic spontaneous urticaria is a common skin disease characterised by the recurrence of transient weals, angioedema, or both for at least 6 weeks. For people with mild urticaria with an identifiable and avoidable trigger (e.g. alcohol, drugs), urticaria may be self-limiting without the need for pharmacological treatment. Where treatment is required, licensed doses of long-acting non-sedating second-generation antihistamines are widely used but are not completely effective in many patients. A number of national and international clinical guidelines include the option of using higher doses off-label. There is limited evidence from small scale studies and case series that antihistamines used off-label in higher doses can be effective for some people and are well-tolerated. However, well-designed large-scale trials comparing their efficacy and safety with other treatment options are lacking.

Prescribers should ensure that patients are aware of unlicensed use of high-dose antihistamines in these circumstances and understand the limitations of the evidence for their efficacy and safety. Patients should be regularly reviewed to assess response to treatment with high-dose antihistamines.

[R=randomised controlled trial; M=meta-analysis]

- 1 Powell RJ et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2015; 45: 547–65.
- 2 Bernstein JA et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014; 133: 1270–7.
- 3 Zuberbier T et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update. *Allergy* 2014; 69: 868–87.
- M 4 Sharma M et al. H₁-antihistamines for chronic spontaneous urticaria. *Cochrane Database Syst Rev* 2014; 11: 10.1002/14651858.CD006137 [Last assessed as up-to-date June 2014].
- 5 Maurer M et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy Eur J Allergy Clin Immunol* 2011; 66: 317–30.
- 6 Ferrer M et al. Management of urticaria: not too complicated, not too simple. *Clin Exp Allergy* 2014; 45: 731–43.
- 7 Kolkhir P et al. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. *J Allergy Clin Immunol* 2017; 139: 1772–81.
- 8 Sabroe RA et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; 140: 446–52.
- 9 Mathias S et al. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2012; 108: 20–4.
- 10 The National Institute for Health and Care Excellence, 2017. *Clinical knowledge summaries: scenario: managing urticaria* [online]. Available: <https://cks.nice.org.uk/urticaria> [Accessed 21 March 2018].
- 11 Mathias S et al. The minimal important difference for measures of urticaria disease activity: Updated findings. *Allergy Asthma Proc* 2015; 36: 394–8.
- 12 Baiardini I et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy* 2005; 60: 1073–8.
- 13 Shah RR. The significance of QT interval in drug development. *Br J Clin Pharmacol* 2002; 54: 188–202.
- 14 Joint Formulary Committee. *British National Formulary*. Edition 74. London: BMJ Group and Pharmaceutical Press, September 2017.
- M 15 Guillén-Aguinaga S et al. Updosing nonsedating antihistamines in patients with CSU: a systematic review and meta-analysis. *Br J Dermatol* 2016; 175: 1153–65.
- R 16 Okubo Y et al. Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: a prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life. *J Dermatol Treat* 2013; 24: 153–60.
- R 17 Kameyoshi Y et al. Increasing the dose of cetirizine may lead to better control of chronic idiopathic urticaria: an open study of 21 patients. *Br J Dermatol* 2007; 157: 803–4.
- R 18 Zuberbier T et al. Efficacy of cetirizine in cholinergic urticaria. *Acta Derm Venereol* 1995; 75: 147–9.
- R 19 Zuberbier T et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatol* 1996; 193: 324–7.
- R 20 Staevska M et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol* 2010; 125: 676–82.
- R 21 Gimenez-Arnau A et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. *Allergy* 2007; 62: 539–46.
- 22 Godse KV et al. Fexofenadine in higher doses in chronic spontaneous urticaria. *Indian Dermatol Online J* 2010; 1: 43.
- 23 van den Elzen MT et al. Effectiveness and safety of antihistamines up to fourfold or higher in treatment of chronic spontaneous urticaria. *Clin Transl Allergy* 2017; 7:4.
- 24 Grattan C, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; 157: 1116–23.
- 25 The National Institute for Health and Care Excellence, 2014. *Chronic urticaria: off-label doses of cetirizine* [online]. Available: <https://www.nice.org.uk/advice/esuom31/resources/chronic-urticaria-offlabel-doses-of-cetirizine-pdf-54116459057003461> [Accessed 21 March 2018].
- 26 General Medical Council, 2015. *Hot topic: prescribing unlicensed medicines* [online]. Available: <https://www.gmc-uk.org/guidance/28349.asp> [Accessed 21 March 2018].

DOI: 10.1136/dtb.2018.4.0614

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to
<http://www.bmj.com/company/products-services/rights-and-licensing/2018>