Up-Dosing Antihistamines in Chronic Spontaneous Urticaria: Efficacy and Safety.

A Systematic Review of the Literature

Short running title: Chronic Spontaneous Urticaria: Up-Dosing

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ABSTRACT

**Background:** According to current guidelines, oral antihistamines are the first line treatment for chronic spontaneous urticaria (CSU). Up-dosing antihistamines up to fourfold the licensed dose is recommended if control is not achieved. Such indications are based mainly on expert’s opinions.

**Objectives:** To critically review and analyze clinical evidence regarding to efficacy and safety of higher-than-licensed dosage of second-generation oral antihistamines in CSU treatment.

**Material and Methods:** A systematic literature review following a sensitive search strategy was performed. All articles published in MEDLINE, EMBASE, and Cochrane Library between 1961 and October 2018 were examined. Publications with CSU patients treated with prescribed second-generation antihistamines in monotherapy comparing with either placebo, licensed dosage and/or higher dosage were included. Articles were evaluated by peer revisors. Quality was evaluated using Jadad and Oxford scores.

**Results:** We identified 337 articles, 14 were included in the final evaluation; 6 focus on fexofenadine, 2 on cetirizine, levocetirizine, rupatadine and desloratadine, and 1 for ebastine and bilastine. Only 5 studies were placebo-controlled. The number of included patients ranged from 20 to 439. Observation lapse was ≤ 16 weeks. High fexofenadine doses produced dose-dependent significant response and controlled urticaria in a majority of patients. Cetirizine, levocetirizine, rupatadine and bilastine showed an increased effectiveness when up-dosing. Most frequent adverse events were headache and drowsiness.

**Conclusion:** The low quality and heterogeneity of the articles reviewed made impossible to reach any robust conclusions and unveil the need to develop large-scale randomized clinical trials.

**Keywords:** Chronic urticaria. Antihistamines. Treatment. Up-Dosing. Efficacy. Safety. Systematic review.
RESUMEN

Antecedentes: Según las guías actuales, los antihistamínicos orales de segunda generación constituyen el primer escalón terapéutico en la urticaria crónica espontánea (UCE). Si el control no se alcanza con la dosis licenciada en ficha técnica, se recomienda aumentarla hasta cuatro veces al día. Estas indicaciones están basadas principalmente en opiniones de expertos.

Material y Métodos: Se realizó una revisión sistemática de los artículos publicados en MEDLINE, EMBASE, y Cochrane Library entre 1961 y octubre de 2018. Se incluyeron publicaciones de pacientes con UCE tratados con antihistamínicos de segunda generación en monoterapia comparando dosis licenciadas con dosis superiores controladas o no con placebo. Los artículos fueron revisados por pares. Su calidad se evaluó siguiendo la puntuación de Jadad y Oxford.

Resultados: Identificamos un total de 337 artículos, en la evaluación final seleccionamos 14; 6 sobre fexofenadina, 2 de cetirizina, levocetirizina, rupatadina y desloratadina, y 1 de ebastina y bilastina. El número de pacientes incluidos en los estudios se encontraba en un rango entre 20 y 439. El tiempo de observación fue ≤ 16 semanas. Solo 5 estudios estaban controlados con placebo. Dosis altas de fexofenadina produjeron una respuesta significativa y controlaron la urticaria en la mayoría de los pacientes. Cetirizina, levocetirizina, rupatadina y bilastina mostraron mayor eficacia al subir la dosis. Los efectos secundarios más frecuentemente referidos fueron cefalea y somnolencia.

Conclusiones: La baja calidad y heterogeneidad de los artículos revisados hace imposible obtener conclusiones válidas y nos indica la necesidad de desarrollar ensayos clínicos aleatorizados a mayor escala.

Palabras clave: Urticaria crónica, Antihistamínicos, Tratamiento, “Up-Dosing”, Eficacia, Seguridad, Revisión sistemática.
Introduction

Chronic spontaneous urticaria (CSU) is a disease characterized by recurrent itchy wheals and/or angioedema, that persist for at least 6 weeks. CSU origin is still unknown, appearing for no identifiable reason. CSU is thought to affect 0.5-1% of the general population. The female - male ratio is 2:1 and it is more common in adults than in children [1].

The cellular and molecular mechanisms are not accurately known, but there is evidence of the basophil and mast cell participation. Histamine and other mast cell mediators (platelet activating factor (PAF), cytokines, proteases, kinins, etc…) are the main mediators of this process [2]. The chronic course of CSU and the lack of well-defined etiology produce an important impairment in patient’s quality of life that leads to a high physical, emotional and social impact.

According to recent guidelines, second-generation antihistamines are the first-line symptomatic treatment for CSU. These drugs act as an inverse-agonists on H1 receptor, stabilizing it in its inactive form. However, in patients with inadequate control of symptoms with licensed dosages, up-dosing up to fourfold is recommended as the second step in European Guidelines. This recommendation is based on expert opinion. In those patients where control is not achieved omalizumab is recommended [3][4].

The interest of our group has been to analyze available data about the efficacy of second-generation antihistamines at higher doses than licensed to treat CSU, in order to evaluate if there exists enough information to accurately ascertain the efficacy and the safety risks of this step.
Material and methods

We performed a systematic literature review following the PRISMA checklist and the Cochrane Collaboration recommendations.

Search strategy

With the help of an expert documentalist, a comprehensive, computerized literature search was performed in Medline, Embase, and Cochrane Database to identify studies published from 1961 to October 2018. We used Mesh and free text terms including “Histamine H1 Antagonists”, “Non-Sedating” or “chronic spontaneous urticaria”

Eligibility criteria

We included studies in English or Spanish language that met all the following criteria: 1) Patients older than 12 years old with CSU with or without histaminergic angioedema, dermographism or delayed pressure urticaria; 2) treated on a regular regimen (not on demand) with second generation antihistamines (cetirizine, loratadine, ebastine, desloratadine, bilastine, levocetirizine, rupatadine, fexofenadine) in monotherapy (neither associated with different antihistamines nor with other drugs); 3) the studies must compare with either placebo, licensed dosage and/or higher dosage groups with comparable information about efficacy and safety; 4) Regarding to study design we selected: randomized controlled trials and prospective and retrospective observational studies.

Studies with patients with other pruritic dermatological conditions or inducible urticaria different from delayed pressure urticaria and dermographism were excluded.
Study Selection

The studies selection was performed in pairs independently (MA and BV; MO and PI; TU and GP; AR and TG). For this purpose, the articles retrieved from the search strategies were distributed among pairs of reviewers. Then, duplicates were removed and, in the first selection round, each pair of reviewers, following inclusion and exclusion criteria, selected the articles by title and abstract. The studies (at least preliminarily) fulfilling inclusion criteria and those without abstract were then evaluated in a second selection process. In case of multiple studies analyzing the same patients, the one with the most comprehensive population was selected. The detailed evaluation of each resulting paper was also performed individually. Discrepancies in the selection processes were resolved by discussion with an expert methodologist.

Data extraction and quality assessment

The reviewers also conducted the data extraction and summarized the information in specific Tables. The following characteristics were recorded from each study: 1) First author’s name and year of publication, type of the study and time of observation; 2) Patient information: sample size, age range and gender; 3) Intervention: type of antihistamine, dosages and time of exposition; 4) Patient outcomes: results of efficacy (including scales used for evaluation) and secondary effects.

The quality of the studies was evaluated using the levels of evidence of Oxford Center for Evidence-based Medicine [5] and Jadad scale [6]. The latter evaluates the quality of randomization, double-blinding and loses to follow up and establishes a range from 0 to 5. Studies with 5 points are considered high quality and less than 3 points as poor quality.
**Statistical Analysis**

A table of evidence (Table 1) was produced to describe the main characteristics of the studies. A qualitative analysis was performed with the information collected by type of study, population, study quality and specific results.

Due to the lack of homogeneity between the studies we rejected the possibility of performing a meta-analysis.

**Results**

We initially identified 337 articles; 73 were duplicates. After analyzing the remaining 264 according to inclusion and exclusion criteria, 254 were excluded: 225 eliminated by title and abstract and 29 eliminated after a close reading. A total of 4 articles were included by a manual secondary search. Finally, 14 articles were analyzed in detail. The PRISMA template for the study flow chart is shown in Figure 1.

The main characteristics and results of the 14 studies included in the present review are described in Tables 1 and 2. They differ in population size, type of antihistamines used, design and quality. We found that 6 of them focus on fexofenadine up-dosing (maximum dose was 720 mg), 2 studies on levocetirizine, rupatadine and desloratadine, and there is one article for each one of these antihistamines: ebastine and bilastine. The number of participants of the studies ranged from 20 to 439. Finn’s fexofenadine study has the largest number of patients[7]. All the studies had a short duration (from 2 to 8 weeks) except for Magen’s fexofenadine [8], that lasted for 16 weeks. Only 5 of them, 3 with fexofenadine and 2 with rupatadine, were placebo-controlled. In Table 3, licensed doses are referred.
Fexofenadine

Regarding fexofenadine up-dosing, studies showed different results. A multicenter, double-blind, randomized, parallel-group and placebo-controlled study by Paul et al., analyzed 222 patients treated with fexofenadine or placebo at doses of 60 mg, 120 mg, 180 mg or 240 mg once a day for 6 weeks [9]. The authors found that increasing the dose of fexofenadine to 180 mg daily achieves better control. The efficacy measures were the mean daily total symptom score (TSS) that included pruritus score (PS) and number of wheals score (NWS). The 180 mg and 240 mg fexofenadine doses resulted in significant reductions in TSS and PS compared to placebo, and the response was found to be dose-dependent. Only the 180 mg treatment group demonstrated significant reductions in the number of wheals. Since there was no significant difference between the 180 mg/day and 240 mg/day doses, the authors recommended fexofenadine 180 mg/day as the optimal dose. The most frequently reported treatment-related adverse event was headache and no patient experienced drowsiness.

An uncontrolled clinical trial by Tanizaki et al. supported that increasing doses of fexofenadine from 120 mg to 240 mg daily, reduced symptoms of CSU [10] in 20 patients, assessing pruritus severity by the visual analog scale score and the severity index. Histamine-induced skin responses by iontophoresis was also evaluated, and seems to be stronger suppressed with 240 mg. None of patients reported adverse effects.

On the other hand, Finn et al. [7] suggested that there are no differences in urticaria control despite increasing the dose of fexofenadine. They reported similar efficacy in the 60 mg, 120 mg and 240 mg twice a day (bid) groups. They performed a multicenter, double-blind, randomized trial compared with placebo in 439 patients treated with fexofenadine at doses of 20 mg, 60 mg, 120 mg, or 240 mg bid, for 4 weeks. They found that all doses of fexofenadine were statistically superior to placebo for the disease
control (reduction in pruritus and number of wheals), and reported less interference with sleep and daily activities than placebo. The 240 mg bid doses had a better efficacy (64%) in reducing pruritus. All groups had similar incidence of adverse events, with headache being the most frequently communicated.

Nelson et al. [11], performed a similar study to Finn et al. during 4 weeks as well, with 418 patients taking fexofenadine 20 mg, 60 mg, 120 mg, and 240 mg bid. A total of 282 patients completed the study. All fexofenadine doses achieved patient significant relief of urticaria symptoms compared with placebo except for 20 mg bid that seems to be suboptimal. In all efficacy measures, 60 mg bid had similar effect than 240 mg bid dose. The results of this study suggest that fexofenadine 60 mg bid (120 mg day) is the optimal effective dose. All doses had similar safety profile.

Godse et al. [12], performed a non-randomized, uncontrolled clinical trial for 4 weeks in 37 patients. All of them started with fexofenadine 180 mg and were reviewed at weekly intervals for 4 weeks. For symptomatic patients the dose of fexofenadine was doubled to 360 mg at the end of week 1 and 540 mg at the end of week 2. They registered Urticaria Activity Score (UAS). Adverse effects were sedation in one patient and two patients reported headache with higher doses. They concluded that fexofenadine in higher doses controlled urticaria in the majority of patients.

Magen et al.[8], in an uncontrolled nonrandomized open-label clinical trial, studied prospectively 276 patients that started with fexofenadine 180 mg per day. At week 8, 172 improved their UAS in 50 % or greater from baseline, and treatment was continued. In 83 patients, whose UAS improvement at week 8 was 50% or less, fexofenadine was increased to 2, 3 or 4 tablets per day every 7 days during 16 weeks. Most of them showed a significant benefit while up-dosing to 2 or 3 tablets, but 21 (25%) of them continued to suffer from urticaria despite increasing to 720 mg.
**Cetirizine**

Cetirizine seems to be more effective with increasing doses. Kameyoshi et al. [13], proposed that increasing cetirizine doses may lead to better control of urticaria activity in patients who did not respond to initial doses. They performed a study including 21 patients with a poor response to 10 mg daily in a 1-2-week screening period. Patients were randomly assigned to group A or group B. Initially, all patients were given an increased dose of 20 mg daily for 1 or 2 weeks. After, patients in group A continued with cetirizine 20 mg and group B received 10 mg during 1 to 2 weeks. Both groups registered urticarial activity scores (number and duration of wheals and severity of itch). These were significantly lower in both groups while treated with 20 mg, and these lower levels were improved in group A while maintaining 20 mg in the second period. In group B, urticarial activity scores were higher while descending dose in the second period. Only 2 patients complained of drowsiness with increased dose.

A study published by Asero [14] involving 22 non-responder patients to cetirizine 10 mg concluded, after rising doses to 30 mg daily during one week, that the number of patients with severe CSU who respond to an off-label dosage is very low, as they only observed a clinical benefit in 1 of them. 13 patients (59%) referred tiredness and somnolence with 30 mg.

**Levocetirizine**

Levocetirizine could be more effective when dose is increased according to Godse et al. [15]. They performed a unicentric, non-randomized, uncontrolled clinical trial with levocetirizine 5 mg, 10 mg or 20 mg daily in 20 patients during 4 weeks, increasing doses in the first 2 weeks depending on urticaria control. They registered UAS at day 0 and week 2. The rate of patients who achieved control with 5 mg, 10 mg and 20 mg was...
60%, 30% and 10% respectively. Only 10% of patients needed fourfold dose of levocetirizine to be controlled. Adverse events registered were mild sedation in 2 patients with doses of 10 and 20 mg.

Staevska et al. [16], in a randomized, double-blind cross-over study, analyzed the efficacy of levocetirizine and desloratadine increasing doses if control was not achieved. In our revision we have decided to analyze the first part of their study and both antihistamines separately. The study recruited 80 patients, 40 for each antihistamine.

Levocetirizine doses started at 5 mg increasing weekly to 10 and 20 mg if symptoms were not controlled. 9 patients responded to 5 mg, 8 to 10 mg and 5 to 20 mg. The proportion of responders reporting more than 50% improvement in discomfort were 52%, 65% and 74% with 5, 10 and 20 mg respectively. Regarding side effects, 75% patients were not affected by somnolence, and patients taking 20 mg didn´t report more somnolence than with lower doses. 6 patients complained of adverse reactions, most of them not drug-related.

Desloratadine doses started at 5 mg increasing weekly to 10 and 20 mg if symptoms were not controlled. 4 patients responded to 5 mg, 7 to 10 mg and 1 to 20 mg. The proportion of responders reporting more than 50% improvement in discomfort were 41%, 56% and 63% with 5, 10 and 20 mg respectively. 55% patients didn´t referred somnolence. As with levocetirizine, fourfold doses didn´t affect somnolence. 11 patients complained of adverse reactions, most of them not drug-related.

One patient suffered from palpitations, but not EKG changes were observed in none.
**Ebastine**

Regarding efficacy of ebastine, Godse et al. [17] performed a unicentric, non-randomized, uncontrolled clinical trial with 30 patients for 4 weeks. All patients started with ebastine 10 mg and were reviewed on weekly intervals. For symptomatic patients, the dose of ebastine was doubled to 20 mg at the end of week 1 and 40 mg at the end of week 2. They registered UAS. Only one patient reported mild sedation with dose of 40 mg. They concluded that 20 mg of ebastine seemed superior to 10 mg. The 2 patients that remained symptomatic with 20 mg, were controlled with 40 mg.

**Rupatadine**

Dubertret et al. [18], in a multicenter, randomized, placebo controlled trial in 277 patients treated with rupatadine at doses of 5 mg, 10 mg or 20 mg once daily for 4 weeks, found that rupatadine 10 and 20 mg provided fast and long-lasting relief from itching and symptoms, though a clear dose-response effect was observed in favor of the 20 mg dose. Therefore, the minimum daily dose capable of effectively relieving itching and symptoms at four weeks was the 10 mg dose. According to investigator´s and patient´s opinion rupatadine 10 mg and 20 mg contributed to significantly improve urticaria symptom´s interference with daily activities and sleep.

In a second study of similar design, 334 patients were randomized to rupatadine 10 mg, 20 mg or placebo once daily for 4-6 weeks, Giménez-Arnau et al. [2] found no difference in efficacy among doses. Rupatadine at doses of 10 and 20 mg significantly reduced the severity of urticaria, showing rapid therapeutic action with objective clinical improvement as early as seven days after treatment that persisted during the six weeks of the clinical trial. The 10 mg dose does not show significant differences in
efficacy compared to the 20 mg dose and a better adverse effect profile is observed. There’s evidence that rupatadine 10 mg is useful and safe in urticaria management.

Lastly, Giménez-Arnauet al. [19] published another study analyzing pooled data from the two previous trials. A total of 538 patients were included. Responder rates were defined as the percentage of patients who exhibited a reduction of symptoms by at least 50% or 75% as compared to baseline after 4 weeks of treatment. They evaluated pruritus, mean number of wheals and mean UAS. The study concluded that both doses of rupatadine, 10 and 20 mg, elicit a significantly superior response versus placebo, though with the 20 mg dose a higher number of patients obtained a response of 75% improvement. In summary, according to this study, there is evidence of a somewhat greater effect with rupatadine 20 mg daily.

**Bilastine**

Weller et al. [20], in an open label study, depicted the effects of bilastine at 20 mg, 40 mg and 80 mg daily in 3 consecutive 2 week-periods. A total of 29 CSU patients were treated with an initial dose of 20 mg that was increased to 40 mg after 2 weeks in patients with UAS7 > 3, the same criteria were adopted 2 weeks after with 80 mg. They concluded that bilastine at standard dose is effective and up-dosing to double the licensed dose appeared to be sufficient for most of patients. Tiredness was reported by 6 patients on 20 mg bilastine but only by 1 at 40 mg or 80 mg each.

**Quality Assessment of the included studies**

The quality of the included studies was variable. Only 5 were placebo-controlled (Paul, Finn, Nelson, Dubertret, and Giménez-Arnau) and 5 had a Jadad score ≥ 3. The studies...
performed by Godse, Kameyoshi and Weller et al. respectively analyzed up-dosing responses in patients who did not respond to standard doses.

**Discussion**

In this review, as clinicians, we tried to answer these two questions: is there enough scientific evidence for up-dosing? Is it really safe when we prescribe these off-label doses?

International guidelines on the management of CSU support up-dosing second generation antihistamines up to four-fold times the licensed dose when control is not achieved but this recommendation is based mainly on expert opinions and lack large well-design double blind clinical trials.

Regarding to efficacy, we analyzed 14 articles and only 6 had a high-quality level score and 5 were placebo controlled. These corresponded to fexofenadine and rupatadine. No placebo effect was analyzed with the other antihistamines (levocetirizine, cetirizine, ebastine and bilastine).

Unfortunately, the heterogeneity of the included studies (control definition, design, quality, lack of active comparator, small sample size, outcomes) and their short duration made the comparisons difficult.

As in Ferrer revision [21], and similar to Guillén-Aguinaga´s systematic review and meta-analysis [4], that found that licensed doses control 31% of patients and up-dosing only reaches 63.2% in symptom´s control, we found that there are a predominance of studies that don´t find significant differences in up-dosing. Taking all into account, we can conclude that up-dosing fexofenadine could be a good clinical practice, but due to the studies´ limitations, more research is needed to confirm this observation. 3 of them were published almost 20 years ago and the doses they recommended, 180 mg or 120
mg depending on the study, are the licensed doses nowadays. Magen’s finds better control when up-dosing to 360 and 720 mg [8] and no additional benefit was considered except for pruritus score with 480 mg in Finn’s [7]. This goes in the same direction as Guillén-Aguinaga’s meta-analysis, as they found no differences in wheal number or response rates but significant differences in pruritus control [4].

In the case of rupatadine, 20 mg is the optimal dose recommended by Giménez-Arnau et al. [19], when they analyzed pool data from two studies [2,18], but examining both studies separately those differences were not significant. There is no additional information about four-fold in CSU, but up-dosing rupatadine up to four-fold is supported in Chronic Inducible Urticaria such as Cold Urticaria (ColdU), with studies proving its efficacy. Abajian et al.[22], showed that 30% and 50% of patients with ColdU had no wheal formation while testing with TempTest 3.0 after treatment with two-fold (20 mg) and four-fold (40 mg) standard rupatadine dosages for 7 days, respectively. However, there was no significant difference in Cold Temperature Threshold reduction and Cold Stimulation Time Threshold prolongation between 20 and 40 mg of rupatadine. Metz et al found that 52% of patients were complete responders when receiving 20 mg (two-fold) of rupatadine for 7 days compared with only 5% of the placebo group [23].

The previous comparative analysis by Sanchez-Borges [24] confirms our results as they found that doubling doses of fexofenadine and rupatadine show an objective improvement in most of patients that respond to antihistamine.

With cetirizine, from the two studies we selected, we don’t have sufficient evidence to recommend up-dosing as Kameyoshi[13] only doubled the licensed dose and Asero [14] does not find any benefit in three or four-fold doses.
Further evidence is also needed to recommend up-dosing in CSU with levocetirizine, desloratadine, bilastine, and ebastine. The quality of these studies, and the short time of treatment, cannot assure the benefit, although our clinical practice confirms that up-dosing benefits patients that remain symptomatic.

Besides safety measures are different between studies are not referred or unclear, we agree with Sanchez-Borges revision [24] that, although insufficiently evaluated in the studies we analyzed, we don’t demonstrate predictable or newer adverse effects. In the highest quality studies, it seems that adverse events are similar in all the groups with different doses and placebo. Relevant clinical information, as hepatic enzymes evaluation, or electrocardiographic values are not collected. The lack of patients in special situations (elderly, polypharmacy, renal or hepatic impairment, heart disease…) in these studies, might limit the supposed safety to healthy volunteers or patients without comorbidities. Headache was the most frequent adverse event reported with fexofenadine and rupatadine across studies, although these results are similar to the observed with placebo. Tiredness was reported by Godse et al. in some patients with ebastine, but as shown previously, it does not seem to be dose-related. Drowsiness was also referred with cetirizine at double the licensed dose. Somnolence or sedation was uncommon except with those treated with rupatadine 20 mg. Staevska et al. [16] reported that higher doses of desloratadine and levocetirizine showed a paradoxical decrease in somnolence, attributed to symptom’s relief. The short treatment duration in all the studies (except Magen’s for fexofenadine that was 16 weeks) may be insufficient to conclude any of these observations, although up-dosing is accepted in real life practice and no severe adverse effects are reported.
Conclusion

Although in daily clinical practice up-dosing is effective and safe when we prescribe antihistamines according to current guidelines in CSU, our review shows that currently, efficacy and safety of high-dose H1 antihistamines in CSU, has a low level of evidence, based mainly on consensus opinion: few randomized controlled trials (RCTs) and low-quality clinical studies. In the studies analyzed we found evidence in up-dosing up to two-fold (rupatadine, fexofenadine) or three-fold. Regarding to licensed doses of second-generation antihistamines in CSU in Spain, there is not enough evidence to support up-dosing to fourfold. Safety data is not evaluated in most of the studies and we do not have long-term data.

Hence high-quality and well-designed studies are needed to validate guidelines´ recommendations and to clarify which non-sedating antihistamines should be used, the optimal dose, and treatment duration in patients not responding to the standard treatment so as to prescribe them according to the leaflet.

Previous presentations

The authors state that this material has not been previously presented or published elsewhere.

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The authors assure that no financial sources were obtained to prepare this manuscript.
Conflicts of interest

Dr. Usero Bárcena reports non-financial support from NOVARTIS, during the conduct of the study; personal fees and non-financial support from NOVARTIS, non-financial support from ALMIRALL, non-financial support from SANOFI, non-financial support from ABBIE, non-financial support from JANSEN, outside the submitted work.

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The remaining authors have no conflicts of interest to declare.

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### Tables and Figures

**Table 1. Global evidence**

| Study    | Design          | No. of patients (withdraws) | Patients       | Intervention | Efficacymeasures | Safety | Quality |
|----------|-----------------|----------------------------|----------------|--------------|-------------------|--------|---------|
|          |                 |                            | Sex(% female) | Agerange (years) | Duration (weeks) | Antihistamine | Dailydosage (mg) |         | Oxford | Jadad   |
| Paul     | Multicenter     | 222 (76)                   | 58%           | ≥18           | 6                 | Fexofenadine | 60 | PS* (0-3) | Yes     | 2a     | 3       |
| 1998 (9) | Randomized     |                            |               |              |                   |           | 120 | NWS** (0-4) |         |        |         |
|          | Double-blind    |                            |               |              |                   |           | 180 | TSS*** (0-7) |         |        |         |
|          | Placebo-controlled |                        |               |              |                   |           | 240 | Interference with sleep and daily activities (0-3) |         |        |         |
|          | Parallel        |                            |               |              |                   |           | 240 | PS* (0-4) |         |        |         |
|          |                 |                            |               |              |                   |           | 480 | NWS**(0-4) |         |        |         |
|          |                 |                            |               |              |                   |           |    | TSS*** |         |        |         |
| Finn     | Multicenter     | 439 (19)                   | 74%           | 12-65         | 4                 | Fexofenadine | 40 | PS* (0-4) | Yes     | 2a     | 3       |
| 1999 (7) | Randomized     |                            |               |              |                   |           | 120 | NWS**(0-4) |         |        |         |
|          | Double-blind    |                            |               |              |                   |           | 240 | TSS*** |         |        |         |
|          | Placebo-controlled |                        |               |              |                   |           | 480 | Interference with sleep and daily activities (0-3) |         |        |         |
| Study    | Design            | Note                  | Participants | Treatment | Dose     | Outcomes                                | Improvement | Score | Notes |
|----------|-------------------|-----------------------|--------------|-----------|----------|-----------------------------------------|-------------|-------|-------|
| Nelson   | Multicenter       | 2000 (11)             | 418 (136)    | Fexofenadine | 40       | PS* (0-4)                              | Yes         | 2a    | 3     |
|          | Randomized        |                       |              |           |          | NWS** (0-4)                            |             |       |       |
|          | Double-blind      |                       |              |           |          | Interference with sleep and daily activities (0-3) |             |       |       |
|          | Placebo-controlled|                       |              |           |          |                                         |             |       |       |
|          | Clinical Trial    |                       |              |           |          |                                         |             |       |       |
| Godse    | Unicenter         | 2010 (12)             | 37 (unknown) | Fexofenadine | 180      | UAS§                                    | Yes         | 4     | NA†   |
|          | Non-randomized    |                       |              |           |          |                                         |             |       |       |
|          | Non-controlled    |                       |              |           |          |                                         |             |       |       |
|          | Clinical Trial    |                       |              |           |          |                                         |             |       |       |
| Tanizaki | Unicenter         | 2013 (10)             | 20 (unknown) | Fexofenadine | 120      | VAS++ (pruritus)                        | Yes         | 3b    | 0     |
|          | Non-randomized    |                       |              |           |          | Severity Index                         |             |       |       |
|          | Non-controlled    |                       |              |           |          |                                         |             |       |       |
| Clinical Trial | Unicenter | Multicenter | Non-randomized | Non-controlled | Clinical Trial | 276 (unknown) | NA | >18 | 16 | Fexofenadine | 180 | 360 | 540 | 720 | NA | 3b | 0 |
|----------------|-----------|-------------|----------------|----------------|----------------|----------------|----|-----|----|--------------|------|-----|-----|-----|----|----|---|
| Magen 2012 (8) |           |             | Non-randomized | Non-controlled | Clinical Trial |                | NA |     |    |              |      |     |     |     |    |    |   |
|                |           |             | Mean (Group A) | Mean (Group B) |                | 42,5           | 36,9          | 2-4 | 2   | 2  |              |      |     |     |     |    |    |   |
|                | Kameyoshi 2007 (13) |         | Randomized | Non-controlled | Clinical Trial | 21 (unknown) | NA |     |    | Cetirizine | 20 (Group A) | 20-10 (Group B) | NWS** (0-3) | DWS** (0-3) | Severity of itch (0-3) | Yes | 3a | 2 |
|                | Asero 2007 (14) |         | Non-randomized | Non-controlled | Clinical Trial | 22 (0)         | 13% | 28-67|    | Cetirizine | 10            | 30            | VAS** on Urticaria severity | Yes | 3a | 0 |
| Study | Design | Participants | Efficacy | Comparator | Treatment | Comparator | Outcomes | Quality |
|-------|--------|--------------|----------|------------|-----------|------------|----------|---------|
| Staevska | Unicenter Randomized Double arm | 40 (0) | 60% | 19-61 | 3 | Levocetirizine | 5 | CU-QoL+++ | VAS++ | Yes | 1b-2a | 3 |
| Staevska | Unicenter Randomized Double arm | 40 (3) | 72% | 19-67 | 3 | Desloratadine | 5 | CU-QoL+++ | VAS++ | Yes | 1b-2a | 3 |
| Godse | Unicentric Non-randomized Non-controlled Clinical trial | 20 (unknown) | 60% | 20-60 | 4 | Levocetirizine | 5 | UAS§ | Yes | 4 | NA

**Note:**

- **CU-QoL+++**: Clinical Utilities-Quantified Quality of Life ( +++ indicates high)
- **VAS++**: Visual Analog Scale ( +++ indicates high)
- **UAS§**: Urticaria Activity Score (§ indicates total)
- **PS* (0-4)**: Pruritus Score (0-4 indicates mild to severe)

**References:**

- Dubertret 2007 (18)
- Godse 2010 (15)
- Godse 2011 (17)
- Staevska 2010 (16)
| Study | Design | N | Percent 77% | Duration | Treatment | Follow-up | Results |
|-------|--------|---|-------------|----------|-----------|-----------|---------|
| Giménez-Arna | Multicenter Randomized Double-blind Placebo-controlled Parallel | 334 | 77% | 12-65 | 4 y 6 | Rupatadine | 10 | NWS** (0-4) TSS*** Perception global of efficacy (0-4) Interference with sleep and daily activities (0-3) |
| Weller | Open-label study | 29 | 79,3% | 20-85 | 6 | Bilastine | 20 | UAS7/UAS7§ Severity of CSU† |

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Table 2. Results

| Study     | Antihistamine | Results                                                                 | Difference with high doses in urticaria control | Adverse events                                      |
|-----------|---------------|-------------------------------------------------------------------------|-------------------------------------------------|----------------------------------------------------|
| Paul 1998 (9) | Fexofenadine  | ANCOVA‡‡: Mean PS*: Any dose better than placebo. Dose dependent effect | No difference between 180 and 240 mg            | Similar or lower than placebo                      |
|           |               | NWS**: 180 mg and 240 mg daily doses superior than placebo             |                                                 | Most frequently reported event: headache (12% in active group, 14% in placebo group) |
|           |               | TSS***: 180 mg and 240 mg daily doses are associated with statistically significant values |                                                 | No relationship between doses                      |
|           |               | 60 mg/d and 180 mg/d are associated with better patient’s assessment of effectiveness |                                                 |                                                    |
|           |               | Only 180 mg/d is associated with better physician assessment           |                                                 |                                                    |
| Finn 1999 (7) | Fexofenadine  | ANCOVA ‡‡: Mean PS*: All doses superior to placebo                     | No, except for 480 mg better efficacy in PS*    | Similar in all treatment groups and to placebo     |
|           |               | Mean NWS**: All doses superior to placebo                              |                                                 | Most frequently reported event: headache          |
|           |               | Mean TSS***: All doses superior to placebo                             |                                                 |                                                    |
|           |               | Interference with sleep and daily activities: All doses superior to placebo |                                                 |                                                    |
| Study     | Dose       | Fexofenadine | ANCOVA‡‡:                                                                 | Mean PS*: All doses superior to placebo, linear trend | Mean NWS**: All doses fexofenadine doses superior to placebo, dose-trend | Interference with sleep and daily activities: All dose group better to placebo, linear trend | No statistical differences between doses | Similar in all treatment groups | Most frequently reported event: headache |
|-----------|------------|--------------|---------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------|---------------------------------------|--------------------------------------|
| Nelson    | 2000 (11)  | Fexofenadine | ANCOVA‡‡:                                                                 | Mean PS*: All doses superior to placebo, linear trend | Mean NWS**: All doses fexofenadine doses superior to placebo, dose-trend | Interference with sleep and daily activities: All dose group better to placebo, linear trend | No statistical differences between doses | Similar in all treatment groups | Most frequently reported event: headache |
| Godse     | 2010 (12)  | Fexofenadine | Symptom free patients:                                                    |                                                     |                                                                         |                                                                                 | Yes                            | Headache (2/37) with 540 mg/d     | Drowsiness (1/37) with 540 mg/d |
|           |            |              | 180 mg/d: 11/37                                                          |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
|           |            |              | 360 mg/d: 12/26                                                          |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
|           |            |              | 540 mg/d: 13/14                                                          |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
| Tanizaki  | 2013(10)   | Fexofenadine | 240mg: 100% VAS** score and severity index decreased                     |                                                     |                                                                         |                                                                                 | Yes                            | None of the patients complained of fatigue and/or sleepiness |
| Magen     | 2012(8)    | Fexofenadine | 1800mg:                                                                  |                                                     |                                                                         |                                                                                 | Yes                            | NA                                   |                                      |
|           |            |              | 62,3%: >50% improvement UAS§                                                  |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
|           |            |              | 360-720mg:                                                               |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
|           |            |              | 75% control urticaria                                                    |                                                     |                                                                         |                                                                                 |                                |                                       |                                      |
| Study | Drug | Effectiveness | Side Effects | Somnolence |
|-------|------|---------------|--------------|------------|
| Kameyoshi 2007 (13) | Cetirizine | Better control of urticarial activity with 20 mg/d than 10 mg/d | Yes | Drowsiness: 20 mg/d: 2 patients, 10 mg/d: none |
| Asero 2007(14) | Cetirizine | Only 1 of 22 patients (5%) reached clinical benefit | No | Tiredness and somnolence were reported by 13 patients (59%) |
| Staevska 2010(16) | Levocetirizine | Levocetirizine responders: 5 mg/d: 9/40, 10 mg/d: 8/40, 20 mg/d: 5/40 | Yes | Somnolence: 75% no change or reduction in somnolence, No difference with higher doses, Other side effects (low probability of association with the drug): Hip pain, anxiety, nausea, fatigue, headache, oral discomfort, kidney pain, stomach ache, viral infection, palpitations (no changes in EKG) |
|   | Desloratadine | Desloratadineresponders: 5 mg/d: 4/40, 10 mg/d: 7/40, 20 mg/d: 1/20 | Yes | Somnolence: 55% no change or reduction in somnolence, No difference with higher doses |
| Author (Year) | Drug | Symptom free patients: | Yes/No | Drowsiness: |
|--------------|------|------------------------|--------|------------|
| Godse (2010) | Levocetirizine | 5 mg/d (12/20) | Yes | 10 mg/d group: 1 patient |
|              |      | 10 mg/d (6/8)         |        | 20 mg/d group: 1 patient |
|              |      | 20 mg/d (2/2)         |        |                          |
| Godse (2011) | Ebastine | 10 mg/d (17/27)       | Yes   | Mild sedation in 1 patient in 40 mg/d group |
|              |      | 20 mg/d (8/10)        |        |                          |
|              |      | 40 mg/d (2/2)         |        |                          |
| Dubertret (2007) | Rupatadine | ANOVA‡‡‡<br>Mean PS*: Doses of 10 and 20 mg are superior to placebo with a linear trend | Yes, between 5 and 10/20, not between 10 and 20 | Drowsiness (2.90% for placebo, 4.29% for 5 mg, 5.41% for 10 mg and 21.43% for 20 mg) |
|              |      | Mean NWS**: No differences between the 10 and 20 mg doses, though dose-response effect was observed with 20 mg dose |        | Headache (4.35% for placebo, 2.86% for 5 mg, 4.05% for 10 mg and 4.29% for 20 mg) |
|              |      | Mean TSS***: 10 mg and 20 mg are superior to placebo |        |                          |
|              |      | Dose of 5 mg no significant differences compared to placebo in these parameters |        |                          |
|              |      | Perception global efficacy: 10 mg and 20 mg are associated with better efficacy by |        |                          |
| Study | Drug | ANOVA | Mean PS* | Mean NWS** | Mean TSS*** | DLQI† | VAS‡‡ | Headache | Drowsiness |
|-------|------|-------|----------|------------|-------------|--------|-------|-----------|------------|
| Giménez-Arnaú 2007(2) | Rupatadine | ANOVA | Doses of 10 and 20 mg are superior to placebo, but not significantly different between 10 and 20 mg | Doses of 10 and 20 mg are superior to placebo from the first week, were not significantly different between 10 and 20 mg | Dose of 10 and 20 mg were not significantly different at any time | 20 mg improve all the subdomain scores to a greater extent than placebo over the time | 20 mg significantly decrease the baseline compared to placebo, 10 mg also reduce it although these was not significant compared with placebo | No | Headache (8% for placebo, 4.5% for 10 mg and 8.3% for 20 mg) |
| | | | | | | | | Drowsiness (5.3% for placebo, 2.7% for 10 mg and 8.3% for 20 mg) |
| Weller 2018(20) | Bilastine | UAS7§§ reduction: | 20 mg: 37% reduction from baseline | 40 mg: 23% further reduction after up-dosing | Yes between 20 and 40, not with 80 mg | Tiredness: | 20 mg/d group: 6 patients | Tiredness: | 20 mg/d group: 1 patient |

*Mean PS: Doses of 10 and 20 mg are superior to placebo, linear trend
**Mean NWS: Doses of 10 and 20 mg are superior to placebo, linear trend
***Mean TSS: Doses of 10 and 20 mg are superior to placebo, linear trend
†DLQI: Dose of 10 and 20 mg are superior to placebo, linear trend
‡‡VAS: Doses of 10 and 20 mg are superior to placebo, linear trend
§§UAS7: Doses of 10 and 20 mg are superior to placebo, linear trend

Giménez-Arnaú 2007(2)
Weller 2018(20)

Investigators and patients

Interference with sleep and daily activities: 10 mg and 20 mg better to placebo, linear trend

Publicidad
|          | 80 mg: 7% further reduction after up-dosing, not statistically significant | 80 mg/d group: 1 patient |
|----------|--------------------------------------------------------------------------|----------------------------|

(*) PS: Pruritus Score

(**) NWS: Number of Wheals Score

(***) TSS: Total Symptom Score

($) UAS: Urticaria Activity Score

(§) UAS7: 7days Urticaria Activity Score

(§§) DWS: Duration of Wheals Score

(‡) CSU: Chronic Spontaneous Urticaria.

(‡‡) ANCOVA: Analysis of Covariance

(‡‡‡) ANOVA: Analysis of Variance

(+) DLQI: Dermatology Life Quality Index

(++) VAS: Visual Analog Scale

(+++) CU-Q2oL: Chronic Urticaria Quality of Life questionnaire

(¥) NA: Not applicable
Table 3. Antihistamines evaluated and licensed daily doses.

| Antihistamines  | Maximum licensed doses (mg/day) |
|-----------------|---------------------------------|
| Desloratadine   | 5 mg/day                        |
| Loratadine      | 10 mg/day                       |
| Levocetirizine  | 5 mg/day                        |
| Cetirizine      | 10 mg/day                       |
| Ebastine        | 20 mg/day                       |
| Fexofenadine    | 180 mg/day                      |
| Rupatadine      | 10 mg/day                       |
| Bilastine       | 20 mg/day                       |

Source: Agencia Española de Medicamentos y Productos Sanitarios (AEMPS):
Data sheet Desloratadine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/76344/FT_76344.html.pdf
Data sheet Loratadine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/58518/FT_58518.pdf
Data sheet Levocetirizine. (Revised may 27, 2020). In: http://cima.aemps.es/cima/pdfs/es/ft/64287/64287_ft.pdf
Data sheet Cetirizine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/58481/FT_58481.pdf
Data sheet Ebastine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/63366/FichaTecnica_63366.html.pdf
Data sheet Fexofenadine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/79718/79718_ft.pdf
Data sheet Rupatadine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/p/64053/P_64053.pdf
Data sheet Bilastine. (Revised may 27, 2020). In: https://cima.aemps.es/cima/pdfs/es/ft/73027/FT_73027.html.pdf
**Figure 1.** Studies flow-chart

- **PubMed** n=94
- **Embase** n=118
- **Cochrane** n=125

Number of publications included:

- n=33
- Duplicates removed: n=73
- Secondary research n=4
- Excluded by title and abstract n=225
- Excluded after fulltext examination n=29

N= number of publications included