Diphenhydramine versus nonsedating antihistamines for acute allergic reactions: A literature review

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ABSTRACT

First-generation antihistamines can have adverse effects on the central nervous system and thereby complicate discharge planning from the emergency department (ED). Newer antihistamines are potentially safer, causing less sedation with similar efficacy. The aim of this study was to review the literature to better define which antihistamines are good options for the treatment of acute allergic reactions. A Medline search was conducted to identify English language articles published between January 1975 and March 2006 on antihistamines, sedation, and acute allergic reactions. Bibliographies from included studies were further investigated. We focused on sedative potential, effect on cognitive function, efficacy, onset of clinical activity, and cost of antihistamines. Diphenhydramine impairs psychomotor performance and cognitive function. Loratadine and desloratadine are nonsedating but less efficacious than cetirizine or fexofenadine. The incidence of sedation with cetirizine is less than that of first-generation antihistamines but is greater than placebo. Cetirizine has the fastest onset of action among the newer antihistamines. Fexofenadine does not impair psychomotor or cognitive skills and shows no dose-related increase in sedation but has a slower onset of action than diphenhydramine and cetirizine. Newer antihistamines cost ~$0.52–2.39 more per dose than diphenhydramine ($0.37). Newer antihistamines provide similar efficacy as first-generation antihistamines but with less sedation. We believe this benefit outweighs the small increase in cost and that newer antihistamines should be considered in the management of acute allergic reactions. Although comparative ED-based trials are not available, newer antihistamines are an option for management of acute allergic reactions when sedation is a concern.

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Key words: Acute allergic reaction, anaphylaxis, antihistamines, cognitive function, cost, diphenhydramine, impairment, psychomotor performance, sedation, urticaria

Acute allergic reactions, ranging from simple urticaria to anaphylaxis, account for ~1 million emergency department (ED) visits each year.[1] The lifetime prevalence of anaphylaxis, the most severe allergic reaction, is ~1% in the United States or almost 3 million Americans at risk of experiencing an episode of anaphylaxis during their lives.[2] Although the diagnosis and classification of acute allergic reactions is not simple, empiric therapy includes epinephrine, corticosteroids, and antihistamines, in addition to supportive therapy with volume replacement and bronchodilators. Antihistamines are an integral part of initial therapy for the spectrum of acute allergic reactions, but the risk of sedation from this class of medication is significant.[3,4] Additionally, in children, although first-generation antihistamines often are administered without apparent harm, data suggest that central nervous system (CNS) impairment occurs far more often than is generally recognized.[5]

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Despite the known sedative effects, diphenhydramine remains the most commonly used antihistamine in the ED for the treatment for acute allergic reactions.[6,7] In a recent multicenter study of food-related allergic reactions in the ED, 72% of patients received antihistamines, with 90% receiving diphenhydramine.[6] In a similar study of insect sting–related allergic reactions, 57% of ED patients received antihistamines, with 90% receiving diphenhydramine.[7] Treatment with antihistamines improves outcomes[8] and therefore is necessary. Although there are many effective first-generation antihistamines, we focus this review on diphenhydramine not only because it is the most commonly used antihistamine in the ED but also because diphenhydramine has been Food and Drug Administration (FDA) approved for use as an adjunct to epinephrine and corticosteroids in the treatment of acute allergic reactions.

Although recognizing that epinephrine is the most important initial treatment for anaphylaxis, we sought to determine if nonsedating, newer antihistamines offer a reasonable alternative to diphenhydramine in treatment of the spectrum of acute allergic reactions—from simple urticaria to anaphylaxis. Sedation is reported to be significantly decreased with the newer class of H_1-receptor blockers.[4,9] The newer antihista-

mines differ in their chemical structures and are believed to generally lack CNS effects because of, in large part, their inability to cross the blood–brain barrier.[10,11] We reviewed the current literature regarding various H_1-blockers to better define which antihistamines are the best options for the treatment of acute allergic reactions with efficacy similar to diphenhydramine but without impairment of cognitive function.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

A literature review was conducted using the Medline database. To qualify, studies satisfied the following criteria[1]: an English language journal from January 1975 through March 2006[2]; key words antihistamines, sedation, or acute allergic reactions[3]; human studies and[4] diphenhydramine, loratadine, desloratadine, cetirizine, or fexofenadine as one of the drugs evaluated. We focused on antihistamines available in the United States. Bibliographies from included articles were further investigated. In addition to articles found on Medline, package inserts for each drug,[12–15] the Physician's Desk Reference,[16,17] and Lexi-Comp[18] were reviewed to determine the onset of clinical activity. Lexi-Comp is the official drug reference guide for the American Pharmacists Association. Data regarding the sedative potential, effect on cognitive function, efficacy, onset of clinical activity, and cost of diphenhydramine and newer antihistamines were considered. The most common reason for article exclusion was presentation of anecdotal evidence without actual performance or sedation measures.

Sedative Potential and Cognitive Function Reported Outcomes

The effects of antihistamines on driving are difficult to measure; therefore, surrogates such as a driving simulator and brake reaction time (BRT) in a laboratory setting can be used. Cognitive and psychomotor tests selected to simulate real-world activities along with mood and sedation scales can be used to assess the effects of antihistamines on the CNS.

Driving Simulation and BRT. The Iowa Driving Simulator[19] allows collection of data on driving performance measures in a manner not available with on-street driving. The simulator consists of a domed enclosure mounted on a hexapod motion platform. The inner walls of the dome act as a screen on which correlated images are projected. The experimental drive is conducted in varying weather and traffic conditions.

BRT is the amount of time that elapses between the recognition of an object or hazard in the roadway and the application of the brakes. The length of BRT varies widely between individual drivers. BRT can be variable depending on driver characteristics such as attitude, level of fatigue, and experience.

Cognitive and Psychomotor Performance Tests. These tests simulate real-world activities and include simple reaction time, mathematical processing, backward digit span, digit symbol substitution scores, divided attention test, dual task test, tracking, and vigilance tasks.

Mood and Sedation Scales. These tests include visual analog scales, Stanford sleepiness scale, and mood scale.

Evaluation of Efficacy

Articles comparing the efficacy of antihistamines, individually or in comparison with one another, for the reduction of symptoms of allergic disorders (*e.g.*, allergic rhinitis and chronic idiopathic urticaria) were reviewed. Unfortunately, data on the efficacy of newer antihistamines in the treatment of acute allergic reactions are lacking.

Evaluation of Cost

Three different sources were evaluated to compare the cost of diphenhydramine to the newer antihistamines: www.drugstore.com, www.cvs.com, and www.walgreens.com. The data from each source were combined to determine the average cost per dose of medication.

RESULTS

The Medline search combining the words acute allergic reactions, sedation, and antihistamines limited to the English language, humans, and published after 1975 identified a total of 146 articles. Another 40 articles identified from the bibliographies of these initial articles were reviewed also. Table 1 provides an overview of diphenhydramine and the newer antihistamines available in the United States.

Diphenhydramine

Overview. Diphenhydramine has been available in the United States since 1945, and its potential adverse effects were reported as early as 1947.[20] In 1981, diphenhydramine was first sold over the counter (OTC) and within 20 years diphenhydramine was the top-selling OTC antihistamine with 40% market share.[21] Diphenhydramine is a first-generation H_1-receptor antagonist. This antagonism also can produce anticholinergic effects and antiemetic effects.

Sedative Potential and Cognitive Function. Studies show impairment of psychomotor performance and

Table 1 **Diphenhydramine vs newer-generation antihistamines**

	Diphenhydramine	Loratadine	Desloratadine	Cetirizine	Fexofenadine
Common trade name	Benadryl	Claritin, Alavert	Clarinex	Zyrtec	Allegra
OTC vs Rx	OTC (1981)	OTC (2002)	Rx	Rx	Rx
Generic available	Yes	Yes	No	No	Yes
Onset of action*	15–60 min	1–3 hr	1–3 hr	15–30 min	60 min
Duration of action*	4–7 hr	≥24 hr	≥24 hr	≥24 hr	≥24 hr
Half-life*	2–8 hr	12–15 hr	27 hr	8 hr	14.4 hr
Excretion*	Urine	Urine and feces	Urine and feces	Mainly urine	Mainly feces
Adult dose	25–50 mg as needed	10 mg daily	5 mg daily	10 mg daily	60 mg b.i.d., 180 mg daily
Pediatric dose	6.25–25 mg as needed	5–10 mg daily	1–5 mg daily	2.5–10 mg daily	30–60 mg daily
Dose adjustments	Elderly patients	Liver and renal disease	Liver and renal disease	Liver and renal disease	Renal disease
Supplied	Chewable tab, dissolvable tab, suspension, cream, elixir, gel, and pill	Dissolvable tab, pill, and syrup	Dissolvable tab, pill, and syrup	Syrup, chewable tab, and pill	Pill
Approved age	2 yr	2 yr	6 mon	6 mon	12 yr
Pregnancy category	B	B	C	B	C
FDA-approved indications	AR, CIU, insomnia, Parkinsonism, motion sickness, and anaphylaxis	AR and CIU	AR and CIU	AR and CIU	AR and CIU

**Lexi-drugs.*[18]

Rx = prescription; AR = allergic rhinitis; CIU = chronic idiopathic urticaria.

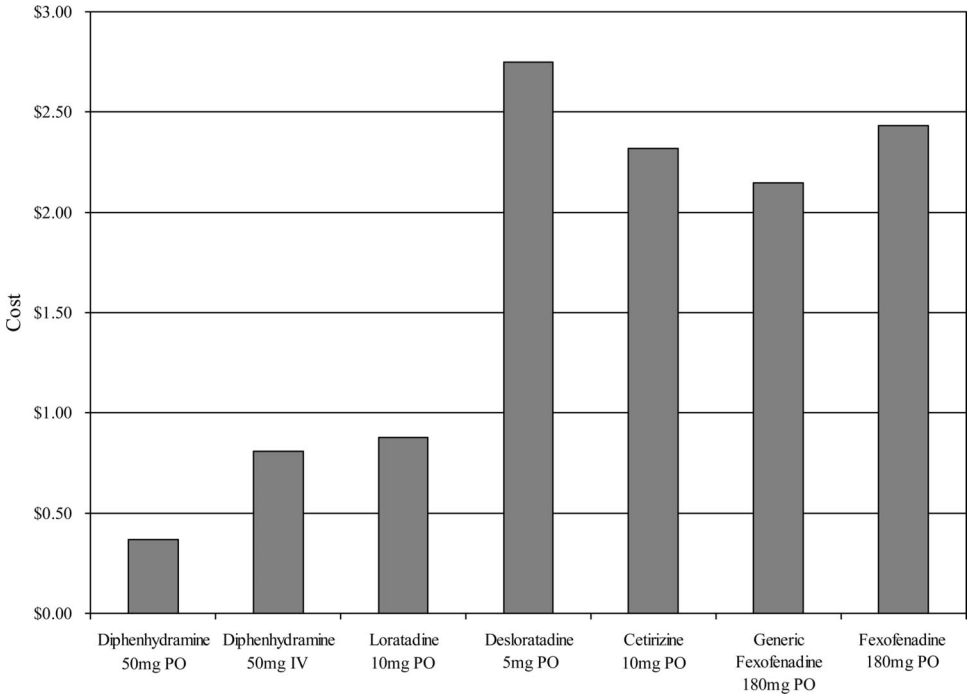

Figure 1. *Average cost of one dose of antihistamine.*

cognitive function after 50 mg of diphenhydramine, a standard dose used in acute allergic reactions. Using an automobile driving simulator and digit symbol substitution scores, mental impairment was apparent for 2 hours after 50 mg p.o. of diphenhydramine, while significant feelings of drowsiness were present for up to 6 hours.[3] Diphenhydramine has been shown to have a greater impact on the complex task of operating an automobile than alcohol.[4]

The effects of diphenhydramine on tasks that would mimic the demands of the modern workplace were evaluated.[22] This investigation suggested that a 50 mg p.o. of diphenhydramine increased the risk of errors when performing psychomotor tasks and decreased motivation that is likely to translate into decreased productivity. The suggestion that nurses in intensive care units or operators of heavy machinery taking diphenhydramine may be at risk for significant errors leading to potential hazards and decreased work productivity is more disturbing.[23]

Efficacy and Cost. Diphenhydramine is effective in the treatment of acute allergic reactions with a very rapid onset of action.[8] Oral diphenhydramine appears in plasma within 15 minutes with peak plasma concentrations within 1–4 hours.[24–27] Intravenous diphenhydramine maximally suppresses the wheal and flare response induced by intradermal histamine at 1–3 hours.[25] Similarly, diphenhydramine acts rapidly in the treatment of allergic rhinitis[28,29] and chronic idiopathic urticaria symptoms.[28,30] The cost is low, ~$0.37 for 50 mg p.o., and 50 mg i.v. is $0.81/dose at our institution. (Fig. 1).

Overview of Newer Antihistamines

Drowsiness caused by first-generation antihistamines has been attributed to the blockade of central histaminergic receptors and antagonism of other brain receptors (*i.e.*, serotonergic, cholinergic, and central α-adrenergic).[11] The newer antihistamines are typically large, lipophobic molecules with a charged side chain and are extensively bound to albumin, therefore limiting transfer across the blood–brain barrier. Loratadine, desloratadine, cetirizine, and fexofenadine have excellent safety records. Their safety has been established in drug-interaction studies, elevated-dose studies, and clinical trials.[31] These antihistamines also have proven safe in special subpopulations, including children and elderly patients.[31]

Loratadine and Desloratadine. Loratadine was first sold in the United States in 1993 and has been available OTC since 2002. Desloratadine has been available as a prescription medication in the United States since 2002. Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity. Loratadine is racemic mixture of active and inactive isomers, and desloratadine is a metabolite of loratadine made up only of the therapeutically active isomer.

Cetirizine. Cetirizine has been available in the United States as a prescription medication since 1996. Cetirizine is a major metabolite of hydroxyzine, a first-generation antihistamine. As with other antihistamines the principal effects of cetirizine are mediated by selective inhibition of peripheral H_1 receptors.

Fexofenadine. Fexofenadine tablets were first introduced in the United States in 1996. In the United States, fexofenadine is now available in the generic form but still requires a prescription. Fexofenadine, the major active metabolite of terfenadine, has selective peripheral H_1-receptor antagonist activity and does not cross the blood–brain barrier.

Sedative Potential and Changes in Cognitive Function with Newer Antihistamines

In terms of CNS safety, meta-analyses[32,33] have shown, in comparison with diphenhydramine, much less impairment with loratadine and cetirizine and almost no impairment with fexofenadine. Similarly, positron emission tomography imaging studies show 77% of H_1-receptor occupation by a first-generation antihistamine (chlorpheniramine, 2 mg p.o.) and 20 mg p.o. of cetirizine occupied 20–50% of the H_1-receptors and 120 mg p.o. of fexofenadine occupied <1% of the H_1-receptors.[34]

Loratadine and Desloratadine. There is no difference between loratadine, 10 mg p.o., and placebo for any measure of cognitive or psychomotor test performance, mood, or sedation.[23] Other studies also have shown that loratadine, 10 mg p.o., does not interfere with visuomotor coordination, digit symbol substitution, short-term memory, the ability to operate aircraft simulators, or performance in driving tasks.[35–37] Similarly, desloratadine is safe and nonsedating.[38] Psychomotor performance, BRT, and driving performance were not impaired by desloratadine.[39,40]

Cetirizine. A double-blind, placebo-controlled, randomized study in children, aged 7–14 years, showed cetirizine to have sedative properties.[41] Cetirizine also was reported to have a mild detrimental effect on driving ability[42] and sedative effects by visual analog scale and psychomotor activity.[31,43,44] Sedation has been reported in up to 14% of those taking cetirizine, 10 mg/day. Conversely, some reports show no impairment in driving tests, cognitive and psychometric tests, and specific questionnaires after 10 mg p.o. of cetirizine.[45] In comparison with loratadine, cetirizine has been shown to be associated with increased somnolence and less motivation to perform activities during the workday.[46] In psychomotor testing and sedation scales, cetirizine was more impairing that fexofenadine.[43]

Fexofenadine. Fexofenadine is a highly specific, H_1-receptor antagonist with a safety profile similar to placebo.[4,9,43] Unlike loratadine or cetirizine, fexofenadine is truly nonsedating, showing no dose-related increase in sedation, even at doses as high as 360 mg/day.[47,48] The effects of fexofenadine at doses of 120, 180, and 240 mg were evaluated in six patients. Results showed no changes in performance or sleepiness with any dose of fexofenadine at any time point.[47] BRT with and without cellular phone usage as well as driving simulations in fexofenadine-treated subjects did not differ from placebo.[49,50] Cognitive testing with fexofenadine was similar to placebo.[51]

Efficacy of Newer Antihistamines

The newer antihistamines have shown similar efficacy in the treatment of allergic rhinitis and chronic urticaria to first-generation antihistamines.[52–54] We are not aware of any studies directly comparing the effectiveness of first-generation versus newer antihistamines for acute allergic reactions.

Although loratadine has been shown in multiple studies to be nonsedating, there is concern that it is less effective than other newer antihistamines in reducing symptoms associated with environmental allergies.[55] Several studies[56–58] suggest that the effectiveness of cetirizine is greater than loratadine. Two double-blind, randomized, placebo-controlled studies compared cetirizine, 10 mg daily, with loratadine, 10 mg daily, in patients with seasonal allergic rhinitis.[56,57] These studies both found greater benefit from cetirizine using symptom complex scores and patient assessments. A third study,[58] among children aged 2–6 years, found histamine wheal response to be decreased more significantly with cetirizine compared with loratadine while eosinophil counts and investigator and patient global symptoms scores were similar between the two groups. Fexofenadine was superior to loratadine in terms of improving itchy eyes, nasal congestion, and quality of life in patients with seasonal allergic rhinitis.[59] Using total symptoms scores for evaluation of patients with seasonal allergic rhinitis, cetirizine, 10 mg daily; fexofenadine, 120 mg daily; and fexofenadine, 180 mg daily, were similar in efficacy.[60]

In chronic urticaria, numerous studies have shown equal if not improved effectiveness with newer antihistamines when compared with first-generation antihistamines.[28,61,62] Cetirizine has shown better efficacy in comparison with fexofenadine[63] and loratadine.[64] Despite these data, some physicians prefer antihistamines such as desloratadine and fexofenadine because they are less sedating and this becomes more important when patients need antihistamines daily.[65]

Onset of Action. Onset of action of the newer antihistamines has been shown to be rapid in after pollen

challenge in subjects with seasonal allergic rhinitis.[66–68] Other studies show that loratadine and desloratadine exhibit their antihistaminic effect within 1–3 hours and that this effect can last over 24 hours.[14,15,18] Cetirizine is rapidly absorbed with maximum concentration within 1 hour of oral administration.[18,69] Fexofenadine has an onset of action of ~60 minutes.[12,18]

Cost of Newer Antihistamines

Loratadine is OTC and offers the cheapest available "nonsedating" antihistamine whereas cetirizine and fexofenadine require prescriptions and are more expensive as shown in Fig. 1. The average cost per usual adult single dose of loratadine (10 mg), desloratadine (5 mg), cetirizine (10 mg), generic fexofenadine (180 mg), and fexofenadine (180 mg) is $0.88, $2.75, $2.32, $2.15 and $2.43, respectively. Diphenhydramine (50 mg) remains the least expensive antihistamine at $0.37. In the context of the cost of a typical ED visit being $383–560,[70,71] these cost differences are minimal.

DISCUSSION

Diphenhydramine is the most frequently used medication in the treatment of acute allergic reactions in the ED.[6,7] Unfortunately, first-generation antihistamines, such as diphenhydramine, can be highly sedating and introduce hazard for activities such as driving cars, flying planes, or using heavy machinery or for nurses administering medications to patients in the hospital.[9,23,72] Our review suggests that newer antihistamines (such as loratadine, desloratadine, cetirizine, and fexofenadine) may offer equal efficacy with less sedation[43] than diphenhydramine. Therefore, the newer antihistamines provide an attractive option for either the acute care setting or prescription on discharge from the ED.

The sedative potential is not trivial. For example, driving performance was worse in patients treated with diphenhydramine than in patients drinking alcohol. A single dose of diphenhydramine is equivalent to a blood-alcohol content of 0.1—higher than the 0.08 level that makes a driver legally drunk.[4] Despite this potential for psychomotor impairment and laws enacted in 37 states and the District of Columbia against driving after taking OTC first-generation antihistamines,[22,73] many individuals continue to drive and prosecutions are rare. The Allergic Rhinitis and Its Impact on Asthma guidelines, along with other experts, already suggest using the newer antihistamines for allergic rhinitis because of favorable efficacy and excellent safety profiles.[74,75] Despite the lack of data in the ED setting, we believe that this could be extended to the management of acute allergic reactions. On discharge from the ED after an acute allergic reaction, prescription of newer antihistamines, rather than diphenhydramine, should be considered. This would be in addition to the prescription for self-injectable epinephrine in appropriate populations (*e.g.*, anaphylaxis).[6,7]

In comparing the newer antihistamines (Table 1), both loratadine and cetirizine are safe in pregnancy but require dose adjustment in the presence of hepatic or renal impairment. Fexofenadine is FDA approved down to age 6 years, and loratadine and cetirizine can be used after age 2 years and 6 months, respectively. Loratadine is the only newer antihistamine available without a prescription. The newer antihistamines are not available in i.v. forms and although no data exist, oral dissolvable or liquid syrup forms of loratadine and desloratadine may offer an easier method of treating patients with acute allergic reactions without needing i.v. access. Similarly, cetirizine is available as both a chewable tablet and liquid syrup.

Although loratadine seems less efficacious and fexofenadine appears to have the least sedation, the data regarding cetirizine are less clear. Some studies report cetirizine to be sedating[41,46] and others do not.[45] However, to summarize a 1998 national task force, the incidence of sedation is less that that seen with first-generation antihistamines but is greater that that seen with placebo.[76] Furthermore, use of a larger dose of loratadine (40 mg/day) or cetirizine (20 mg/day) is clearly linked with an increased incidence of sedation.[3,37,77,78] Loratadine, desloratadine, and fexofenadine at the recommended doses are classified by the FDA as nonsedating antihistamines and are approved for use by airline pilots by the Federal Aviation Administration, unlike cetirizine.[51,79–81]

Approximately 5–20% of individuals with anaphylaxis have an unusual pattern of symptoms, *viz.*, either biphasic anaphylaxis or protracted anaphylaxis.[82,83] Biphasic anaphylaxis refers to anaphylaxis that resolves but then recurs 1–8 hours later. Protracted anaphylaxis refers to anaphylaxis that persists for up to 48 hours despite treatment. These two patterns are especially common among subjects who develop symptoms >30 minutes after exposure and subjects who are exposed to an allergen by the oral route. Although we recognize that epinephrine is a crucial part of initial management, many patients also will (and should) receive antihistamines.[6,7] In such cases, the longer-acting newer antihistamines may provide benefit with less frequent dosing, leading to improved patient compliance after ED discharge. Diphenhydramine needs to be taken every 4–6 hours to maintain benefit whereas the newer antihistamines can be taken once a day.

The main limitation of our review arises from the lack of evidence regarding the effectiveness of newer antihistamines for the specific treatment of acute allergic reactions. Similar efficacy might be expected based on their effectiveness in blocking histamine in allergic

rhinitis and chronic urticaria. This lack of data may deter some physicians from using newer antihistamines but provides a clear area for further research. Regardless, it is important to increase awareness of sedation and factor that into the selection of antihistamines for ED and post-ED use. With regard to speed of onset, unlike diphenhydramine, i.v. formulations are not available for the newer antihistamines. Although a faster onset of action is critical to treating patients with severe acute allergic reaction, data regarding the onset of clinical activity suggest only small differences between newer antihistamines such as cetirizine, with an onset of action of 15–30 minutes,[18] and diphenhydramine. Again, we lack data on the role of dissolvable newer antihistamines such as loratadine and desloratadine and liquid cetirizine in the ED.

The significantly lower price for OTC diphenhydramine has resulted in almost one-half of the patients in the United States using sedating (versus nonsedating) products.[84] Although we recognize that newer antihistamines are more expensive, outpatient studies have indicated that ED visits, inpatient admissions, and physician office visits were significantly lower for patients using newer antihistamines[85]; these outcome differences led to significantly lower total direct healthcare treatment costs per patient for those using newer antihistamines versus first-generation antihistamines.[85] This evidence should be considered when prescribing antihistamines for a patient on discharge from the ED.

CONCLUSION

In summary, we believe that newer antihistamines are an option for treatment of acute allergic reactions when antihistamines are needed and sedation is a potential concern. Although there are sparse data on this exact issue, circumstantial data suggest that nonsedating antihistamines offer safer options with equal efficacy to first-generation antihistamines. Although onset of action is critical, the treatment decision also should consider the increased driving hazards, work-related decrease in productivity, and risk of errors after discharge. Loratadine and desloratadine are available as liquid syrup and oral dissolvable tablets for ease of administration in the acute setting. Cetirizine is available as liquid syrup and chewable tablet formulations and is more potent. Fexofenadine may offer the best overall balance of effectiveness and safety but is only available in pill form. With ~1 million ED visits each year for acute allergic reactions,[1] we hope that this review will encourage consideration of newer treatments and spur ED-based clinical research to more directly address the issues covered in our literature review.

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