

## Risk of first-generation H<sub>1</sub>-antihistamines: a GA<sup>2</sup>LEN position paper

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**To cite this article:** Church MK, Maurer M, Simons FER, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, Holgate ST, Zuberbier T. Risk of first-generation H<sub>1</sub>-antihistamines: a GA<sup>2</sup>LEN position paper. *Allergy* 2010; **65**: 459–466.

### Keywords

adverse event; allergic rhinitis; cognitive function; sedation.

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Accepted for publication 11 December 2009

DOI:10.1111/j.1398-9995.2009.02325.x

Edited by: Thomas Bieber

### Abstract

**Background:** First-generation H<sub>1</sub>-antihistamines obtained without prescription are the most frequent form of self-medication for allergic diseases, coughs and colds and insomnia even though they have potentially dangerous unwanted effects which are not recognized by the general public.

**Aims:** To increase consumer protection by bringing to the attention of regulatory authorities, physicians and the general public the potential dangers of the indiscriminate use first-generation H<sub>1</sub>-antihistamines purchased over-the counter in the absence of appropriate medical supervision.

**Methods:** A GA<sup>2</sup>LEN (Global Allergy and Asthma European Network) task force assessed the unwanted side-effects and potential dangers of first-generation H<sub>1</sub>-antihistamines by reviewing the literature (Medline and Embase) and performing a media audit of US coverage from 1996 to 2008 of accidents and fatal adverse events in which these drugs were implicated.

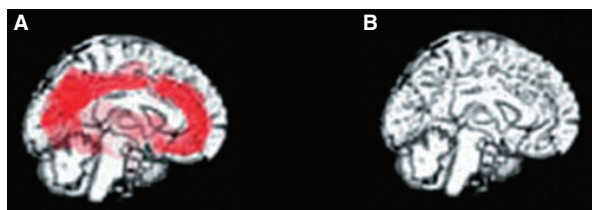
**Results:** First-generation H<sub>1</sub>-antihistamines, all of which are sedating, are generally regarded as safe by laypersons and healthcare professionals because of their long-standing use. However, they reduce rapid eye movement (REM)-sleep, impair learning and reduce work efficiency. They are implicated in civil aviation, motor vehicle and boating accidents, deaths as a result of accidental or intentional overdosing in infants and young children and suicide in teenagers and adults. Some exhibit cardiotoxicity in overdose.

**Conclusions:** This review raises the issue of better consumer protection by recommending that older first-generation H<sub>1</sub>-antihistamines should no longer be available over-the-counter as prescription-free drugs for self-medication of allergic and other diseases now that newer second-generation nonsedating H<sub>1</sub>-antihistamines with superior risk/benefit ratios are widely available at competitive prices.

H<sub>1</sub>-antihistamines are inverse agonists that combine with and stabilize the inactive conformation of H<sub>1</sub>-receptors and thus interfere with the actions of histamine at H<sub>1</sub>-receptors. They are widely used for the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, coughs, colds and insomnia. These drugs are usually classified as older 'first-generation H<sub>1</sub>-antihistamines' and newer 'second-generation H<sub>1</sub>-antihistamines'.

First-generation H<sub>1</sub>-antihistamines, many of which have been in clinical use since the 1940s and 1950s, derive from the same chemical stem from which cholinergic muscarinic antagonists, tranquilizers, antipsychotics and antihyperten-

sive agents were also developed (1). As a consequence, they have poor receptor selectivity and often interact with receptors of other biologically active amines and causing antimuscarinic, anti- $\alpha$ -adrenergic and antiserotonin effects. They penetrate the blood–brain barrier readily (Fig. 1A). Their proclivity to interfere with neurotransmission by histamine at central nervous system (CNS) H<sub>1</sub>-receptors potentially leads to drowsiness, sedation, somnolence, fatigue leading to impairment of cognitive function, memory and psychomotor performance. In addition, the H<sub>1</sub>-antihistaminic effects in the brain are primarily responsible for the potentially life-threat-



**Figure 1** The penetration (red colouring) of (A) diphenhydramine, a first-generation H<sub>1</sub>-antihistamine, and (B) bepotastine, a second-generation H<sub>1</sub>-antihistamine, into human brain shown by positron emission tomography [reproduced from reference (3)].

ening toxicity of first-generation H<sub>1</sub>-antihistamines in overdose. The adverse effects of these drugs have been widely reported, beginning shortly after they were introduced six decades ago (2).

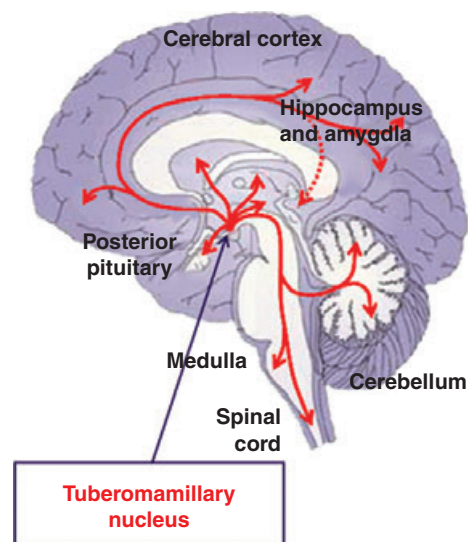
A major advance in antihistamine development occurred in the 1980s with the introduction of second-generation H<sub>1</sub>-antihistamines (4), which are minimally or nonsedating because of their limited penetration of the blood–brain barrier (Fig. 1 B). In addition, these drugs are highly selective for the histamine H<sub>1</sub>-receptor and have no anticholinergic effects.

Despite the recommendations of the WHO Guideline ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines (in collaboration with AllerGen, GA<sup>2</sup>LEN and WHO) for use of second-generation H<sub>1</sub>-antihistamines (5), oral first-generation H<sub>1</sub>-antihistamines are widely used in both adults and children for self-medication of diverse allergic symptoms, particularly allergic rhinitis, allergic conjunctivitis and urticaria and also for relief of symptoms of upper respiratory tract infections, and nonspecific cough, disorders in which there is little or no support for their use (6, 7). In addition, they are the most commonly used medications worldwide for relief of insomnia. Their ubiquitous use is related to the following, largely fallacious, reasons.

The primary reason for their choice by adults as over-the-counter medications is that first-generation H<sub>1</sub>-antihistamines have been available for decades, and, as such, patients are very familiar with them and consider that ‘they must be both effective and safe’. In fact, patients believe them to be so safe that the warnings on the label that the drugs may cause drowsiness often go unheeded, or even unread.

For infants and children, the justification for the preference for first-generation H<sub>1</sub>-antihistamines is twofold. First, because of their widespread use for many years, first-generation H<sub>1</sub>-antihistamines are assumed, particularly by the general public, to be as safe as the newer second-generation drugs. Second, many physicians still advise the use of sedating antihistamines at night to ensure a better sleep. The logic of these recommendations is not supported by scientific studies (8) but rather on ‘felt-experience’. Recent studies of the effects of first-generation antihistamines on brain function suggest that they produce an unnatural sleep, as is described later.

In line with creating the international guidelines in allergy, GA<sup>2</sup>LEN, the Global Allergy and Asthma European Network, set up a taskforce to investigate the risk/benefit ratio of first-generation sedating H<sub>1</sub>-antihistamines in the treatment of



**Figure 2** A map of histaminergic neurons emanating from the tuberomammillary nucleus in the brain [adapted from reference (9)].

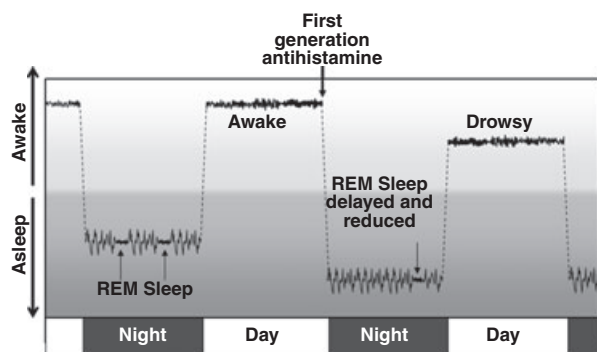
allergic and pruritic diseases. The taskforce reviewed the literature (Medline and Embase) to evaluate the level of side-effects of first-generation H<sub>1</sub>-antihistamines in controlled studies and published reports. As there is a bias in reporting of adverse events towards newly licensed drugs vs old drugs, a screen was performed using a media audit of US coverage from 1996 to 2008 of accidents and fatal adverse events in which first-generation H<sub>1</sub>-antihistamines were implicated.

### Impact of first-generation antihistamines on cognitive functions – implications for presenteeism and learning

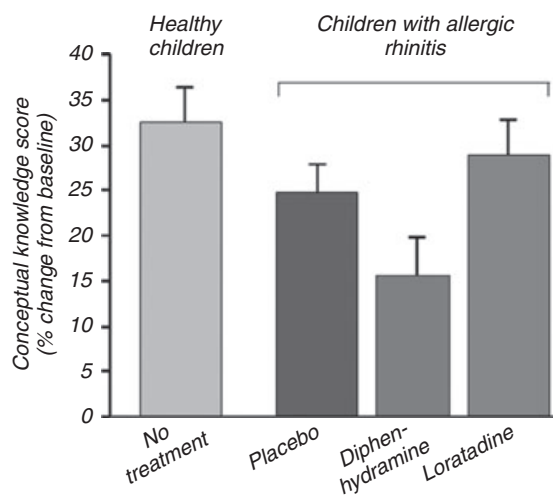
There are approximately 64 000 histamine-producing neurones, located in the tuberomammillary nucleus of the human brain. When activated, these neurones stimulate H<sub>1</sub>-receptors in all of the major parts of the cerebrum, cerebellum, posterior pituitary and spinal cord (Fig. 2) (9).

The actions of histamine on H<sub>1</sub>-receptors in the brain have been implicated in arousal in the circadian sleep/wake cycle, reinforcement of learning and memory, fluid balance, suppression of feeding, control of body temperature, control of cardiovascular system and mediation of stress-triggered release of ACTH and β-endorphin from the pituitary gland (10). Furthermore, as neurotransmitter amines in the brain do not work individually but in a complex integrated network, the central anticholinergic effects of first-generation H<sub>1</sub>-antihistamines may contribute to their unwanted CNS effects (11).

First-generation H<sub>1</sub>-antihistamines markedly alter the circadian sleep/wake cycle (Fig. 3). The release of histamine during the day causes arousal, whereas its reduced production at night results in a passive reduction of the arousal response. It is well established that taking first-generation H<sub>1</sub>-antihistamines in doses commonly recommended for the treatment of allergic disorders frequently leads to daytime



**Figure 3** A theoretical diagram of the sleep/wake cycle and the effects of a first-generation H<sub>1</sub>-antihistamine leading to somnolence during the day and abnormal sleep at night. This diagram is based on data from references (19–21).



**Figure 4** The effect of allergic rhinitis on learning in children and the influence of a first-generation (diphenhydramine) and second-generation (loratadine) H<sub>1</sub>-antihistamine. The conceptual knowledge score of children with allergic rhinitis taking diphenhydramine was significantly ( $P = 0.0167$ ) lower than that of healthy children. There was no significant difference between healthy children and those with allergic rhinitis taking loratadine [adapted from reference (23)].

somnolence, sedation, drowsiness, fatigue and impaired concentration and memory (12–15). The incidence of subjectively reported somnolence has been reported to vary from 40% with chlorpheniramine or brompheniramine to 80% after hydroxyzine (16). However, lack of drowsiness does not mean that an individual is able to drive a vehicle without impairment because subjective somnolence and impairment of the ability to perform tasks are not necessarily correlated, some individuals denying subjective adverse effects despite objective evidence of impairment, while others complain of somnolence and yet are able to perform psychomotor tests adequately (17).

At night, first-generation H<sub>1</sub>-antihistamines increase the latency to the onset of rapid eye movement (REM) sleep and

reduce the duration of REM sleep (18–21) (Fig. 3). Furthermore, residual effects, or hang-over, are still present the next morning. Such effects include impairment in divided attention, vigilance, working memory and sensory-motor performance, and reduced latency to daytime sleep (20, 22).

Allergic rhinitis reduces learning ability in children and is associated with poor examination performance in teenagers. This situation is worsened by first generation, but not second-generation, H<sub>1</sub>-antihistamines (Fig. 4) (23–25). Furthermore, in an analysis of 1834 teenage students in the UK taking national examinations, those with untreated allergic rhinitis were 40% more likely to drop one or more grades compared with healthy teenagers. However, if they took a first-generation H<sub>1</sub>-antihistamine, the likelihood to drop one or more grades increased to 70% (26).

### Summary of the effects of first-generation H<sub>1</sub>-antihistamines on the central nervous system

First-generation H<sub>1</sub>-antihistamines cause drowsiness, especially with the initial doses. Indeed, their packaging carries a warning that they may cause drowsiness and, if affected, not to drive or operate machinery. It is clear that many patients either ignore this warning or think it applies only to the period immediately following drug ingestion, believing that there will be no impairment in the morning when having taken the drug the previous evening. Below is a summary of the most common CNS effects of first-generation H<sub>1</sub>-antihistamines.

- Impairment of function is produced even by the lowest doses of first-generation H<sub>1</sub>-antihistamines that are recommended by manufacturers; for example, chlorpheniramine 4 mg, diphenhydramine 25 mg, promethazine 10 mg and triprolidine 5 mg (27, 28).
- Effects of first-generation H<sub>1</sub>-antihistamines on the CNS are similar to and additive with those produced by alcohol (ethanol) or other CNS-sedatives, such as benzodiazepines (14, 15, 29).
- Bedtime dosing may not decrease functional impairment during the next day because first-generation H<sub>1</sub>-antihistamines have long elimination half-life values with consequential hang-over effects the following morning (14, 20, 22, 30, 31).
- Some patients are especially vulnerable to the CNS effects, for example: women; the elderly; persons with a small body mass hepatic or renal dysfunction; or those with a pre-existing CNS disorder (14, 15).
- Tolerance to sedation and psychomotor impairment, although suggested from some studies (14, 32–34), does not necessarily occur (15, 35).

### Antihistamines and accidents – an underestimated danger of cognitive impairment

#### Antihistamines and airplane crashes

The Manual of Civil Aviation Medicine published by the International Civil Aviation Organization states that ‘a pilot

with allergic symptoms severe enough to require medication should be treated with a nonsedating antihistamine, such as fexofenadine or loratadine' (36–38). While this is rigorously enforced with random drug screening tests for military and commercial airline pilots, it is clear that this recommendation is blatantly disregarded by many other civil aircraft pilots, particularly those who fly private or small aircraft. Sen and colleagues (39) used the Civil Aerospace Medical Institute's (CAMI's) Toxicology Database to examine the incidence of first-generation H<sub>1</sub>-antihistamines usage in pilot fatalities in civil aircraft accidents that occurred during a 16-year (1990–2005) period. Of 5383 fatal aviation accidents from which CAMI received specimens, there were 338 accidents (6% of total) where the pilot's blood sample was found to contain first-generation H<sub>1</sub>-antihistamines (brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine and triprolidine). First-generation H<sub>1</sub>-antihistamines, varying in blood levels from the sub-therapeutic to the toxic range, were detected alone in 103 fatalities (1 antihistamine in 94 and 2 antihistamines in 9 cases), while other drug(s) and/or ethanol were also present in the remainder. The National Transportation Safety Board determined the use of first-generation H<sub>1</sub>-antihistamines to be the cause of 13 and a contributory factor in 50 of the 338 accidents. First-generation H<sub>1</sub>-antihistamines were found in approximately 4% of the fatalities/accidents in 1990 and 11% in 2004.

Civil aviation pilots often exceed the manufacturer's recommended dose of first-generation H<sub>1</sub>-antihistamines but continue with their everyday lives regardless (40). Soper and colleagues reported that during the period 1991–1996, 47 (2.2%) accidents involved chlorpheniramine. In 16 of these cases, only chlorpheniramine was detected with the average blood concentration of 100 ng/ml, some ten times higher than its therapeutic level.

#### Antihistamines and other accidents

Documentation of accidents involving other means of transport, such as motor vehicles (including buses), trains and boats, is poor because drivers are usually tested for only ethanol or illegal drugs after a crash. For this reason, the authors undertook a media audit of US coverage of such accidents from 1996 to 2008 in which first-generation H<sub>1</sub>-antihistamines were implicated. This revealed 54 fatalities, likely a gross underestimation of the true figure. A similar audit performed on second-generation H<sub>1</sub>-antihistamines found no media articles that insinuated them as a source of impairment or inebriation that might lead to an accident or other hapless result. In fact, an important message of the coverage as a whole is that second-generation drugs are exonerated from many of the harmful side-effects of their predecessors.

#### Danger of potentially lethal overdose by first-generation antihistamines

Overdosage, either by accident or as a suicide attempt, is common with first-generation H<sub>1</sub>-antihistamines and often

leads to death. Intoxication symptoms during emergency admission are variable and to some extent dose-dependent and age-dependent. Adults and adolescents often exhibit CNS-suppressive symptoms, including somnolence and coma (41, 42). Infants and children often exhibit initial paradoxical CNS stimulation, including agitation, hallucinations, confusion and convulsions before progressing to coma. Diphenhydramine overdoses are so frequently reported to poison control centres in the United States that evidence-based guidelines have been published to facilitate their management (43). In contrast, a search of the literature found no deaths associated directly with overdoses of second-generation H<sub>1</sub>-antihistamines.

Over-the-counter medicines containing first-generation H<sub>1</sub>-antihistamines for the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, coughs, colds and insomnia have been used for many years. Because of this, they are presumed by the general population to be efficacious and safe. However, they came into use before randomized controlled clinical trials were required to demonstrate efficacy and safety in patients of any age, including children. In February 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK (44) advised that cough and cold remedies containing certain ingredients, including first-generation H<sub>1</sub>-antihistamines, should no longer be used in children under six because the balance of benefit and risks has not been shown to be favourable. This followed their advice in March 2008 stating that they should not be used in children under the age of 2 years. Reports submitted to regulators stated that more than 3000 people have reported adverse reactions to these drugs and that diphenhydramine and chlorpheniramine were mentioned in reports of 27 and 11 deaths, respectively (44).

In the United States, reports of serious and often life-threatening adverse events of promethazine in children led to a 'boxed warning' (the so-called 'black box') being added in 2004 to the labelling of promethazine. The warning included to a contraindication for use in children <2 years of age and a strengthened warning with regard to use in children 2 years of age or older (45). In March 2007, a group of senior paediatricians urged the Federal Drug Administration (FDA) to issue a public statement explaining that many over-the-counter paediatric cough and cold medications, including first-generation H<sub>1</sub>-antihistamines, had not been shown to be safe and effective for children under six, and to take action against misleading marketing, and to revise its monograph accordingly. The FDA committee voted 13–9 in favour of immediate action against the use of cough and cold medications in children under 6 years of age. However, these preparations are still marketed for children between 2 and 5 years of age. Because the original monograph is still in effect, the products and their 'toddler'-friendly, good-tasting liquid formulations are still being widely advertized to parents in ways that suggest that they are known to be safe, effective and recommended by most paediatricians. Furthermore, despite their own proposal that the use of these products for sedation be stopped, companies are still marketing 'nighttime' preparations containing sedating antihistamines (46).

### Cardiac toxicity

Much has been written about the propensity of two second-generation H<sub>1</sub>-antihistamines introduced in the 1980s, astemizole and terfenadine, to block the I<sub>Kr</sub> current, prolong the QT interval, and potentially cause serious polymorphic ventricular arrhythmias such as torsades de pointes (47–49). These two drugs are no longer approved by regulatory agencies in most countries. Although cardiac toxicity is not a class effect and does not occur through the H<sub>1</sub>-receptor, some first-generation H<sub>1</sub>-antihistamines, such as promethazine (50), brompheniramine (51, 52), diphenhydramine (53, 54), may be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or overdoses. No clinically significant cardiac effects have been reported for the second-generation H<sub>1</sub>-antihistamines loratadine, fexofenadine, mizolastine, ebastine, azelastine, cetirizine (55, 56) desloratadine (57, 58) and levocetirizine (59).

### H<sub>1</sub>-antihistamines in infants

Even more alarming is the practice of using first-generation H<sub>1</sub>-antihistamines as sedatives/sleeping aids in infants. Although reports of fatal intoxications are uncommon and are usually accidental, infant homicides have also been reported (60). For example, five cases of fatal diphenhydramine intoxication were reported in infants from 6 to 12 weeks old. In one case, the child's father admitted giving the infant diphenhydramine in an attempt to induce the infant to sleep; in another case, a daycare provider admitted putting diphenhydramine in a baby bottle (61).

Over-the-counter cold medications can also contain first-generation H<sub>1</sub>-antihistamines and their use in children may also be potentially lethal, even when the manufacturer's instructions are followed. In a report of ten infant deaths in Ohio over an 8-month period in which these drugs were at least a contributory factor to death, two of the cases were the result of possible child abuse. In the remainder, caregivers were under the mistaken notion that over-the-counter cold medications formulated for children were also safe for use in infants. These cases clearly demonstrate that administration of some over-the-counter cold medications to infants can result in toxicity that can lead to death (62, 63).

These reports contrast markedly with the report of an 18-month-old boy, weighing only 13 kg, who drank approximately 18 ml of cetirizine solution, corresponding to a dose of 180 mg, some 50 times the recommended dose. The toddler tolerated the overdose with virtually no complications (64). Although this single case is no proof of the harmlessness of a major overdose of second-generation H<sub>1</sub>-antihistamines, it is supported by six other less dramatic reports of cetirizine (65) and one of loratadine (66) overdoses in children. Indeed, the overall safety profiles of the second-generation H<sub>1</sub>-antihistamines are similar to placebo. This has been confirmed in randomized, double-blind, placebo-controlled trials of cetirizine, loratadine and levocetirizine lasting 12–18 months (67–69).

### H<sub>1</sub>-antihistamines in the elderly

The elderly are particularly vulnerable to the adverse effects of first-generation H<sub>1</sub>-antihistamines. Twenty-five per cent of individuals older than 65 years of age have some cognitive impairment, often with no overt sign of dysfunction (70), and histamine neurotransmission is disrupted in individuals with neurodegenerative disease (71). Administration of first-generation H<sub>1</sub>-antihistamines in this population is associated with an increased risk of inattention, disorganized speech, altered consciousness and impaired function or alertness (72, 73).

### H<sub>1</sub>-antihistamines in pregnancy

The first-generation H<sub>1</sub>-antihistamines chlorpheniramine and diphenhydramine have a favourable FDA category B rating, i.e. they are recommended for use in pregnancy because of their lack of teratogenicity. The only orally administered second-generation H<sub>1</sub>-antihistamines that have a favourable category B rating at present and are recommended for use in pregnancy are cetirizine, levocetirizine and loratadine (14).

However, the main concern about the first-generation H<sub>1</sub>-antihistamines in pregnancy is their use in large doses or overdose just before parturition when they cause contractions because of their oxytocin-like effects (74). Furthermore, if a large dose is taken immediately before delivery, the neonate may exhibit withdrawal symptoms including tremulousness and irritability (75).

### Discussion and Conclusions

The results of this taskforce report clearly show that the risks of first-generation H<sub>1</sub>-antihistamines have been clearly underestimated in the medical field, particularly when purchased as nonprescribed over-the-counter medications. As they are old drugs introduced before regulatory agencies existed and licensed before the era of randomized controlled trials and modern evidence-based medicine, H<sub>1</sub>-antihistamines are under less strict surveillance of the regulatory authorities worldwide.

Based on the concept that 'what has been good for my grandparents and my parents must be good for me and my child', first-generation H<sub>1</sub>-antihistamines have been widely recommended in textbooks to be safe and have been used in pregnancy, infancy and childhood as preferred drugs. Furthermore, they have often been advised to facilitate a good night's sleep for patients with allergic rhinitis or urticaria. This, however, is no longer logical or acceptable.

First, screening of the public media shows clearly that there is a high rate of fatal accidents attributed to the use of first-generation H<sub>1</sub>-antihistamines. This is easily explained because, even at recommended doses, the level of impairment produced by these medications is similar to or exceeds that produced by alcoholic beverages. For example, diphenhydramine 50 mg is more impairing than alcohol sufficient to produce a blood concentration of 0.1% (29). Furthermore, in many instances, individuals often exceed the recommended doses of first-generation H<sub>1</sub>-antihistamines to achieve rapid

relief from their symptoms (40). While there is a high level of awareness by the general public of the dangers of drinking alcohol and driving, too little attention has been given to similar dangers caused by drugs, especially those available over-the-counter. These problems can be avoided by the use of nonsedating second-generation H<sub>1</sub>-antihistamines instead.

Secondly, it is clear that first-generation H<sub>1</sub>-antihistamines have detrimental effects on sleep and learning, exacerbating the impairment caused by the allergic disease itself. The REM phases of sleep are changed and because these are important in brain development and learning, it is no surprise that in clinical studies of first generation, H<sub>1</sub>-antihistamines also impaired the learning capabilities of children. The effect on learning is a concern because, in our knowledge-based society, learning at school and at university is of the utmost importance. In contrast, newer nonsedating second-generation H<sub>1</sub>-antihistamines are not only free from these unwanted side-effects but reduce the detrimental effects on mental functions caused by allergic disease.

Given the risks of first-generation H<sub>1</sub>-antihistamines, there is no good argument today for these older sedating drugs to be available as over-the-counter medications. However, we do not suggest that their prescription by medical practitioners should be prevented because, as stated in the 2008 EAACI/GA<sup>2</sup>LEN/EDF/WAO Guideline on the management of urticaria, special situations may arise for the specialist to employ them outside the outcome treatment algorithm (76).

It has been pointed out in the past that first-generation H<sub>1</sub>-antihistamines are cheaper and especially in countries of the third world or evolving countries the only way people can afford a treatment for allergic rhinitis. However, with the advent of many generic versions of nonsedating antihistamines, this is no longer true. For example, on the Internet site of a major supplier, generic cetirizine was priced at \$5.95 and loratadine at \$5.04 per 100 tablets (dosage 1 tablet per day), while chlorpheniramine was priced at \$2.95 per 100 tablets (dosage 4 tablets per day ≡ \$11.8 per day treatment) (77).

The debate in favour of the availability of the old sedating H<sub>1</sub>-antihistamines as over-the-counter medications is based

primarily on emotion rather than on science. The most worrisome point, however, is that, in general, old drugs are under a less strict surveillance by regulatory authorities and the public awareness of their possible dangers is less than with new drugs. In the United States of America, the 1951 Durham-Humphrey amendment to the original Federal Food, Drug and Cosmetic Act of 1938 requires that: 'a drug be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance'. But when a first-generation antihistamine is purchased from an open display in a pharmacy, patients assume that it is a perfectly harmless medication; after all it has been available in this way for several generations. For acute exacerbations of allergic diseases, such as allergic rhinitis and urticaria, or in the treatment of troublesome cold or cough symptoms, individuals often exceed the manufacturers recommended dose so as to obtain instant relief from symptoms. They seldom pay attention to the warnings of sedation on the label and continue with their normal everyday activities as usual, sometimes with disastrous consequences.

In conclusion, had first-generation H<sub>1</sub>-antihistamines been filed for registration with the clear cut criteria for evidence-based medicine studies expected today, it is very unlikely that regulatory authorities would approve prescription-free sales. Because the potentially dangerous unwanted effects of these drugs are not recognized by the general public, consumer protection needs to be paramount. Therefore, we ask that the case for allowing the prescription-free sale for self-medication of old sedating first-generation H<sub>1</sub>-antihistamines should be re-examined now that we recognize more fully the dangers of this class of drugs and as modern nonsedating antihistamines are now available at competitive prices.

### Acknowledgments

The authors acknowledge the help and valuable comments of the members of the GA<sup>2</sup>LEN Executive Committee, including Jean Bousquet, Paul van Cauwenberge, Peter Burney, Magnus Wickmann, Karin C. Lodrup Carlsen and Ewa Nizankowska-Mogilnicka.

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