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REVIEW

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Diphenhydramine: It is time to say a final goodbye

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ABSTRACT

Diphenhydramine, once a pioneering antihistamine, is now overshadowed by second-generation antihistamines with similar efficacy and fewer adverse effects. Current data suggest that the adverse side-effect profile of diphenhydramine is higher among children and older adults. This has led to countries such as Germany and Sweden restricting access to first-generation antihistamines and societal guidelines advocating for the use of second-generation antihistamines. Despite its well-documented problematic therapeutic ratio, diphenhydramine remains available in over 300 formulations, most of which are over-the-counter.

Based on a comprehensive evaluation of practice patterns and the prevalence and incidence of adverse clinical events, we believe that diphenhydramine has reached the end of its life cycle, and in its class of therapies it is a relatively greater public health hazard. We recommend it should no longer be widely prescribed or continue to be readily available over the counter.

Keywords: Diphenhydramine, Histamine H1 antagonists, Antihistamines, Second-generation

INTRODUCTION

Similar to humans, medications have natural life cycles. They are discovered and researched with the hope of providing effective interventions for the underlying causes and symptoms of specific diseases. Over time, as a medicine's usage grows, its indications may be expanded, and its safety profile becomes better understood, Fig. 1. Eventually, competition from newer medications with equal or better efficacy or fewer adverse events exceeds the comparative risk-benefit ratio of the earlier medication, often decreasing it to the point where it should be retired.

We believe that diphenhydramine has reached the end of its life cycle, and in its class of therapies is a relatively greater public health hazard. We recommend it should no longer be widely prescribed or continue to be readily available over the counter.

PREVALENCE AND USE OF DIPHENHYDRAMINE

It is difficult to find precise data on diphenhydramine prescriptions and over-the-counter purchases. In the United States, there are over 1.5 million prescriptions per year.[1] In addition, there appears to be far greater acquisition of diphenhydramine in over-the-counter products than is determined in the number of prescriptions. In a national Harris Poll survey of 500 adults and

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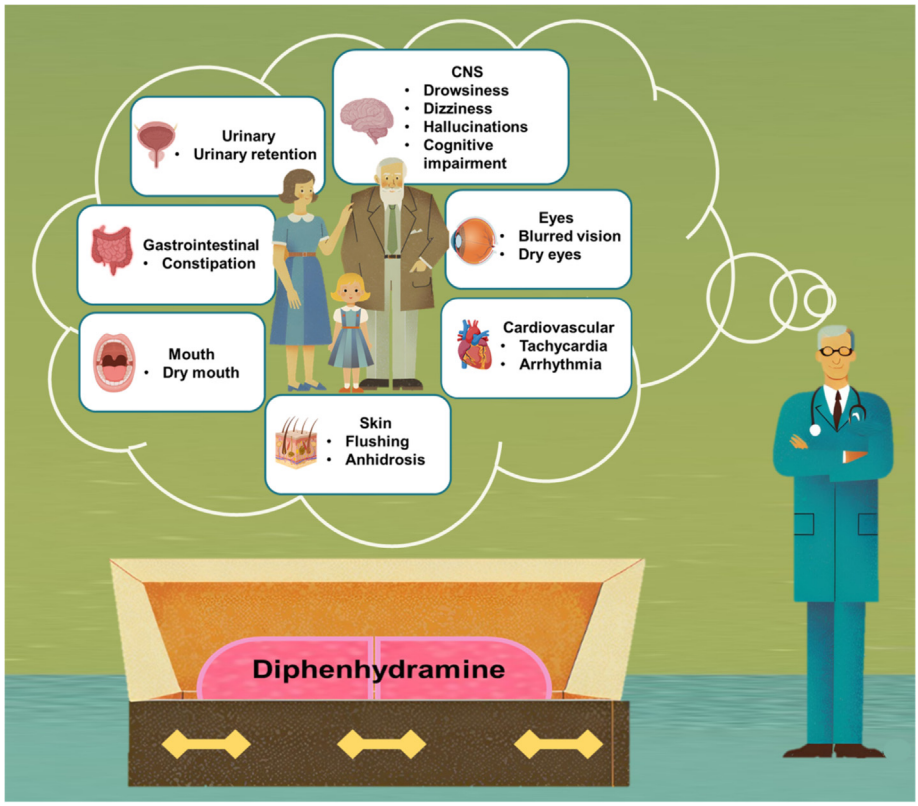

Fig. 1 Adverse effects of diphenhydramine.

501 parents of children ages 12–17 years, respondents reported they generally managed doctor-diagnosed seasonal allergic rhinitis with over-the-counter oral medications (62% of adults and 51% of children). Furthermore, overall, only 32% reported to be "very or extremely" satisfied with this treatment.[2] Parents consider diphenhydramine to be safe for their children and themselves because they have been using it since their childhood.[3] Thus, millions of adults and children are exposed to diphenhydramine yearly.

Diphenhydramine was the first antihistamine approved by the US Food and Drug Administration (FDA) to become available for treating allergies in 1946 when current rigorous medication testing standards were not in place.[4] Diphenhydramine now appears in more than 300 formulations, most of which are over-the-counter in the therapeutic categories of allergy, cough and cold medicine, and sleep aids. It is available in multiple formulations (liquid, tablet, capsule, injectable, topical for skin) in single (eg, Benadryl, Sominex) and combination (eg, Robitussin Severe Multi-Symptom Cough Cold + Flu Nighttime, Sudafed PE Day/Night Sinus Congestion) products.

Diphenhydramine has been used for its therapeutic efficacy in pruritus and dermatologic eruptions, including urticaria, food, medication, insect allergy reactions, allergic rhinitis, and associated ocular symptoms. It can mitigate nasal itch, sneezing, and rhinorrhea. However, as with other oral antihistamine monotherapies, it does not significantly reduce the most common and usually most problematic nasal complaint of congestion.[5]

ADVERSE EFFECTS, ABUSE POTENTIAL, AND SAFER ALTERNATIVES TO DIPHENHYDRAMINE

Multiple clinical conditions have been treated with both daytime and nighttime dosing with diphenhydramine. Over the years, due to this therapy, sedation and anticholinergic adverse effects have become apparent. In the 1970s, the pharmaceutical industry took advantage of these adverse effects and incorporated diphenhydramine into over-the-counter cough and cold products and sleep aids. However, there is increasing awareness of the magnitude of diphenhydramine's adverse effects, abuse potential, and the presence of safer alternatives. Current reassessment of

diphenhydramine's therapeutic ratio, the ratio of therapeutic benefits to the toxic effects, also referred to as risk/benefit, and risk/reward, has found diphenhydramine wanting.

Sedation is a concern with all first-generation antihistamines, and diphenhydramine is a prime example. In addition to being able to cross the blood-brain barrier, first-generation antihistamines lack specificity for H1-receptors. Consequently, these agents act to block the neurotransmitter effect of endogenous histamine within the central nervous system, leading to various adverse events, including sedation, drowsiness, and psychomotor impairment.[6] Similar adverse effects are reduced (eg, with cetirizine or loratadine) or absent (eg, fexofenadine) in second-generation antihistamines.[7] The half-life of diphenhydramine can vary based on age group, with the pediatric cohort's reported half-life as low as 4 h and the elderly patients' reported half-life as long as 18 h.[8] When used as a sleep aide, its long elimination half-life is paradoxically associated with daytime sedation beyond the night of sleep, poor concentration and consequent poor attention, reduced memory, poor sensory-motor performance, and compromised school performance.[9] Yet, patients are frequently unaware of the potential for these well-established effects.[3] This scenario has resulted in vehicular accidents in patients who have underestimated their sedation after taking such medications.[10] One study found that diphenhydramine demonstrated a more significant impact on driving than alcohol.[11] Consequently, the European Union has added diphenhydramine to its "do not drive" category due to its sedative potential.[9] In a simulated car-driving study, it was demonstrated that while diphenhydramine adversely impacted the psychomotor performance of subjects, this was not noted with second-generation antihistamines.[12] Such findings are reflected by the US Federal Aviation Authority (FAA) legislation, which forbids medical certification of pilots taking sedating antihistamines, whereas non-sedating antihistamines, including fexofenadine and desloratadine, remain permissible.[13]

Sleep aids containing diphenhydramine are available without a prescription and may provide temporary relief. Lifestyle changes, however, are usually the best approach for chronic insomnia, especially given the rapid development of tolerance to the sedative effects of diphenhydramine. First-generation antihistamines have also been demonstrated to interfere with sleep quality.[14–16]

The magnitude of the sedative effect from first-generation antihistamines led to the development of the second-generation, less or non-sedating antihistamines. Although there are virtually no studies directly comparing the efficacy of diphenhydramine and second-generation antihistamines, numerous double-blinded, randomized, placebo-controlled clinical trials show the efficacy of non-sedating antihistamines in treating allergic rhinitis. In multiple *in vivo* studies, second-generation antihistamines have demonstrated superior pharmacokinetic and pharmacodynamic properties, such as 24-h coverage after a single dose and better receptor binding.[17] They are safer with fewer adverse reactions, widely available, and similarly priced. They also have equivalent onset and longer-lasting treatment effects. Thus, they have much better therapeutic ratios than diphenhydramine.

Until 2019, parenteral (intravenous, IV or intramuscular, IM) diphenhydramine and hydroxyzine (another first-generation antihistamine) were the only medications in this class of agents for patients reporting to an emergency department with acute urticaria or anaphylaxis. Intravenous cetirizine has more recently been approved for use in urticaria.[18] It is as effective as IV diphenhydramine in preventing urticaria and has a 24-h duration with less sedation, requires a shorter emergency room stay, and results in fewer treatment-related adverse events.

Diphenhydramine is not recommended for people with specific health problems, including closed-angle glaucoma, dry eyes, peptic ulcer, constipation, and urinary retention. In addition, regular use of diphenhydramine poses risks for women who are pregnant or breastfeeding.[19] Due to anticholinergic properties, cumulative use of first-generation antihistamines confers risks for people over age 65, including Alzheimer's disease and other forms of dementia.[20]

Paradoxical stimulation with agitation and confusion is often the presenting sign of harm from first-generation medications in children, followed by extreme sedation and coma.[21] Consuming

more than the recommended dose has produced cardiac toxicity because of prolonged QTc and arrhythmias.[22]

The anticholinergic effect of reducing respiratory secretions by diphenhydramine has resulted in it becoming a frequent component in over-the-counter cough and cold products. Wang and colleagues looked at accidental unsupervised ingestions in the morbidity associated with cough and cold medicine exposure in children.[23] Most cases (61.3%) occurred in children aged 2 to younger than 4 years. Most exposures occurred in the child's residence (94.9%), and 43.8% were admitted to a health care facility (22.0% to a critical care unit). Dextromethorphan and diphenhydramine, when packaged alone or in combination products, contributed to 96.0% of accidental unintentional ingestions. Single-ingredient pediatric liquid diphenhydramine (30.1%) and single-ingredient pediatric liquid dextromethorphan (21.4%) were the most common specific products involved. There were 3 deaths from solid diphenhydramine formulations. Honey is likely better than diphenhydramine in reducing cough frequency.[24]

As people seek legal alternative medications for abuse, which have ease of obtaining information via online forums, there has been an increase in the number of cases involving excessive use of diphenhydramine. During the pandemic years, the TikTok "Benadryl Challenge" led to some hospitalizations and deaths.[25] In response, the FDA has issued warnings that taking higher than recommended doses of the antihistamine diphenhydramine can lead to serious heart problems, seizures, coma, or even death.[26]

Countries outside the United States, including Germany, the Netherlands, and Sweden, have taken action to limit diphenhydramine's accessibility by making it available by prescription only.[27] Canadian, United States. and British healthcare agencies recommend against cold medications containing diphenhydramine for children younger than 5 (United States) and 6 (Canada and Britain).[28–30]

The United States Practice Parameter Guidelines for Rhinitis recommended the use of second-generation in favor of first-generation antihistamines.[31] The Canadian Society of Allergy and Clinical Immunology (CSACI) recommends that first-generation antihistamines should only be considered a behind-the-counter medication.[9] This strategy was applied to pseudoephedrine in the United States because of its potential to be converted to methamphetamines. For diphenhydramine, it would give the pharmacist a role in recommending safer alternative medicines and preventing abuse.

CONCLUSION

The presence of effective and safer second-generation antihistamines, frequent and sometimes severe adverse reactions to first-generation agents, as well as its demonstrated abuse potential, strongly suggest it is time to remove diphenhydramine's availability from both the prescription and over-the-counter markets. Diphenhydramine's problematic therapeutic ratio has been known since the 1980s, and this significant disadvantage has not to date succeeded in stopping over a million prescriptions being written each year. The behind-the-counter status would help the pharmacist suggest safer alternatives and hopefully prevent many adverse consequences, including abuse. Furthermore, a more serious and potent action plan would be to remove diphenhydramine from the market. In the past, it has been a useful medication that has helped millions of patients; however, its current therapeutic ratio is matched or exceeded by second-generation antihistamines, especially due to their markedly reduced adverse reactions. It is time to say a final goodbye to diphenhydramine, a public health hazard.

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