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COMPARATIVE EFFICACY AND SAFETY OF FIRST-VERSUS SECOND- GENERATION OVER-THE-COUNTER ANTIHISTAMINES: A REVIEW

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ABSTRACT

Background: Oral H1-antihistamines remain among the most frequently purchased over- the-counter (OTC) medications worldwide for allergic and non-allergic conditions. Despite evolving clinical guidelines favoring newer agents, sedating first-generation antihistamines continue to be widely used. **Objective:** To critically evaluate and compare the clinical efficacy and safety profiles of first- and second-generation OTC H1-antihistamines, with special consideration of vulnerable populations and real-world self-medication patterns. **Methods:** This narrative review integrates findings from randomized clinical trials, systematic reviews, pharmacovigilance databases, observational cohort studies, and professional guideline statements. Outcomes assessed include symptom control in allergic rhinitis and chronic urticaria, effectiveness in viral upper respiratory infections, central nervous system (CNS) and cardiovascular safety, fall risk in older adults, pediatric safety, and public health implications of OTC access. **Results:** ‘For allergic rhinitis and chronic urticaria, second-generation antihistamines provide symptom relief comparable to or greater than first-generation agents, with substantially fewer adverse effects. First-generation drugs demonstrate modest benefit in common cold–related rhinorrhea and sneezing but are consistently associated with sedation, psychomotor impairment, anticholinergic burden, delirium risk, falls, and cardiovascular concerns in high-risk groups. Modern second-

generation agents exhibit minimal CNS penetration and strong cardiac safety at recommended doses, although post- marketing surveillance continues to monitor rare adverse signals associated with specific molecules. **Conclusion:** In routine allergy management, second-generation OTC antihistamines represent the preferred first-line option due to a more favorable balance between efficacy and safety. First-generation agents should be restricted to short-term, carefully selected circumstances and avoided in populations at increased risk of adverse outcomes.

KEYWORDS: H1-antihistamines; over-the-counter medications; allergic rhinitis; chronic urticaria; sedation; geriatric safety; pediatric pharmacology; cardiovascular risk.

INTRODUCTION

Allergic rhinitis and chronic urticaria affect a significant proportion of the global population and are associated with sleep disturbance, reduced productivity, impaired academic performance, and diminished quality of life. Oral antihistamines constitute a central component of treatment strategies for these disorders.

The availability of many antihistamines without prescription has shifted much of their use into the realm of self-care. Patients frequently select products based on cost, familiarity, or perceived strength rather than safety considerations. Consequently, understanding the comparative effectiveness and adverse effect profiles of these agents is essential for clinicians, pharmacists, and public health stakeholders.

First-generation antihistamines were introduced decades ago and were once the primary pharmacologic option for allergic symptoms. However, their pharmacodynamic properties—particularly high lipophilicity and non-selective receptor binding— contribute to prominent central and peripheral adverse effects. In response, second- generation antihistamines were developed to enhance peripheral H1 selectivity while minimizing central nervous system exposure.

This review examines whether the continued widespread use of first-generation OTC antihistamines is supported by contemporary evidence when compared with newer alternatives.

Pharmacological Distinctions Between Generations First-Generation Antihistamines

Older antihistamines, including diphenhydramine, chlorpheniramine, promethazine,

dimenhydrinate, brompheniramine, and hydroxyzine, readily cross the blood–brain barrier. Their lack of receptor specificity results in antagonism not only at H1 receptors but also at muscarinic, adrenergic, and serotonergic sites.

Clinically relevant consequences include.

- Sedation and cognitive slowing
- Anticholinergic symptoms such as dry mouth and urinary retention
- Visual disturbances
- Short elimination half-lives requiring repeated daily dosing

These characteristics underlie both their therapeutic effects and their toxicity.

Second-Generation Antihistamines

Second-generation agents—such as loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, and bilastine—were engineered to act primarily on peripheral H1 receptors while demonstrating limited central penetration.

Key properties include.

- Greater receptor selectivity
- Longer duration of action (typically once-daily dosing)
- Minimal anticholinergic activity
- Markedly reduced sedative effects

Although mild drowsiness can occur with certain agents (notably cetirizine or levocetirizine), the overall central adverse effect burden is significantly lower than that of earlier drugs.

Clinical Effectiveness in Allergic Rhinitis

Allergic rhinitis represents one of the most common reasons for OTC antihistamine purchase. Evidence from controlled trials and meta-analyses consistently demonstrates that second-generation antihistamines effectively reduce sneezing, nasal pruritus, rhinorrhea, and ocular symptoms in both seasonal and perennial disease.

Comparative studies suggest that while differences between individual second-generation drugs are generally modest, certain agents may exhibit faster onset or slightly greater symptom score reduction under experimental conditions. Importantly, symptom relief achieved with modern agents occurs without meaningful impairment of alertness in most patients.

In contrast, first-generation antihistamines are also effective in reducing histamine- mediated symptoms but do so at the expense of sedation and diminished functional performance. For individuals who drive, operate machinery, or engage in cognitively demanding tasks, this trade-off is clinically significant.

Management of Chronic Spontaneous Urticaria

International guidelines identify second-generation antihistamines as first-line pharmacotherapy for chronic spontaneous urticaria. Escalation of dose up to four times the standard amount is recommended in refractory cases, with evidence supporting improved symptom control and acceptable tolerability.

Sedation becomes more likely at higher doses of certain agents; however, even dose-escalated second-generation antihistamines typically produce fewer impairing effects than standard doses of first-generation drugs.

Given the chronic nature of urticaria, long-term exposure to anticholinergic and sedative medications is undesirable. Thus, first-generation antihistamines have limited rationale in sustained management strategies.

Role in Viral Upper Respiratory Infections

An important exception to the general superiority of second-generation agents lies in the management of common cold symptoms. First-generation antihistamines demonstrate modest reductions in sneezing and rhinorrhea during viral infections, likely attributable to central and anticholinergic mechanisms rather than pure histamine blockade.

Second-generation antihistamines, lacking these central effects, generally do not provide meaningful relief for cold-related nasal symptoms.

Nevertheless, any short-term symptomatic benefit must be weighed against sedation, next-day impairment, and risk of accidental injury—particularly in children and older adults.

Central Nervous System and Functional Impact

Sedation remains the most clinically relevant distinction between generations. First-generation antihistamines are associated with.

- Reduced reaction time
- Impaired divided attention

- Memory deficits
- Increased accident risk
- Decreased workplace and academic productivity

These impairments are not merely subjective but demonstrable in psychomotor testing and epidemiologic studies of motor vehicle collisions.

Second-generation agents exhibit minimal influence on psychomotor function at therapeutic doses. While some variability exists among molecules, the overall cognitive safety profile is substantially improved.

Geriatric Considerations: Falls and Delirium

Older adults face heightened vulnerability to anticholinergic and sedative medications. Age-related pharmacokinetic changes, polypharmacy, and baseline fall risk amplify adverse outcomes.

Observational research links first-generation antihistamines with.

- Increased incidence of falls and fractures
- Higher rates of hospital-associated delirium
- Greater overall anticholinergic burden

Accordingly, geriatric prescribing frameworks classify these agents as potentially inappropriate medications.

Second-generation antihistamines, when appropriately dose-adjusted, present a considerably safer alternative for older individuals requiring allergy therapy.

Cardiovascular Safety

Historical concerns regarding QT prolongation and arrhythmia stem from earlier antihistamines withdrawn from the market. Currently available second-generation OTC agents demonstrate strong cardiovascular safety at recommended doses.

However, overdose and off-label use of first-generation antihistamines can precipitate serious arrhythmias, particularly in pediatric populations. Ongoing pharmacovigilance surveillance also monitors rare adverse event reports associated with individual second- generation drugs, though causality remains uncertain in many cases.

Pediatric Use

Children frequently receive antihistamines for allergic symptoms and colds. Contemporary evidence supports preferential use of second-generation formulations due to reduced sedation and improved safety margins.

First-generation agents may cause paradoxical excitation, respiratory depression, seizures, or cardiotoxicity in overdose. Regulatory warnings in several jurisdictions discourage use of sedating antihistamines in very young children.

Clear caregiver education regarding age-appropriate dosing is essential.

Public Health and OTC Implications

OTC availability enhances accessibility but may obscure risk perception. Many consumers equate non-prescription status with safety, potentially underestimating the cognitive and cardiovascular risks associated with sedating agents.

Transition of several second-generation antihistamines to OTC status has been associated with reduced healthcare utilization costs and possibly fewer sedation-related accidents. Nonetheless, unsupervised long-term use warrants attention.

Pharmacists play a pivotal role in guiding consumers toward safer therapeutic choices.

Practical Recommendations

1. **Allergic rhinitis and urticaria:** Prefer second-generation antihistamines as initial therapy.
2. **Children:** Avoid first-generation agents whenever possible.
3. **Older adults:** Treat first-generation antihistamines as generally inappropriate.
4. **Common cold:** If used, limit sedating antihistamines to short courses in carefully selected adults.
5. **OTC counselling:** Emphasize that “non-prescription” does not equate to “risk- free.”

CONCLUSION

When assessed across efficacy, tolerability, functional impact, and safety in vulnerable populations, second-generation OTC antihistamines demonstrate a clearly superior risk–benefit profile for most allergic conditions. While first-generation drugs retain limited short-term roles, routine or prolonged use—particularly in self-medication contexts— conflicts with contemporary safety standards.

Healthcare professionals should actively encourage transition toward modern, minimally

sedating antihistamines to optimize patient outcomes and reduce preventable harm.

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