# Antihistamines and Mental Status

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Histamine receptor antagonists (known as antihistamines) are one of the most commonly used family of drugs. Antihistamines are typically used for allergic diseases, including asthma, food allergy, rhinitis, and atopic dermatitis. The incidence of these diseases has been steadily increasing for the last 20 years, despite better awareness and protective measures (eg, air conditioners, filters, pollen count reports, etc).[1–10] Moreover, the number of other conditions with an atopic component such as chronic fatigue syndrome, fibromyalgia syndrome, interstitial cystitis/bladder pain syndrome, and psoriasis has also been on the rise.[11] As a result, the use of antihistamines has also increased and warrants a re-evaluation of their possible adverse effects.

## Classes of Antihistamines

The first generation of histamine-1 receptor antagonists, such as diphenhydramine (Benadryl), chlorpheniramine (Dimetane), hydroxyzine (Atarax, Vistaril), and ketotifen (Zaditen) are sedating because they enter the brain.[12,13] At least, diphenhydramine has been shown to undergo active uptake at the blood-brain barrier.[14] Diphenhydramine is also intentionally used as a sedative.[15] There is a positive correlation between its plasma concentration and sedative effect, but at concentrations of 25 to 50 ng/mL, there was sufficient antihistaminic effect without significant sedation.[16] Hydroxyzine is also sedating, but daily use at bedtime minimizes its sedative effect during waking hours, while still retaining its antihistaminic actions.[17]

The second-generation histamine-1 receptor antagonists, such as cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin), are not usually sedating at the prescribed doses[18,19] because they are substrates for the blood-brain barrier P-glycoprotein, which is an efflux pump that prevents them from entering the brain.[20] Rupatadine (Rupafin) is a second-generation histamine-1 receptor reverse agonist that also blocks the action of platelet-activating factor.[21] These second-generation antihistamines all have the potential of being sedating at higher doses.

Tricyclic antidepressants, such as amitriptyline (Elavil) and doxepin (Sinequan), also have antihistaminic actions.[22] In fact, doxepin was reported to be 800 times as potent as diphenhydramine in antagonizing the histamine-1 receptor.[23] These tricyclic antidepressants can be particularly sedating.

## Mastocytosis

Antihistamines are the main line of treatment for mastocytosis and mast cell activation.[24] However, control studies on the overall benefit to the patients are limited.[25] Only 1 double-blind, randomized, placebo-controlled trial (n = 33) using rupatadine (20 mg/d for two 28-day treatment periods) in indolent systemic mastocytosis showed significant improvement of pruritus and quality of life.[26] A small (n = 10) crossover, randomized, placebo-controlled trial using ketotifen (2 mg twice a day for three 30-day treatment periods) in cutaneous mastocytosis patients reported significant reduction in pruritus but was not adequately blinded, because 40% of patients on the treatment arm experienced fatigue.[27] Moreover, unlike rupatadine, which inhibits histamine release from mast cells,[28,29] ketotifen not only did not inhibit skin mast cells, but it actually stimulated them at high doses.[30]

Regardless of these studies, patients with mastocytosis are often prescribed large doses (>300 mg/d) of antihistamines, especially diphenhydramine. It is therefore of interest that one of the most common symptoms reported by such patients is what they often collectively describe as "brain fog."[31,32] It is hard to discern whether this problem is related to the underlying mastocytosis or the use of antihistamines, although both may occur.

## Antihistaminic Effects on Cognition

Some reports seem to suggest that antihistaminics may contribute to "mental clouding" characterized by cognitive impairment, confusion, as well as transient deficits in cognition, communication, and memory. For instance, 1 study assessed 1627 individuals aged 65 years or older between 1987

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and 1989 and then they were reassessed between 1996 and 1998. It reported a significant association between diphenhydramine use and cognitive impairment, as judged by Mini-Mental State Examination scores (OR, 6.7; $P = 0.005$), but only in those persons without dementia (n = 652, as judged by the Clinical Dementia Rating).[33]

One population-based longitudinal study of persons aged 65 years or older (n = 3434) with no dementia, based on the Cognitive Abilities Screening Instrument, found a significant association between higher cumulative use of drugs with anticholinergic activity and higher adjusted hazard risk of 1.54 (95% confidence interval compared with nonusers) of all-cause dementia and Alzheimer disease.[34] The "high-risk" group included those patients who took the equivalent of 50 mg each day of diphenhydramine or doxepin for longer than 3 years or 25 mg per day for longer than 6 years.[34] However, this article did not account for the contribution of any comorbidities present.

Histamine-2 receptor antagonists, such as famotidine (Pepcid) or ranitidine (Zantac), are often used together with histamine-1 receptor antagonists.[35] Surprisingly, even these may result in altered mental status in older adults.[36] One population-based cohort study compared patients older than 65 years who were prescribed either "standard dose" of ranitidine or famotidine (300 or 200 mg/d, respectively) or "low dose" (30 or 20 mg/d, respectively) for 30 days. Only the standard dose was associated with a 30-day increased risk of hospitalization requiring urgent head neuroimaging with computed tomography and all-cause mortality with a relative risk increase of 1.33 (95% confidence interval).[36]

## Mechanism of Mental Clouding

Antihistaminics may contribute to cognitive impairment because they block the action of histamine, which is a neurotransmitter[37,38] involved in cognition,[38–40] memory,[41] learning,[42] and motivation.[43] Moreover, blockade of the histamine-1 or even histamine-2 receptors may shift histamine to activating the histamine-3 autoinhibitory receptors in the brain,[44] further limiting histaminergic transmission.[45] In fact, 1 histamine-3 reverse receptor agonist (Pitolisant) is clinically available for the treatment of patients with narcolepsy and possibly also those with attention-deficit/hyperactivity disorder and dementias, because it increases wakefulness, attention, learning, and other cognitive processes.[45]

## Paradoxical Antihistaminic Effects

Despite the potential for cognitive impairment discussed previously, some patients taking diphenhydramine get paradoxically stimulated.[46] This may be especially true in individuals who are CYP2D6 ultrarapid metabolizers.[47] Moreover, high doses of the sedating antihistamines,[48–51] especially diphenhydramine,[52–55] have been associated with increased seizure activity mostly in children. Assuming 1 compartment model of 40 kg (40 L) and equal distribution, a diphenhydramine dose of 250 mg corresponds to approximately 6.25 μg/mL; blood concentrations greater than 5 μg/mL have been regarded as potentially lethal.[56–59]

The need for high diphenhydramine doses may be caused by development of tolerance or psychological dependence. For instance, 5 case reports of children and adolescents with chronic hematologic or oncologic illnesses using diphenhydramine were found to exhibit apparent drug-seeking behavior toward this antihistamine.[60] Other possible causes of a need for higher doses of antihistamines could be deficiency of the histamine-metabolizing enzyme, diamine oxidase,[61] and/or consumption of foods rich in histamine,[62] both of which could create an excess of histamine in the body.

## CONCLUSIONS

Antihistaminics, when selected and used properly, can have significant beneficial effects. However, caution should be exercised using high doses, because they may contribute to mental status changes, especially in vulnerable populations. Nevertheless, it is complicated to interpret dose-related adverse effects from pharmacoepidemiological studies unless taking into account pharmacokinetic and pharmacodynamic mechanisms, genetic polymorphisms, and drug-drug and drug-food interactions.[63]

## AUTHOR DISCLOSURE INFORMATION

*The authors declare no conflicts of interest.*

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