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# Hydroxyzine:

## *An Effective Antihistamine and the Drug of Choice for Pruritus*

# Table of Contents

## Panel Members

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# Message From President and Hon. Secretary-General

IMA, as the largest professional association of modern medicine doctors in India, with 3,51,258 members across 1700 local branches, has always been at the forefront of promoting and advancing medical and allied sciences. In pursuit of our objective to enhance public health and medical education in India, IMA regularly publishes guidelines and monographs to keep its members abreast of evolving clinical practices.

Indian Medical Association (IMA) is proud to announce a collaborative effort by a distinguished panel of 8 esteemed doctors, comprising a General Practitioner, Endocrinologist, Dermatologist, and Paediatrician. This eminent group has convened to create a comprehensive booklet on "Hydroxyzine: An Effective Antihistamine and the Drug of Choice for Pruritus" This publication aims to simplify the intricacies of Urticaria management in India.

We take great pleasure in announcing the culmination of this collaborative effort, and the final recommendations from the meeting have been published. This valuable resource is now accessible to all, and we extend our heartfelt gratitude to all the experts for their invaluable contributions. These recommendations are intended to be a practical guide for General Practitioners, enabling them to diagnose and manage allergy effectively in the Indian scenario.

IMA remains committed to serving as the platform for the medical fraternity, fostering academic discourse, advocating for the profession, and addressing the health concerns of the people. We thank the dedicated panel members for their commitment to advancing medical knowledge and improving healthcare practices.

**Dr Sharad Agrawal**
National President, 2023
Indian Medical Association

**Dr Anilkumar Nayak**
Hon. Secretary-General (HSG), 2023
Indian Medical Association

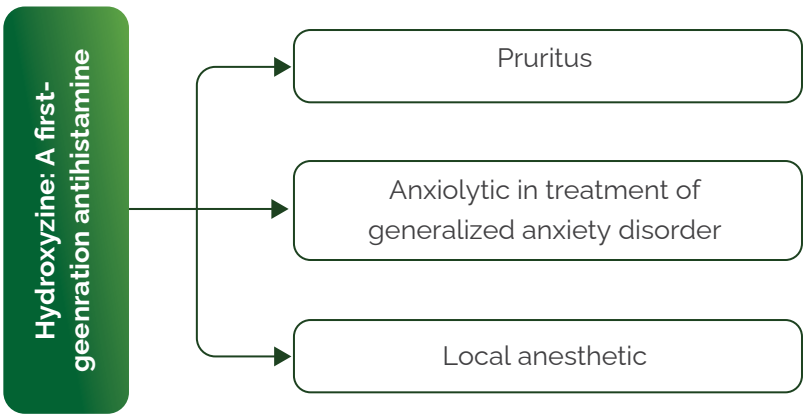
# *Hydroxyzine: An Effective Antihistamine and the Drug of Choice for Pruritus*

## Introduction to Hydroxyzine

- Most commonly used first-generation H1 antihistamine from diphenylethane class.[1,2]
- Displays antipruritic, anxiolytic, antispasmodic, antiemetic, anticholinergic, and sedative behavior in addition to being a histamine (H1) blocker.[1-3]
- Considered as the most potent antihistamine in managing chronic pruritus.[4]
- Used in the management of pruritus due to allergic conditions such as chronic urticaria, atopic and contact dermatitis, and in histamine-mediated pruritis.
- Used for symptomatic relief from anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.
- The most thoroughly tested and the only FDA-approved antihistamine for anxiety.[5]
- Exhibits a rapid onset of antipruritic action with prolonged duration.

## Clinical Uses of Hydroxyzine (Figure 1)

**Figure 1: Clinical uses of hydroxyzine**




- Exhibits excellent antipruritic behavior.[4]
- Most common H1 anti-histamine drug used to control pruritus in Atopic dermatitis.[1]
- Proven effectiveness and safety in **generalized anxiety disorder** with good anti-depressive effects.[6-7]
- Superior to placebo and comparable to other anxiolytic agents in a Cochrane review on generalized anxiety disorder.[8]
- Effective treatment for diabetes related itch.[9,10]

- Used in pediatrics as a mild sedative drug.[11]
- Used in management of pediatric pruritus.[12, 13]

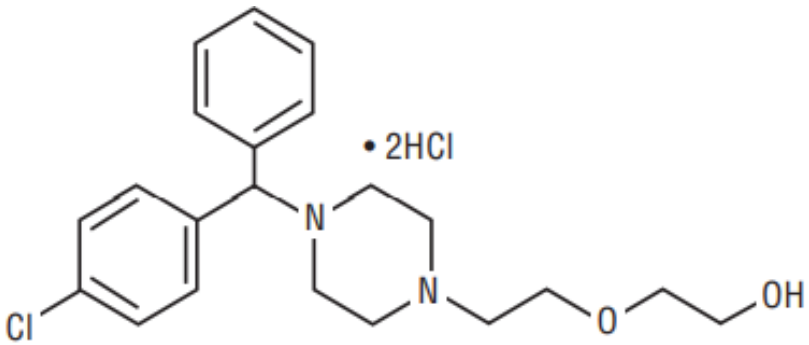
## History and Pharmacology of Hydroxyzine

- Synthesized by biopharmaceutical company Union Chimique Belge in 1955; later authorized its commercialization by Pfizer in the US.
- Food and Drug Administration (FDA) approved the abbreviated new drug application confirming its safety in 1956.
- On April 6, 2023, FDA considered including hydroxyzine on the 503B Bulks List of FD&C Act.
- Authorized in the majority of countries to treat anxiety, typically in combination with physical symptoms like pruritus, urticaria, dyspepsia, irritable bowel syndrome, and bronchospasm (Figure 1).[6,14]
- No known complaints of dependence, abuse, or memory impairments.[6]
- Most common adverse effect is sedation, which generally fades with continued treatment.[6]

**Chemical Name:** 2-[2-[4-(p-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol dihydrochloride synthesized by the alkylation of 1-(4-chlorobenzohydril) piperazine with 2-(2-hydroxyotoxy) ethylchloride.[11]

**Chemical Formula:** C_21 H_27 ClN_2 O_2•2HCl (Figure 2).

**Figure 2: Chemical Structure of hydroxyzine**




**Molecular Weight:** 447.83 g/mol

**Dosage Forms:** Available as tablets or capsules (10, 25, 50 and 100 mg), oral suspension/ syrup and liquid for intramuscular injection

## Dosage

- Doses used for pruritus are generally lower than those for anxiety and tension.[15,16] For use in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses and in histamine-mediated pruritus:
  - **Adults:** Starting dose: 25 mg at night increasing as necessary to 25 mg three or four times daily.[15]
  - **Elderly:** Maximum daily dose: 50 mg per day.[15]
  - **Children over 6 years:** Starting at 15-25mg and increasing to 50-100mg daily in divided doses adjusted according to the child's weight.

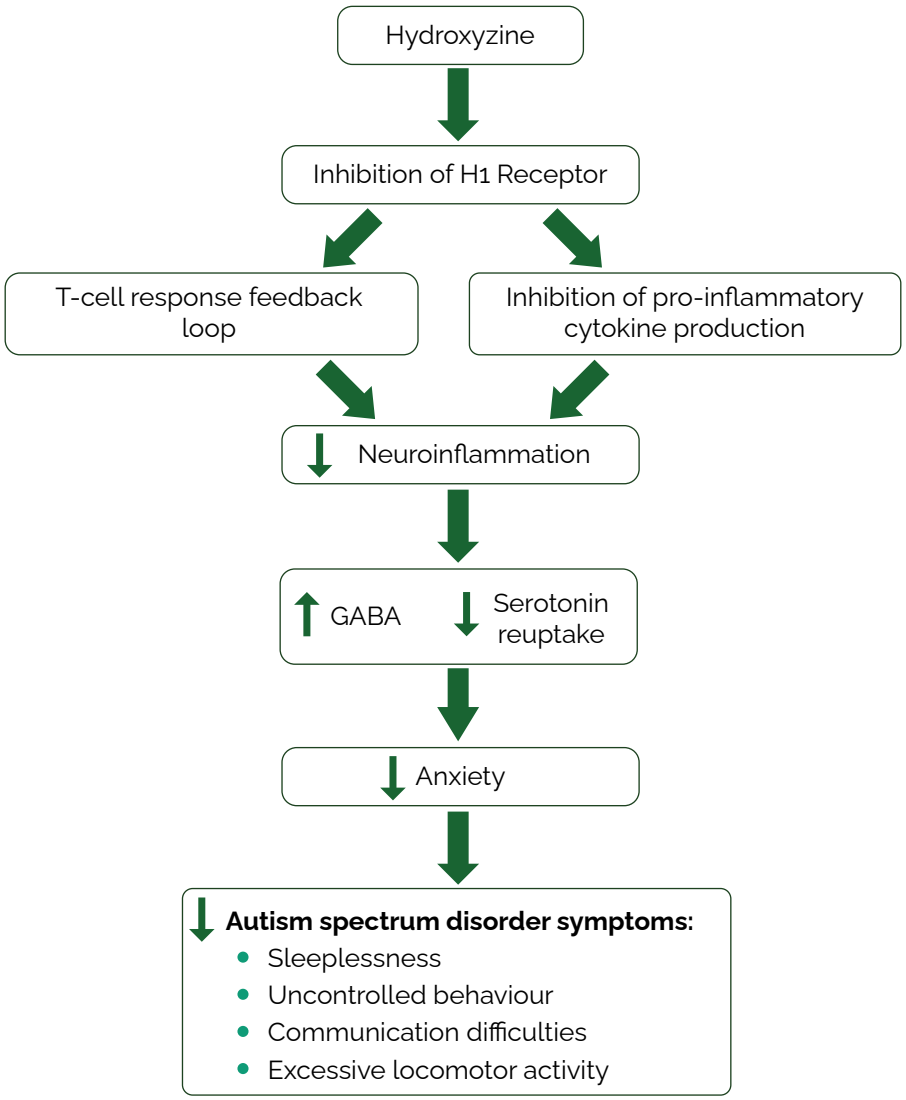
    Maximum daily dose in children up to 40 kg in bodyweight: 2 mg/kg/day.[15]

- Chronic pruritus: 50 mg daily. Maximum daily dose: 100 - 200 mg per day (adult dose).
- For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested:
  - **Adults:** 50-100 mg daily in divided doses.[15]
- The dosage should be adjusted according to the patient's response to therapy.[15]

## Mechanism of Action - Explained

- Functions as a potent H1 receptor antagonist and serotonin reuptake inhibitor.
- It was thought that hydroxyzine suppressed some hypothalamus nuclei along with having a peripheral effect in the sympathetic portion of the autonomic nervous system.[17]
- Has minimal impact on the cerebral, thalamic, or spinal cord areas, except at extremely high dosages.[17]
- Suppresses extreme responses to stimuli, whether external or internal, without impairing the patient's perspective or sense of value.[17]
- Inhibition of H1 receptors reduces neuro inflammation by suppressing production of inflammatory cytokines and activation of brain mast cells.[18]

**Figure 3: Hydroxyzine mechanism of action**



- Induces a T-cell response, Gamma-Aminobutyric Acid (GABA) and serotonin reuptake inhibition.[18]
- Hydroxyzine's immunomodulatory effect: Stimulates macrophage inflammatory activity by reduction in the levels of p38 Mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) proteins.[19]
- Alleviates anxiety and autism spectrum disorder symptom.

## Pharmacokinetics

- **Terminal Elimination Half-life** ($t_{1/2}$): Adults: 24 hours
  Children: 7.1 hours.[20]
- **Onset of action:** Rapid absorption from the gastrointestinal system, with clinical effect beginning within 15-30 minutes after oral administration.[20]
- **Time to Maximum Plasma Concentration (Tmax) after a Single Dose:** 2.1 hours.[21]
- **Duration of action:** 3-4 hours.[20]
- **Clearance:** Adults: 9.8 ± 3.3 mL/min/kg
  Children: 31.1 ± 11.1 mL/min/kg.[20]
- **Protein binding:** Binds to human albumin in-vitro, however extent of protein binding in plasma not been determined.[20]
- **Metabolism:** Metabolized in the liver by drug metabolizing enzymes CYP3A4 and CYP3A5.[20]
- **Route of elimination:** Cetirizine, an active hydroxyzine metabolite, is excreted unchanged in urine in approximately 70% of cases.[20]

## Contraindications

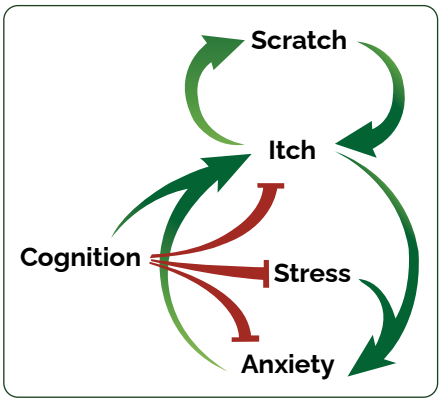
- Contraindicated in patients with known acquired or congenital QT interval prolongation, or with a known risk factor for QT interval prolongation such as cardiovascular disease, family history of sudden cardiac death, significant bradycardia, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia, Hyponatremia), or concomitant use of drugs known to prolong the QT interval and/or induce torsades de pointes.[22]
- Shoud not be co-administered with other drugs causing QT prolongation.
- May inhibit human Ether-à-go-go-Related Gene (hERG) and other cardiac channels, according to European Medical Agency (2015) and Health Canada (2016) advisories.[22,23]
- May show deleterious impact on cardiac rhythm, such as QT interval prolongation and manifestation of cardiac arrhythmia.[22,23]
- Contraindicated in early stages of pregnancy, breastfeeding and individuals with a history of hypersensitivity to hydroxyzine.[15]
- Considerd as Cateogry C drug in pregnancy. (Risk cannot be ruled out, there are no satisfactory studies in pregnant women).

**In elderly:**

- Not generally prescribed in elderly patients due to sedative effects, as it may lead to fall and increased risk of fractures.
- Also leads to frequent urination due to hyponatremia with its anticholinergic effects.
- Due to reduced hydroxyzine clearance and higher sensitivity to anticholinergic effects, use of hydroxyzine is not recommended.
- To be used with caution in patients with bradycardia or on hypokalaemia-inducing medications.
- To be used in caution with medications known to be potent inhibitors of alcohol dehydrogenase or CYP3A4/5.[22]

## Itch scratch cycle

Chronic itch is linked to heightened stress, anxiety, and mood disorders. This creates a detrimental cycle where stress and anxiety intensify the itch, leading to increased scratching and further deteriorating the prognosis and quality of life for patients. This pattern is observed across various chronic itch conditions, including those with varying etiologies, and is even present to some degree in healthy individuals. This implies that the central nervous system, serving as the ultimate processing pathway for itch, significantly influences the connection between itch and anxiety. Encouragingly, treatments targeting anxiety, both pharmacological and non-pharmacological, have demonstrated potential in alleviating itching symptoms.[24]




## Pruritus and its Burden/ Implications

**A** Humans scratch to relieve itching by inducing discomfort/ pain at the itch site, thereby alleviating the unbearable itch and often producing a pleasurable experience owing to release of serotonin while scratching.[24-26]

**B** The itch-scratch cycle, on the other hand, contributes to epidermal barrier damage by elevating water loss and drying and creating ideal conditions for skin pathogens to cause infection and symptom flare-ups.[24-26]

**C** Aside from physical injury, Itch can have major psychological consequences (such as depression, anxiety attacks, and suicide ideation), disrupt sleep, hinder performance at work or school, and degrade quality of life and self-esteem.[27-30]

**D** As eczema has a profound impact on quality of life, most patients assess the severity of eczema based on the degree of pruritus.[31]

**E** The severity of the illness affects quality of life regardless of the specific psoriasis variation, as shown in a recent cross-sectional, binational study that included a wide range of clinical psoriasis subtypes including large- and small-plaque, palmoplantar, scalp, erythrodermic, palmo plantar pustular, etc.[32]

**F** Because of the intricate etiology of pruritus in atopic dermatitis and the implications of pruritus on patients' lives, itching continues to be an issue for dermatologists, although it **may be managed with symptomatic treatment with non-inflammatory drugs such as antihistamines.**[25,26]

## Pruritus - Overview and Burden

Atopic dermatitis is a common chronic or recurrent inflammatory skin disorder that causes itching.[24-25] Itching, or pruritus, is described as an unpleasant feeling of the skin that creates the desire to scratch. Human itch may be divided into four clinical categories (Table 1).[26,27]

## Table 1: Types of itch and their characteristics based on clinical features

| S.No. | Type of itch | Characteristics |
|---|---|---|
| 1. | Pruritoceptive or cutaneous | ▶ Most common<br>▶ Due to biological mechanisms that emerge from the skin's layers and produce the somatic sensation of itch<br>• Peripheral pruritogens: Histamine, dust mites, cytokines, endothelin-1, tryptase, substance P, and capsaicin<br>• Central pruritogens: Serotonin and opoids[26] |
| 2. | Systemic | ▶ Caused by organ system illnesses other than skin such as diabetes, renal failure, or liver disease[27] |
| 3. | Neuropathic | ▶ Caused by a primary lesion or pathological changes or damaged central or peripheral afferent neurons |
| 4. | Psychogenic or functional pruritus | ▶ Have a psychosomatic or psychiatric origin<br>▶ May be related to a stressful lifestyle, which aggravates itch-causing conditions such as eczema, urticaria, and psoriasis[26] |

## Pruritus classification based on duration

### Acute Pruritus

- Sudden and intense itching of the skin, involves a rapid and strong itchiness sensation
- Can either be limited to a particular area or affect the entire body; intensity varying from mild to severe[33]

### Chronic Pruritus

- Persistent itching on a daily or nearly daily basis
- Lasting for over 6 weeks[33]

## Potential Causes of Chronic Pruritus

### Disease-Related Causes of Pruritus[34]

#### A. Skin diseases causing chronic pruritus

| | |
|---|---|
| **Abnormal vascular responses** | Urticaria, erythema multiforme, stevens-johnson syndrome, erythema nodosum etc. |
| **Inflammation induced by scratching** | Atopic dermatitis, contact dermatitis, xerosis, psoriasis, drug reactions, urticaria, lichen simplex chronicus, lichen sclerosus, prurigo nodularis, chronic renal disease etc. |
| **Infectious** | Scabies, folliculitis, mycotic infection, impetigo, viral infection, etc. |
| **Autoimmune** | Dermatitis herpetiformis, bullous pemphigoid, dermatomyositis, etc. |
| **Genetic** | Ichthyoses, Darier's disease, Hailey-Hailey disease, etc. |
| **Dermatoses of pregnancy** | Pruritic urticarial papules and plaques of pregnancy (PUPPP) or polymorphic eruption of pregnancy (PEP), pemphigoid gestationis, prurigo gestationis, pruritic folliculitis of pregnancy, Atopic eruption of pregnancy etc. |

## B. Systemic and other non-cutaneous diseases causing chronic pruritus

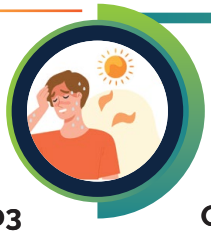
| | |
|---|---|
| **Chronic renal insufficiency** | Chronic Kidney disease, reactive perforating collagenosis, increase in Blood Urea Nitrogen (BUN), etc. |
| **Liver associated disease** | Cholestatic liver diseases (CLD), primary biliary cirrhosis, primary sclerosing cholangitis, obstructive biliary disease, etc. |
| **Metabolic** | Diabetic pruritus, acute diabetic complications like balanoposthitis, pruritus vulvae, skin/ soft tissue infections, itching, and and chronic microvascular complications causing itch |
| **Neuropathic** | Post-herpetic neuralgia, vulvodynia, notalgia paresthetica, brachioradial pruritus, multiple sclerosis, brain tumor, cerebral infarction, small fiber neuropathy, etc. |
| **Infectious** | HIV infection, parasitosis, helminthiasis, etc. |
| **Hematological** | [Hodgkin's disease,non-Hodgkin's lymphoma, leukemia, multiple myeloma, plasmacytoma, polycythemia vera, etc. |
| **Neoplasms** | Endocrine tumors (MEN-syndromes), metastasis |
| **Drugs** | Opioids, hydrochlorothiazide, estrogen, ACE inhibitors, allopurinol, simvastatin, amiodarone, etc. |
| **Psychogenic** | Depression, anxiety disorders, schizophrenia, obsessive-compulsive disorders, bipolar disorder, delusional parasitosis, etc. |

## Exposure-Related Causes of Pruritus[34-35]

### 01 Allergic contact dermatitis

- Allergic reactions from contact with substances like cosmetics and black hair dye, latex, laundry detergents, fabric softeners, nickel, concentrated inert oil ointments, paint-on tattoos, tattoo dyes, and Rhus oil (e.g., poison ivy).
- Pruritus triggered by topical medications like benzocaine and neomycin.
- Photo allergic disorder, photo contact dermatitis, Photodermatoses, solar urticaria, cold urticaria etc.

### 02 Heat exposure



- Cholinergic urticaria, which is a response to factors like hot baths, fever, and exercise.
- Miliaria rubra, commonly known as prickly heat.

### 03 Occupational factors

- Occupational exposure to substances like fiberglass, glyceryl monothioglycolate (found in permanent-wave solutions), methyl methacrylate (used in products like Plexiglas), potassium dichromate (found in cements and dyes), rosin and epoxy resins (used in adhesives), and rubber.

## 04 Systemic medications

- Itching caused by systemic medications, including antifungal agents like fluconazole, itraconazole, and ketoconazole.
- Itching triggered by aspirin, B vitamins (including niacinamide), drug hypersensitivity reactions to medications like rifampin (Rifadin) and vancomycin (Vancocin), nitrates (used as food preservatives), quinidine, and spinal narcotics (resulting in pruritus affecting the face, neck, and upper chest).

## 05 Water exposure

- Aquagenic pruritus, causing itching within 15 minutes of water contact.
- Itching caused by conditions like polycythemia vera.
- Swimmer's itch, resulting in a seven-day eruption after swimming in freshwater.

## Diagnosing the Cause of Pruritus[33,36]

An approach to the diagnosis of pruritus is presented in Figure 4.

**Figure 4: Diagnostic algorithm for pruritus**

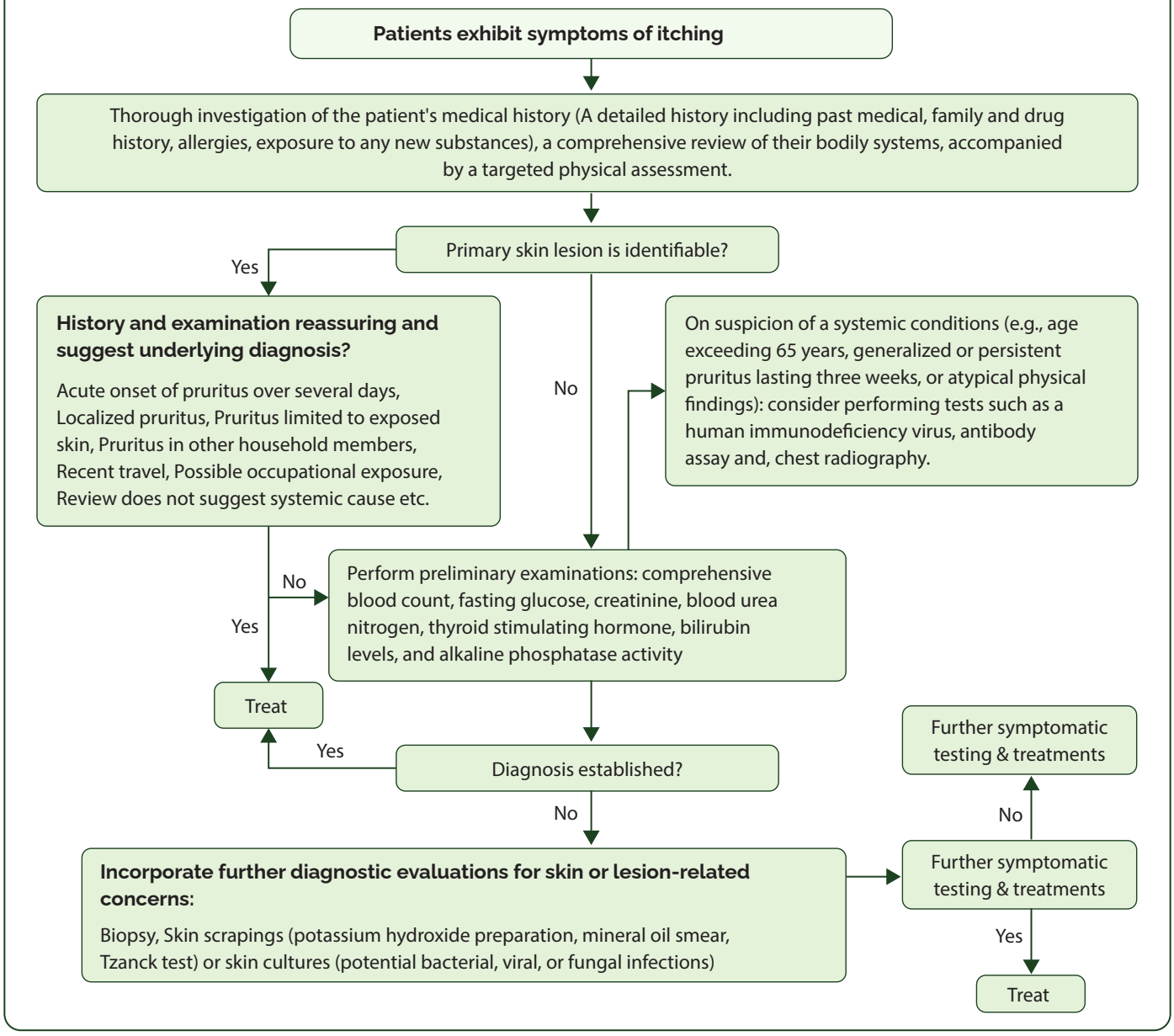
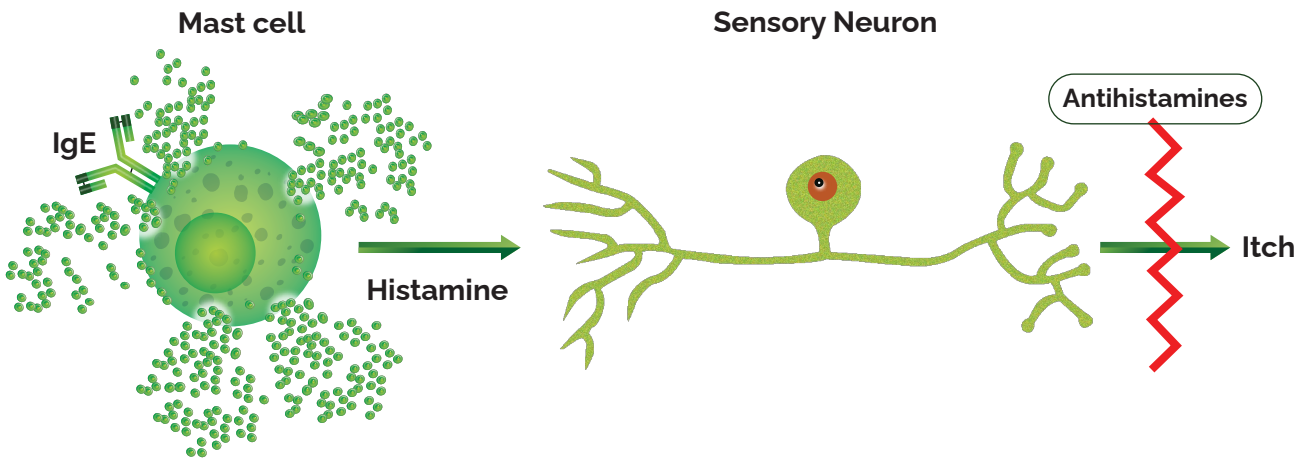


**Figure 5: Classic histaminergic itch pathway**




Histamine is a key modulator of allergic reactions and is responsible for hives, itching, discomfort, smooth muscle contraction, and enhanced vascular permeability.[37]

Activation of the high-affinity cell-surface receptor by IgE leads to the degranulation of mast cells, resulting in the release of histamine, which in turn triggers the activation of neurons responsible for sensing itch.

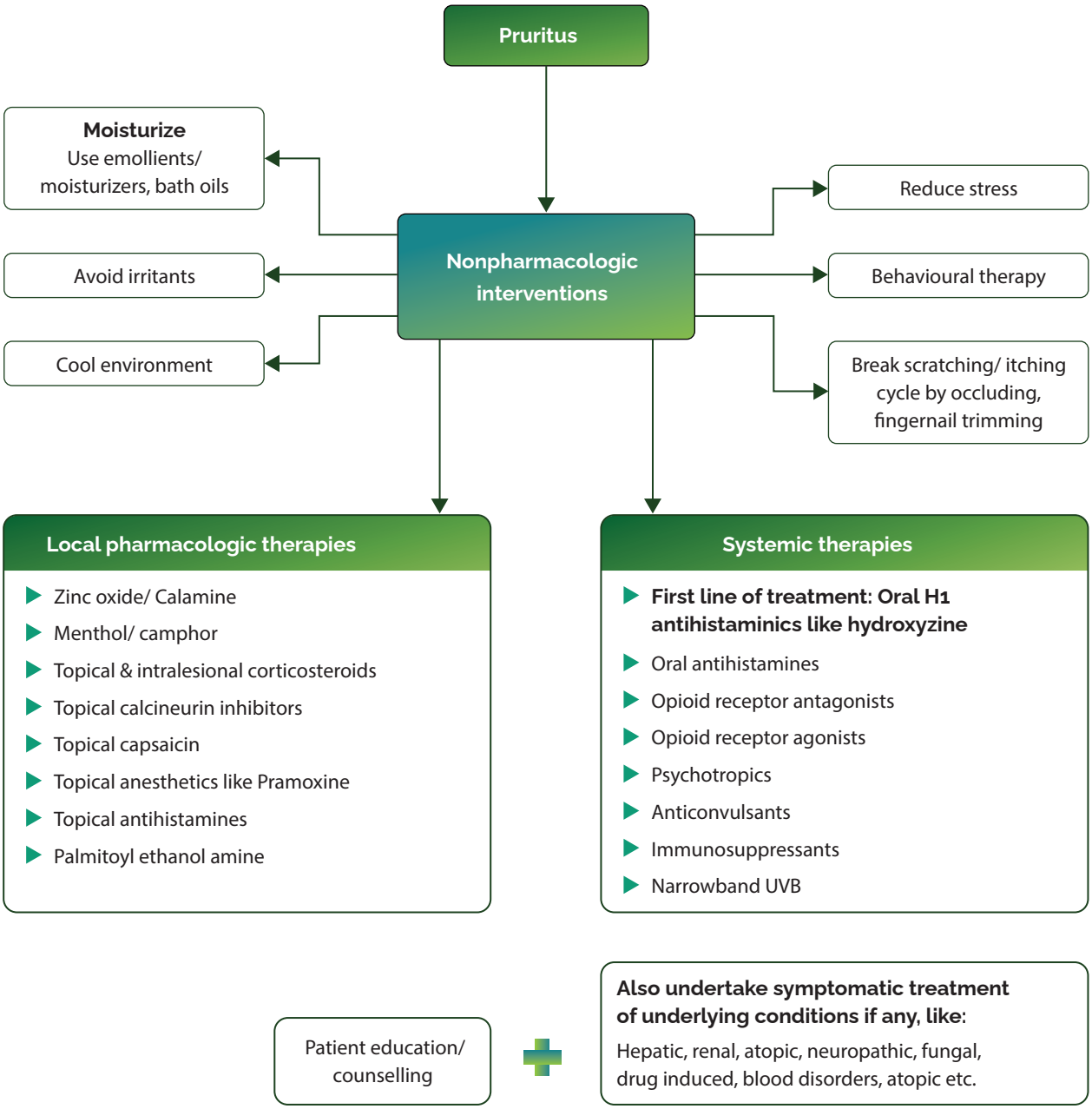
Approximately 90 years ago, the enhanced sensitivity or reactivity of the cutaneous vessels to histamine was noted, evidenced by increase in skin temperature and emergence of erythema, leading to atopic dermatitis.[38]

Antihistamines are deemed safe and are used worldwide to treat allergies and pruritus[36]. The success of antihistamines in other dermatologic illnesses, such as chronic urticaria, has contributed to their use in atopic dermatitis.[24]

## Treatment Algorithm for Pruritus[39-41]

Specific management strategies for pruritus are provided in Figure 6.

**Figure 6: Treatment algorithm for management of acute and chronic pruritus management**




**For acute pruritic conditions, oral H1 antihistaminics like Hydroxyzine** are considered **first line of treatment** along with focus on general non-pharmacological interventions and local pharmacological therapies like calamine, anaesthetics, palmitoyl ethanol amine. Apart from these, symptomatic treatment of other underlying conditions like fungal/ bacterial/ viral infections, scabies, pediculosis, hepatic, renal or blood disorders etc. is undertaken.

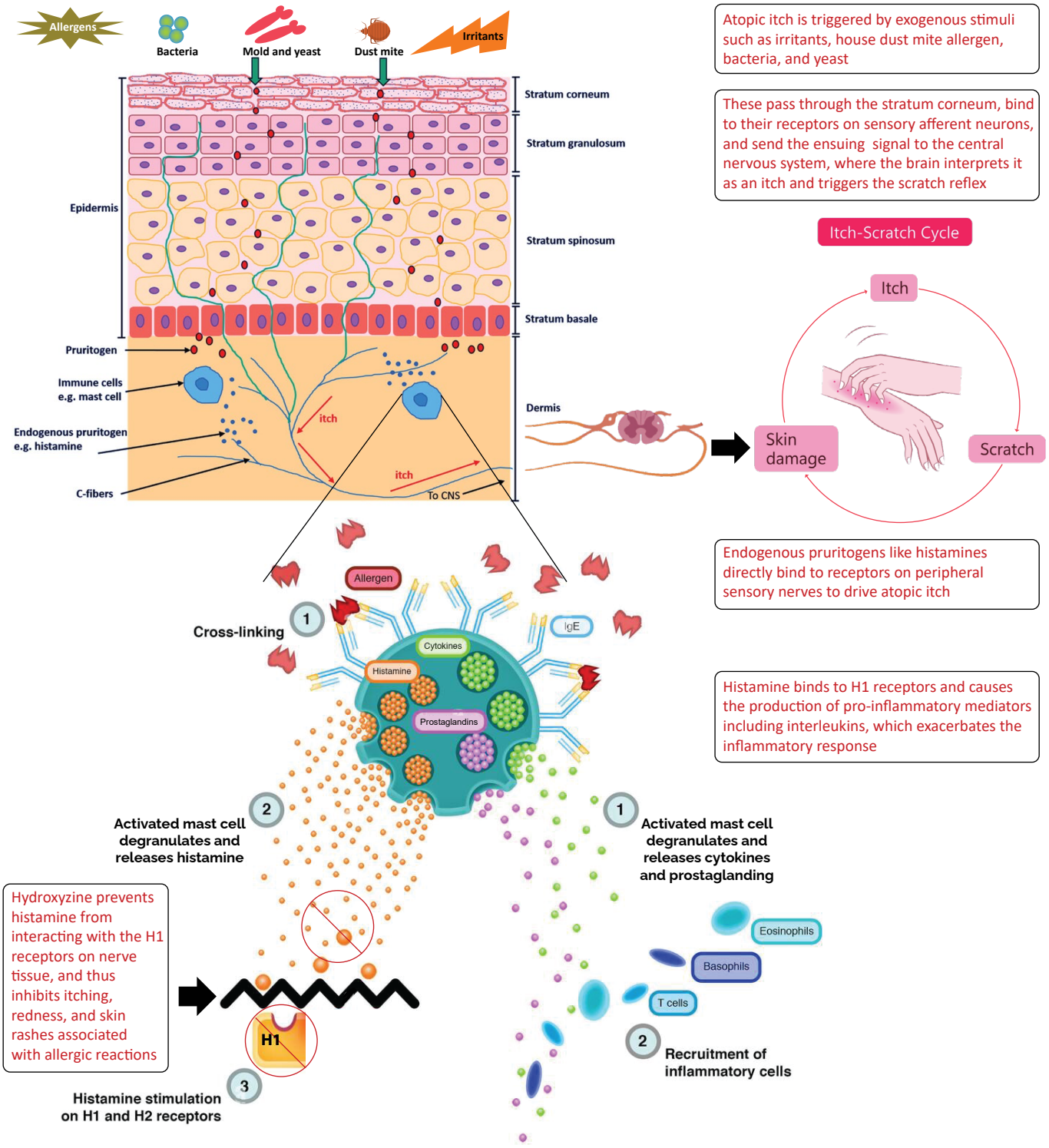
**Table 2: Hydroxyzine vs other commonly used anti histaminics**

| Category | Hydroxyzine | Cetirizine | Loratadine | Fexofenadine | Bilastine |
|---|---|---|---|---|---|
| Adult Dosage | 25 mg t.i.d. | 10 mg daily | 10 mg daily | 12 years old: 120 mg daily or 60 mg BID | 20 mg daily |
| Pediatric dosage | <6 years: 50 mg daily; >6 years: 50-100 mg daily; in divided doses | 12+ years: 5-10 mg daily 6-11 years: 5-10 mg daily 2-10 years 2.5-5 mg daily | 2-5 years: 5 mg daily >5 years: 10 mg daily | Approved 12 years: 60 mg BID (off-label: 6 months-2 years: 15 mg BID 2-11 years 30 mg BID) | 1 hr before or 2 hours after food No $P_{450}$ interactions P-Glycoprotein interactions |
| Safety considerations[42] | Avoid in elderly due to risk for delirium, QT prolongation risk, Sedative and Somnolence effects[42] | Dose adjust for chronic renal or liver impairment (5 mg daily) Most sedating 2nd Gen | Dose adjust for severe hepatic impairment, avoid in severe renal impairment | No dose adjustment for elderly, hepatic impairment Start half dose if renal impairment | 1 hr before or 2 hours after food P-Glycoprotein interactions |
| Half life[43] (hours) | 20 | 7-11 | 8-11 | 17 | 14.5 |
| Sedative effects[44] | Significant | Minimal | Minimal | None | None |
| Onset of action | **15-30 min**[20] | 45 minutes[44] | 2 hours[44] | 1-3 hours[44] | 2 hours[44] |

# Mechanism of Action of Hydroxyzine in Itch

## Figure 7: a) Mechanism of action of hydroxyzine in pruritus; b) Hydroxyzine competing with histamine for active site binding

**a.**




Atopic itch is triggered by exogenous stimuli such as irritants, house dust mite allergen, bacteria, and yeast

These pass through the stratum corneum, bind to their receptors on sensory afferent neurons, and send the ensuing signal to the central nervous system, where the brain interprets it as an itch and triggers the scratch reflex

**Itch-Scratch Cycle**

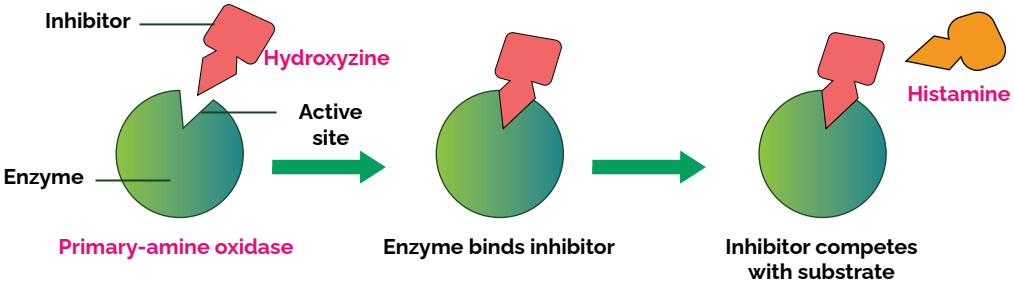



Endogenous pruritogens like histamines directly bind to receptors on peripheral sensory nerves to drive atopic itch

Histamine binds to H1 receptors and causes the production of pro-inflammatory mediators including interleukins, which exacerbates the inflammatory response

Hydroxyzine prevents histamine from interacting with the H1 receptors on nerve tissue, and thus inhibits itching, redness, and skin rashes associated with allergic reactions

**b.**



**Exogenous Triggers:** The onset of atopic itch is initiated by external factors like irritants, house dust mite allergens, bacteria, and yeast. These elements penetrate the outer layer of the skin, bind to receptors on sensory nerves, transmitting signals to the central nervous system, leading to the perception of itch and prompting the reflex to scratch.

↓

**Endogenous Pruritogens:** Internal pruritogens, such as histamines, directly attach to receptors on peripheral sensory nerves, contributing to the development of atopic itch.

↓

**Inflammatory Response:** Binding to H1 receptors, histamine induces the release of inflammatory mediators, notably interleukins, intensifying the overall inflammatory reaction.

↓

**Hydroxyzine** acts by obstructing the interaction between histamine and H1 receptors on nerve tissue, effectively mitigating itching, redness, and allergic skin reactions.

Other pathways, such as activity against H4 receptors, anti-muscarinic, anti-adrenergic, and anti-serotonin effects, may also contribute to further beneficial effects due to its central sedative action.[1,45] Though hydroxyzine is more likely to be sedating, but even if the itch is not mediated by histamine, they frequently help patients with nocturnal itch.[46]

Being a lipophilic drug, it easily crosses blood brain barrier and excerts its sedative action, causing relief to the patient

## Hydroxyzine in Management of Pruritus and Allergies

### Hydroxyzine in Pruritus Management

For generalized pruritus, oral H1 antihistamines like hydroxyzine are typically the first line of treatment.[1,41]

According to European guidelines, H1 antihistamines are regarded as first symptomatic treatment for pruritus for >6 weeks as well as chronic spontaneous urticarial.[1]

Hydroxyzine and cetirizine have an ameliorative effect on disorders like atopic dermatitis by providing necessary sedation and relief from pruritus. In addition to its antipruritic and H1 antihistaminic effects, it demonstrates anti-inflammatory action, further supporting the therapeutic management of atopic dermatitis.

Table 3 summarizes the studies assessing efficacy and safety of hydroxyzine therapy in pruritus.

## Diabetic Itch

Diabetes mellitus is a prevalent and disabling condition that impacts various parts of the body, including the skin. Typical skin manifestations of diabetes encompass skin infections, dryness, and itching. Skin issues are present in 79.2% of individuals with diabetes and can either emerge as the initial indication of the disease or develop at any stage of its progression.

Diabetes is more often linked to localized itching, particularly affecting the scalp, ankles, feet, torso, or genital area. People with diabetes and those with neuropathy are at a heightened risk of experiencing diabetic itching, especially if they have dry skin (xerosis).[47]

Pathogenesis: Dry skin (xerosis cutis) and diabetic peripheral neuropathy are the two main factors associated with pruritus in diabetes mellitus.[48,49]

**Figure 8 a: Factors associated with pathogenesis of pruritus in diabetes**

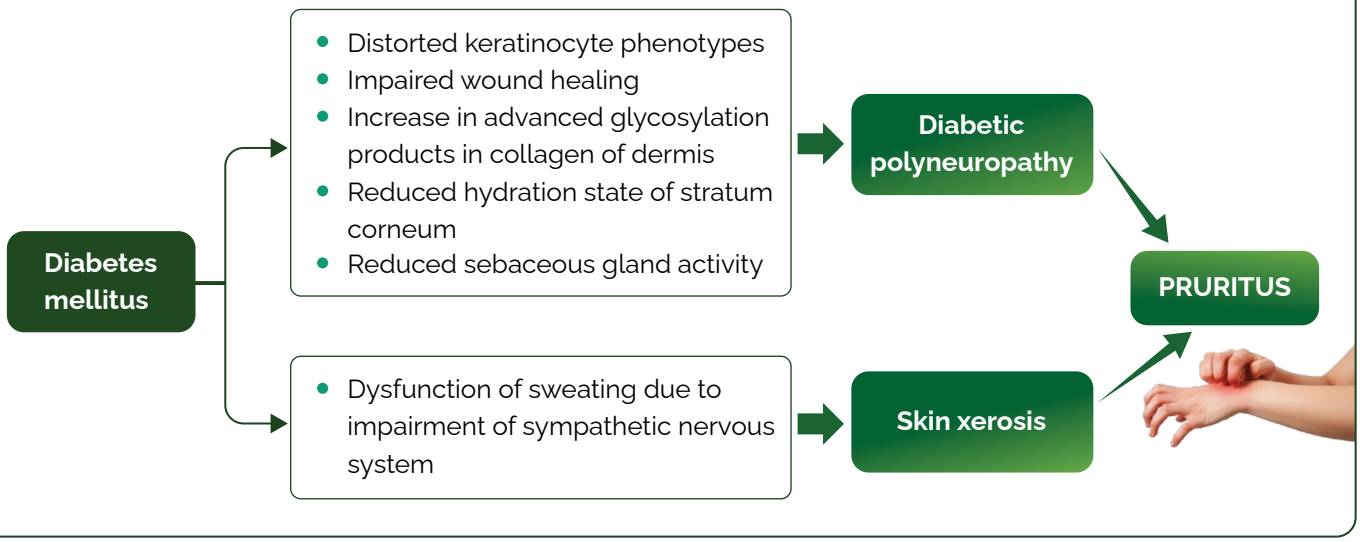
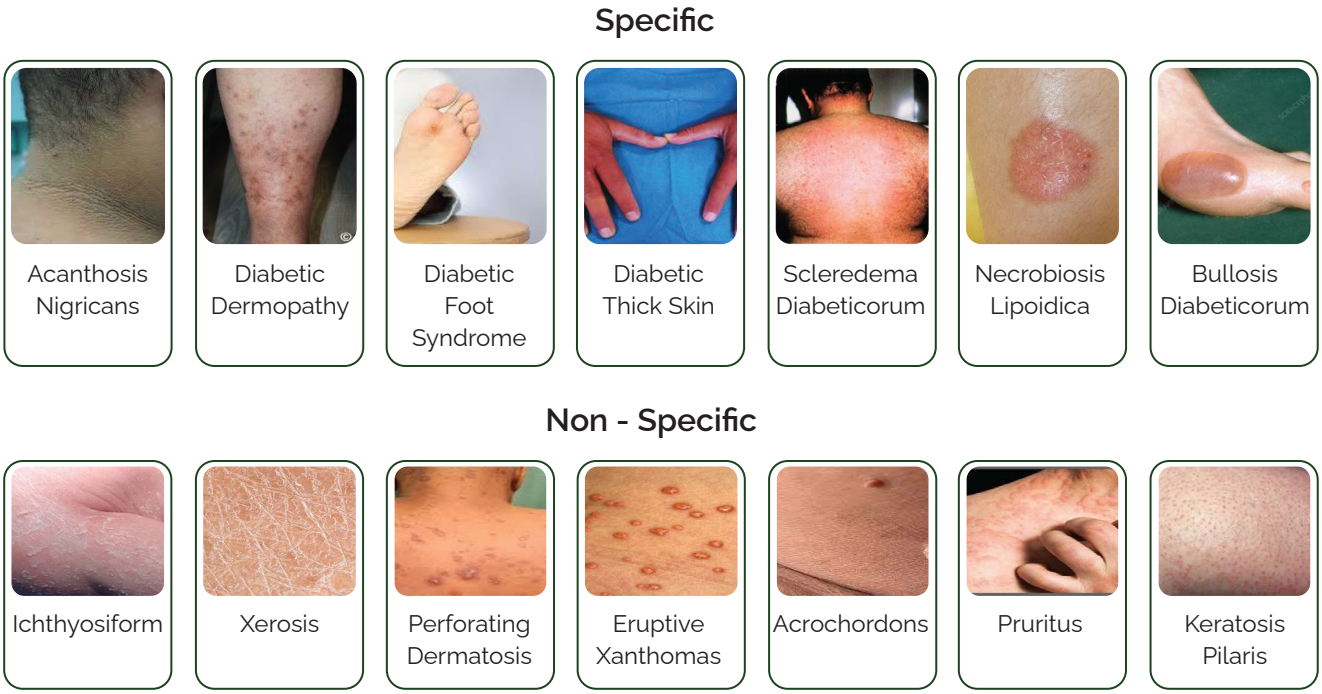



**Figure 8 b: Skin complications of diabetes**




Pruritus or itching can arise from both acute and chronic complications of diabetes. Acute complications, such as balanoposthitis, pruritus vulvae, and skin/soft tissue infections, contribute to immediate discomfort. Chronic complications, including microvascular ones like nephropathy, retinopathy, and neuropathy, as well as macrovascular complications, are long-term outcomes associated with diabetes that leads to diabetic pruritus.

## Diabetic Polyneuropathy and itch[47]

- Diabetes mellitus stands as the predominant cause behind small-fiber polyneuropathy.
- When neurons responsible for processing pruritoception suffer damage, whether in the peripheral or central nervous system, it instigates neuropathic itch.
- This itching is observed in approximately 8% of chronic itch cases, and it often tends to be overlooked as a symptom in neuropathic conditions.

### Pruritus as a microvascular equivalent

- Itchiness, a common symptom in systemic and localized skin conditions, is also prevalent in diabetic painful neuropathy associated with diabetes mellitus.
- The primary pathophysiology of diabetic neuropathy revolves around small fiber neurons, particularly C-fibers responsible for transmitting both pain and itch sensations.
- Although pain and itching are typically associated with distinct neural circuits, there is evidence suggesting communication or cross-talk between these pathways.

**Pruritus can manifest as a symptom of diabetic neuropathy, mirroring the clinical implications observed in microvascular disease associated with diabetes.**

**Treatment:** Since diabetic itch/pruritus is majorly a microvascular equivalent of neuropathy, it warrants a similar level of attention and care in treatment. Addressing it not only alleviates discomfort but also enhances the overall quality of life.Therapeutic approaches include:

- Adequate glycaemic control
- Skin care measures
- Anti-pruritic topical therapies like pramoxine
- Systemic therapies like hydroxyzine
- Optimal management of neuropathy, and
- Adjuvant therapies like acupuncture or hypnosis

Systemic antihistamines are the most used drugs for relieving symptoms of chronic pruritus due to dermatological and non-dermatological causes.

- Hydroxyzine is considered to be the most potent antihistamine in managing chronic diabetic pruritus.[49]
- Anxiolytic effects of Hydroxyzine help in handling of diabetic distress (stress related to treatment/ management of diabetes causing anxiety) and can be used as an adjuvant therapy.
- Post therapeutic neuralgia is additional effect associated with many antidiabetic drugs and Hydroxyzine works perfectly in controlling the itching related to it.

## Pediatric Pruritus

The most common causes of chronic nocturnal itching in children are atopic dermatitis and psoriasis, with lichen simplex chronicus and prurigo nodularis contributing to lesser degrees.[50]

The most troubling consequence of nocturnal itching is poor quality of sleep leading to:[50]

- ✓ Neurocognitive
- ✓ behavioral, and
- ✓ physiologic outcomes

Such changes lead to various debilitating effects such as:

- ✓ Poor Performance In School
- ✓ Attention Deficit Hyperactivity Disorder
- ✓ Short Stature
- ✓ Hypertension

- ✔ Obesity, and
- ✔ Impaired immune function.

- **Treatment:** Conservative, nonpharmacologic measures are used in conjunction with topical and systemic treatments.
- First-generation antihistamines like diphenhydramine, hydroxyzine etc. work by antagonizing H1 receptors and are commonly used as first-line therapy for the treatment of nocturnal pruritus in children.[50]

## Other Indications of Hydroxyzine

Hydroxyzine, a first-generation H1-receptor antagonist, is among the most prescribed antihistamines with a range of therapeutic indications[51]

- Hydroxyzine is used to alleviate **rhinorrhea** by blocking histamine receptors and reducing excessive nasal mucus production associated with allergic reactions. It provides symptomatic relief for runny nose in allergic conditions.[44]
- It is used in the treatment of **Generalized Anxiety Disorder (GAD)**, supported by numerous studies, without the risk of addiction[51]. Hydroxyzine selectively antagonizes the histamine H1 receptor, reducing histamine's activity and producing sedative and anxiolytic effects.
- It efficiently penetrates the central nervous system, and beyond its primary antihistaminic activity, may interact with serotonergic, dopaminergic, and GABAergic neurotransmission[51]. It exhibits **tranquilizing and sedative properties** due to its weak antagonism of serotonin 5-HT2A, dopamine D2, and α1-adrenergic receptors.[51]
- Hydroxyzine is also commonly prescribed to manage stress **and anxiety arising from neurotic conditions and specific physical ailments.** It has been shown to have muscle-relaxing, pain-relieving, local anesthetic, and anti-nauseatic effects. In anesthesia contexts, it has utility both pre- and post-procedure, potentiating the effects of meperidine and barbiturates.[51]
- It is frequently prescribed in pediatrics as a mild sedative and for managing anxiety in children and adolescents with **Avoidant Restrictive Food Intake Disorder (ARFID)**.[52]
- Of particular interest are emerging findings that suggest hydroxyzine's potential role against **COVID-19**[52]. Preliminary evidence has highlighted its in-vitro antiviral effects against Middle East respiratory syndrome and hepatitis C virus, indicating possible interactions with the SARS-CoV-2 cellular entry process that could be beneficial in attenuating disease progression.[53-55]
- In oncology, hydroxyzine has demonstrated potential as a therapeutic agent against **Triple Negative Breast Cancer (TNBC)** by inducing apoptosis via mitochondrial superoxide generation and suppression of Janus Kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3) signaling.[56]
- It's also been combined with haloperidol for treating **overactive delirium**[57], and with codeine phosphate for chronic pain management.[58]
- Recent findings also suggest hydroxyzine's potential role in modulating **cardiac autonomic activity**[59] and as a therapeutic consideration in cases unresponsive to behavioral treatment for childhood masturbation.[60]
- Used in **palmoplantar hyperhidrosis** at a dose of 10 mg twice a day, in patients dealing with anxious situations (exam writing stress etc.) and where anticholinergics are not well tolerated.[61,62]
- Hydroxyzine is sometimes prescribed for **nodular prurigo**, a skin condition characterized by intensely itchy nodules. Its antihistaminic effects can help alleviate itching and discomfort associated with nodular prurigo, providing symptomatic relief.[4]
- It works excellently in scrotum dermatitis and vulvar dermatitis and conditions like **balanoposthitis and pruritus vulvae**.[63]

- **Drug induced urticaria** and specially opoid drug induced urticaria is controlled very well with Hydroxyzine.
- In **Scabetic itch**, it is comparatively more useful to other oral anti-histamitines.[64]
- **Insect bite reaction**[65], **mastocytosis**[66] are also very well controlled by Hydroxyzine.
- It has been used in cases of **Bullous pemphigoid** to control excessive itching and provide relief.[67]

**Table 3: Summary of the studies assessing efficacy and safety of hydroxyzine therapy in pruritus**

| No. of patients | Condition | Intervention and dose | Duration | Control/ Comparator | Efficacy outcomes | Conclusion | Most common AEs associated to Hydroxyzine therapy |
|---|---|---|---|---|---|---|---|
| **1. Thomas et al., 2019[4] – A prospective, non-comparative study** | | | | | | | |
| 400 | Indian patients with chronic pruritus | Hydroxyzine up to 25 mg four times daily | 12 weeks | – | DLQI and 5-D itch scores | Hydroxyzine significantly improves symptoms of pruritus and quality of life in patients with chronic pruritus due to dermatological causes over 12 weeks, indicating its long term safety | Mild to moderate AEs; Dizziness (1.0%), constipation (0.5%), drowsiness (0.5%), dry mouth (0.5%), sedation (0.3%) |
| **2. Mohammadi Kebar et al., 2020[68] - Double blind randomized clinical trial** | | | | | | | |
| 32 | Pruritus in dialysis patients | Hydroxyzine 25 mg orally per day | 6 weeks | Gabapentin capsule (100mg) orally per day | Severity and frequency of itching before and after treatment using Pruritus Scale questionnaire | Both Hydroxyzine and Gabapentin significantly improved and controlled pruritus in dialysis patients but no significant difference was observed between two drugs | Not assessed |
| **3. Klein and Galant, 1980[69] - Double-blind study** | | | | | | | |
| 20 | Children with atopic dermatitis | Hydroxyzine 1.25/mg/kg/ day or 3 times daily | 1 week | Cyproheptadine 0.25/mg / kg/day 3 times daily | Pruritus score, improvement of the dermatitis | Hydroxyzine is apparently more effective than cyproheptadine for the management of pruritus associated with atopic dermatitis in children | Not assessed |

| No. of patients | Condition | Intervention and dose | Duration | Control/ Comparator | Efficacy outcomes | Conclusion | Most common AEs associated to Hydroxyzine therapy |
|---|---|---|---|---|---|---|---|
| **4. Monroe, 1992[70]- Double-blind study** | | | | | | | |
| 59 | Chronic idiopathic urticaria and atopic dermatitis aged 18 to 65 years | 25 mg of hydroxyzine thrice daily | — | 10 mg of loratadine once daily, placebo twice daily or placebo thrice daily | Symptom relief, Daily symptom scores | Loratadine is as effective as hydroxyzine in the treatment of urticaria and demonstrates a significant antipruritic effect in atopic dermatitis, but does not have the central nervous system effects of hydroxyzine | Somnolence or sedation |
| **5. Kalili *et al.*, 2006[71] - Comparative study** | | | | | | | |
| 30 | Pruritus in patients with chronic renal failure. | Hydroxyzine 25 mg TDS | 2 weeks | 2 weeks ketotifen therapy 1mg BID, 2 weeks chlorphenir-amine 4mg BD | Pruritus severityusing Pruritus Severity Score | Pruritus Severity Score improve-ment with hydroxyzine and chlorpheniram-ine was statistically significant | Not assessed |
| **6. Shohrati *et al.*, 2007[72] - Randomized, double-blind safety and efficacy study** | | | | | | | |
| 50 | Chronic pruritus due to exposure to sulfur mustard | Hydroxyzine 25 mg/day | 4 weeks | Doxepin 10 mg/day | Pruritic score | Both hydroxyzine and doxepin are effective and have equivalent results in controlling the symptoms of patients with chronic pruritus due to exposure to sulfur mustard | Not assessed |

| No. of patients | Condition | Intervention and dose | Duration | Control/ Comparator | Efficacy outcomes | Conclusion | Most common AEs associated to Hydroxyzine therapy |
|---|---|---|---|---|---|---|---|
| **7. Gall-Ianotto *et al.*, 2021[73] - Multicentric, double-blind, double-placebo, randomized trial** | | | | | | | |
| 80 | Patients with myelopr-oliferative neoplasia suffering from Persistent Aquagenic Pruritus | Hydroxyzine (25 mg daily) + placebo | 14 days | Aprepitant (80 mg daily) + placebo | Reduction of pruritus intensity below (or equal) at 3/10 on VAS, number of patients with a reduction or cessation of AP, evaluation of QoL and AP characterist-ics with MPN-SAF and AP question-naires, modification of plasmatic concentrati-ons of cytokines and neurope-ptides | Ongoing | — |

## Place of Hydroxyzine in Pruritus Management

First-generation antihistamines, such as hydroxyzine are known to bind not only to H1-receptors, but also to muscarinic, α-adrenergic, dopamine or serotonin receptors and have a central effect.

- As per an expert opinion consensus to manage pruritus in Indian settings, systemic oral antihistamines such as hydroxyzine and diphenhydramine are generally considered the first line of treatment for generalized pruri-tus.[41]
- In conditions like atopic dermatitis, hydroxyzine show an ameliorative effect by producing essential sedation and pruritus relief.[41]
- H1-type antihistamines are the most clinically investigated drugs for managing pruritus. First-generation antihistamines are considered to be highly effective & hydroxyzine is considered to be the most potent antihis-tamine in managing chronic pruritus.[33]
- As per an expert consensus review for management of chronic pruritus, hydroxyzine in the dose of 75-100 mg/day and 1-2.5 mg/kg/day is recommended the treatment of chronic pruritus for adults and children, respectively.[33]
- The European guidelines on chronic pruritus recommends use of hydroxyzine as a first choice in treatment of pruritus occurring as a result of several etiologies due to its antipruritic, anxiolytic and sedative properties.[36]

## Hydroxyzine in Allergic Disorders

Hydroxyzine is used in various allergic disorders as provided in Figure 9.

**Figure 9: Use of hydroxyzine in various allergic disorders**

**Hydroxyzine**

Dosage: in adults, 25 mg t.i.d. or q.i.d.; children under 6 years, 50 mg daily in divided doses; and over 6 years, 50-100 mg daily in divided doses[74]

**Contact/Atopic dermatitis**

Hydroxyzine demonstrates a significant antipruritic effect in atopic dermatitis and have CNS effects as well[4,75,76]

**Chronic Urticaria**

Hydroxyzine significantly improves symptoms of pruritus and quality of life in patients with chronic pruritus[76]

**Histamine-mediated pruritus**

Most efficacious and longest acting antihistamine in suppressing the wheal and flare response to histamine
Most potent antihistamine in managing chronic pruritus[4]

## Drug Delivery Methods of Hydroxyzine

Traditional drug delivery methods are intended for instant drug release for rapid absorption. Sustained release systems overcome the related shortcomings with traditional delivery.

**Sustained/controlled drug delivery systems: Latest technological development in hydroxyzine**

Created to address the shortcomings of conventional drug delivery systems

Advantages of novel drug delivery systems[77,78,79]:

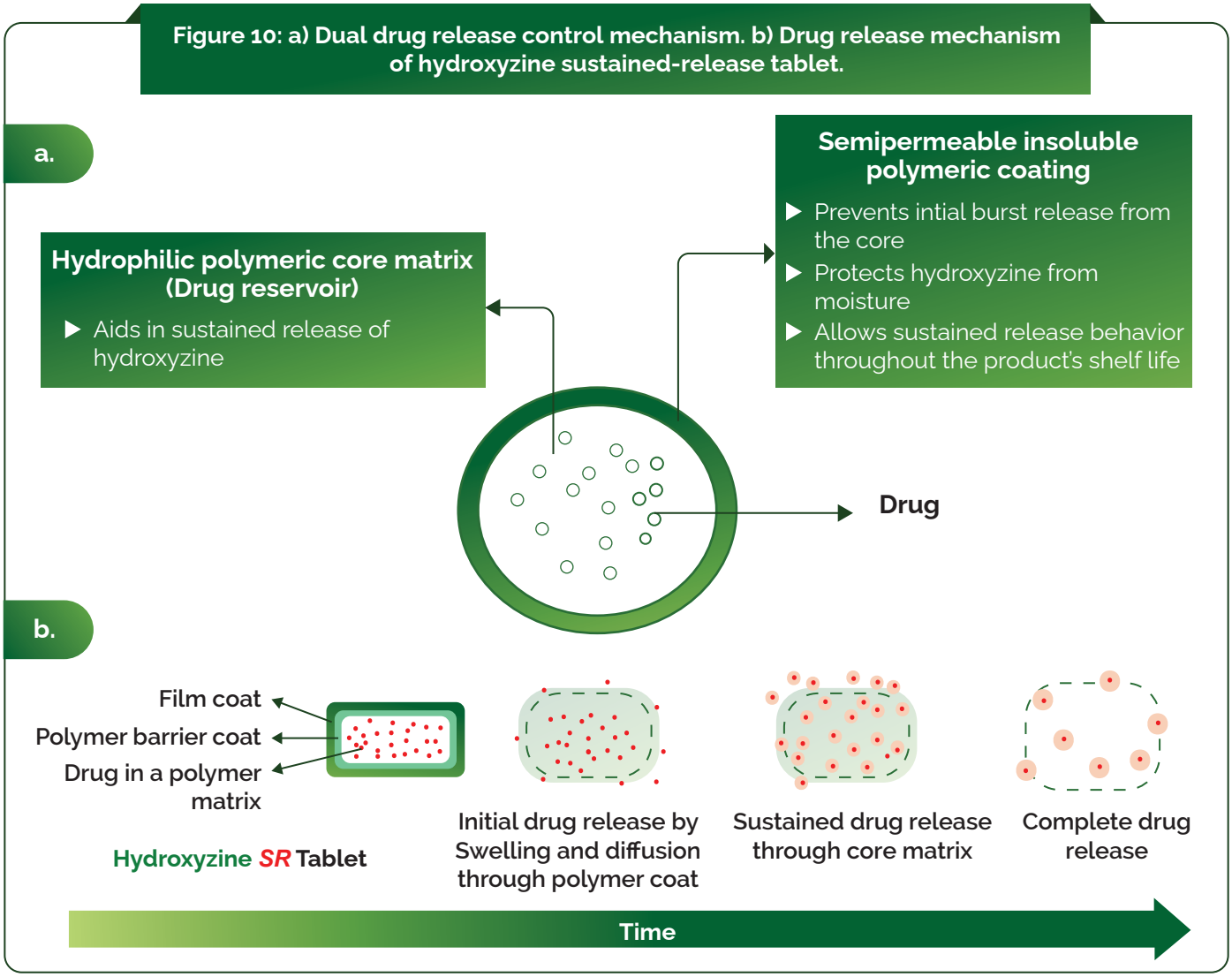
- Help lower fluctuations in drug levels in the blood
- Reduce drug-related side effects
- Has uniform pharmacological response
- Has uniform drug plasma concentrations for prolonged period of time
- Improved treatment efficiency and patient compliance

To mask bitter taste of hydroxyzine hydrochloride, a palatable dosage form was formulated using with strong and weak cation exchange resins[80]

## Hydroxyzine Hydrochloride Sustained Release Tablet: Matrixeal Technology

- A platform appropriate for highly water-soluble and hygroscopic pharmaceuticals such as hydroxyzine.
- Employs a dual drug release control mechanism (Figure 10) and comprises:
  - Outer semipermeable insoluble polymeric coating
  - Inner hydrophilic polymeric core matrix
- Drug is distributed in the inner hydrophilic matrix and is predominantly released by a diffusion mechanism.[81]
- Hydrophilic polymer matrix is frequently utilized in oral controlled drug delivery because of:[82]
  - Its usefulness in achieving a suitable drug release profile
  - Cost effectiveness
  - Broad regulatory acceptability

**Figure 10: a) Dual drug release control mechanism. b) Drug release mechanism of hydroxyzine sustained-release tablet.**

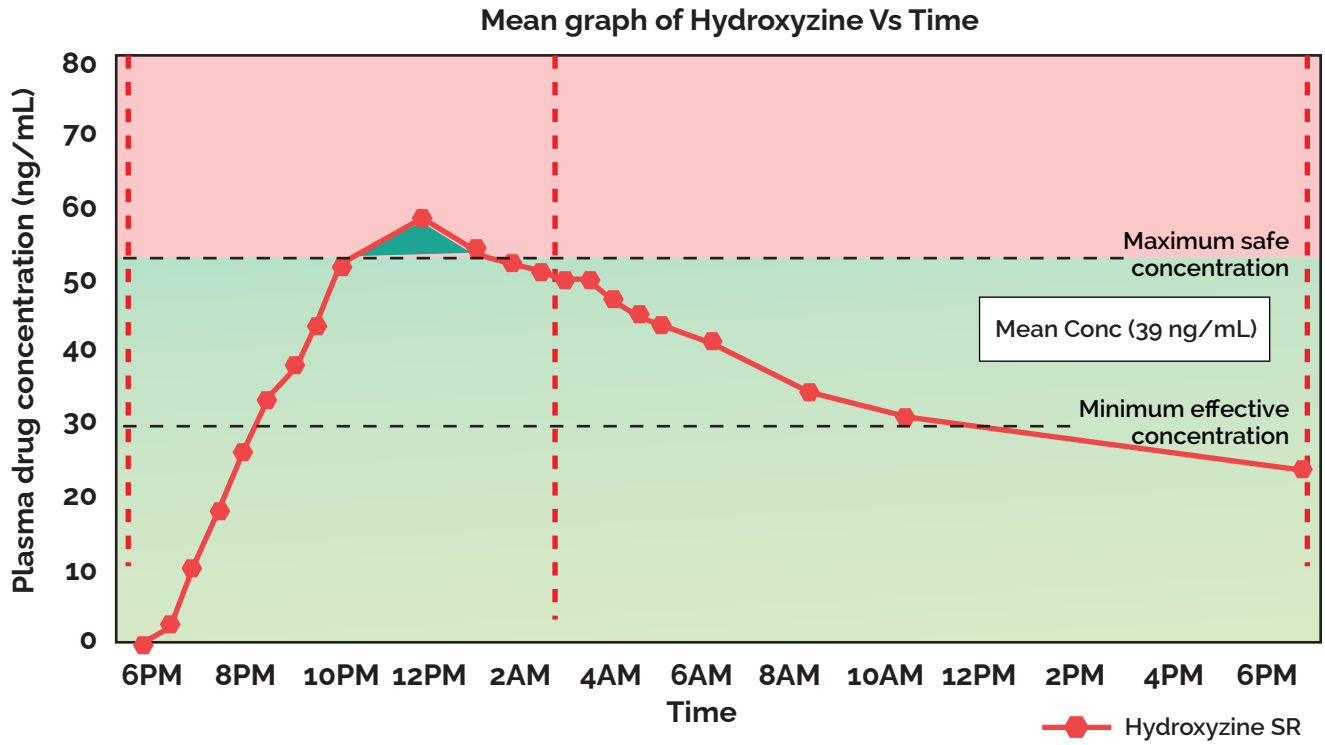



## Hydroxyzine SR - Comparative Bioavailability Study

Dr Reddy's Laboratories performed the pharmacokinetic study in a randomized, open label, balanced, two-treatment, two period, two sequence, single dose, crossover, comparative bioavailability study of hydroxyzine hydrochloride SR tablet 50 mg of Dr. Reddy's Laboratories Limited, India, comparing with Hydroxyzine Immediate Release (IR) 25 mg (Hydroxyzine Hydrochloride Tablet I.P. 25 mg) x 2 tablets of Dr. Reddy's Laboratories Limited, in 72 normal healthy adult human subjects under fasting conditions.

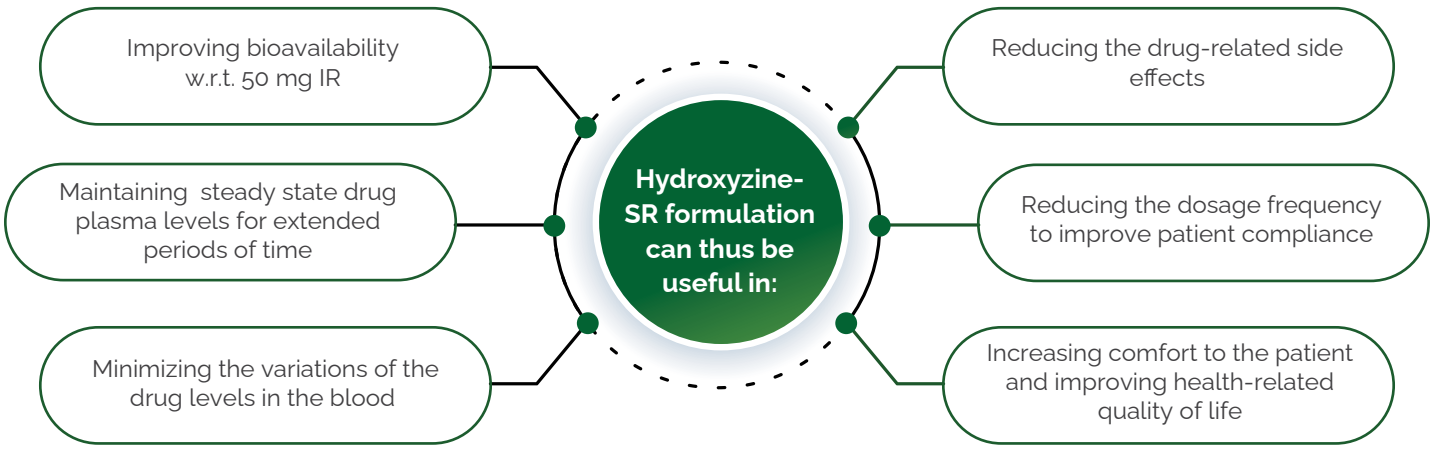
- Hydroxyzine SR release pattern over 24 hours were evaluated.

**Figure 11: Results of the comparative bioavailability study**




The comparative study showed the below advantages of SR formulation:

- Concentrations of Hydroxyzine-SR formulation were steadily increased, and the maximum concentration observed was 58.344 ng/mL at 6 hrs post-dose, but the reference IR formulation showed the maximum concentration of 75.132 ng/mL observed at 2.5 hrs post-dose which potentially showed Hydroxyzine-SR has desired concentration with maximum effect with reduced sedation over reference product as shown in the Figure 11.
- Hydroxyzine-SR formulation was able to maintain consistent plasma concentration above 9 ng/ml (efficacious concentration) from 1.5 hr to more than 24 hr post dose not exceeding beyond 58.344 ng/mL which was desired concentration with maximum effect with reduced sedation.
- Hydroxyzine SR only stays in the high sedation zone for two hours due to the blunting of the Cmax by Matrixeal technology, but the IR formulation stays in the high sedation zone for five to six hours.
- Hydroxyzine SR provides maximum comfort with better compliance and less adverse reactions.



## Table 4: Dosing charts for use of Hydroxyzine in pruritus

| Pharmaceutical form: Film coated tablets | |
|---|---|
| **Recommendation** | Should be used at the lowest effective dose and for the shortest possible duration |
| **Maximum daily dose** | 100 mg/day in adults and children over 40 kg in weight |
| **For anxiety** | 100 mg/day in adults and children over 40 kg in weight<br>▶ 50 mg/day in 3 separate administrations of 12.5-12.5-25 mg<br>▶ In more severe cases doses of up to 100 mg/day can be used |
| **For pruritus** | Starting dose of 25 mg before resting, to be followed, if necessary, with doses up to 25 mg 3 to 4 times daily |
| **In elderly** | ▶ It is advised to start with half the recommended dose due to a prolonged action<br>▶ Maximum daily dose is 50 mg/day |
| **In patients with hepatic impairment** | Recommended to reduce the daily dose by 33% |
| **In patients with moderate or severe renal impairment** | Dosage should be reduced due to decreased excretion of its metabolite cetirizine. In patients with chronic renal failure, the dosage is reduced, up to 1/3rd of the usual adult dose is recommended based on the creatinine levels. |
| **In pediatric population (Children, six months and above)** | ▶ Up to 40 kg weight: Maximum daily dose is 2 mg/kg/day<br>▶ Over 40 kg in weight: Maximum daily dose is 100 mg/day<br>For symptomatic treatment of pruritus:<br>▶ 1 mg/kg/day up to 2 mg/kg/day in divided doses |
| **Pharmaceutical form: Oral Solution** | |
| **For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested** | ▶ **Adults:** 50 to 100 mg four times daily<br>▶ **Children under 6 years:** 50 mg daily in divided doses<br>▶ **Children over 6 years:** 50 to 100 mg daily in divided doses |
| **For management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus** | ▶ **Adults:** 25 mg three times to four times daily<br>▶ **Children under 6 years:** 50 mg daily in divided doses<br>▶ **Children over 6 years:** 50 to 100 mg daily in divided doses |

| | |
|---|---|
| **As a sedative when used as a premedication and following general anesthesia** | ▶ **Adults:** 50 to 100 mg<br>▶ **Children:** 0.6 mg/kg in children |
| **Recommendations** | ▶ When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally.<br>▶ Dosage should be adjusted according to the patient's response to therapy |
| **Pharmaceutical form: Injection** | |
| **For adult psychiatric and emotional emergencies, including acute alcoholism** | ▶ Intramuscular 50-100 mg immediately, and every 4-6 hours, when necessary |
| **Nausea and vomiting excluding nausea and vomiting of pregnancy** | ▶ **Adults:** 25-100 mg intramuscular<br>▶ **Children:** 0.5 mg/ body weight intramuscular |
| **Pre- and post-operative adjunctive medication** | ▶ **Adults:** 25-100 mg intramuscular<br>▶ **Children:** 0.5 mg/ body weight intramuscular |
| **Pre- and post-partum adjunctive medication** | ▶ 25-100 mg intramuscular |
| **Recommendations** | Do not administer parenteral preparation by sub-Q, intra-arterial, or IV injection high.<br>▶ **Adults:** Preferably inject deeply into the midlateral thigh or the upper outer quadrant of the gluteus maximus. Use the deltoid area with caution and only if well developed to prevent radial nerve injury. No administration in the lower and middle third of the upper arm<br>▶ **Children:** Administer into the midlateral muscles of the thigh. Infants and small children: If intramuscular injection is required, administer in the periphery of the upper outer quadrant of the gluteus maximus. Oral therapy should replace IM therapy as soon as possible |

**Table 5: Use of hydroxyzine in various age groups along with safety considerations, oral dosage and comorbid conditions**

| Patient Profile: Chronic Urticaria Sufferers | Age group | Treatment History | Impact on Daily Life | Safety Considerations | Tailored Dosage | Comorbidities | Pediatric and Geriatric Considerations | Patient Education |
|---|---|---|---|---|---|---|---|---|
| **Adults with Urticaria (Acute chronic, angiodema, solar urticaria\ etc.)** | Age range: 18 to 65 years | Previous Antihistamines | -Sleep disturbances, work, and social activities affected | Drowsiness and dizziness, caution while driving and operating machinery | Initial Dosage: 25mg orally 3 times daily (or as prescribed) | Anxiety or Insomnia | Consider age-related kidney and liver function decline | Importance of Compliance to treatment |
| **Pediatric Patients with Chronic Urticaria** | Age range: 6 months to 17 years (<40 kg bodyweight) | Previous Treatments | Impact on school attendance and playtime | Age-Appropriate Dosage | Dosage Adjustment: Based on weight and response | Allergy-Related Sleep Disturbances | Avoid use in premature infants | Educating Parents/ Caregivers |
| **Geriatric Patients with Chronic Urticaria** | Age range: 65 years and above | Treatment Response | Mobility and daily living activities affected | Potential Drug Interactions | Dosage Modification based on renal function | Comorbidities (e.g., Insomnia) | Evaluate risks of polypharmacy and drug interactions | Medication Management |
| **Patients with Comorbid Anxiety or Insomnia** | Age range: 18 to 65 years | Combined Therapy (e.g., SSRIs) | Impact on mental health and sleep patterns | Addressing Drowsiness, potential for CNS depression | Adjusted Dosage: 10-25 mg orally as needed | Allergy Management, Psychological Considerations | Avoid use in acute alcohol intoxication | Coping Strategies for Anxiety/ Insomnia |
| **Allergic Asthma Patients with Chronic Urticaria** | Age range: 6 months and above | Co-existing Medications | Respiratory and Skin Symptoms, Asthma Exacerbation | Asthma Safety Measures | Dosage based on age and weight | Asthma-Allergy Connection, Allergy Management | Consider asthma severity and control | Allergy-Asthma Management |

## Summary

- H1-receptor antagonist '**hydroxyzine**' is an old molecule that has proved its efficacy and safety in a wide range on of pathologies.
- It is used for the management of:
  - anxiety and tension states in adults, psychomotor agitation and acute stress situations like those accompanying minor surgical procedures or allergic states, and
  - Histamine-mediated pruritus as well as allergic diseases such chronic urticaria, atopic dermatitis, and contact dermatitis
- Hydroxyzine success in other dermatologic illnesses, such as chronic urticaria, has contributed to its **use in atopic dermatitis.**
- It is safe and commonly utilized in acute and chronic settings including pruritus.
- When hydroxyzine is used as a treatment for allergic reactions, it prevents histamine from interacting with the H1 receptors on nerve tissue, and thus inhibits itching, redness, and skin rashes associated with allergic reactions.
- Other pathways, such as activity against H4 receptors, anti-muscarinic, anti-adrenergic, and anti-serotonin effects, may also contribute to further beneficial effects due to its central sedative action.
- Thus, hydroxyzine is considered as first drug of choice in treatment of pruritus Owing to these antipruritic, anxiolytic, and sedative properties.
- Technological advancements have led to the development of **sustained/controlled drug delivery systems** of hydroxyzine to further aid in therapy with more favorable efficacy and side effect profiles.

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