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Hydroxyzine:

An Effective Antihistamine and the Drug of Choice for Pruritus

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Message From President and Hon. Secretary-General

Indian Medical Association (IMA), as the largest professional association of modern medicine doctors in India, with around 4 lakhs members across 1760 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.

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

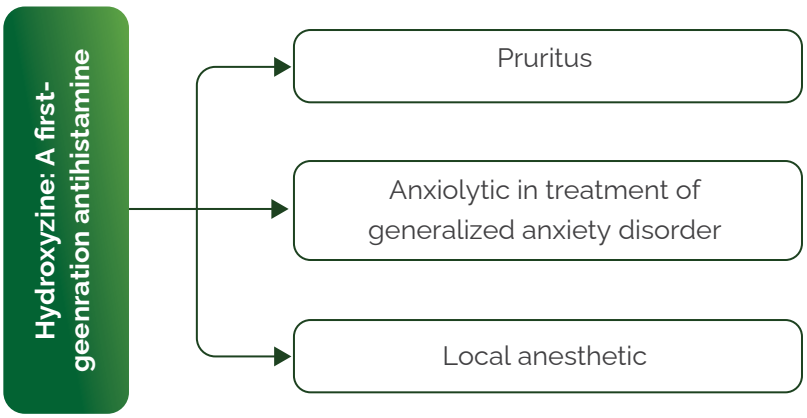
Hydroxyzine: An Effective Antihistamine and the Drug of Choice for Pruritus

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]

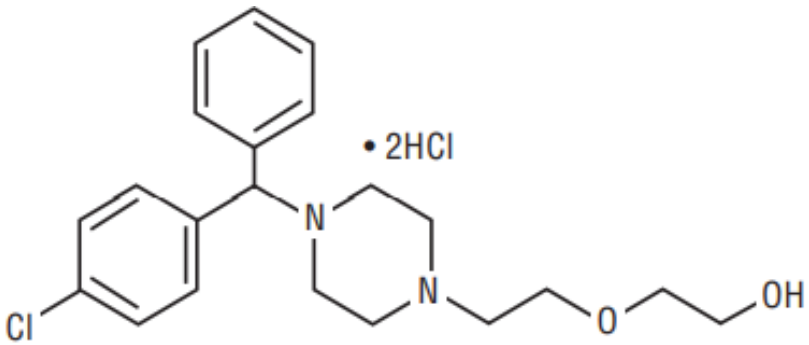
History and Pharmacology of Hydroxyzine

- 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.

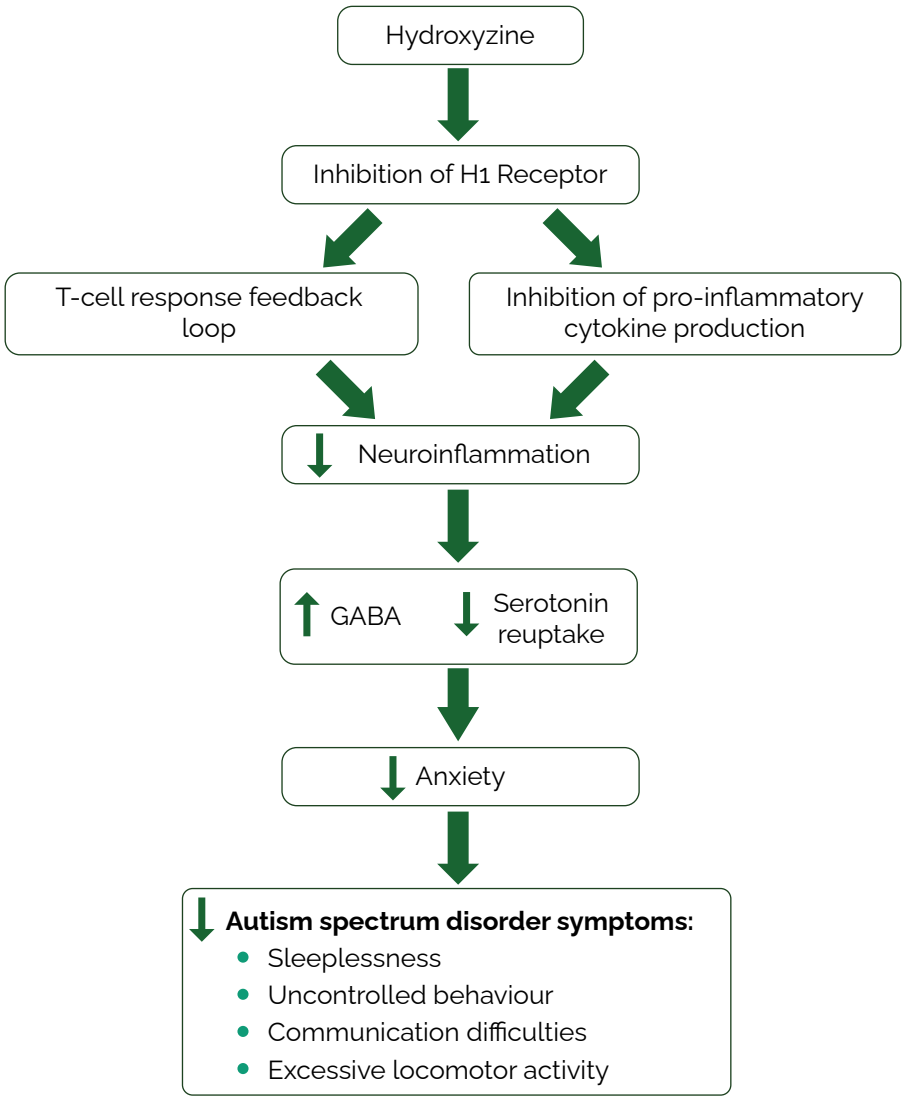
    Maximum daily dose in children up to 40 kg in bodyweight: 2 mg/kg/day.[15]

- 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

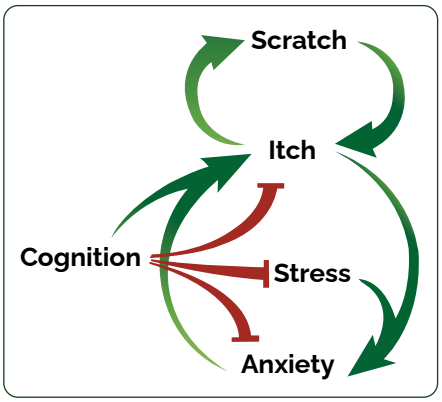
- Contraindicated in patients with known acquired or congenital QT interval prolongation, or with a known risk factor for QT interval prolongation such as cardiovascular disease, family history of sudden cardiac death, significant bradycardia, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia, 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 ▶ Due to biological mechanisms that emerge from the skin's layers and produce the somatic sensation of itch • Peripheral pruritogens: Histamine, dust mites, cytokines, endothelin-1, tryptase, substance P, and capsaicin • 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 ▶ 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

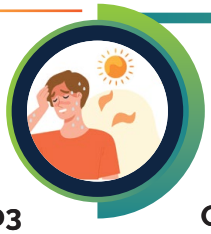
Chronic renal insufficiency	Chronic Kidney disease, reactive perforating collagenosis, increase in Blood Urea Nitrogen (BUN), etc.
Liver associated disease	Cholestatic liver diseases (CLD), primary biliary cirrhosis, primary sclerosing cholangitis, obstructive biliary disease, etc.
Metabolic	Diabetic 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

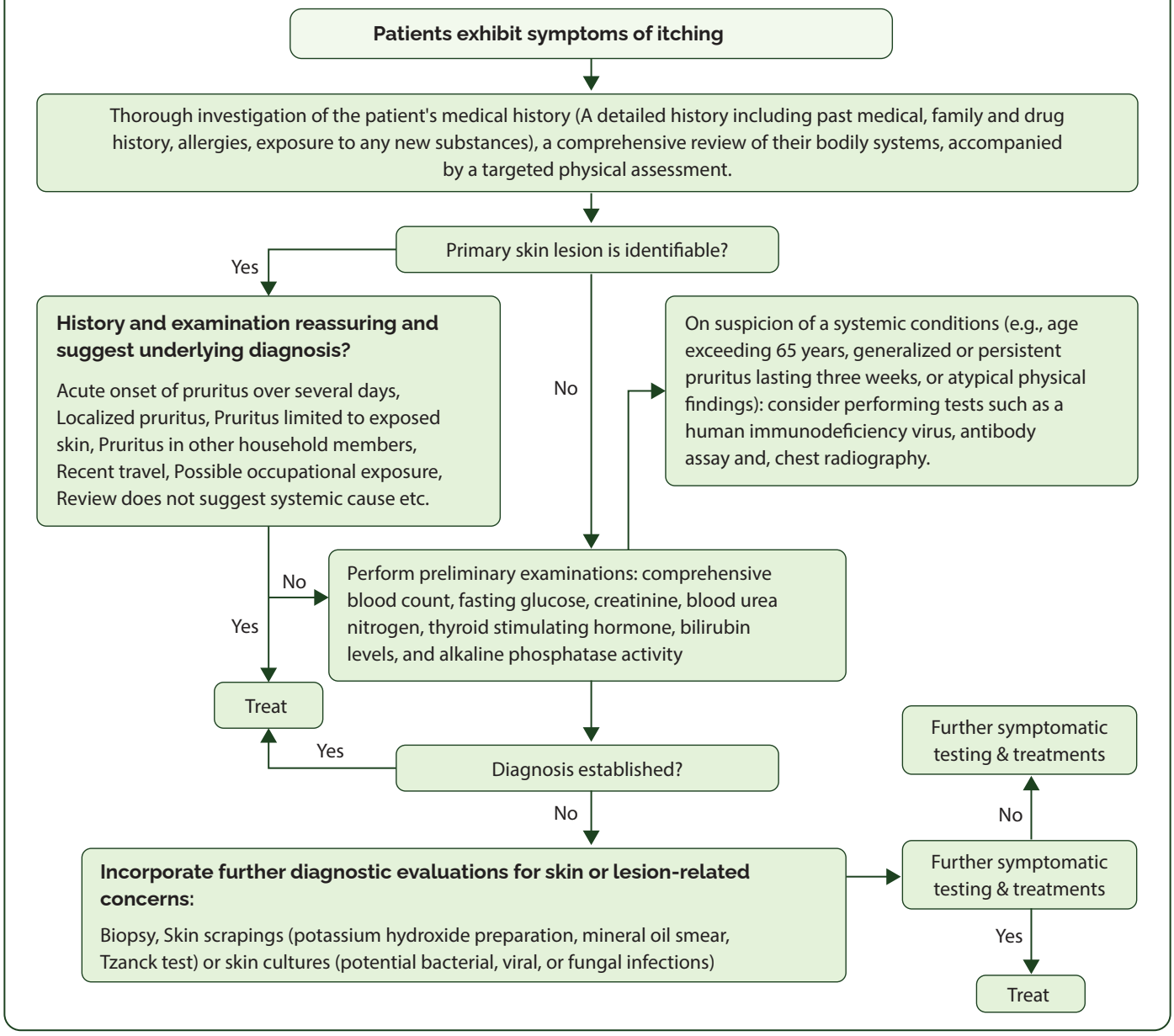
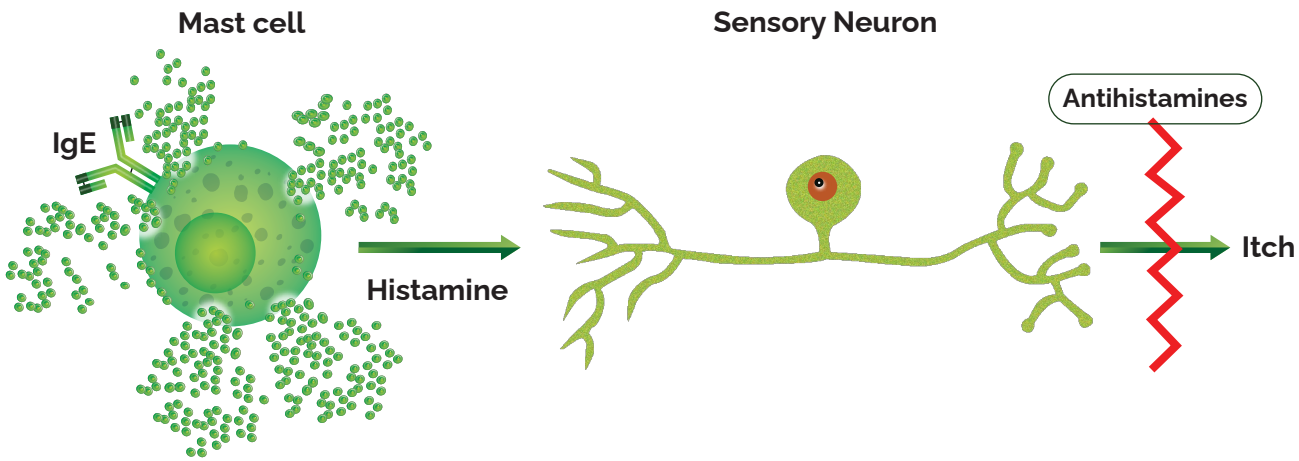


Figure 5: Classic histaminergic itch pathway



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.

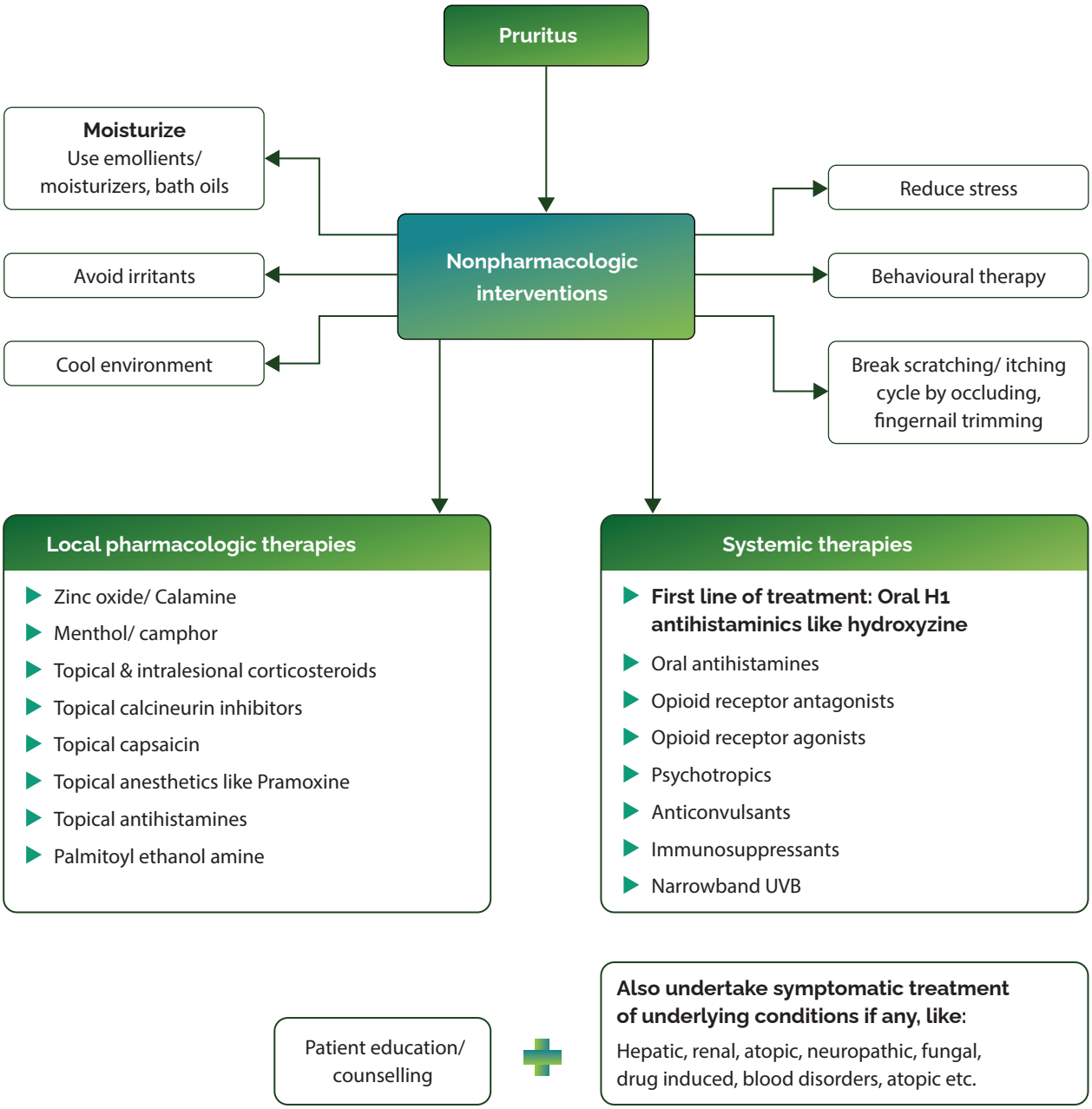
Approximately 90 years ago, the enhanced sensitivity or reactivity of the cutaneous vessels to histamine was noted, evidenced by increase in skin temperature and emergence of erythema, leading to atopic dermatitis.[38]

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.

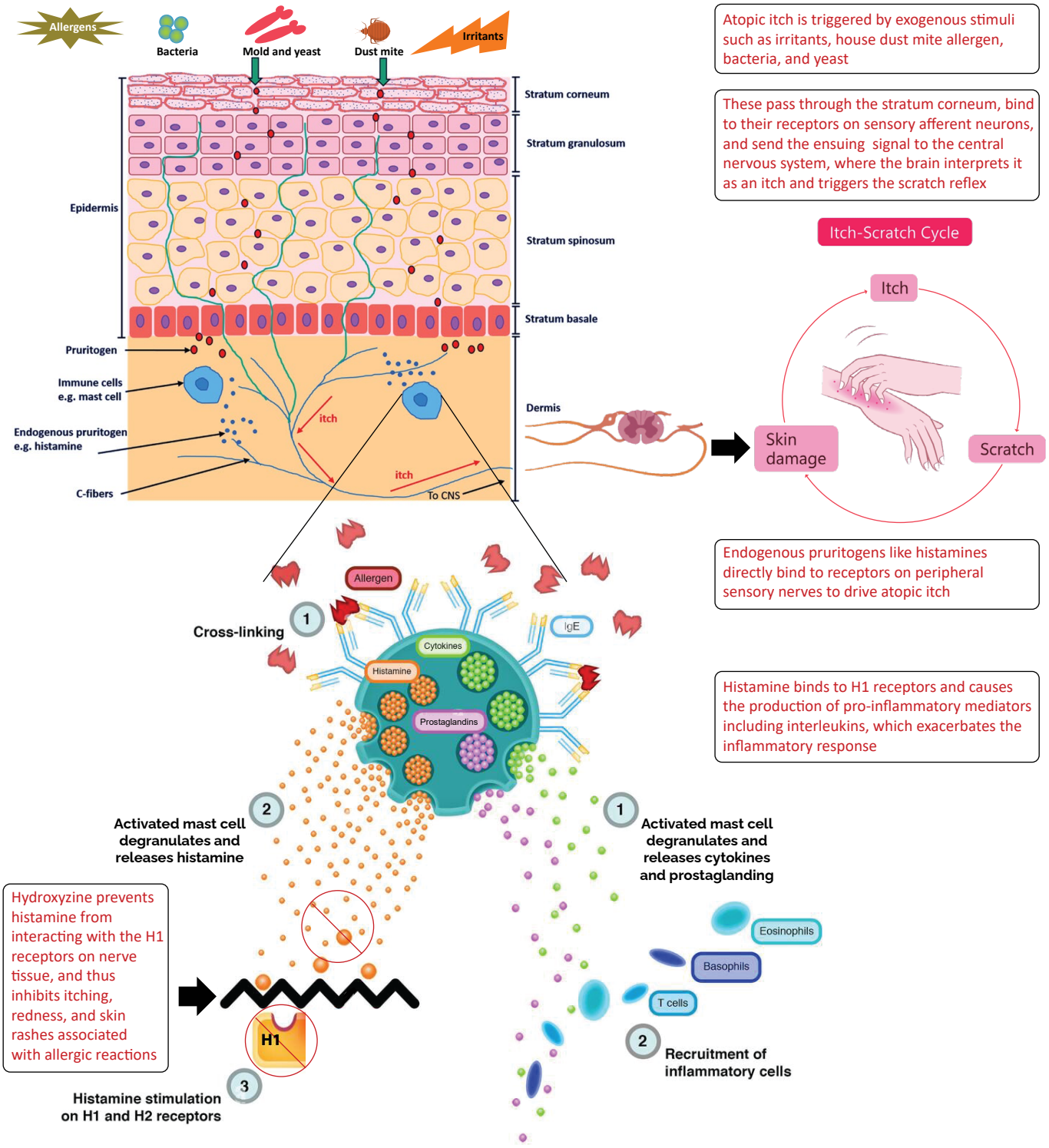
Table 2: Hydroxyzine vs other commonly used anti histaminics

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

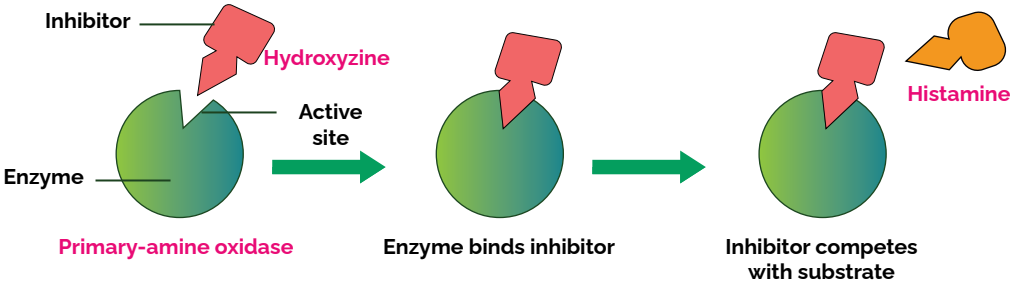
Itch-Scratch Cycle

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

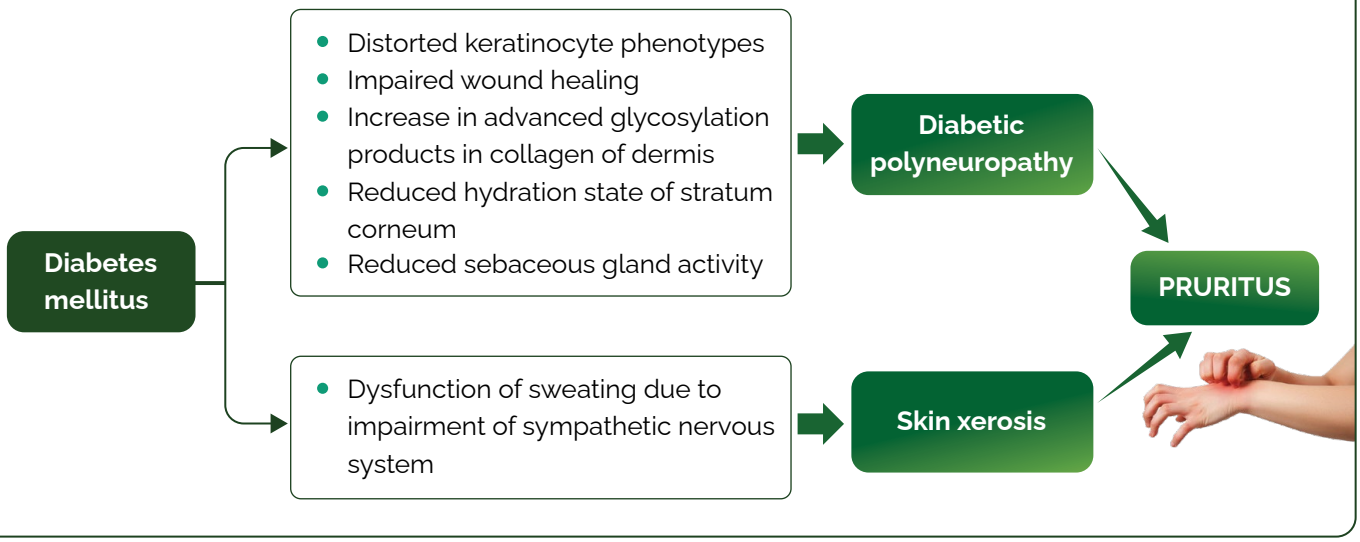
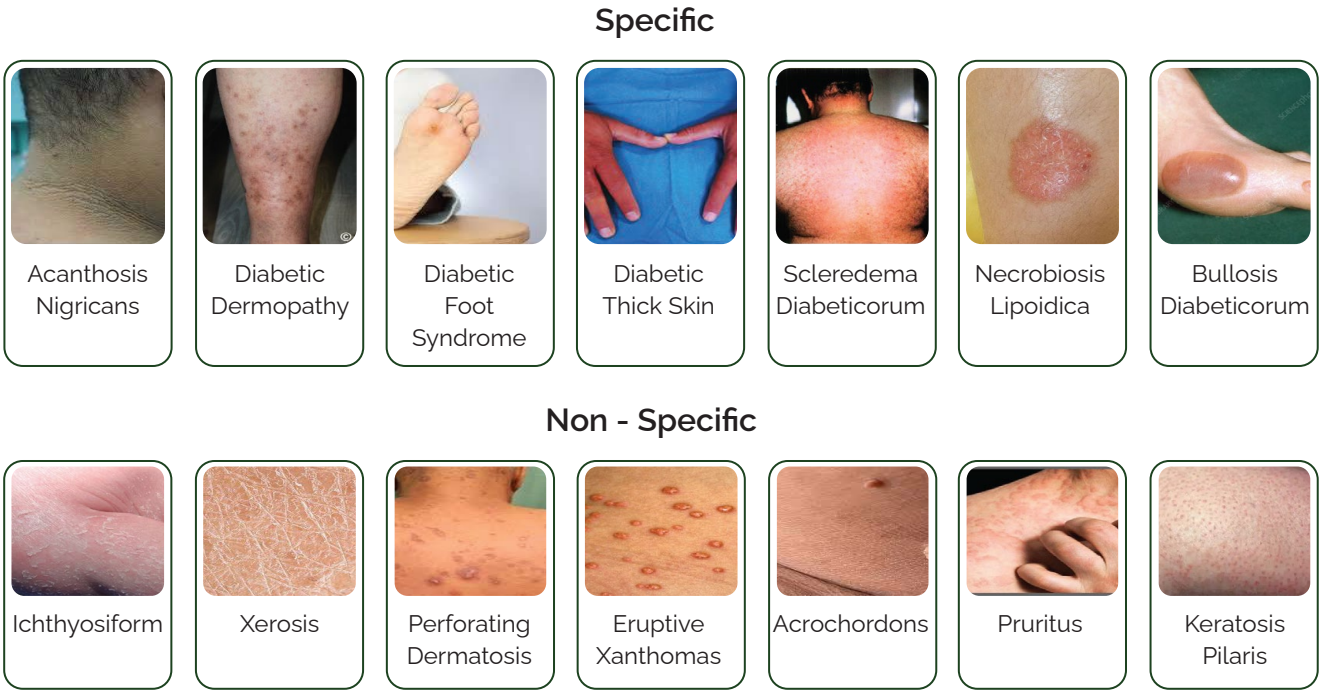


Figure 8 b: Skin complications of diabetes



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]:

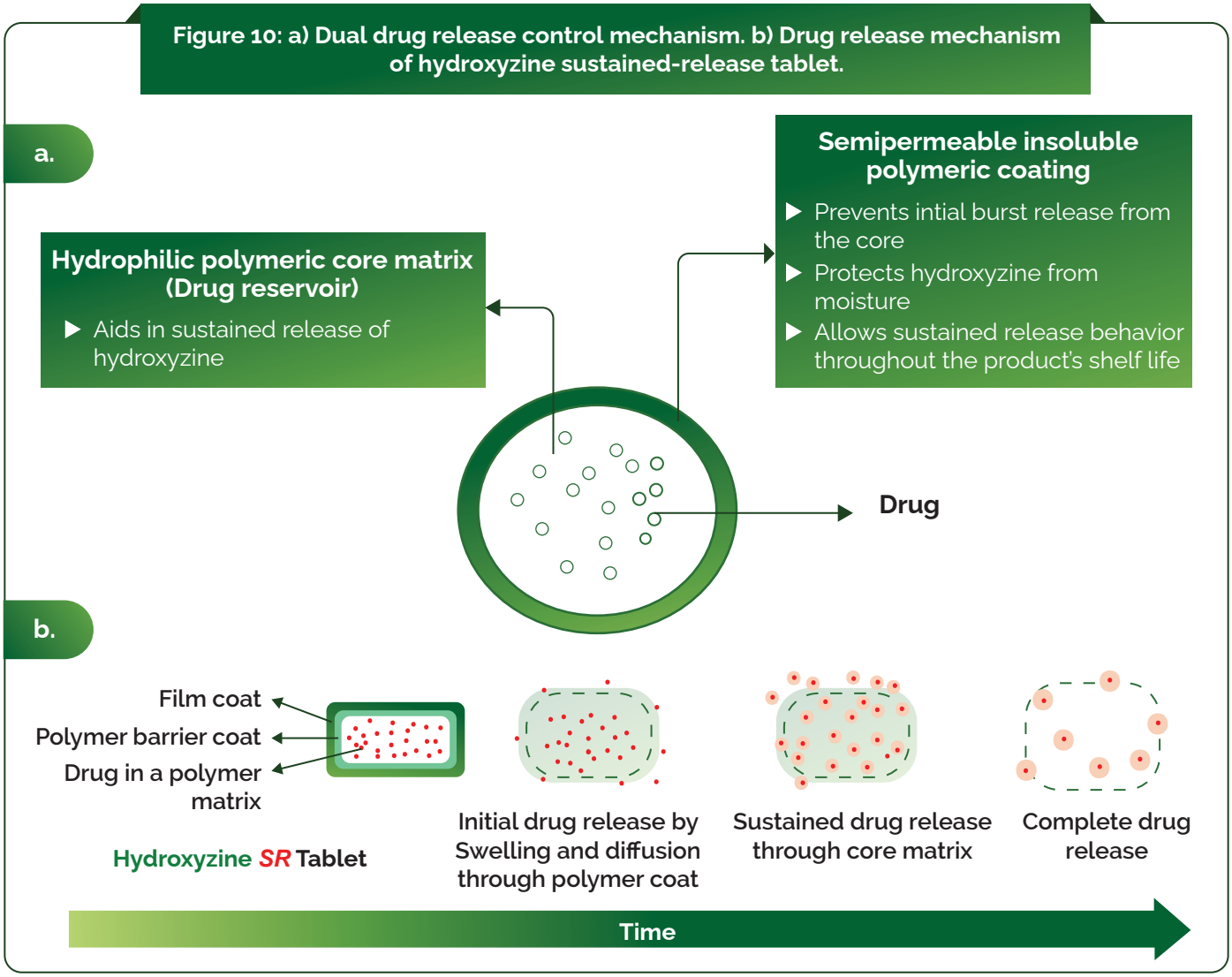
- Help lower fluctuations in drug levels in the blood
- Reduce drug-related side effects
- Has uniform pharmacological response
- Has uniform drug plasma concentrations for prolonged period of time
- Improved treatment efficiency and patient compliance

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.

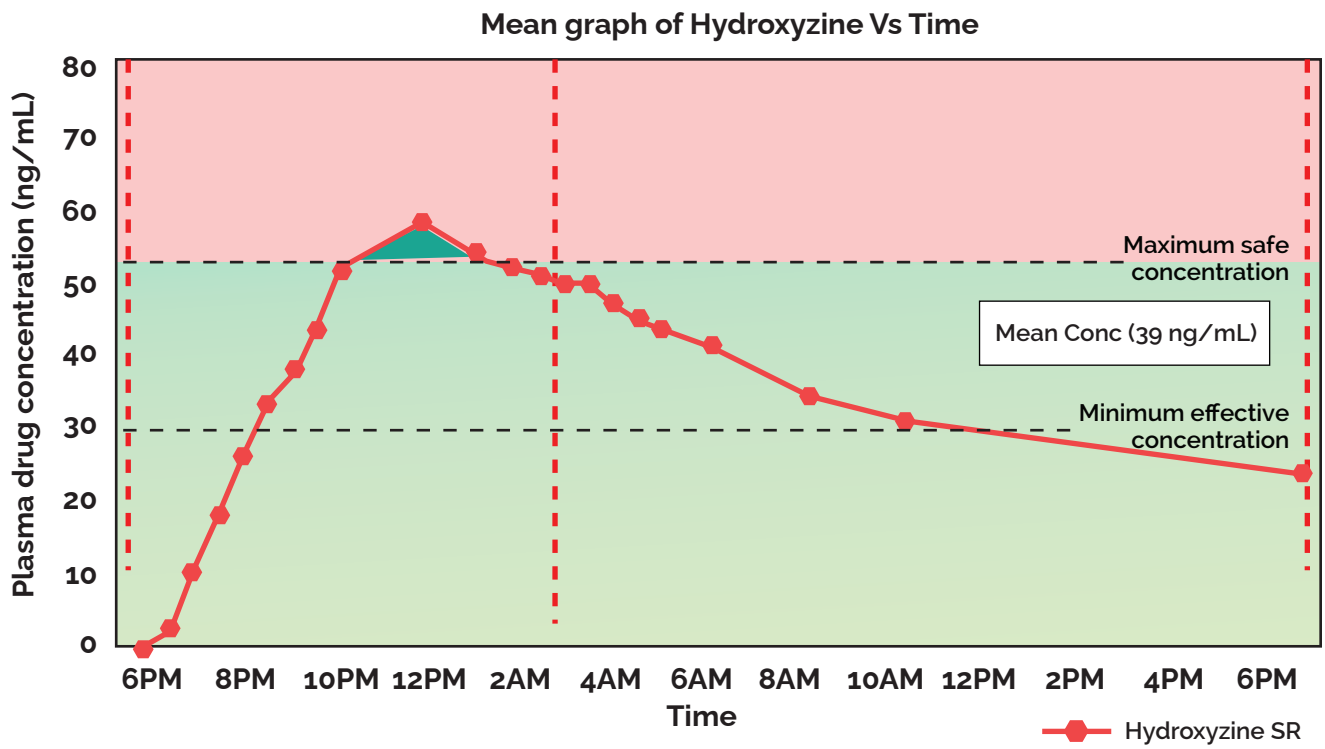


Hydroxyzine SR - Comparative Bioavailability Study

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.

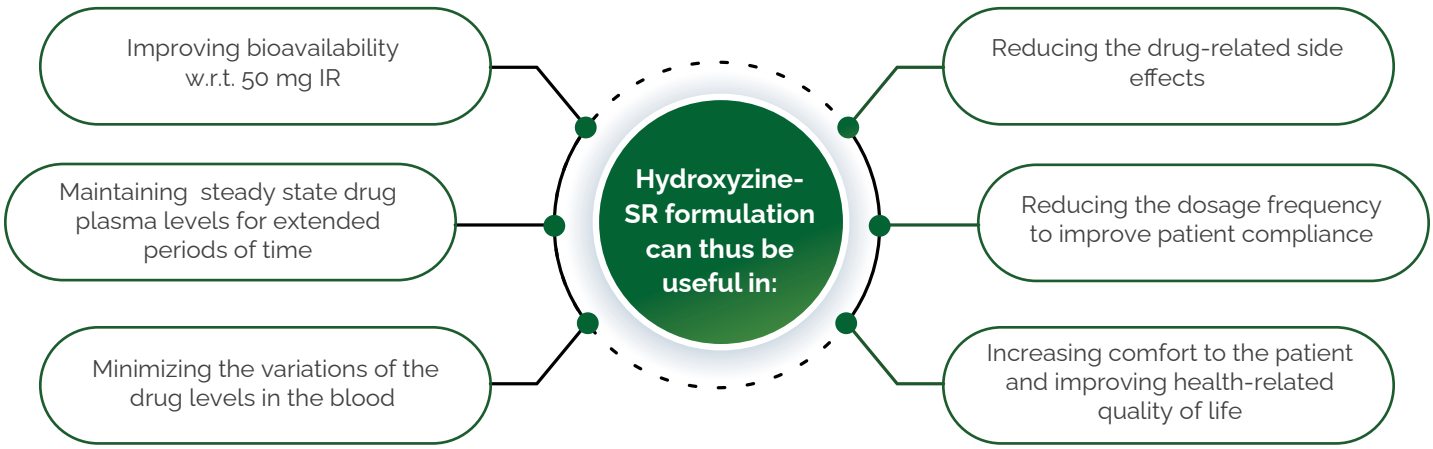


Table 4: Dosing charts for use of Hydroxyzine in pruritus

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 ▶ 50 mg/day in 3 separate administrations of 12.5-12.5-25 mg ▶ 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 ▶ 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 ▶ Over 40 kg in weight: Maximum daily dose is 100 mg/day For symptomatic treatment of pruritus: ▶ 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 ▶ **Children under 6 years:** 50 mg daily in divided doses ▶ **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 ▶ **Children under 6 years:** 50 mg daily in divided doses ▶ **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 ▶ **Children:** 0.6 mg/kg in children
Recommendations	▶ When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally. ▶ 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 ▶ **Children:** 0.5 mg/ body weight intramuscular
Pre- and post-operative adjunctive medication	▶ **Adults:** 25-100 mg intramuscular ▶ **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. ▶ **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 ▶ **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.

References

1. Weisshaar E, Szepietowski JC, Dalgard FJ, Garcovich S, Gieler U, Giménez-Arnau AM, et al. European S2k guideline on chronic pruritus. Acta Derm Venereol. 2019;99(5):469–506.
2. Malamed SF, editor. Chapter 7 - Oral Sedation. In: Sedation (Sixth Edition) [Internet]. Mosby; 2018. p. 95–119. Available from: https://www.sciencedirect.com/science/article/pii/B978032340053400007X
3. Saxen MA. Pharmacologic management of patient behavior. In: McDonald and Avery's Dentistry for the Child and Adolescent. Elsevier; 2016. p. 303–27.
4. Thomas J, Saple DG, Jerajani HR, Netha NRG, Rangasamy DU, Shaikh R, et al. Real-world, non-interventional, observational study of hydroxyzine hydrochloride in chronic pruritus: A prospective, non-comparative study. Dermatol Ther (Heidelb). 2019;9:299–308.
5. Garakani A, Murrough JW, Freire RC, Thom RP, Larkin K, Buono FD, et al. Pharmacotherapy of anxiety disorders: current and emerging treatment options. Front Psychiatry. 2020;1412.
6. Lader M, Scotto JC. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology (Berl). 1998;139:402–6.
7. Llorca PM, Spadone C, Sol O, Danniau A, Bougerol T, Corruble E, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. Journal of Clinical Psychiatry. 2002;63(11):1020–7.
8. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database of Systematic Reviews. 2010;(12).
9. Lipman ZM, Ingrasci G, Yosipovitch G. Approach to the patient with chronic pruritus. Medical Clinics. 2021 Jul 1;105(4):699-721.
10. Russell M, Zare M. How to assess and relieve that perplexing rashless itch. The Journal of family practice. 2020 Nov 1;69(9).
11. Vardanyan R, Hruby V. Synthesis of essential drugs. Elsevier; 2006.
12. Fitzsimons R, van der Poel LA, Thornhill W, du Toit G, Shah N, Brough HA. Antihistamine use in children. Archives of Disease in Childhood-Education and Practice. 2015 Jun 1;100(3):122-31.
13. Gurnani P, Miloh T, Chandar J, Landau DA, Hajjar F, Yosipovitch G. Systemic causes of non-dermatologic chronic pruritus in the pediatric population and their management: An unexplored area. Pediatric dermatology. 2021 Sep;38(5):1051-60.
14. Ferreri M, Hantouche E. Recent clinical trials of hydroxyzine in generalized anxiety disorder. Acta Psychiatr Scand. 1998;98:102–8.
15. HYDROXYZINE HYDROCHLORIDE. Summary of Product Characteristics. Available from: https://www.hpra.ie/img/uploaded/swedocuments/Licence_-PA22749-025-001_02122022155612.pdf.
16. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Hydroxyzine [Internet]. 2017 [cited 2023 Jul 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548128/
17. Kopel HM. Hydroxyzine as a pre-operative sedative: a double blind study with apprehensive children. Anesth Prog. 1971;18(6):127.
18. Wiley TS, Raden M, Haraldsen JT. H1R antagonists for brain inflammation and anxiety: targeted treatment for autism spectrum disorders. J Pharm Drug Deliv Res. 2015;4(3).
19. YETKİN D. Investigation of the Anti-Inflammatory Activity of Hydroxyzine Hihydrochloride in Mammalian Macrophages on the PI3K and P38 Pathway. Sakarya Tıp Dergisi. 2022;12(3):560–5.
20. Maita D, Gupta J. Formulation And Evaluation Of Hydroxyzine Hydrochloride Sustain Release Tablet. International Journal of Pharmaceutical Research and Applications. 2022;7(4):1407–12.
21. Simon FER, Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organization Journal. 2008;1(9):145–55.
22. Medicines Agency E. New restrictions to minimise the risks of effects on heart rhythm with hydroxyzine-containing medicines [Internet]. 2015. Available from: www.ema.europa.eu/contact
23. Health Canada, Canada.ca. Safety Reviews Summary Safety Review-Hydroxyzine (ATARAX and generics)-Assessing the Potential Risk of Abnormal Heart Rhythm [Internet]. 2016 [cited 2023 Jul 2]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-hydroxyzine-atarax-generics-potential-risk-abnormal-heart.html
24. Sanders KM, Akiyama T. The vicious cycle of itch and anxiety. Neuroscience & Biobehavioral Reviews. 2018 Apr 1;87:17-26.
25. Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. In: Seminars in cutaneous medicine and surgery. NIH Public Access; 2011. p. 71.
26. Rinaldi G. The itch-scratch cycle: a review of the mechanisms. Dermatol Pract Concept. 2019;9(2):90.
27. Harrison IP, Spada F. Breaking the itch–scratch cycle: topical options for the management of chronic cutaneous itch in atopic dermatitis. Medicines. 2019;6(3):76.
28. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. Journal of Investigative Dermatology. 2015;135(4):984–91.
29. Thyssen JP, Hamann CR, Linneberg A, Dantoft TM, Skov L, Gislason GH, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy. 2018;73(1):214–20.
30. Ho PY, Shen D, Hsu CJ, Chan TC, Cho YT, Tang CH, et al. Effects of disease severity on sleep and quality of life in Taiwanese patients with atopic dermatitis. JAAD Int. 2022;8:92.

31. Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. Exp Dermatol. 2002;11(1):12–24.
32. Jaworecka K, Rzepko M, Marek-Józefowicz L, Tamer F, Stefaniak AA, Szczegielniak M, et al. The impact of pruritus on the quality of life and sleep disturbances in patients suffering from different clinical variants of psoriasis. J Clin Med. 2022;11(19):5553.
33. Rajagopalan M, Saraswat A, Godse K, Shankar DSK, Kandhari S, Shenoi SD, et al. Diagnosis and management of chronic pruritus: an expert consensus review. Indian J Dermatol. 2017;62(1):7.
34. Steinhoff M, Cevikbas F, Yeh I, Chong K, Buddenkotte J, Ikoma A. Evaluation and management of a patient with chronic pruritus. Journal of Allergy and Clinical Immunology. 2012;130(4):1015–6.
35. Moses S. Pruritus. Am Fam Physician. 2003;68(6):1135–42.
36. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. Acta Derm Venereol. 2012;92(5):563–81.
37. Johansen P, Weiss A, Bünter A, Waeckerle-Men Y, Fettelschoss A, Odermatt B, et al. Clemastine causes immune suppression through inhibition of extracellular signal-regulated kinase–dependent proinflammatory cytokines. Journal of allergy and clinical immunology. 2011;128(6):1286–94.
38. Williams DH. Skin temperature reaction to histamine in atopic dermatitis (disseminated neurodermatitis). Journal of Investigative Dermatology. 1938;1(2):119–29.
39. Nowak D, Yeung J. Diagnosis and treatment of pruritus. Canadian Family Physician. 2017;63(12):918–24.
40. Steinhoff M, Cevikbas F, Ikoma A, Berger TG. Pruritus: management algorithms and experimental therapies. In: Seminars in cutaneous medicine and surgery. NIH Public Access; 2011. p. 127.
41. Godse K, Sangolli PM, De A, Sharma N, Girdhar M, Shankar K, et al. Management of pruritus in Indian settings: An expert opinion. Am J Dermatol Venereol. 2021;10:31–43.
42. Fourzali K, Yosipovitch G. Safety considerations when using drugs to treat pruritus. Expert Opin Drug Saf. 2020;19(4):467–77.
43. Simon FER, Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organization Journal. 2008;1(9):145–55.
44. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: Newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. Allergy, Asthma & Clinical Immunology. 2019;15(1):1–6.
45. Kumbukattu Abraham A, Bhokare A, Anna Varghes A, Kumar A, Godara D, Singh KG, et al. Hydroxyzine for the Management of Pruritus [Internet]. Vol. 23, International Journal of Scientific Study. 2022. Available from: www.ijss-sn.com
46. Patel T, Yosipovitch G. Therapy of pruritus. Expert Opin Pharmacother. 2010;11(10):1673–82.
47. Labib A, Rosen J, Yosipovitch G. Skin manifestations of diabetes mellitus. InEndotext [Internet] 2022 Apr 21. MDText. com, Inc..
48. Wijaya L, Melanie A, Veronica V, Christy G. Pruritus in diabetes mellitus (DM) and its pathophysiology-based treatment. Journal of the Medical Sciences (Berkala Ilmu Kedokteran). 2022;54(1).
49. Sanjay Kalra, Asit Mittal, Sarita Bajaj, Nitin Kapoor, Prabhakar M. Sangolli, Mangesh Tiwaskar, Ashok Kumar, Kapil Vyas, Navneet Agrawal, Roheet Rathod, Amey Mane, Snehal Muchhala, Management of Diabetic Pruritus: An Expert Consensus, American Journal of Dermatology and Venereology, Vol. 11 No. 1, 2022, pp. 7-1.
50. Boozalis E, Grossberg AL, Püttgen KB, Cohen BA, Kwatra SG. Itching at night: A review on reducing nocturnal pruritus in children. Pediatric dermatology. 2018 Sep;35(5):560-5.
51. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
52. Mahr F, Billman M, Essayli JH, et al. Selective serotonin reuptake inhibitors and hydroxyzine in the treatment of avoidant/restrictive food intake disorder in children and adolescents: rationale and evidence. J Child Adolesc Psychopharmacol. 2022;32(2):117-21.
53. Villoutreix BO, et al. Prevention of COVID-19 by Drug Repurposing: Rationale from Drugs Prescribed for Mental Disorders. Drug Discov. Today 2020; 25:1287.
54. Villoutreix BO, et al. Chemoinformatic Analysis of Psychotropic and Antihistaminic Drugs in the Light of Experimental Anti-SARS-CoV-2 Activities. Adv. Appl. Bioinforma. Chem. 2021; 14:71–85.
55. Rivas MD, et al. Hydroxyzine Inhibits SARS-CoV-2 Spike Protein Binding to ACE2 in a Qualitative in Vitro Assay. bioRxiv 2021.
56. Shakya R, et al. Hydroxyzine Induces Cell Death in Triple-Negative Breast Cancer Cells via Mitochondrial Superoxide and Modulation of Jak2/STAT3 Signaling. Biomolecules Therapeutics. 2022;30(6):585.
57. Sato J, Tanaka R. A retrospective comparison of haloperidol and hydroxyzine combination therapy with haloperidol alone in the treatment of overactive delirium. Support Care Cancer. 2022;30(6):4889-96.
58. Bonner D. The Evaluation of Blended Codeine Phosphate with Hydroxyzine Pamoate, Gabapentin, Ondansetron, and Docusate for the Treatment of Chronic Pain: A Patient-Centered Approach to the Pain Management "State of Emergency". J Pain. 2019;20(4):S70.
59. Rezaeyanzade F, et al. Transient modulation of hydroxyzine, an antihistamine and anxiolytic agent, on the cardiac autonomic activity in healthy subjects. Physiology and Pharmacology. 2019;23(1):59-69.
60. Gulec A, et al. The Assessment and Management of Childhood Masturbation: An Analysis of 90 Cases. Neuropediatrics. 2023 Oct 12.
61. Pascher F. How I Treat Hyperhidrosis of the Palms and Soles. Postgraduate Medicine. 1968 Jul 1;44(1):186-7.
62. Tsiskarishvili NV, TsI T. Colorimetric determination of eccrine sudoriferous glands functional condition in case of hyperhidrosis and their correction by belladonna. Georgian Medical News. 2006 Nov 1(140):47-50.

63. Weisshaar E. Successful treatment of genital pruritus using topical immunomodulators as a single therapy in multi-morbid patients. Acta dermato-venereologica. 2008 Jan 3;88(2):195-6.
64. Arnold AJ, Simpson JG, Jones HE, Ahmed AR. Suppression of histamine-induced pruritus by hydroxyzine and various neuroleptics. J Am Acad Dermatol. 1979 Dec;1(6):509-12. doi: 10.1016/s0190-9622(79)80094-8. PMID: 43338.
65. Geller M, Bonalumi Filho A, Siqueira-Batista R, Ribeiro MG, Duque-Estrada EO, Nunes FP. Safety and efficacy of hydroxyzine hydrochloride: a retrospective study. CEP. 2006;25964:000.
66. Kettelhut BV, Berkebile C, Bradley D, Metcalfe DD. A double-blind, placebo-controlled, crossover trial of ketotifen versus hydroxyzine in the treatment of pediatric mastocytosis. J Allergy Clin Immunol. 1989 May;83(5):866-70. doi: 10.1016/0091-6749(89)90097-3. PMID: 2654254.
67. Varpuluoma O, Jokelainen J, Försti AK, Turpeinen M, Timonen M, Huilaja L, Tasanen K. Drugs used for neurologic and psychiatric conditions increase the risk for bullous pemphigoid: A case–control study. Journal of the American Academy of Dermatology. 2019 Jul 1;81(1):250-3
68. Mohammadi Kebar S, Sharghi A, Ghorghani M, Hoseininia S. Comparison of gabapentin and hydroxyzine in the treatment of pruritus in patients on dialysis. Clin Exp Dermatol. 2020;45(7):866–71.
69. Klein GL, SP G. A comparison of the antipruritic efficacy of hydroxyzine and cyproheptadine in children with atopic dermatitis. 1980;
70. Monroe EW, Bernstein DI, Fox RW, Grabiec S V, Honsinger RW, Kalivas JT, et al. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria. Arzneimittelforschung. 1992;42(9):1119–21.
71. Kalili H, Dashti S, Poor PA, Babaei MH, Abdollahi F. Efficacy of anti-pruritis drugs in chronic renal failure: a comparative study. Tehran University of Medical Sciences Journal. 2006;64(4):36–42.
72. Shohrati M, Tajik A, Harandi AA, Davoodi SM, Almasi M. Comparison of hydroxyzine and doxepin in treatment of pruritus due to sulfur mustard. SKINmed: Dermatology for the Clinician. 2007;6(2):70–2.
73. Gall-Ianotto L, Verdet R, Nowak E, Le Roux L, Gasse A, Fiedler A, et al. Rationale and design of the multicentric, double-blind, double-placebo, randomized trial APrepitant versus HYdroxyzine in association with cytoreductive treatments for patients with myeloproliferative neoplasia suffering from Persistent Aquagenic Pruritus. Trial acronym: APHYPAP. Trials. 2021;22(1):1–15.
74. FDA, CDER. VISTARIL® (hydroxyzine pamoate) Capsules and Oral Suspension.
75. Steinhoff M, Cevikbas F, Yeh I, Chong K, Buddenkotte J, Ikoma A. Evaluation and management of a patient with chronic pruritus. J Allergy Clin Immunol [Internet]. 2012 [cited 2023 Aug 16];130(4):1015-1016.e7. Available from: https://pubmed.ncbi.nlm.nih.gov/23021147/
76. Moses S. Pruritus. Am Fam Physician. 2003;68(6):1135–42.
77 Gade R, Makineni A, Murthy T, Rao CB, Nama S. DESIGN AND DEVELOPMENT OF HYDROXYZINE HYDROCHLORIDE CONTROLLED RELEASE TABLETS BASED ON MICROSPONGE TECNOLOGY. Caribbean Journal of Sciences and Technology. 2013;1(1):172–84.
78. Bose S, Kaur A, Sharma SK. A review on advances of sustained release drug delivery system. Int Res J Pharm. 2013;4(6):1–5.
79. Yeo Y, Park K. Recent advances in microencapsulation technology. Encyclopedia of Pharmaceutical Technology. 2005;2005:1–15.
80. Pawar PB, Wagh MP, Hiremath SN, Baviskar A V, Akul MR. Taste Abatement of Hydroxyzine Hydrochloride by Cation Exchange Resins. Research Journal of Pharmaceutical Dosage Forms and Technology. 2011;3(4):130–4.
81. Nardi-Ricart A, Nofrerias-Roig I, Suñé-Pou M, Pérez-Lozano P, Miñarro-Carmona M, García-Montoya E, et al. Formulation of sustained release hydrophilic matrix tablets of tolcapone with the application of sedem diagram: influence of tolcapone's particle size on sustained release. Pharmaceutics. 2020;12(7):674.
82. Kumar AR, Aeila ASS. Sustained release matrix type drug delivery system: An overview. World J Pharma pharm Sci. 2019;8(12):470–80.

Medical initiative supported by:

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