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Learning pharmacology by metaphors: A tale of antihistamines

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ABSTRACT

Learning is facilitated by the use of proper instructional design. There are many creative forms reported for effective learning of medical subjects. Creative writing requires a great deal of intuitiveness and imaginations, using anecdotes, figures of speech, and stories from the literature. Often, homologies and analogies are given in metaphors, transforming inanimate drugs into live human beings, who tell about themselves to convey desired information. By such metaphors difficult topics in pharmacology can be narrated in simplified manner which maintain curiosity and stimulate interest and thus core components can be retained due to vivid rhetoric effect on memory. Here, we describe a metaphor of antihistamine (AH) drugs in which there is lively narration of mechanism of action, therapeutic uses and adverse effects and comparison of sedating older AHs with newer non-sedating second generation drugs. One of the AH drugs acts as a colorful raconteur and narrates evolution of AH therapy.

KEY WORDS: Antihistamines; Inverse agonist; Metaphors; Pharmacology

INTRODUCTION

Learning becomes easier when it is facilitated by proper instructional designs.[1] There are many creative forms used as effective learning tools and some examples are autobiography of drugs, concept maps, music, storytelling, role plays, videos, movie clips, and quizzes.[2,3] These tools increase students' involvement in learning by maintaining curiosity.[4] Recently, a number of metaphors are designed and published as learning aids in pharmacology in an attempt to increase active participation and sustain interest of students to understand difficult topics in pharmacology which otherwise would be monologues and boring when delivered by traditional lectures.[5-8] The new competency based medical education curriculum lays stress on self-directed learning (SDL) to promote experiential learning and making students responsible to adjust their pace of learning.[9] Therefore, using modified tools and techniques would promote SDL. Studies have shown that learning becomes more meaningful when students relate it with daily experiences and therefore important points are retained due to vivid rhetoric effects on memory. This involvement can be enhanced by making topic interesting in the form of anecdotes and metaphors.[10,11] Mathibe showed that 80% nursing students found the teaching interesting while 84% felt there was an improvement in their knowledge when autobiography was used to impart pharmacological knowledge.[12] Jalgaonkar *et al* evaluated the effect of online videos along with traditional teaching on learning drug administration skills. There were statistically higher OSCE scores among video watchers compared to others. Students (93.10%) perceived the online videos as useful teaching tools, which helped them to understand and retain the sequence of procedural steps of the skills better.[2]

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THE METAPHOR

The corona pandemic necessitated isolation and social distancing as an important measure to curb the spread. Several antihistamine (AH) families across three generations [Table 1] which were placed far away from each other took the opportunity to be there in their ancestral native village well before restrictions were imposed so that they would stay together without getting exposed to the threat of corona. Just before trains were cancelled, aerial and surface transports were blocked, 45 members of three generations arrived in the village and started cleaning the hamlet (*Dhani*) to make it habitable for a few weeks. There were seven families in the first generation consisting of octogenarians such as Mr Promethazine (aged 80 years), Mr Diphenhydramine, Mr Dimenhydrinate, Mr Pyrilamine, Mr Pheniramine, Ms Doxylamine, and Mr Doxepin. There were closer septuagenarian cousins; Ms Hydroxyzine, Ms Meclizine, Ms Cinnarizine, and Mr Tripolidine and, sexagenarians; Mr Cyproheptadine, Ms Chlorpheniramine, and Ms Clemastine. Mr Antazoline was the youngest among sedating group. The hallmark of these families, as a group was sedation as a side effect which earned them the name sedating AHs (SAHs). In addition, there were five families of newer generation (second generation) members, aging 40 years or under, who were born in 1980 or later, and included Ms Cetirizine and her daughter, Ms Levocetirizine, uncle Mr Loratidine and his nephew Mr Desloratidine, and Ms Ebastine, and her son Mr Carebastine. Ms Fexofenadine represented her mother Ms Terfenadine and Uncle Mr Astemizole who died prematurely (withdrawn due to ventricular arrhythmogenic potential). She accompanied closer cousins Ms Azelastine and Mr Olapatadine [Table 1]. Unlike SAHs, these drugs were devoid of significant sedative effect and thus were grouped as non-SAHs (NSAHs).

Ms Cetirizine was the first drug to be used as NSAH because she caused negligible disturbance of alertness, psychomotor performance, and attention. It paved the way for the development of more of newer, second generation NSAHs (vide supra). Subsequently, their own kith and kin were young teens designed to be born as "enantiomers and intermediates" with selective and potent peripheral antihistaminic actions compared to their parents! This species, sometimes grouped as third generation AHs, included Ms Levocabastine, Ms Levocetirizine, Masters Dexchlorpheniramine and Dexbrompheniramine, and Ms Desloratidine.[13]

It was indeed a great opportunity for all of them to strengthen bond of relationship and revive fond memories and greet brethren and kins for the 1st time. Soon, tired of long journeys, all of them went to sleep deciding to assemble in the dining room for dinner. The traditional food was prepared by the local cooks. As per the family custom, the senior most member, Mr Promethazine was greeted by all with youngsters bowing to their feet for blessings. The great grandparents were happy to be together with their families. They thanked profusely the Corona virus for providing opportunity to identify and be with them for some time. Here, began the conversation.

"Who are the youngest of us all?" enquired Mr Diphenhydramine.

Ms Cetirizine responded, "Ms Epinastine is about 25 years old. In addition, there are four young ones among us. Two little cute girls Alcaftadine (18 years) and Rupatadine (17 years) and two handsome boys Bepotastine (18 years) and Bilastine (10 years old) are the youngest." All working in health-care sector to serve the mankind! All four stood up and bade "Namaste" to them.

Mr Promethazine began, "Dear children, do you know that all of us have a common mission and vocation, i.e., waging a war against the ubiquitous fugitive lying within cells and organs of animals and human body which when released in large amounts causes allergy and harm to tissues and human organ systems. Do you know its name?"

"No," the young members voiced.

Mr Promethazine continues, "It is called as *Histamine*. Its onslaught is responsible for inflammation, bronchospasm, itching, hives, and fall in blood pressure. Mankind identified this culprit as early as 1910 and relied heavily on our ancestral chemicals of *Phenothiazine group* to protect against its harmful effects. Their hard work produced fruits and I was born in 1940 and became first savior against histamine incursions!"

"Dadu, how do you kill histamine?" asked Ms Levocetirizine.

"I do not kill or destroy histamine but I block the cell membrane receptive sites through which it attacks the susceptible cells in different tissues and organs," explained Mr Promethazine.

"Please clarify further," requested brother Pheniramine.

"OK, there are specific sites on cell membrane on which histamine can bind and divert the sub-cellular machinery (post-receptor signaling mechanism) to act according to its wishes. It intends to produce chemicals which induce inflammation (redness, flare, wheal, itching, and capillary oozing) and to reduce blood pressure, cause smooth muscle spasm, bronchospasm, excessive gastric hydrochloric acid (HCl), and intestinal secretions, all being detrimental to health."

Mr Cyproheptadine said, "Let me elaborate further. Histamine is an endogenous diamine synthesized by most of mammalian cells and lower animals such as insects and bees. It plays important physiological role in humans and

Table 1: Families of antihistamines

Family	1st Generation (sedating)	Main use	2nd Generation### (non-sedating)	Main use	Enantiomers and metabolites of second generation###	Characteristic and use
Phenothiazines	Promethazine*/$ (1940)	Sedative anti-allergic	-	-	-	-
	Methdilazine*/$ (1982)	Anti-allergic	-	-	-	-
Piperazines	Hydroxyzine**/$ (1955)	Sleep-aid and anti-pruritic	Cetirizine % (1987) mild sedation	Anti-allergic anti-pruritic	Levocetirizine (2007)	Twice as potent and quicker onset
	Buclizine## (1987)	Appetite stimulant				
	Cyclizine## (1947)	Anti-vertigo				
	Cinnarizine**/# (1955)	Anti-vertigo				
	Oxatomide*** (1975)	Allergic rhinitis				
	Flunarizine# (1968)	H_1 blocker with CCB^ action used in migraine				
Alkylamines	Pheniramine*/# (1948)	Anti-allergic				
	Chlorpheniramine**/## (1949)	Anti-allergic	-		Dexchlorpheniramine## (1962)	Twice as active as CPM
	Tripolidine**/## (1953)		Acrivastine (derivative of Tripolidine)		-	-
	Brompheniramine**/## (1958)				Dexbrompheniramine (1996)	
Piperidines	Cyproheptadine**/# (1960)	Appetite stimulant (has anti-cholinergic and anti 5-HT actions)	Loratidine (1988)	Anti-allergic	Desloratidine+ (2001)	Twice potent to loratidine
	Azatadine* (1973)		Fexofenadine (1996)	Anti-allergic	-	-
			Ebastine (1990) (Metabolised to carebastine)	Anti-allergic	Levocabastine (1979) ophthalmic solution	Potent and selective antagonist for the neurotensin receptor NTS_2
			Mizolastine (1992)	Anti-allergic		
			Bepotastine (2002)	Ophthalmic solution		
			Rupatadine+ (has PAF antagonist action) (2003)	Anti-allergic anti-pruritic	-	-
			Bilastine (2010)	Like cetirizine		
			Alcaftadine++ (2010)	Ophthalmic solution		
Ethanolamines	Diphenhydramine*/$ (1946)	Motion sickness	-	-	-	-
	Dimenhydrinate*$ (1949)	Motion sickness				
	Doxylamine*/#	Nausea vomiting				
	Clemastine**/## (1967)	Anti-allergic				
Ethylene diamines	Pyrilamine**/$ (1944) (Mepyramine)	Anti-allergic				
	Antazoline@@ (1990)	Ophthalmic solution				
	Tripelennamine	Anti-allergic				

(Contd...)

Table 1: (*Continued*)

Family	1st Generation (sedating)	Main use	2nd Generation### (non-sedating)	Main use	Enantiomers and metabolites of second generation###	Characteristic and use
Tricyclics	Doxepin*/$ (1970) potent H_1 with some H_2 antagonism	Antidepressant, nocturnal itching (5% cream)	Olapatadine (1996)	Ophthalmic solution oral also		
Thiazinones	-		Azelastine (1986) (inhibits release of histamine, LTs and PAF)	Nasal spray in rhinitis	-	-
Miscellaneous related	Betahistine (1970) H_1 agonist, H_3 antagonist/ inverse agonist	Meniere's disease	Epinastine (1994) (mast cell stabilizer and H_2 antagonist)	Ophthalmic solution	-	-

Astemizole and terfenadine were withdrawn because of their proarrhythmic potential due to prolongation of QTc interval (inhibition of rapid component of delayed rectifier K^+ Current in myocytes). *High anti-cholinergic activity, **low anti-cholinergic activity, ***no anti-cholinergic action. $High sedation, #moderately sedative, ##low sedation. ###Non-sedating due to poor penetration across BBB, devoid of anti-cholinergic and proarrhythmic actions, long acting and have additional properties. Enantiomers have quicker action. @@Has anti-arrhythmic action; ++Has Anti H_4 and mast cell stabilizing activities; ^CCB=T-type calcium channel blocker. +Desloratidine is one of the metabolites of rupatadine. %Cetirizine is a metabolite of hydroxyzine

regulates sleep wake cycle, food intake, hydrochloric acid secretion, and blood vessel reactivity (capillary permeability) and is needed for tissue repair. Physiologically, the release of histamine during the day causes arousal, whereas its decreased production at night results in reduction in arousal response.[14] It is stored in mast cells and basophils. Human body releases adequate amount of histamine necessary for its functions. However, as is said, "*Too much of everything is bad*," excessive release of histamine occurs when there is envenomation, bee bite, tissue injury, or untoward drug reaction. A gush of released tissue histamine causes local allergy (itching, hive, redness, and swelling), or systemic allergy, rhinitis, conjunctivitis, generalized itching, hot feeling, and throbbing headache and the severest form is anaphylaxis leading to shock. What is more important to know is that irrespective of mode of release, the effects are similar thereafter, as big brother Promethazine told earlier.

Mr Dimenhydrinate moved towards Mr Promethazine and said, "The sites which you spoke are actually known as histamine receptors and are of four types. Depending on the type occupied and stimulated by histamine, organ specific actions are observed."

Mr Pyrilamine said, "I could not sleep properly at night because of *jet-lag* and thus took opportunity to prepare a table of histamine receptors and actions for developing a holistic view of actions of histamine [Table 2]. Will all of you please go through it tonight?"

"Yes of course," all said in unison. They departed for rest.

Next day they met again and there was a lot of social get together, exchange of gifts and tinkles, and sharing of family pleasures and pains. Sitting under the Bunyan tree discussion resumed.

Ms Chlorpheniramine spoke first, "Can anyone tell me how sedative actions are identified?"

Mr Dimenhydrinate revealed, "There are many methods used during preclinical studies on small animals and currently central H_1 receptor binding is evaluated in mammals and humans by Positron Emission Tomography (PET) technique."[15]

Mr Promethazine elaborated, "We are actually *inverse agonists* at histamine receptors (H_1 receptors) but people erroneously call us as antagonists!

"What is it?" asked Ms Fexofenadine.

"In fact difficult to understand but I shall simplify as possible," said Mr Diphenhydramine.

"*The histamine receptors have basal activity even when not occupied by the histamine molecules. This basal constitutional activity is decreased when receptors are occupied by one of us. This phenomenon of reduction in basal activity by receptor occupation is called as negative intrinsic activity and such effect is called as* "*Inverse agonism.*" *Therefore, we oppose the histamine actions by acting as* "*inverse agonists*" *and not as antagonists as viewed traditionally*."[16]

"Amazing we were so ignorant about ourselves!" coined Mr Loratidine.

"Tell us more about you," he further requested to Mr Promethazine.

"I belong to the oldest group of medicines used by the mankind for relief of allergy and itching. We, the old generation members, are time tested remedies (medicines of choice) in

Table 2: Histamine receptors (GPCRs)[15,24]

Subtype	Distribution	Main function	Sub-cellular mechanism	Agonist	Antagonist
H_1	Smooth muscles of intestine, bronchi, blood vessels and WBCs#, adrenal medulla, CNS (hypothalamus, midbrain), Sensory nerve endings (dendritic cells)	Broncho-constriction ↑Capillary permeability Triple response (redness, wheal and flare) ↓Appetite, wakefulness	$G_{q/11}$ coupled PIP_3/ IP_3/DAG activation. Ca^{++} release	2-Methyl histamine Betahistine* (vestibule)	H_1 Antihistamines
H_2	Gastric parietal cells, blood vessels, WBCs#, heart, brain, mast cells	↑HCl secretion vasodilation	G_s-coupled increase in c-AMP	Amthamine, Dimaprit	Cimetidine and others
H_3	GABAergic, histaminergic, monoaminergic and cholinergic neurones (tuberomammillary nucleus of hypothalamus and project to several parts of extra-pyramidal and cortical neurones) (↓NE release)	Pre-synaptic auto- and hetero-receptors in brain Wakefulness and cognitive function ↓Appetite ↓HCl secretion	$G_{i/0}$ coupled ↓c-AMP, ↓Ca^{++}, K^+ channel opening	Imetit, Rα-methyl histamine	Thioperamide Tiprolisant central acting Clobenpropit, Ciproxan
H_4	Eosinophil, basophil, mast cells, (chronic inflammation) intestines, brain (deeper layers of cortex thalamus, hippocampus)	Chemotaxis, immune response and chronic inflammation	$G_{i/0}$ mediated ↓c-AMP and activation of MAP kinase	4-Methyl histamine	Toreforant

*Betahistine is considered as H_1 agonist with H_3 antagonist or inverse agonist. Betahistine is a structural analogue of histamine that acts as a weak partial postsynaptic histamine H_1 receptor agonist and presynaptic H_3 receptor antagonist with no effect on postsynaptic H_2 receptors. #White blood cells (neutrophils, eosinophils, monocytes, and T & B lymphocytes)

allergic (seasonal) rhinitis, conjunctivitis, control of sneezing, running nose, itching, soreness of throat, and allergic cough; alone and along with many other constituent medicines such as mucolytics, expectorants, and decongestants. I am very effective in acute and chronic urticaria. In fact many of us have been in clinical use for decades making us available '*Over the counter'* cough and cold medicines! In addition, five of us (promethazine, hydroxyzine, doxylamine, doxepin, and pyrilamine) have been used widely as sleep-aids in many countries. Promethazine, Diphenhydramine, and Hydroxyzine are used for conscious sedation and post-operative analgesia. We (promethazine, diphenhydramine, dimenhydrinate, meclizine, and cinnarizine) have antiemetic and anti-motion sickness action."

"That means seniors are useful in all types of vomiting!" exclaimed Levocetirizine.

"No," said Mr Promethazine, "except for me, others (mentioned above) are not so useful in vomiting induced by diseases (jaundice, gastritis, and radiations) and when vomiting center is involved directly without input from chemoreceptor trigger zone in medulla."

Mr Doxepin informed, "Ms Doxylamine could not come due to early imposition of restrictions in her area but she is a good OTC sleep-aid and is commonly prescribed to prevent and treat nausea and vomiting (morning sickness) in early pregnancy. It is coformulated with Vitamin B6 (doxylamine 10 mg and pyridoxine 10 mg) for this purpose. It is considered safe (Category-A) when given up to 4 tablets a day. It causes sedation and dryness of mouth."[17]

"What about anti-motion sickness activity?" asked Mr Desloratidine.

Mr Dimenhydrinate replied, "Some individuals are sensitive to motion while travelling in car, bus, and by sea and develop sense of vomiting or actual vomiting. This is due to disturbance created by turbulence in vestibules of inner ears which give signals to vomiting centers."

"Oh! But how are you useful?" he enquired.

"Because, "histamine" plays belligerent and generates such signals from inner ears!"

"But I have read that Scopolamine is the preferred choice for motion sickness," said Ms Chlorpheniramine.

"That's true, but there are limitations of marked anti-cholinergic effects and availability. For prevention of travel sickness, oral Dimenhydrinate, Cyclizine, Meclizine, Diphenhydramine, or Promethazine is convenient."

"And what about vertigo?" enquired Mr Doxepin.

Ms Meclizine said, "I and Cinnarizine are time honored medicines for it. She inhibits vestibular sensory nuclei and regulates Ca^{++} movement from endolymph to vestibular sensory cells. She is useful in Meniere's disease and vertigo in ischemic neurological disorders."

She continued, "A very special relative, *a friendly foe,* Mr Betahistine, is related to histamine (H_1 agonist) and has H_3

antagonist activity is away today but is found to be useful in vertigo due to vestibular labyrinthitis (Meniere's disease). He works by increasing blood flow to the cochlea and the vestibular labyrinth (improved microcirculation) and acts as a vestibular sedative, i.e. reduces the resting firing rate of the ampulla of semicircular canals."[18]

Ms Levocetirizine said, "I just thought of airline pilots, machine operators and bus and train drivers. Could they use older ones if they develop allergic conjunctivitis or itching?"

"Certainly not," said Ms Cetirizine, "because impaired vigilance, cognition, alertness, fatigue, drowsiness, and sedation can prove to be dangerous."

"So which one of us can be friend to them?" asked Ms Levocetirizine.

"Ms Fexofenadine would be an affable choice because she is least likely to cross blood–brain barrier and does not impair psychomotor performance and multitasking! Loratidine and Desloratidine are second choice medications for them," revealed Cetirizine.

"I may tell you something interesting!" said Mr Promethazine. "I can make an inebriating cocktail, called as *Lytic cocktail*."

"*Lytic cocktail?*" enquired Ms Chlorpheniramine.

Mr Promethazine elaborated, "In 1961, a renowned Indian Obstetrician Dr Menon introduced a mixture of three depressants; Promethazine, Chlorpromazine, and Pethidine (meperidine) to treat eclampsia. This remained a treatment of choice for several years until magnesium sulfate overtook it.[19] I was also used as an anti-itch local cream 2% in dermatitis."

"Actually itching and hives occur due to many underlying causes and many of us are also effective in acute urticaria and relieve itching in dermatoses."

"May I disclose a secret about Cetirizine?" divulged Mr Loratidine.

All eagerly awaited for the disclosure.

Mr Loratidine continued, "It is about treatment of urticaria (hives). Ms Cetirizine and her daughter Levocetirizine are particularly effective in itching and urticaria because they make home in skin by strong and long-lasting binding to cutaneous histamine H_1-receptors.[2] Often, higher than recommended doses are needed for the treatment.[3] Furthermore, addition of H_2 AH (Ranitidine) augments the anti-urticarial effect of H_1 AHs."[20]

"That means Doxepin, a dual blocker (potent H_1 and weak H_2 antagonist) should also be effective," Ms Chlorpheniramine enquired.

"Yes," said Mr Loratidine. "Doxepin is an alternative for the treatment of chronic urticaria in patients who respond poorly to AH therapy."[21]

Ms Cinnarizine said, "Mr Cyproheptadine is unique in increasing appetite by its central anti-serotonin activity and is being (mis)used as a weight gain medicine (syrup) in children."

"He is not alone in that foray. I also have the same action." Ms Buclizine protested.

Madam hydroxyzine observed silently and seemed annoyed by this conversation and thus did not speak a word so far. "Please say something about you," requested Mr Diphenhydramine.

Ms Hydroxyzine said, "I have been in clinical use for over half a century as a sleep aid and anti-itch agent against hives, pruritus, and insomnia. I allay anxiety as well. But times are changing. Now these Gen-X and millennials want to write us off for their own benefits, I suppose."

"Largely because doctors have started opting for NSAHs and avoiding use of older members due to a number of unwanted effects and inconvenience associated with their use." Narrated Mr Loratidine.

"Yes, I do agree," said Ms Rupatadine. "We, the members of NSAHs (Loratidine, Fexofenadine, Mizolastine, Ebastine, Azelastine, Cetirizine, Desloratadine, and Levocetirizine) are virtually devoid of undesirable anti-cholinergic, sedative, α-blocking, anti-serotonin, and CNS toxicities. Patients' heart rate and rhythm remain regular even when he is on poly-therapy! Furthermore, overdose lethal toxicities (30 times therapeutic doses) are unlikely."[15]

"Please permit me to differ," begged Mr Loratidine. "I read that aunty Cetirizine was responsible for impairment of motor reaction time and has higher incidence of drowsiness or fatigue when compared with her daughter Levocetirizine. Tests of car driving appear to be sensitive to the sedative effect of the AHs. Recent evidence has suggested that, in recommended doses, Levocetirizine is less sedative than Cetirizine and Desloratadine causes negligible somnolence,"[15] she corroborated her statement.

Ms Hydroxyzine defended, "Selection of a suitable AH depends on individual needs. If itching or sneezing disturbs sleep at night, then "*old is gold*." However, when attention and fine motor movements are to be preserved, as during driving or machine operating, then newer NSAHs are preferred!"

Mr Loratidine said, "Many of oldies cause fall in BP because of α-blocking actions leading to dizziness and orthostatic hypotension posing serious problems in elderly."

She continued, "Furthermore, a major drawback in SAHs is anti-cholinergic adverse effects such as dryness of eyes, dry mouth, mydriasis, constipation, tachycardia, precipitation of glaucoma, hesitancy, or urinary retention in elderly. Many of first generation compounds may prolong QTc interval by blocking rapid component of delayed rectifying current (blocking of K^+channels). This effect leads to ventricular tachycardia (torsades de pointes), particularly when used with other drugs which inhibit metabolism of these AHs. Terfenadine and Astemizole were withdrawn because of this adverse effect."

"But exceptions are always there," announced Mr Methdilazine.

All stared up at him in amazement.

He said, "We have Mr Antazoline which has shown anti-arrhythmic activity against atrial fibrillation."[22]

Ms Chlorpheniramine added, "In addition, there is potential for overdose toxicity in children and adults. Extreme drowsiness and confusion, delirium and coma, and hypotension and respiratory depression have been reported. Ventricular arrhythmias are seen with overdoses of Cyproheptadine, Diphenhydramine, Doxepin, Hydroxyzine, and Promethazine. Thechildrenwould show excitation, irritability, insomnia, convulsions, and coma. Morning hangover is also reported."

Hydroxyzine appeared cheerful by now as she said, "Have any one seen a movie *City of sizzurp* directed by Thomas Gibson in 2015?"

"No," almost all said, "but, how is it connected to present discussion?" Ms Chlorpheniramine interjected.

Ms Hydroxyzine triumphantly said, "It's concerned on Grandpa!"

"Mr Promethazine had fallen in trap of iniquitous mixtures such as *purple drank* and *sizzurp*. These monikers are coined to concoctions of soda, candy and Promethazine with or without codeine which became recreational beverages in 1990 for teenager rap dancers and pop singers. They induced swooning euphoria with "high" feelings. The misuse was associated with somnolence, stupor, respiratory depression, coma, and death. This menace has nicely been highlighted in this movie which I have watched."[23]

"Oh! An astounding revelation in deed," muttered Mr Diphenhydramine.

Ms Clemastine tried to divert the conversation and asked, "What about others?"

Mr Doxepin said, "My primary role is to treat endogenous depression. I am the only AH that inhibits both H_1 and some H_2 receptors! I also have blocking effects on serotonin, muscarinic, and adrenergic receptors. I am used as anti-pruritic cream (5%) in atopic dermatitis. If taken at night I induce a sound sleep also."

"Me too!" interrupted young Epinastine, "I have H_1 and H_2 blocking actions and prevent release of inflammatory mediators from mast cells."

"But you are useful in allergic conjunctivitis as eye drops only," protested Mr Doxepin

"Yes," she withdrew.

Ms Rupatadine said, "I not only block H_1 receptors but also block PAF receptors and mast cell degranulation. In addition, Desloratidine is my by-product (not only of Loratidine!)."

"And what about Gen-X and millennials?" asked Ms Acrivastine.

Young Alcaftadine came forward. "Don't forget me please. I am endowed with powers to block H_1 and H_4 receptors and vanquish them for longer time (24 h) just as aunts Cetirizine, Fexofenadine, and Rupatadine do. I also stabilize mast cells preventing degranulation and mediator release."

All appreciated her.

Ms Olapatadine and Bepotastine spoke together "We are useful topical anti-allergics in allergic conjunctivitis."

Ms Azelastine contributed in the last, "I am an important topical medicine for allergic rhinitis and conjunctivitis. I have an additional anti-inflammatory action and am available as nasal spray for allergic rhinitis."

Ms Chlorpheniramine briefed, "Montelukast (a leukotriene inhibitor) has become bosom friend of Ms Levocetirizine, Desloratidine, Fexofenadine, and Ebastine. These duos (fixed dose combination of Montelukast with any one of them) work together in allergic bronchial asthma and other allergic disorders. However, the evidence of greater efficacy is not strong."[15]

Let us conclude that the mankind should be grateful to us for over half a century of service rendered to provide them succour from myriads of allergic disorders and our posterity shall confirm to it.

Let us toast to our happy reunion!!

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