AUTACOIDS

Eicosanoids

Platelet Activating Factor (PAF)

Histamine

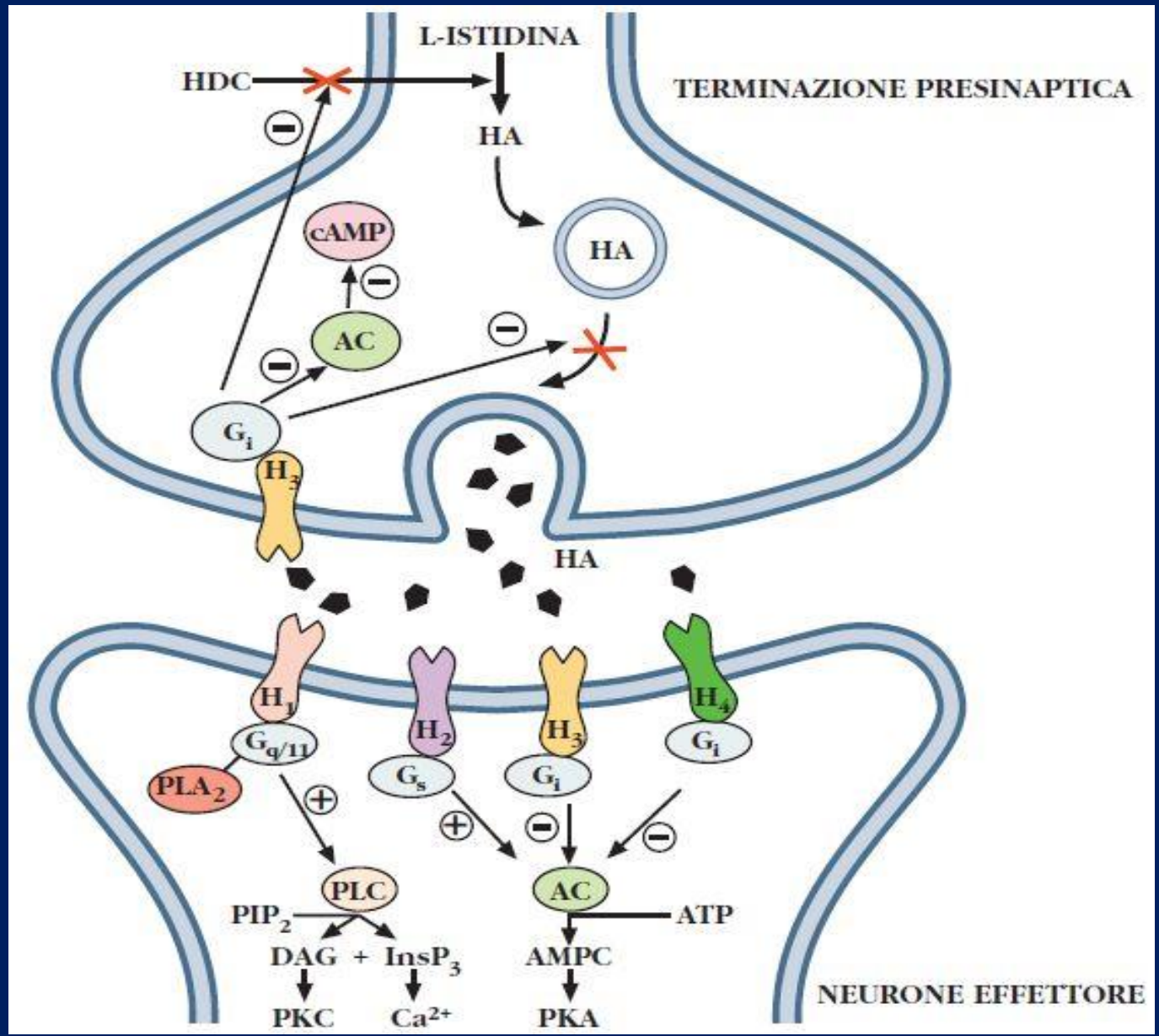
Bradykinin

5-HT

HISTAMINE

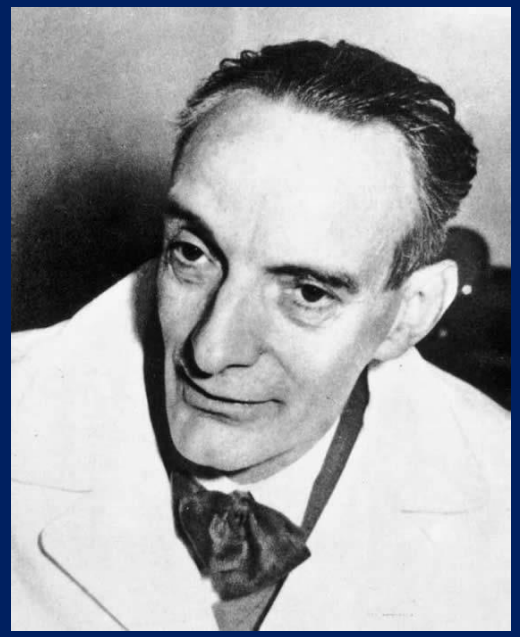
- Histamine is a basic amine, stored in granules within mast cells and basophils and secreted when complement components C3a and C5a interact with specific membrane receptors, or when antigen interacts with cell-fixed IgE.
- It produces effects by acting on H_1-, H_2- or H_3-receptors on target cells.
- The main actions in humans (with the receptors involved) are:
  - —stimulation of gastric secretion (H_2)
  - —contraction of most smooth muscle other than that of blood vessels (H_1)
  - —cardiac stimulation (H_2)
  - —vasodilatation (H_1)
  - —increased vascular permeability (H_1).
- Injected intradermally, histamine causes the 'triple response': reddening from local vasodilatation, wheal by direct action on blood vessels and vasodilatation, and flare from an 'axon' reflex in sensory nerves releasing a peptide mediator.
- The main pathophysiological roles of histamine are:
  - —as a stimulant of gastric acid secretion (treated with H_2-receptor antagonists)
  - —as a mediator of type 1 hypersensitivity reactions such as urticaria and hay fever (treated with H_1-receptor antagonists).
- H_3-receptors occur at presynaptic sites and inhibit the release of a variety of neurotransmitters.

Histamine receptors



HA: histamine
HDC: histidine decarboxylase

Anti-histamine drugs

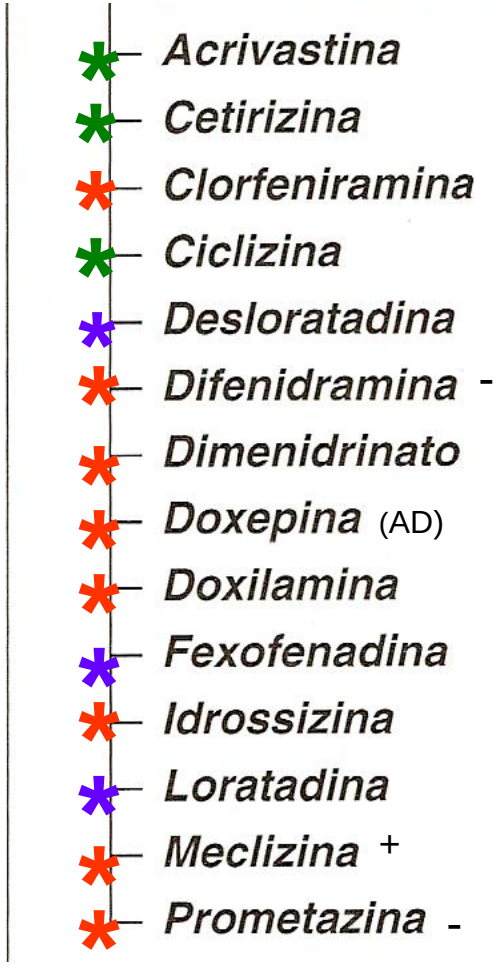


Daniel Bovet 1907-1992
Istituto Superiore di Sanità
Prof. Pharmacology Sassari

Nobel Medicine 1957

Discovery of the first competitive histamine antagonist 1937: (thymoxy-ethyl-diethyl-amine)
1944: pyrilamine

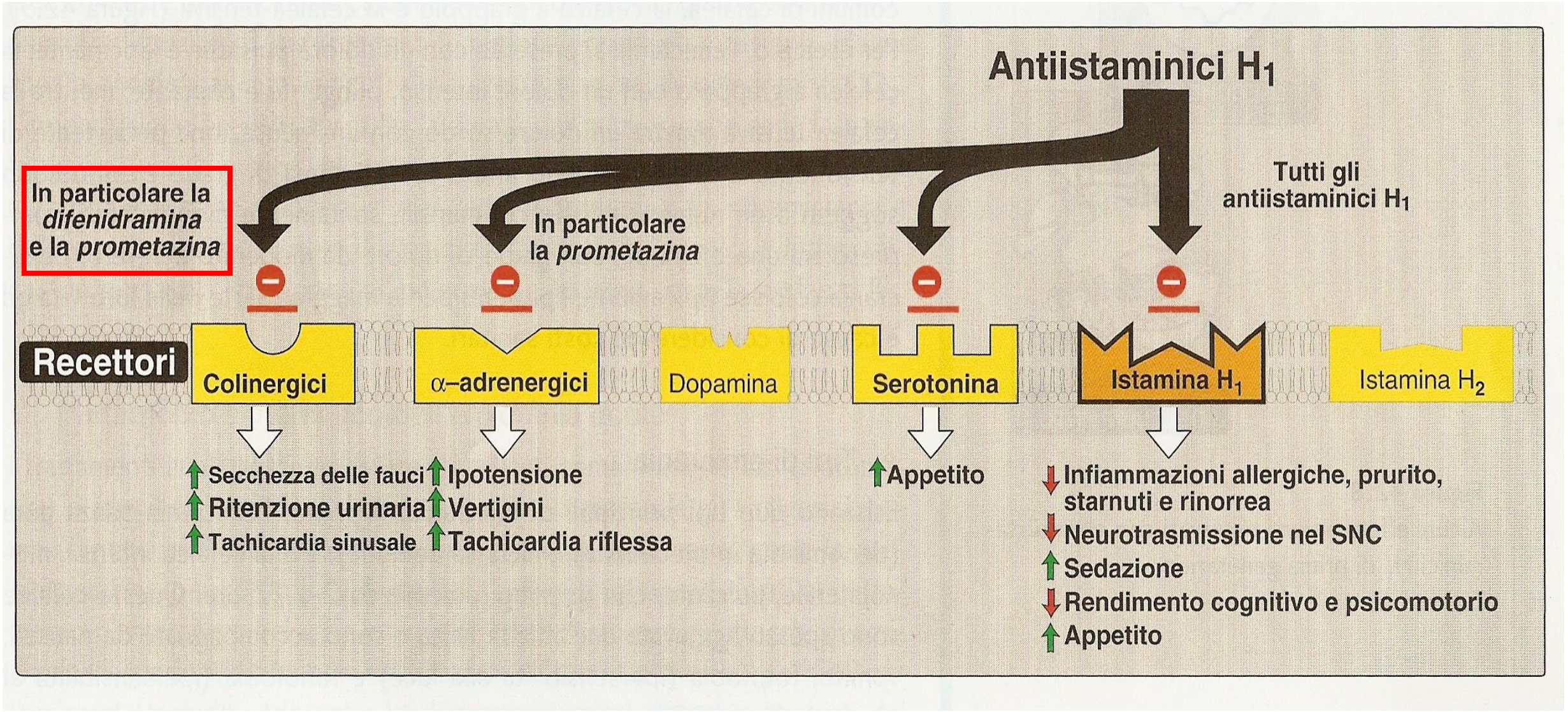
H_1 Receptor Antagonists



Cromoglicate (- Histamine release)

* **first generation**
* **second generation**
* **third generation**

COMPLEX PROFILE OF H1 ANTIHISTAMINES ON CHOLINERGIC, ADRENERGIC AND SEROTONERGIC RECEPTORS



Clinical use of histamine H_1-receptor antagonists

- For allergic reactions including allergic rhinitis (hay fever), urticaria, insect bites, drug hypersensitivities. Drugs that lack sedative or muscarinic receptor antagonist actions (e.g. fexofenadine or cetirizine) are preferred. Topical preparations (e.g. for eye, nose) are available. Injections are used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis.
- As antiemetics for the prevention of motion sickness or other causes of nausea, especially those associated with vertigo (e.g. labyrinthine disorders). Muscarinic receptor antagonist actions of some antihistamines (e.g. cinnarizine, cyclizine) probably contribute to efficacy but also cause side-effects.
- For sedation: some H_1-receptor antagonists (e.g. promethazine; are fairly strong sedatives and may be used for this action.

ANTI-HISTAMINE DRUGS (ANTI-H1)

First Generation

ETHANOLAMINE (Diphenhydramine, Dimenhydrinate)

ALKYLAMINE (Chlorpheniramine)

ETHYLENEDIAMINE (Pyrilamine)

PHENOTHIAZINE (Promethazine, Trimeprazine)

PIPERIDINE (Cyproheptadine)

PIPERAZINE (Cyclizine, Meclizine, Hydroxyzine)

FEATURES

1) Poor receptor specificity
2) High lipophilicity
3) Widely used drugs

ANTI-HISTAMINE DRUGS (ANTI-H_1)

First Generation

KINETIC

-Well absorbed in the gastrointestinal tract

- Uniform distribution throughout the body

- Elimination by the urinary route in the form of metabolites

Therapeutic Uses

1) Allergic syndromes

2) Emesis, motion sickness

3) Sleep disturbances (sedation)

4) Anorexia

ANTI-HISTAMINE DRUGS (ANTI-H_1)

First Generation

Side Effects

1) Central Effects

a) sedation

b) asthenia

c) dizziness

2) inhibition of other receptors (anti-muscarinic effects)

3) hypersensitivity

4) teratogenic effects

ANTI-HISTAMINE DRUGS (ANTI-H_1)

SECOND GENERATION

PIPERIDINE (Loratadine, Terfenadine)

PIPERAZINE (Cetirizine)

CHARACTERISTICS

1) Greater affinity for H1 receptors

2) Less lipophilicity

KINETICS

- Well absorbed in the gastrointestinal tract
- Loratadine, terfenadine: metabolized in the liver by cytochrome P450 to active metabolites
- Excreted in the urine

ANTI-HISTAMINE DRUGS (ANTI-H_1)

THIRD GENERATION

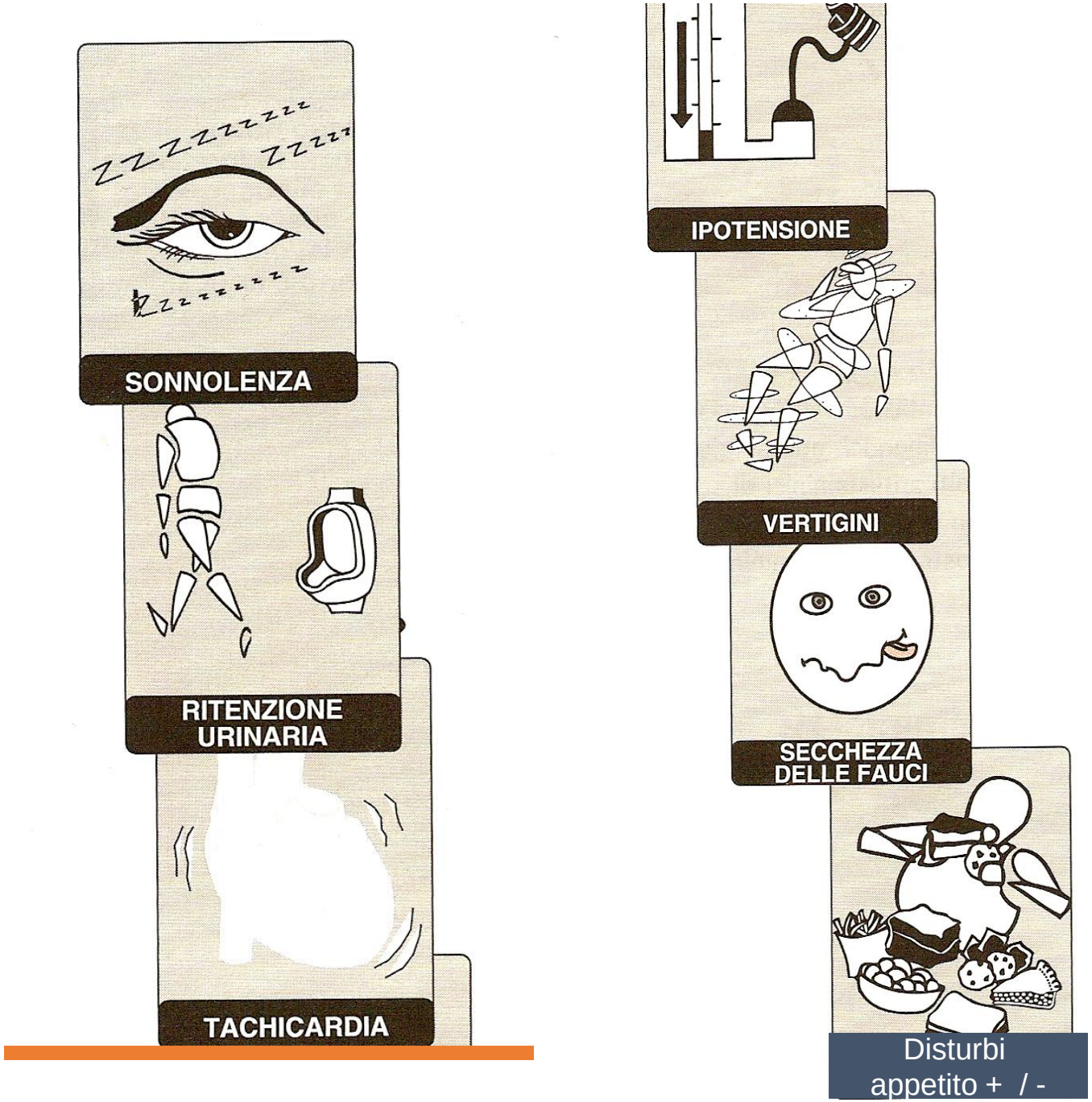
PIPERIDINE (Fexofenadine*, Desloratadine)

PIPERAZINE (Levocetirizine)

CHARACTERISTICS

Active metabolites

No Cardiotoxicity



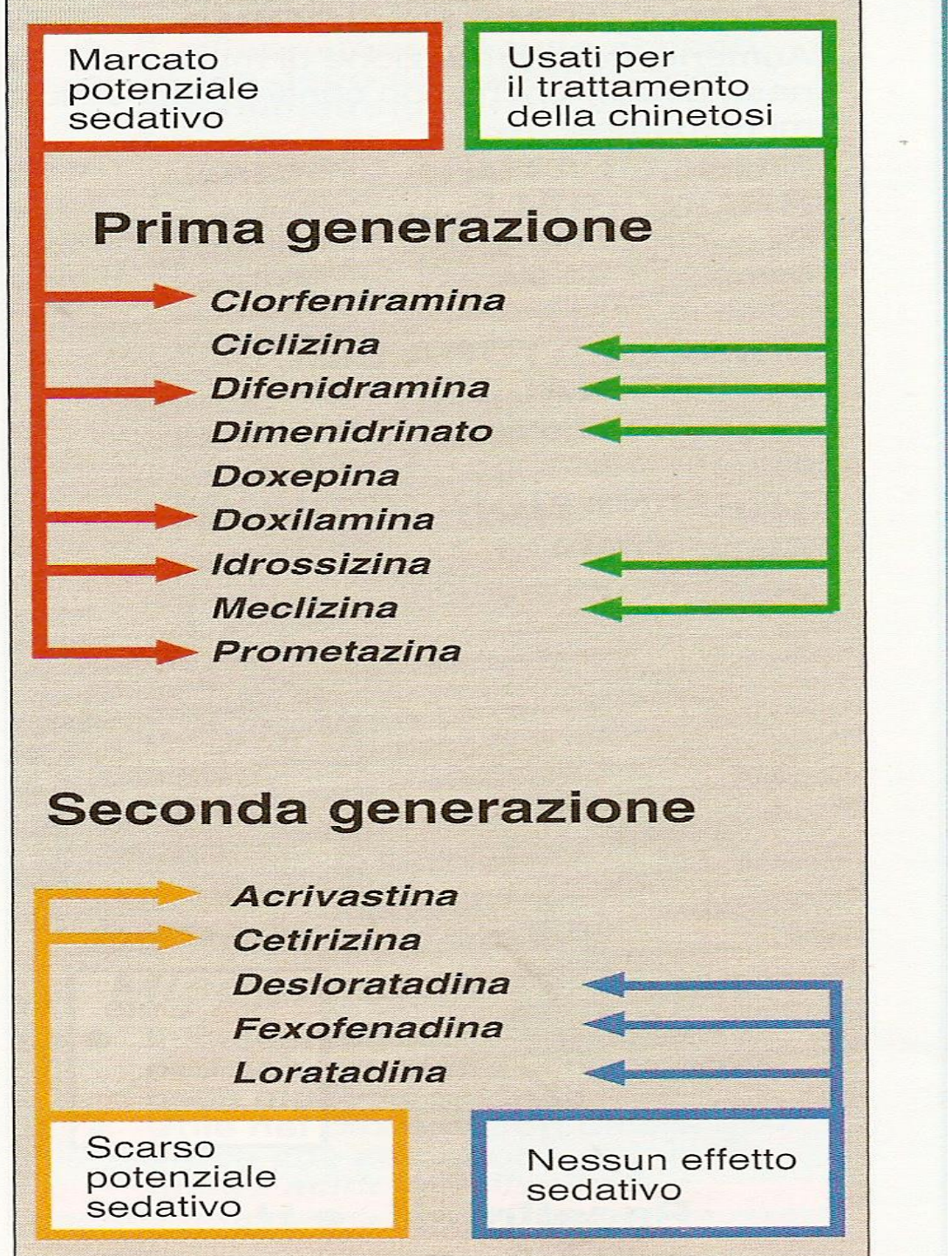
Side effects of H_1 receptor antagonists

Table 14.4 Comparison of some commonly used H1 receptor antagonists

Type	Drug	Common uses: *H*	*U*	*R*	*AE*	*S*	Comments
Non-sedating	Acrivastine	•	•				–
	Cetirizine	•	•				–
	Desloratidine	•	•				Metabolite of loratidine
	Fexofenadine		•	•			Metabolite of terfenadine
	Levocetrizine	•	•				Isomer of cetrizine
	Loratidine	•	•				–
	Mizolastine	•	•				May cause QT interval prolongation
Sedating	Alimemazine		•			•	Used for premedication
	Brompheniramine	•	•			•	–
	Chlorpheniramine	•	•		•	•	–
	Clemastine	•	•			•	–
	Cyproheptadine	•	•			•	Used also for migraine
	Diphenhydramine					•	Mainly used as a mild hypnotic
	Doxylamine					•	Mainly used as an ingredient of proprietary decongestant and other medicines
	Hydroxyzine		•			•	Also used to treat anxiety
	Promethazine	•	•		•	•	Also used for motion sickness
	Triprolidine					•	Mainly used as an ingredient of proprietary decongestant and other medicines

AE, allergic emergency (e.g. anaphylactic shock); H, hay fever; R, rhinitis; S, sedation; U, urticaria and/or pruritis.
(From British Medical Association and Royal Pharmaceutical Society of Great Britain 2005 British National Formulary. BMA and RPSGB,

Disadvantages



Advantages

Pharmacological Interactions

- CNS depressants, alcohol

- Antipsychotics

- MAO inhibitors (aggravate anti-cholinergic effects)

- Induction of hepatic microsomal enzymes

- Overdose (hallucinations, excitement, ataxia, convulsions)