Emesis and antiemetic drugs

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Reference: Pocket Atlas of pharmacology, 4th edition

- In emesis the stomach empties in a retrograde manner. The pyloric sphincter is closed while the cardia and esophagus relax to allow the gastric contents to be propelled orally by a forceful, synchronous contraction of abdominal wall muscles and diaphragm.
- Closure of the glottis and elevation of the soft palate prevent entry of vomitus into the trachea and nasopharynx.

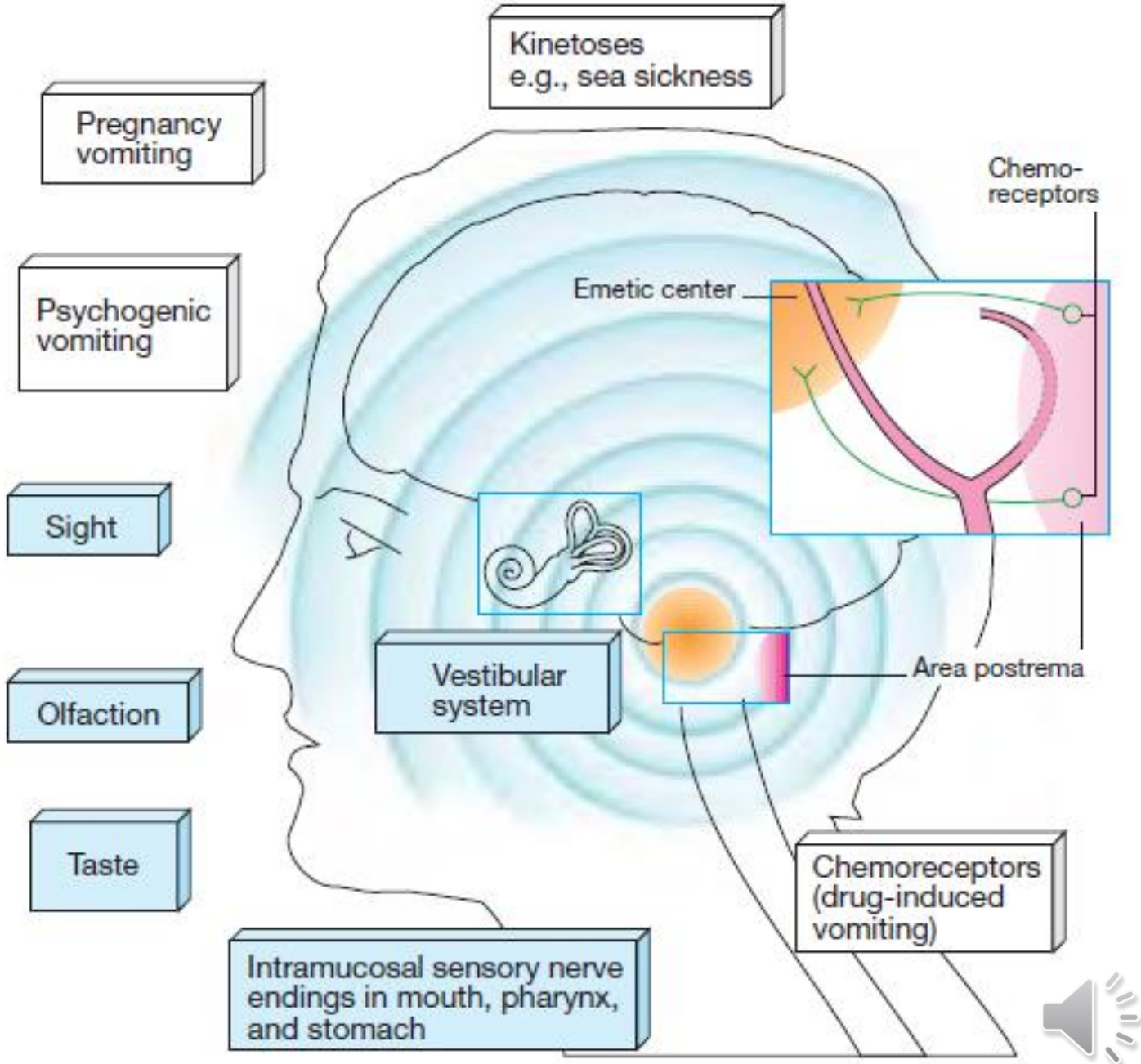
- As a rule, there is prodromal salivation or yawning. Coordination between these different stages depends on the **medullary center for emesis,** which can be activated by diverse stimuli.
- These are conveyed via the: **vestibular apparatus, visual, olfactory, and gustatory inputs,** as well as **viscerosensory afferents** from the upper alimentary tract.
- Furthermore, **psychic experiences** may also activate the emetic center.
- The mechanisms underlying **motion sickness** (kinetosis, sea sickness) and vomiting during pregnancy are still unclear.

- Polar substances cannot reach the emetic center itself because it is protected by the blood-brain barrier. However, they can indirectly excite the center by activating **chemoreceptors** in the **area postrema** or receptors on peripheral vagal nerve endings

- **A. Emetic stimuli and antiemetic drugs**

Chemoreceptor trigger zone

It is also called area postrema.
It is located at the caudal end of the fourth ventricle.
It is outside the blood-brain barrier, but accessible to emetogenic stimuli in the blood and cerebrospinal fluid.
It is rich in dopamine D_2 receptors and opioid receptors, and possibly serotonin 5-HT_3 receptors and NK_1 receptors.



Antiemetic therapy.

- Vomiting can be a useful reaction enabling the body to eliminate an orally ingested poison.

- Antiemetic drugs are used to prevent:
  - kinetosis,
  - pregnancy vomiting,
  - cytotoxic drug-induced
  - postoperative vomiting,
  - as well as vomiting due to radiation therapy

Motion sickness.

- Effective prophylaxis can be achieved with the:
- parasympatholytic scopolamine
- H1 antihistamines of the diphenylmethane type (e.g., diphenhydramine, meclizine).
- Antiemetic activity is not a property shared by all parasympatholytics or antihistamines.
- The efficacy of the drugs mentioned depends on the actual situation of the individual:
    - (gastric filling,
    - ethanol consumption),
    - environmental conditions (e.g., the behavior of fellow travellers),
    - and the type of motion experienced.

Motion sickness.

- The drugs should be taken 30 min before the start of travel and repeated every 4 to 6 h.
- Scopolamine applied transdermally through an adhesive patch can provide effective protection for up to 3 d.

Pregnancy vomiting

- **Pregnancy vomiting** is prone to occur in the first trimester; thus pharmacotherapy would coincide with the period of maximal fetal vulnerability to chemical injury.
- Accordingly, antiemetics (antihistamines, or neuroleptics if required) should be used only when continuous vomiting threatens to disturb electrolyte and water balance to a degree that places the fetus at risk

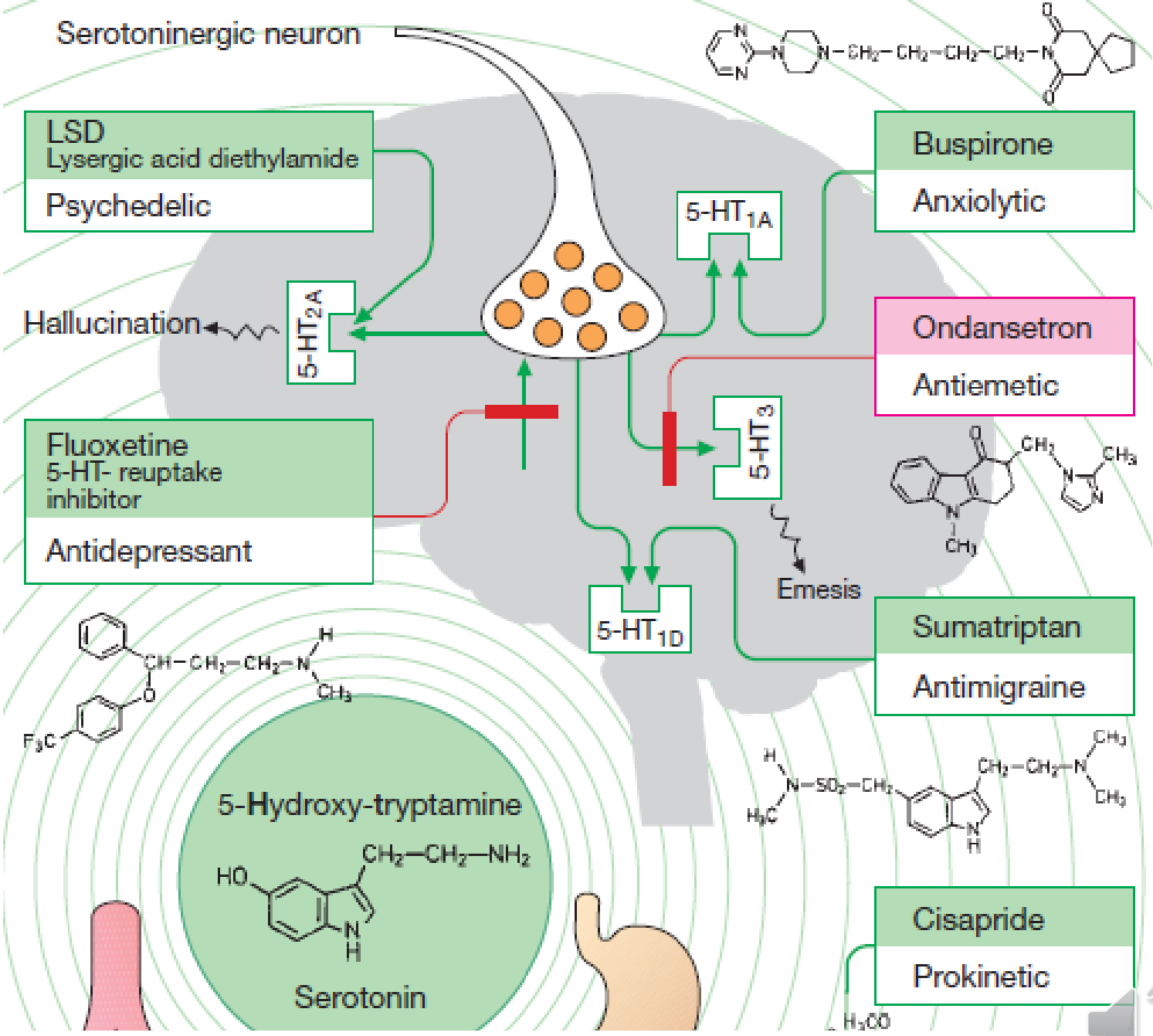
Drug-induced vomiting

- To prevent vomiting during anticancer chemotherapy (especially with cisplatin), effective use can be made of 5-HT3-receptor antagonists (e.g., *ondansetron, granisetron,* and *tropisetron*), alone or in combination with glucocorticoids *(methylprednisolone, dexamethasone).*
- **Dexamethasone 8-20 mg iv. before chemotherapy, followed by 8 mg/d orally for 2-4 days, is commonly administered.**

Central Nervous System.

- Serotoninergic neurons play a part in various brain functions, as evidenced by the effects of drugs likely to interfere with serotonin.
- *Fluoxetine* is an antidepressant that, by blocking re-uptake, inhibits inactivation of released serotonin. Its activity spectrum includes :
- significant psychomotor stimulation
- depression of appetite,
- and anxiolysis.
- *Buspirone* also has anxiolytic properties thought to be mediated by central presynaptic 5-HT1A receptors.
- *Ondansetron,* an antagonist at the 5-HT3 receptor, possesses striking effectiveness against cytotoxic drug-induced emesis, evident both at the start of and during cytostatic therapy.
- *Tropisetron* and *granisetron* produce analogous effects.

- **Serotonin receptors and actions**

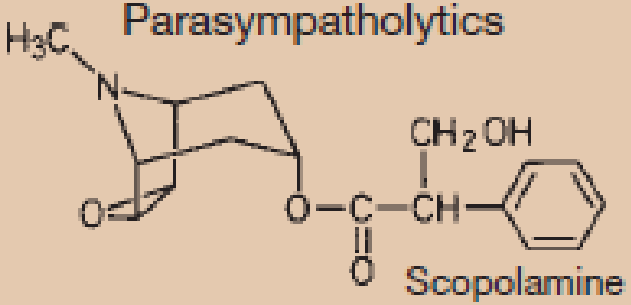


Anticipatory nausea

- **Anticipatory nausea** and vomiting, resulting from inadequately controlled nausea and emesis in patients undergoing cytotoxic chemotherapy, can be attenuated by a benzodiazepine such as *lorazepam.*
- Dopamine agonist-induced nausea in parkinsonian patients can be counteracted with D2-receptor antagonists that penetrate poorly into the CNS (e.g., *domperidone, sulpiride*).

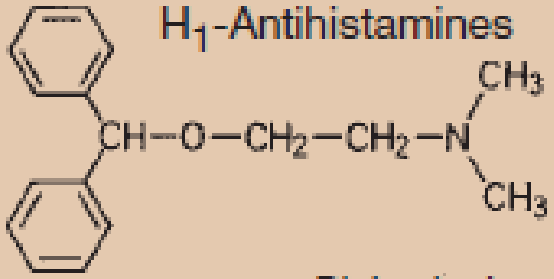
- *Metoclopramide* is effective in nausea and vomiting of gastrointestinal origin (5-HT4-receptor agonism) and at high dosage also in chemotherapy- and radiation- induced sickness (low potency antagonism at 5-HT3- and D2-receptors).
- Phenothiazines (e.g., *levomepromazine, trimeprazine, perphenazine*) may suppress nausea/emesis that follows certain types of surgery or is due to opioid analgesics, gastrointestinal irritation, uremia, and diseases accompanied by **elevated intracranial pressure.**
- The synthetic cannabinoids *dronabinol* and *nabilone* have antinauseant/ antiemetic effects that may benefit AIDS and cancer patients.

Parasympatholytics

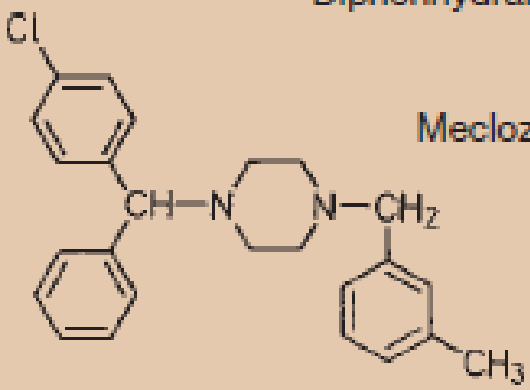


Scopolamine

H_1-Antihistamines

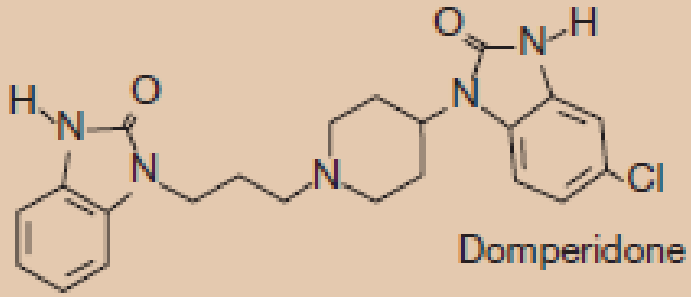


Diphenhydramine

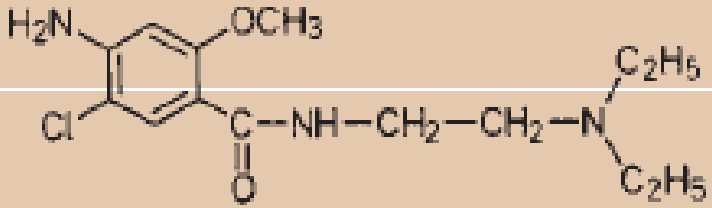


Meclozine

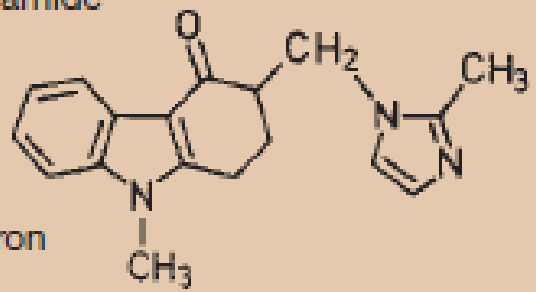
Dopamine antagonists



Domperidone



Metoclopramide



Ondansetron

5-HT_3-antagonist