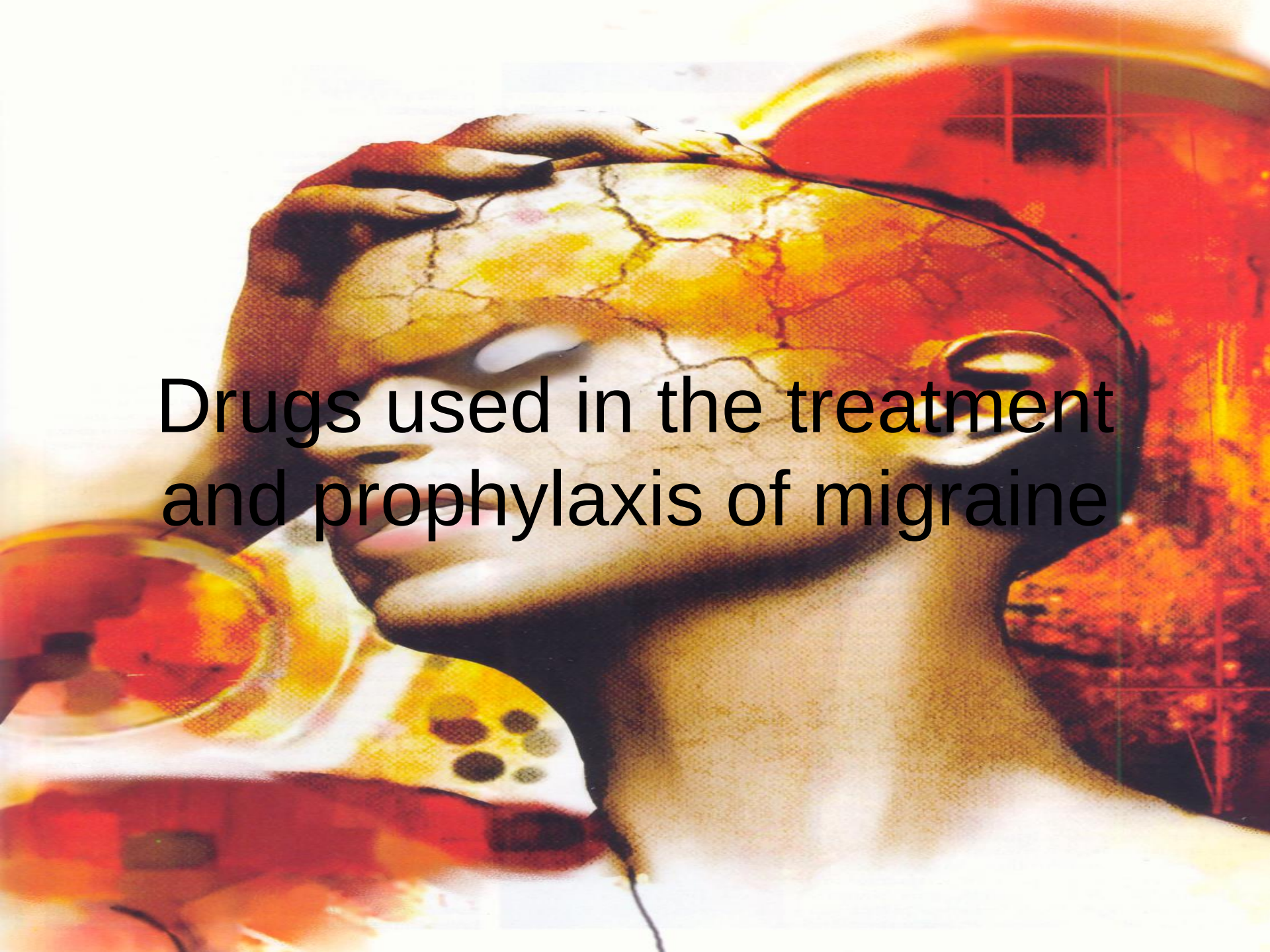


Drugs used in the treatment and prophylaxis of migraine

It is thought that migraine has genetic etiology or is stimulated by external or internal stimuli.

The pathomechanism of migraine involves the adrenergic and serotoninergic systems.

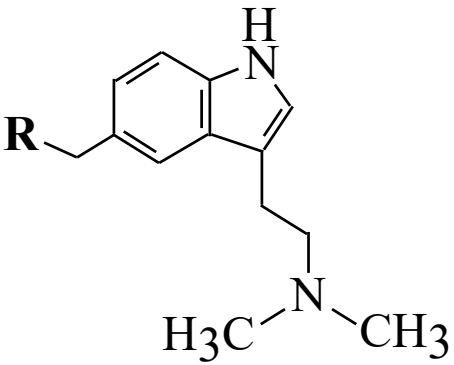
A strong attack of migraine is characterized by an acute headache, which is usually accompanied by nausea, vomiting and a disturbance of the motor activity of the gastrointestinal tract.

- Acetylsalicylic acid, paracetamol or ibuprofen are used as analgesics.
- When a bout of migraine is so intense that it does not disappear under the influence of analgesics, triptanes or dihydroergotamine are used.
- Metoclopramide and domperidone are recommended as antiemetics to stimulate the motor activity of the gastric tract.
- They block peripheral D_2-dopaminergic receptors, but do not act centrally, as they do not permeate the blood-brain barrier.

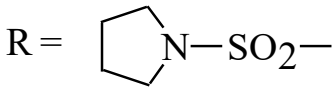
Triptanes

The first triptane introduced into therapy was sumatriptan.

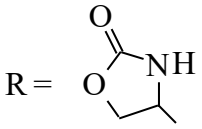
R = H_3C-NH-SO_2-; Sumatriptan, IMIGRAN



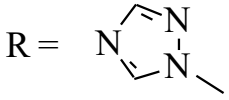
R = H_3C-NH-SO_2-CH-; Naratriptan, NARAMIG



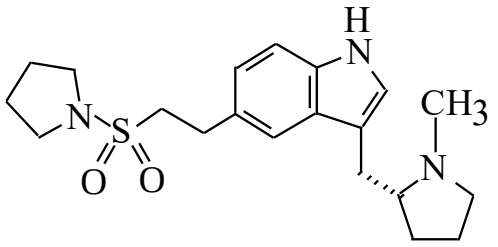
Almotriptan, ALMOGRAN



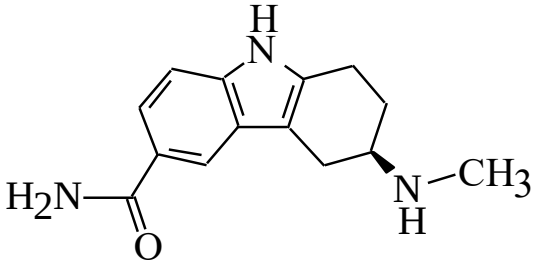
Zolmitripan, ZOMIG



Rizatriptan, MAXALT



Eletriptan, RELPAX



Frovatriptan, ALLEGRO

Sumatriptan is structurally similar to serotonine and is a selective agonist at 5-$HT_{1B/D}$ receptors. These receptors are mainly located in extra- and intracranial blood vessels. The dilation of these vessels is probably the cause of migraine attacks.

Triptanes, as agonists at serotoninergic receptors, especially 5-HT_{1D}, selectively constrict the excessively dilated intracranial vessels and inhibit the peripheral and central release of pain mediators (neuropeptides) such as substance P, vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), which are responsible for the inflammatory process and excessive vasodilatation.

As a result, the normal volume of vessels is restored.

Triptanes also inhibit the activity of the trigeminal nerve, but they are not effective in the treatment of tension headaches.

Caution is recommended when using triptanes in patients after myocardial infarction, with ischaemic heart disease and fluctuating arterial blood pressure. These drugs should not be administrated to children and patients over 65.

Differences between triptanes involve the following:

- **Bioavailability** (sumatriptan – 14%, rizatriptan – 40%, zolmitriptan – 41%, naratriptan – 60%, almotriptan – 70%, eletriptan – 81%, frovatriptan – 22% in men and 35% in women)

- **Half-time** (sumatriptan – 2 hours, zolmitriptan – 2.6 hours, rizatriptan – 3 hours, almotriptan – 3.5 hours, naratriptan – 6 hours, eletriptan - ?, frovatriptan – 26 hours)

- **Intensity of action** (zolmitriptan = naratriptan = frovatriptan > rizatriptan > almotriptan > eletriptan > sumatriptan).

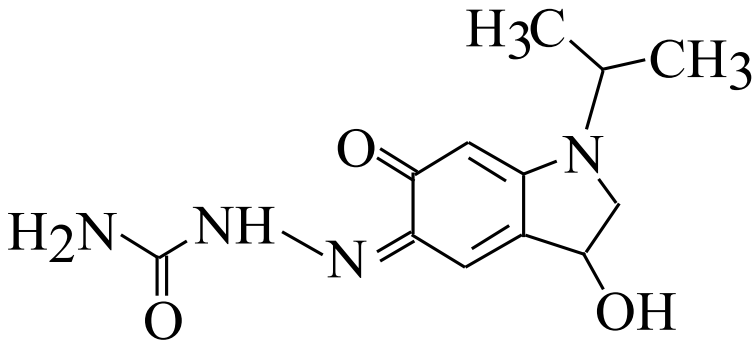
Iprazochrome, MIGRENON

In the treatment of migraine another indol derivative, iprazochrome, is also used.

It acts agonistically at 5-HT-receptors.

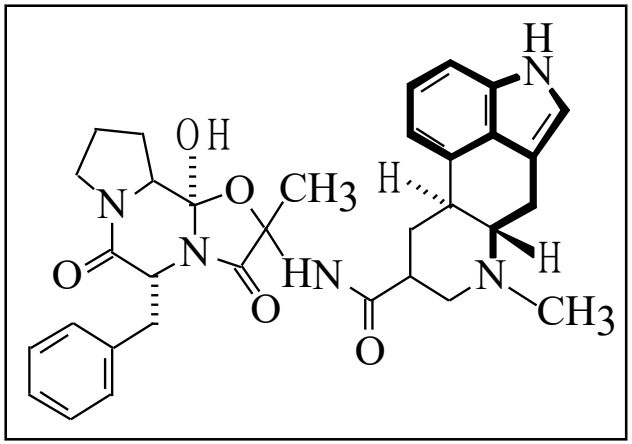
Iprazochrome is used in migraine-like headaches, ophthalmic migraine and cluster headaches.

Although it relieves attacks of migraine, it rarely stops them.



Dihydroergotamine

Dihydroergotamine, whose structure also includes elements of serotonine, does not act as selectively as sumatriptan.



Dihydroergotamine shows strong affinity
not only for

5-HT_{1D}-receptors (agonist)

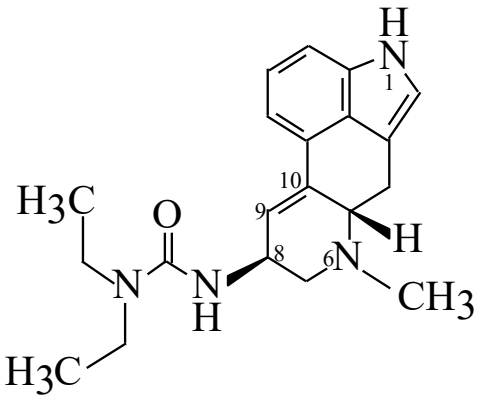
but also at

5-HT_{1A} (agonist),
5-HT_{1C} (agonist) and
5-HT_2 (antagonist) receptors.

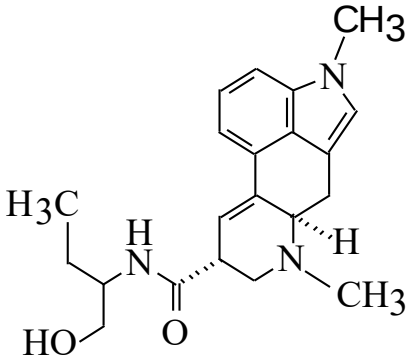
It demonstrates strong affinity for α_1- and α_2 adrenergic receptors and weak affinity for D_2-dopaminergic receptors.

In the case of long-time (48 hours) attacks of migraine and attacks occuring more than twice a month, the following drugs are used to prevent migraine:

- drugs blocking 5-HT-receptors – pizotifen, oxetorone, lisuride, methysergide
- certain β-adrenolytic drugs
- a non-selective blocker of the calcium channel – flunarizine.



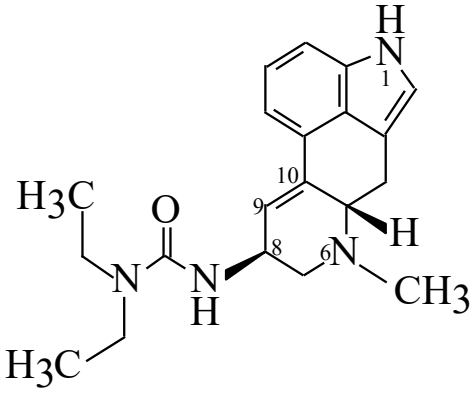
Lisuride, DOPERGIN



Methysergide,
METHYSERGIDE
DESERIL, SANSERT

Lisuride and methysergide are semisynthetic derivatives of isoergoline.

Lisuride acts on

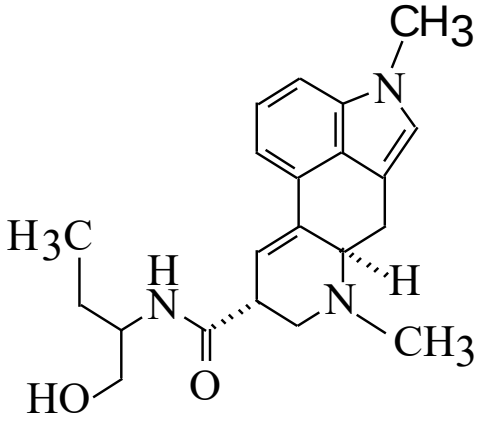


- serotoninergic (5-HT_1≈5-HT_2),
- α-adrenergic (α_2/α_1=2:1) and
- dopaminergic (D_2/D_1 = 2:1) receptors.

The action of lisuride is peripherally antiserotoninergic.

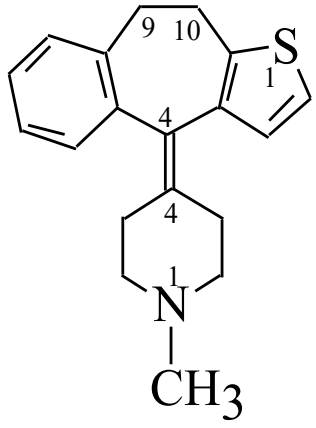
At greater doses lisuride acts centrally as an agonist at D_2-dopaminergic receptors. Because of that it is also used in Parkinson's disease and as the inhibitor of prolactin in the prevention and inhibition of postnatal lactation and in the treatment of hyperprolactinemia.

Methysergide is



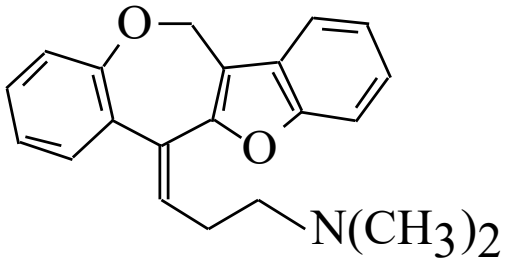
- an agonist at 5-HT_{1B} and
- an antagonist at 5-HT_{1A}, 5-HT_{1C} and 5-HT_2-receptors.

Pizotifen, PIZOTIFEN, POLOMIGRAN, SANDOMIGRAN



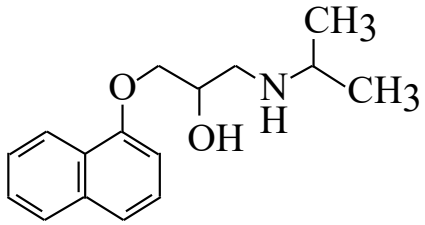
The antiserotoninergic action of pizotifen (antagonist at
5-HT_2-receptors) is stronger than the action of methysergide.
It also demonstrates antihistaminic, weakly sedative and antidepressive properties.

Oxetorone, NOCERTONE

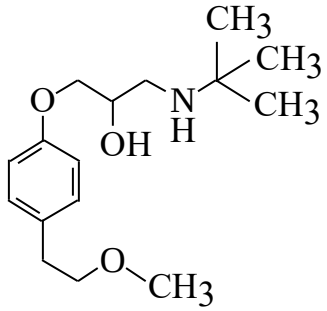


Oxetorone acts antiserotoninergically, antihistaminically, antianaphylactically and antianalgesically.

Propranolol



Metoprolol



Propranolol and metoprolol decrease the number, intensity and duration of migraine attacks.

Flunarizine inhibits the constriction of blood vessels induced by Ca^{2+} ions over a long period of time by blocking the influx of Ca^{2+} ions to the depolarized cells of the smooth muscles of blood vessels.