DRUGS for GOUT, MIGRAINE and ANTIRHEUMATIC DRUGS

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Anti-inflammatory, Antipyretic, and Analgesic Agents

1) NONSTEROIDAL ANTI-INFLAMMATORY DRUGS/ **NSAIDs**
2) ACETAMINOPHEN
3) DISEASE-MODIFYING ANTIRHEUMATIC DRUGS/ **DMARDs**
4) **BIOLOGIC** THERAPIES IN RHEUMATOID ARTHRITIS
5) DRUGS USED FOR THE TREATMENT OF **GOUT**
6) DRUGS USED TO TREAT **MIGRAIN** HEADACHE

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS - DMARDs

DMARDs are used in the treatment of RA and have been shown to:

- ✓ Slow the course of the disease
- ✓ Induce remission
- ✓ Prevent further destruction of the joints and involved tissues.

DMARDs:

- ✓ **Methotrexate**
- ✓ **Hydroxychloroquine**
- ✓ **Sulfasalazine**
- ✓ **leflunomide**

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS - DMARDs

Methotrexate - treatment of patients with rheumatoid or psoriatic arthritis.

- ✓ is a **folic acid antagonist** that inhibits cytokine production and purine nucleotide biosynthesis, leading to **immunosuppressive and anti-inflammatory** effects.
- ✓ Doses of methotrexate required for RA treatment are much lower than those needed in **cancer chemotherapy**
- ✓ side effects (RA) - mucosal ulceration and nausea, cytopenias, cirrhosis of the liver, and an acute pneumonia-like syndrome
- ✓ Taking **leucovorin (folinic acid)** after methotrexate reduces the severity of adverse effects. **Folic acid** taken on off-days is widely used.

DMARDs

Hydroxychloroquine: (used for **early, mild RA**, also used in the treatment of **lupus and malaria**)

Its mechanism of action in autoimmune disorders is **unknown**, and onset of effects takes 6 weeks to 6 months.

Hydroxychloroquine has **less effects on the liver and immune system** than other DMARDs

SE: **ocular toxicity**, including irreversible retinal damage and corneal deposits. CNS disturbances, GI upset, and skin discoloration and eruptions.

DMARDs

Sulfasalazine

Used for **early, mild RA** in combination with methotrexate and/or hydroxychloroquine.

Onset of activity is **1 to 3 months**, and it is associated with leukopenia.

Its mechanism of action in treating RA is unclear.

Glucocorticoids

Glucocorticoids are potent anti-inflammatory drugs that are commonly used in patients with RA

BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

- ✓ **IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA.**

- ✓ When secreted by synovial macrophages, IL-1 and TNF-α stimulate **synovial cells** to proliferate and synthesize **collagenase**, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis.

- ✓ **The TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab)** have been shown to:
  - decrease signs and symptoms of RA,
  - reduce progression of structural damage
  - improve physical function.

- Patients receiving TNF-á inhibitors are at increased risk for **infections** (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia.

BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

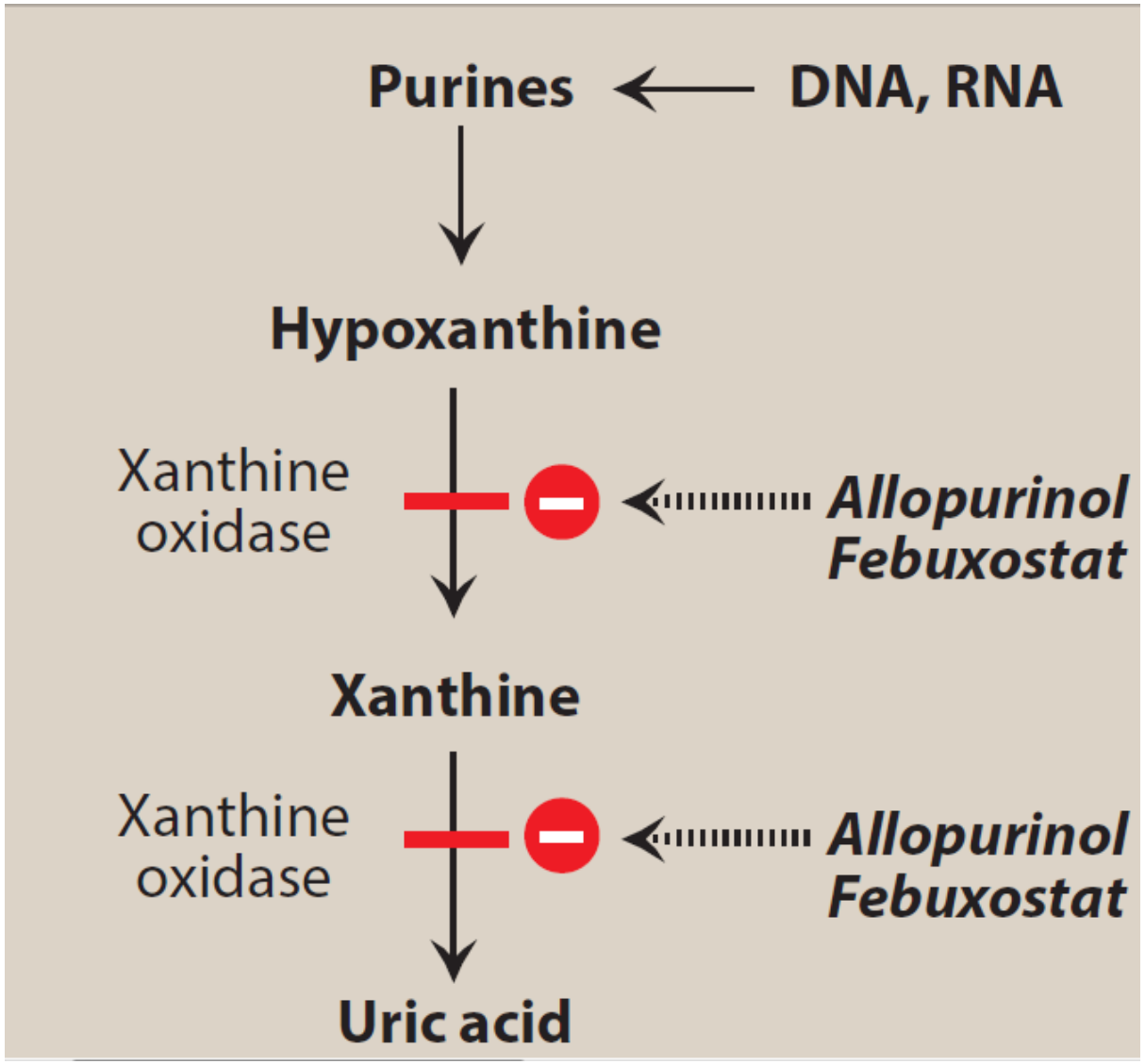
Adalimumab

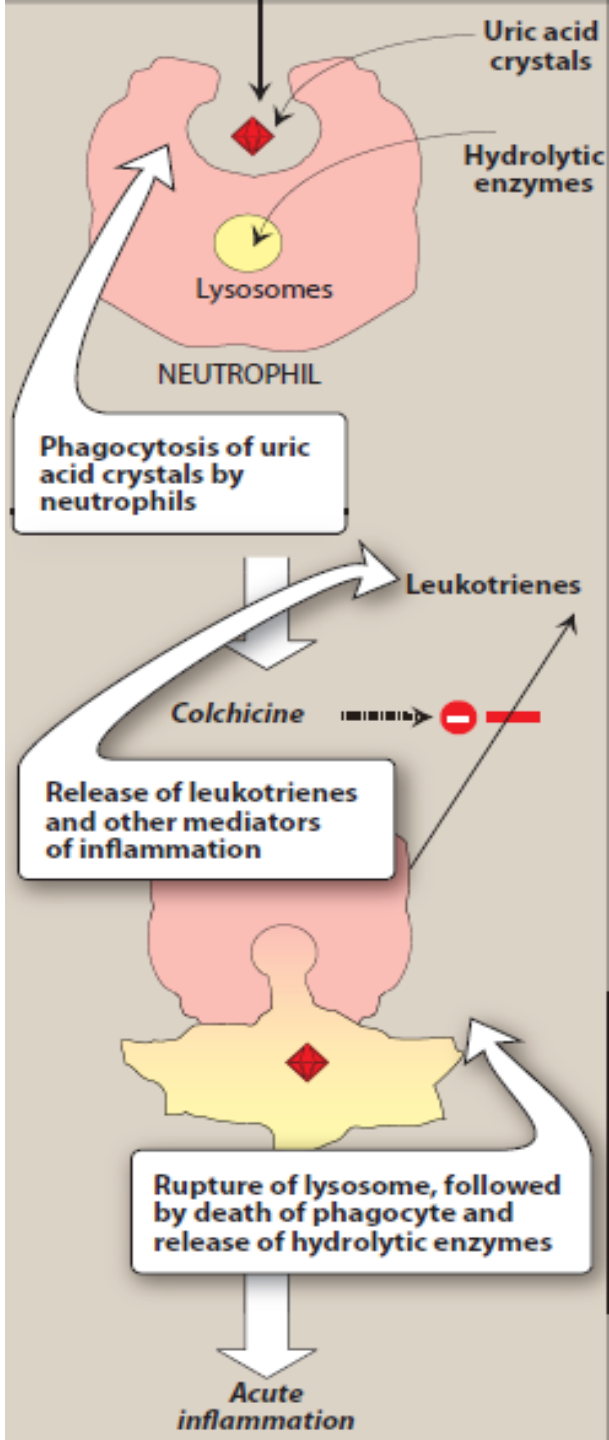
- ✓ is a recombinant monoclonal antibody that binds to **TNF-α**, thereby interfering with endogenous TNF-α activity by blocking its interaction with cell surface receptors.

- ✓ Used:

  RA , psoriatic arthritis, ankylosing spondylitis, and Crohn disease.

DRUGS USED FOR THE TREATMENT OF GOUT





DRUGS USED FOR THE TREATMENT OF GOUT

- Gout is a metabolic disorder characterized by high levels of **uric acid** in the blood (hyperuricemia).
- Hyperuricemia can lead to deposition of **sodium urate crystals** in tissues, especially the joints and kidney.
- Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia.
- The deposition of urate crystals initiates an **inflammatory process** involving the infiltration of granulocytes that phagocytize the urate crystals
- The cause of hyperuricemia is an imbalance between overproduction of uric acid and/or the inability of the patient to excrete it via renal elimination.
- Most therapeutic strategies for gout involve **lowering the uric acid** level, thus preventing the deposition of urate crystals.
- This can be accomplished by interfering with uric acid **synthesis** or increasing uric acid **excretion**.

DRUGS USED FOR THE TREATMENT OF GOUT

Treatment of acute gout

NSAIDs, corticosteroids, or colchicine are effective

Treatment of chronic gout. Treatment strategies include the use of:

- **xanthine oxidase inhibitors** to reduce the synthesis of uric acid (**allopurinol**)
- **uricosuric drugs** to increase its excretion (**probenecid**)

DRUGS USED FOR THE TREATMENT OF GOUT

Colchicine - acute gouty attacks

MoA:

- Colchicine **binds to tubulin**, a microtubular protein, causing its **depolymerization**. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their **migration** into the affected area.
- Furthermore, colchicine blocks cell **division** by binding to mitotic spindles

SE: Colchicine may cause nausea, vomiting, abdominal pain, and diarrhea. Chronic administration may lead to myopathy, neutropenia, anemia.

The drug should not be used in pregnancy,

DRUGS USED FOR THE TREATMENT OF GOUT

Allopurinol - a xanthine oxidase inhibitor, is a purine analog

MoA:

- reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by **xanthine oxidase**

Uses: treatment of **gout** and **hyperuricemia secondary** to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

SE: **Hypersensitivity** reactions, especially skin rashes, are the most common adverse reactions.

DRUGS USED TO TREAT HEADACHE/ Migraine,

	MIGRAINE
Family history	Yes
Sex	Females more often than males
Onset	Variable
Location	Usually unilateral
Character and severity	Pulsating, throbbing
Duration	2–72 hours per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting

DRUGS USED TO TREbAT HEADACHE/ Migraine,

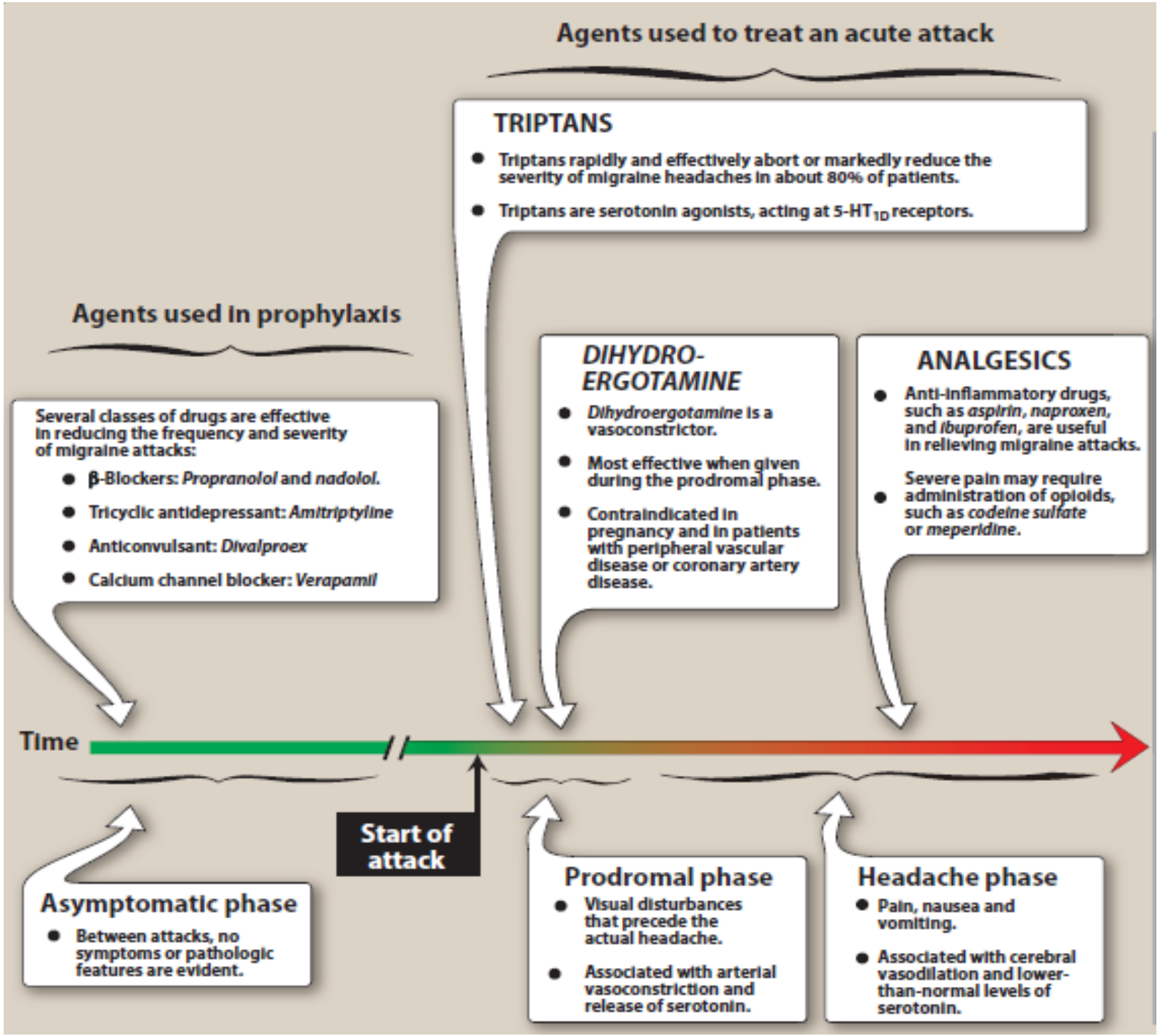
Migraines present as a pulsatile, throbbing pain,

Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually **unilateral**.

The headaches significantly **affect quality of life** and result in considerable health care costs.

Pain of migraine may be due to extracranial and intracranial arterial **vasodilation**, which leads to **release of neuroactive molecules**, such as substance P, neurokinin A, and calcitonin gene–related peptide.

Management of headaches involves **avoidance of headache triggers** (for example, alcohol, chocolate, and stress) and use of abortive **treatments** for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines



TRIPTANS

Almotriptan AXERT
Eletriptan RELPAX
Frovatriptan FROVA
Naratriptan AMERGE
Rizatriptan MAXALT
Sumatriptan IMITREX, ALSUMA
Zolmitriptan ZOMIG

ERGOTS

Dihydroergotamine MIGRANAL, VARIOUS

NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac TORADOL
Naproxen ALEVE, ANAPROX, NAPROSYN

PROPHYLACTIC AGENTS

Anticonvulsants
Beta-blockers
Calcium channel blockers
Tricyclic antidepressants

DRUGS USED TO TREAT HEADACHE/ Migraine,

Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific.

Nonspecific treatment includes:

- **Analgesics such as NSAIDs**
- **Antiemetics (for example, prochlorperazine) to control vomiting.**

Opioids are reserved as rescue medication when other treatments of a severe migraine attack are not successful.

Specific migraine therapy (5-HT1D receptor agonists) includes triptans and ergot alkaloids.

Activation of 5-HT1 receptors leads either to **vasoconstriction** or to inhibition of the release of proinflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

DRUGS USED TO TREAT HEADACHE/ Migraine,

Triptans: (almotriptan, eletriptan, frovatriptan, ratriptan, rizatriptan, **sumatriptan** (prototype) and zolmitriptan)

The triptans are **serotonin agonists**, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature.

The **nausea** that occurs with dihydroergotamine and the **vasoconstriction** caused by ergotamine are much less pronounced with the triptans.

The onset of the parenteral drug sumatriptan is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache.

DRUGS USED TO TREAT HEADACHE/ Migraine,

Triptans:

Elevation of **blood pressure** and other cardiac events have been reported with triptan use.

Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration.

Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. Dizziness and malaise have also been seen with the use of triptans.

DRUGS USED TO TREAT HEADACHE/ Migraine,

Ergot alkaloids: (Ergotamine and dihydroergotamine)

approved for the treatment of migraine headaches.

Ergot alkaloids bind to **5-HT1** receptors, **α receptors**, and **dopamine** receptors.

5-HT1 receptors located on intracranial blood vessels are targets that cause **vasoconstriction** with the use of these agents.

Nausea is a common adverse effect.

DRUGS USED TO TREAT HEADACHE/ Migraine,

Prophylaxis for migraine headache:

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs.

β-Blockers are the drugs of choice for migraine prophylaxis.

Propranolol and other β-blockers, such as metoprolol, atenolol, and nadolol, have been shown to be effective.
The calcium channel blocker verapamil is an alternative.

Anticonvulsants (divalproex) and **antidepressants** (tricyclics) have also shown effectiveness in preventing migraine.