# Neuropharmacology IV

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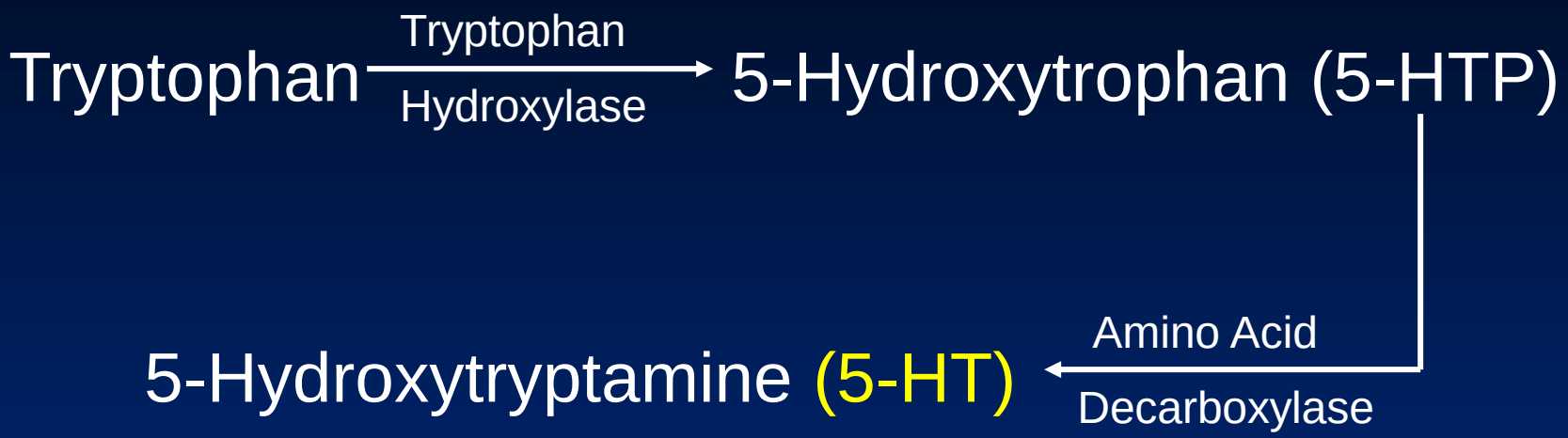
# Objectives

- Discovery of serotonin
  - Synthesis - metabolism
  - Receptor subtypes
- Serotonin drugs used for treatment of
  - Emesis
  - Depression
  - Migraine
- Serotonin toxicity
  - Serotonin syndrome
  - Fibrosis of cardiac valves

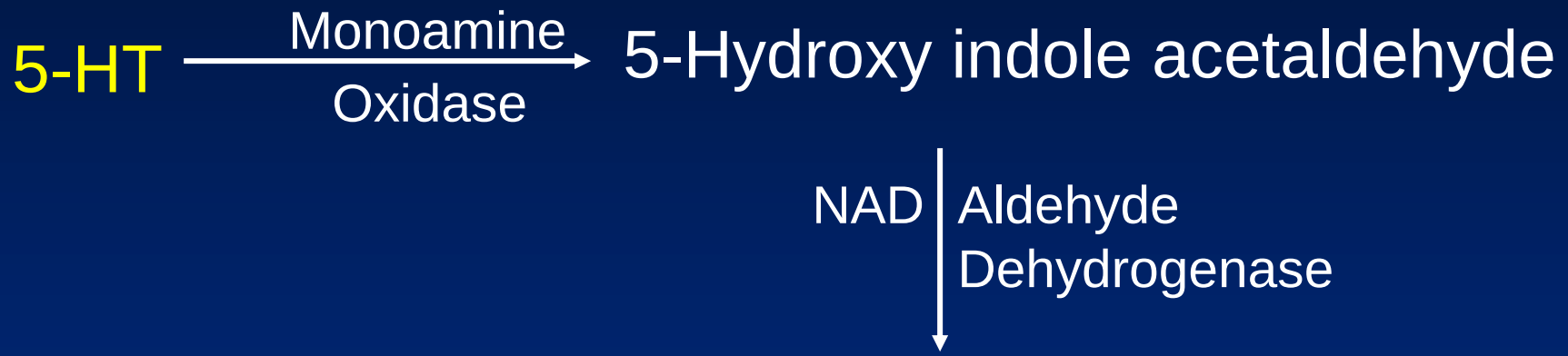
# Serotonin Discovery

- When blood is allowed to clot, platelets release a vasoconstrictor substance
- Initially called Sero-tonin (↑ tone in vessels)
- Also found in the gut and CNS
- 90% of serotonin is in the GI system

# Synthesis


Tryptophan
Tryptophan
Hydroxylase
5-Hydroxytrophan (5-HTP)
Amino Acid
Decarboxylase
5-Hydroxytryptamine (5-HT)

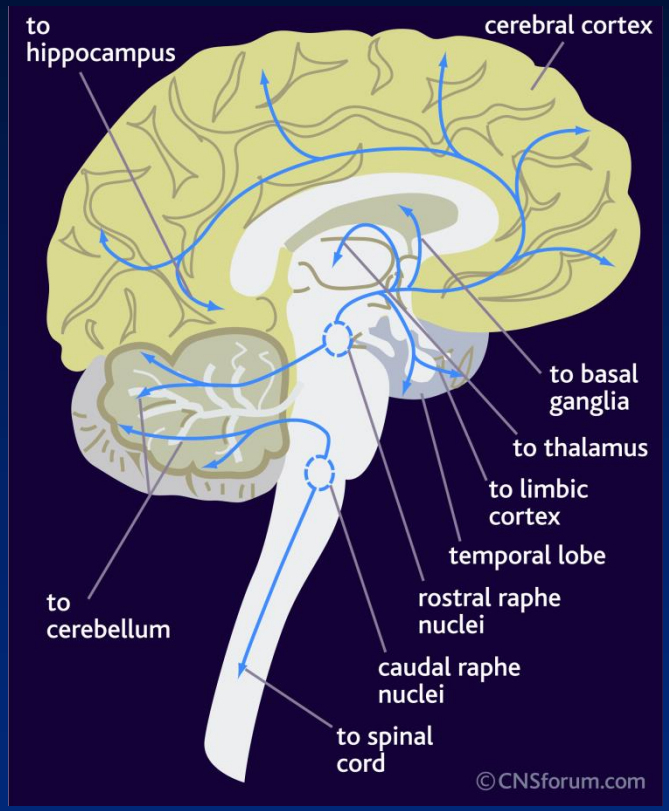
# Metabolism


5-HT
Monoamine
Oxidase
5-Hydroxy indole acetaldehyde
NAD
Aldehyde
Dehydrogenase
5-HIAA: 5-Hydroxy indole acetic acid
(5-HIAA)

# 5-HT Receptor Signaling

| **receptor** | 5HT1 | 5HT2 | 5HT3 | 5HT4 | 5HT5 | 5HT6 | 5HT7 |
|---|---|---|---|---|---|---|---|
| **subtype** | 5HT1A<br>5HT1B<br>5HT1D<br>5HT1E<br>5HT1F | 5HT2A,<br>5HT2B,<br>5HT2C | 5HT3A,<br>5HT3B | | 5HT1A,<br>5HT1B | | |
| **major signaling pathway** | cAMP↓ | IP3↑ | **ion channel** | cAMP↑ | cAMP? | cAMP↑ | cAMP↑ |

# Serotonin in the Brain




- To thalamus, involved in sensation and pain perception
- To limbic cortex, involved in mood and emotions
- To hippocampus, involved in memory and cognition

# Serotonin Effects in the Brain, Working Through Diff. Subtypes

- Depression
- Anxiety
- Obsessive-compulsive disorder
- Panic disorder
- Eating disorders
- Irritable bowel syndrome
- Nausea/vomiting
- Migraine
- Memory loss
- Sleep disorders
- Fibromyalgia
- Reproductive behavior
- Craving
- Hypersensitivity to pain
- Chronic Fatigue Syndrome

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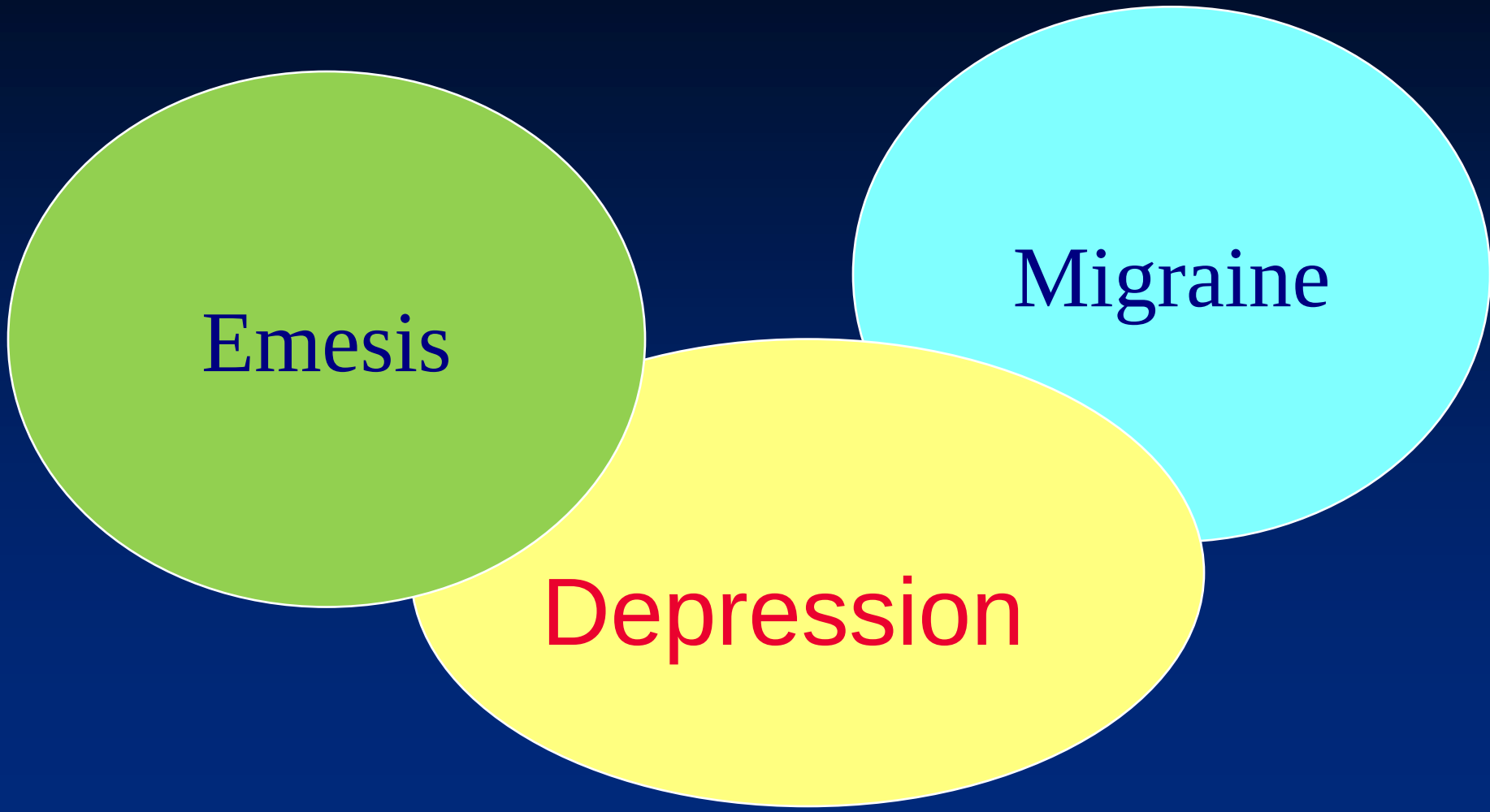
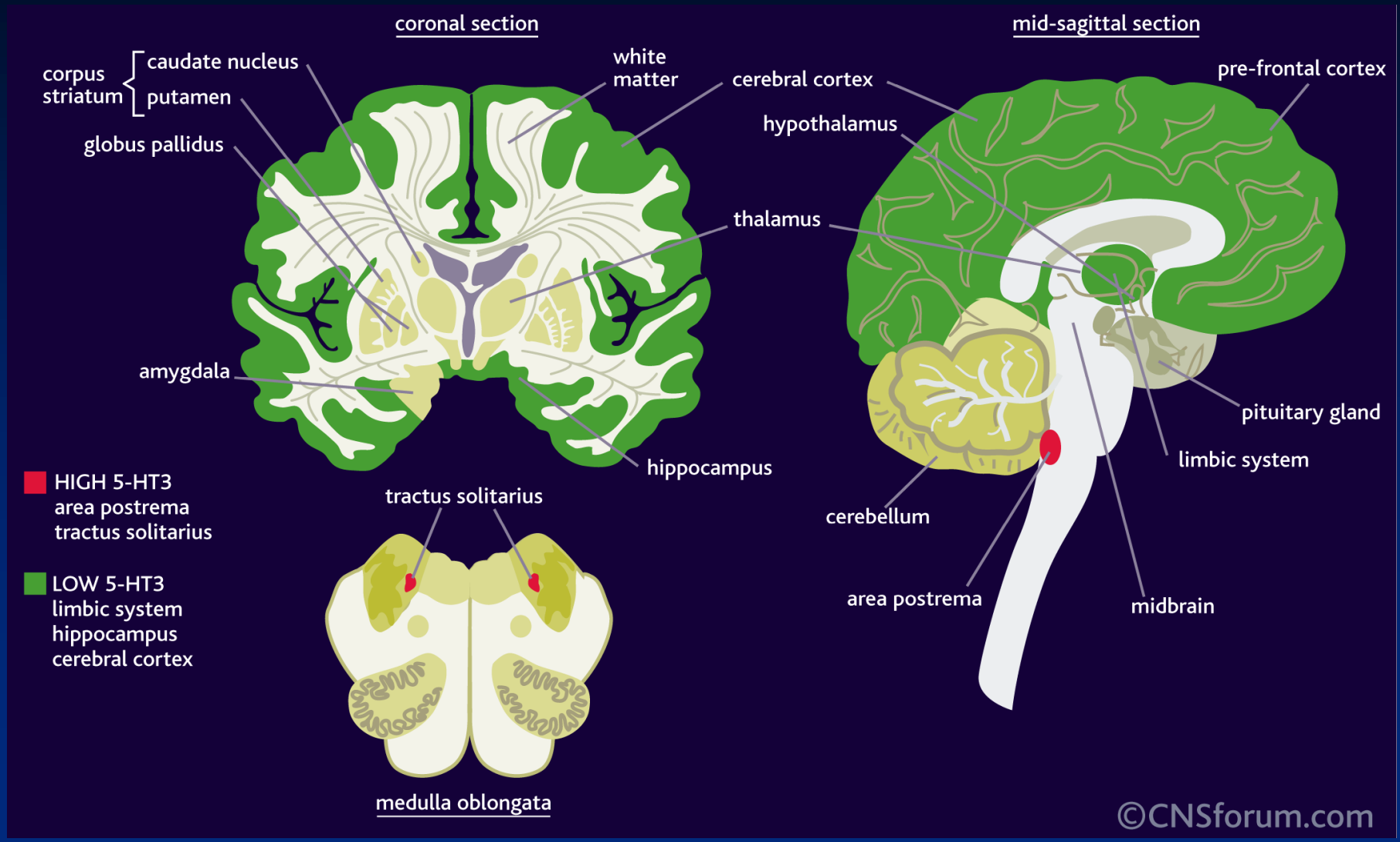
# Serotonin Drugs



# $5HT_3$ receptors: distributed in brain areas important for nausea/vomiting

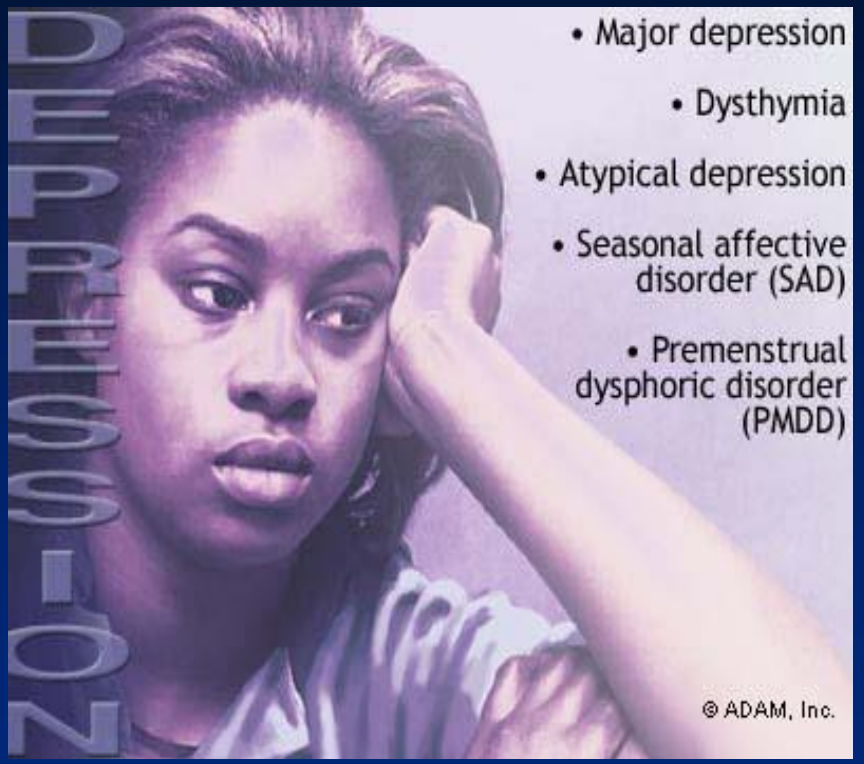


# Serotonin 5-$HT_3$ Antagonists Antiemetics for Chemotherapy

- 90% of 5-HT is in GI enterochromaffin cells
- Highly emetogenic chemo drugs (e.g cisplatin), lyse GI cells → release large amounts of 5-HT
- 5-HT depolarizes neurons (via 5-$HT_3$ receptors) on
  - Vagal afferents
  - Chemoreceptor Trigger Zone
- Blocked by Ondansetron and congeners
- Chemotherapy was formerly an inpatient ordeal – 5-$HT_3$ antagonists have made it an outpatient procedure.

# Depression

Monoamine Hypothesis: Depression and other affective disorders involve dysregulation of CNS serotonin and norepinephrine

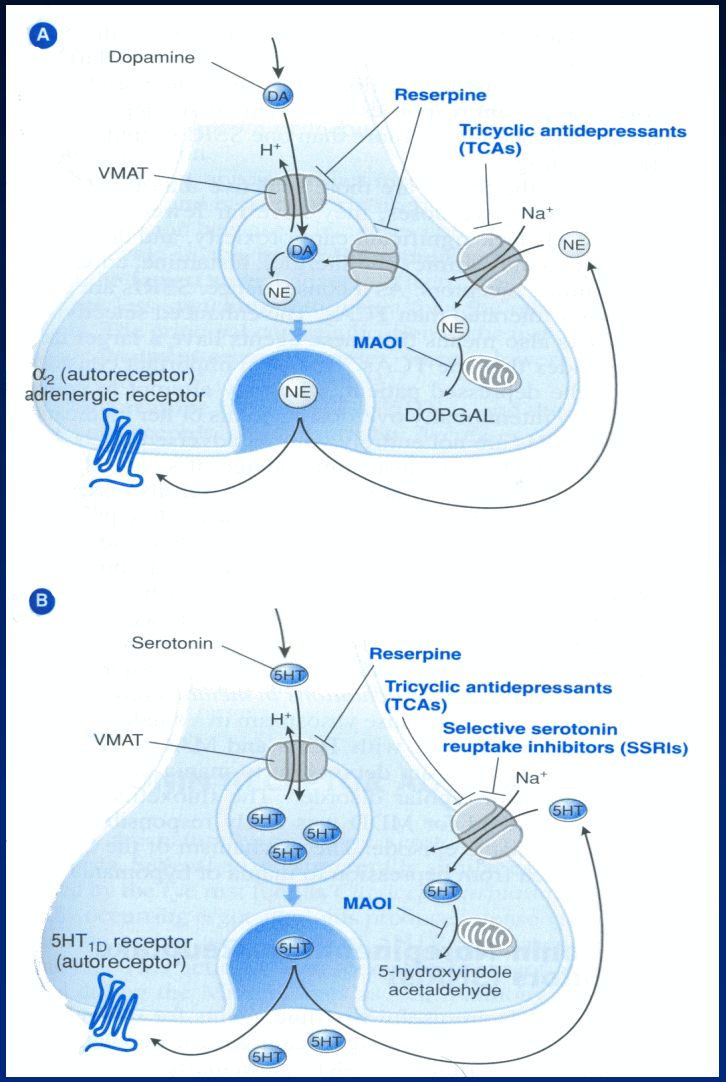


# Case: Depressed secretary

- RW, a 27-year-old secretary, experiences deep sadness after she breaks up with her boyfriend
- Three months later she still feels hopeless, helpless, tearful, and guilty
- Has no appetite, loses weight
- Wonders if life is worth living
- No energy (or interest) to see a physician

# Anti-Depressants

- Tricyclic anti-depressants (TCA)
  - Nortriptyline
  - Amitriptyline
- Selective Serotonin Reuptake Inhibitors (SSRI)
  - Fluoxetine
  - Sertaline
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)
  - Venlafaxine
  - Duloxetine



# Antidepressant Choices

- SSRIs not effective for pain. Usually better for anxious patients with weight loss and insomnia (atypical depression)
- SNRIs effective for pain. Usually better for lethargic patients with excessive sleeping and over-eating (typical depression)
- Tricyclics effective for depression and pain, but toxicity limits use. Usually avoided in the elderly.

# Anti-depressant Toxicity

- SSRIs - well-tolerated
  - Sexual dysfunction
- SNRIs - well tolerated
  - Sexual dysfunction
- TCAs - significant side effects
  - Convulsions, coma, or cardiac arrest (3Cs)
  - Anticholinergic – Constipation, dry mouth, somnolence, arrhythmias, urinary retention
  - Typical Rx is enough for suicide!

# Case (cont.): Depression treatment

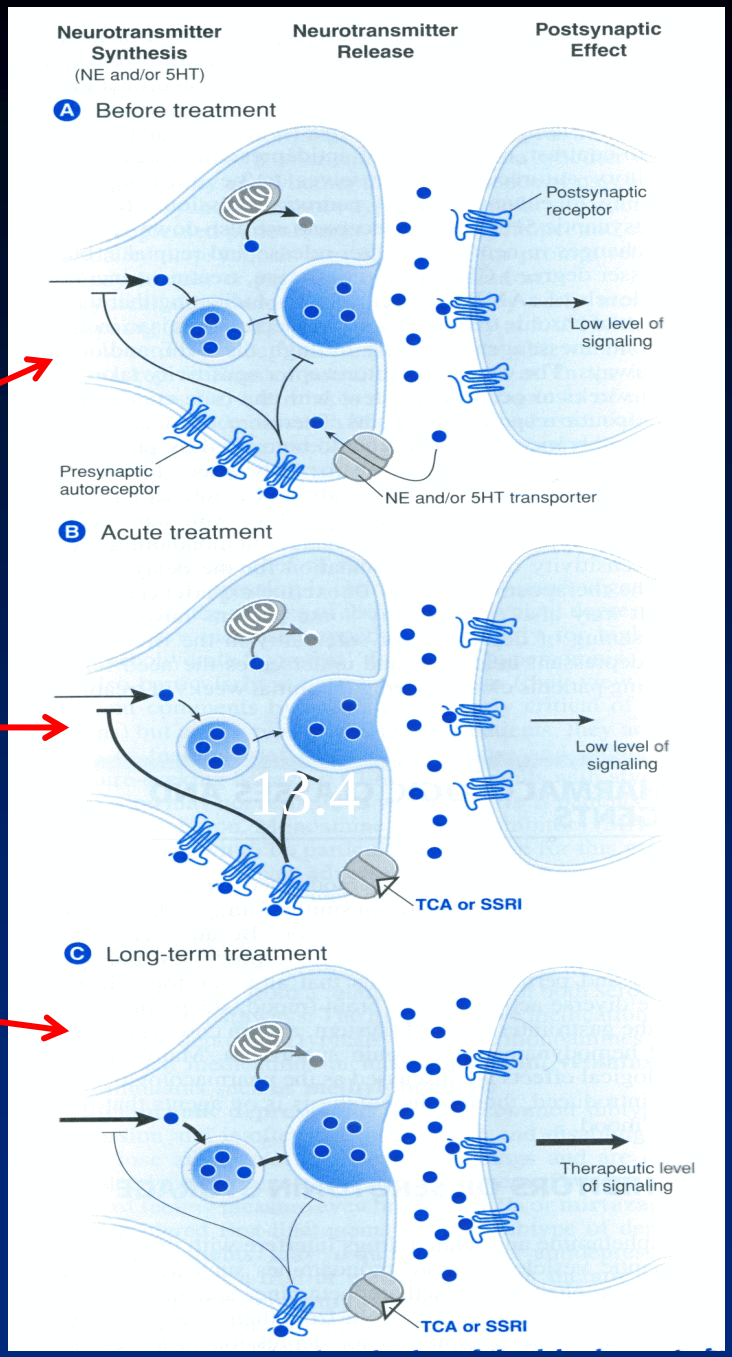
- Prescribed sertaline (SSRI) by her PCP
- Specifically denied suicidal thoughts; a friend agreed to live with her for a couple of weeks
- After 10 days, her symptoms were the same -- her friend was quite concerned.
- Three weeks later, she was much better; she found herself smiling and laughing.

# Why does it take 3-4 weeks for anti-depressants to work?

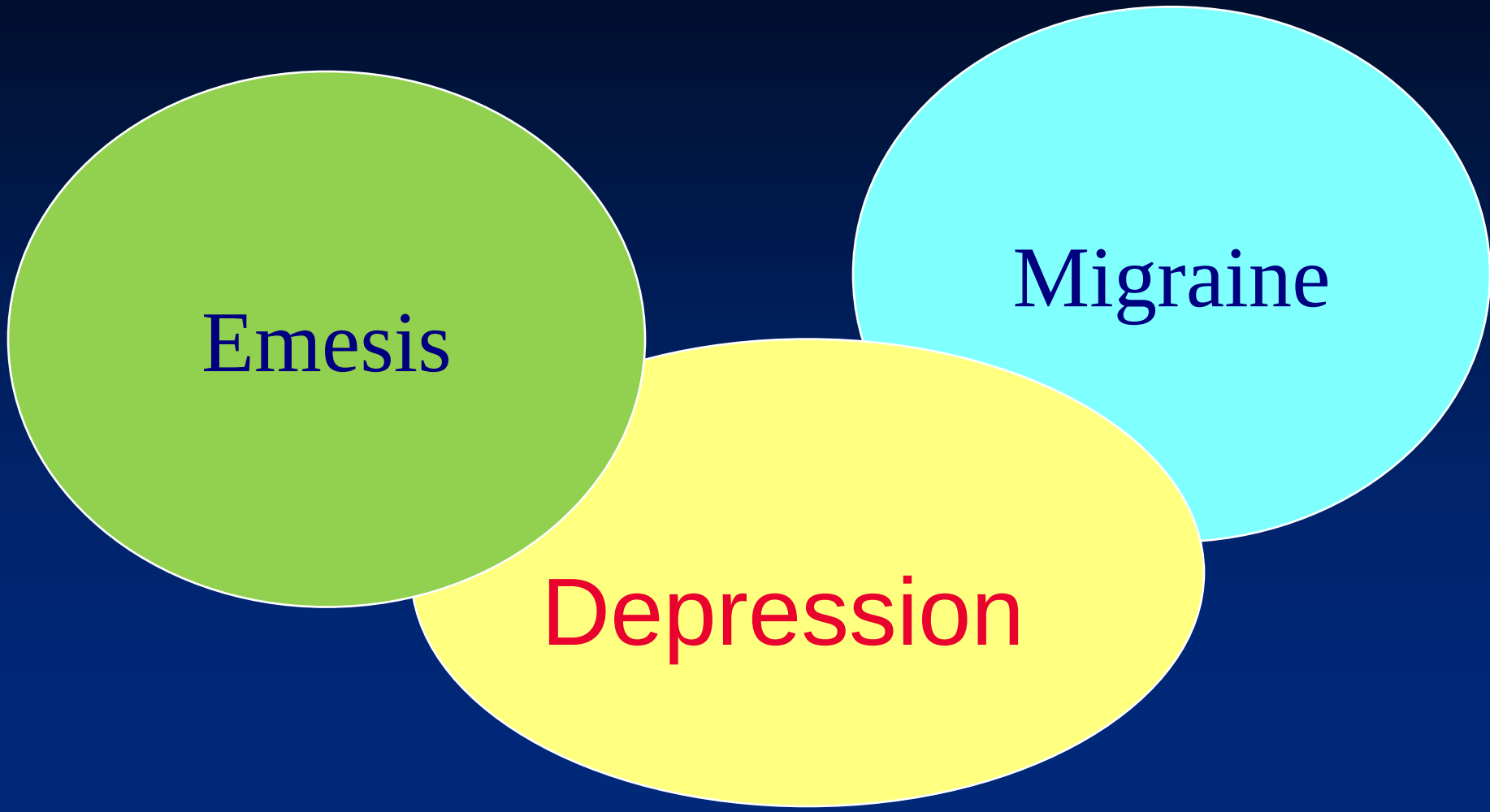
A. Goal is ↑ serotonin

B. Stimulating presynaptic auto-receptors initially ↓ serotonin production

C. With chronic treatment, auto-receptors are down-regulated and serotonin levels rise in the synapse



# Serotonin Drugs



# Case: A physician with severe headaches

- 48 year old physician with history of headaches since medical school
- Severe headaches occurred
  - When children limited his night sleep
  - After a 12 hr shift
  - After consuming pizza or wine
- Sometimes associated with nausea, photophobia, and allodynia
- Twice, he felt “world-spinning” for 10-20 minutes, without accompanying headache

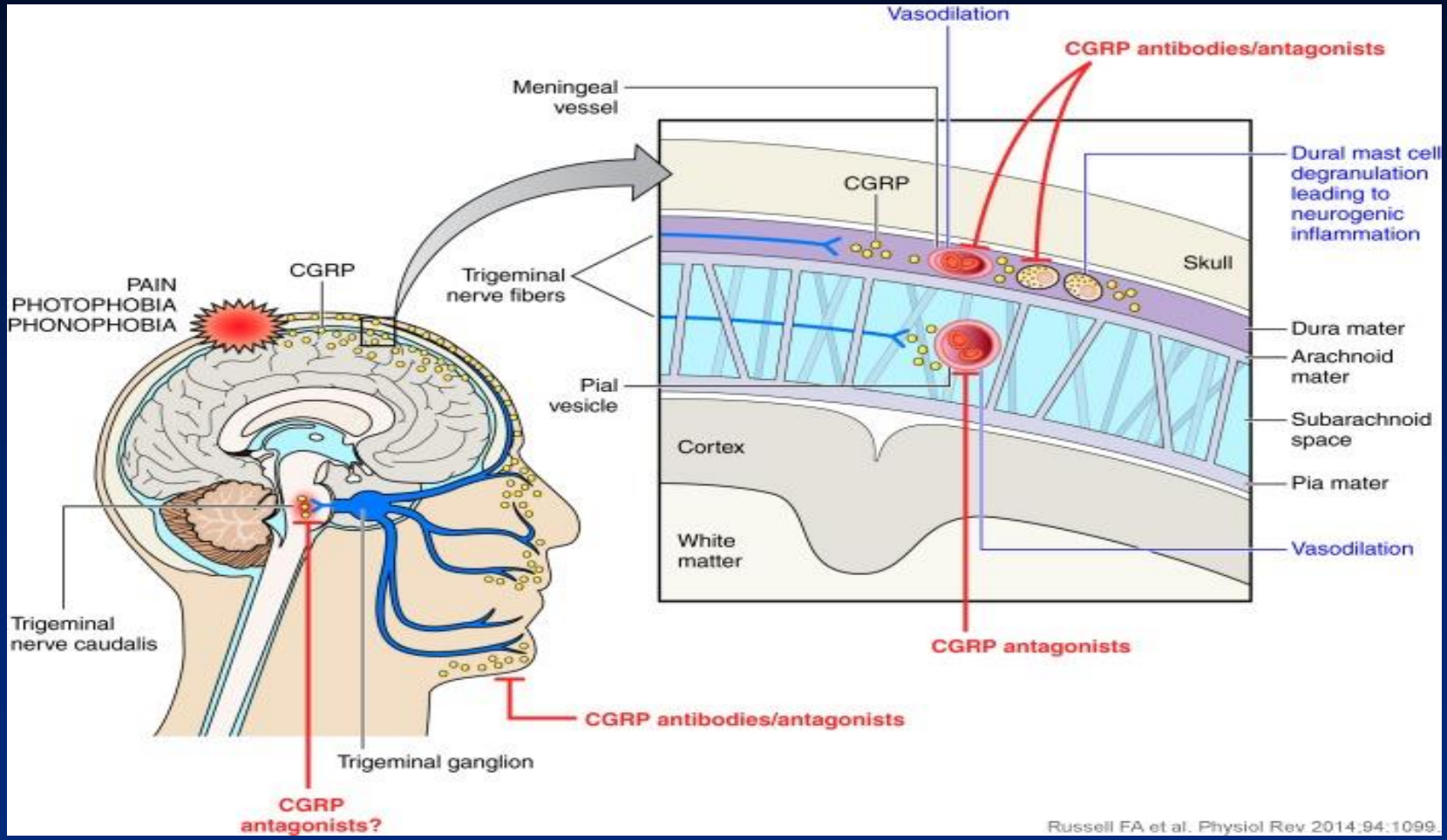
# Classic Migraine – Four phases

- Prodrome
  - Fatigue, cravings, neck stiffness, yawning, irritability
- Aura
  - Vision loss, inability to speak, seeing zig-zag lines or flashing stars, vertigo, allodynia, or paresthesia
- Pain
  - Usually throbbing, unilateral, and severe (variable duration, 4-72 hours)
- Postdrome
  - Difficulty concentrating, mood swings, “hung-over”

# Pathophysiology: Several Theories

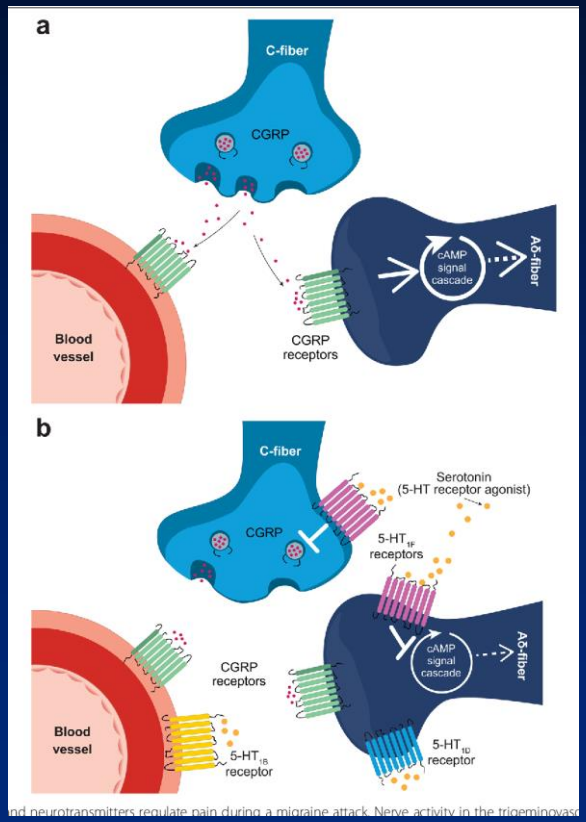
1. Spreading Cortical Depression
2. Activation of brain stem nuclei and stimulation of trigeminal nerve
3. Release of peptides (e.g., CGRP) at nerve terminals on blood vessels → vasodilation, protein extravasation, and inflammation
4. Activation of trigeminal nucleus stimulates pain pathways to thalamus and cortex

# CGRP in Blood Vessels & Brain




https://migraineagain.com/hope-for-new-migraine-drugs/

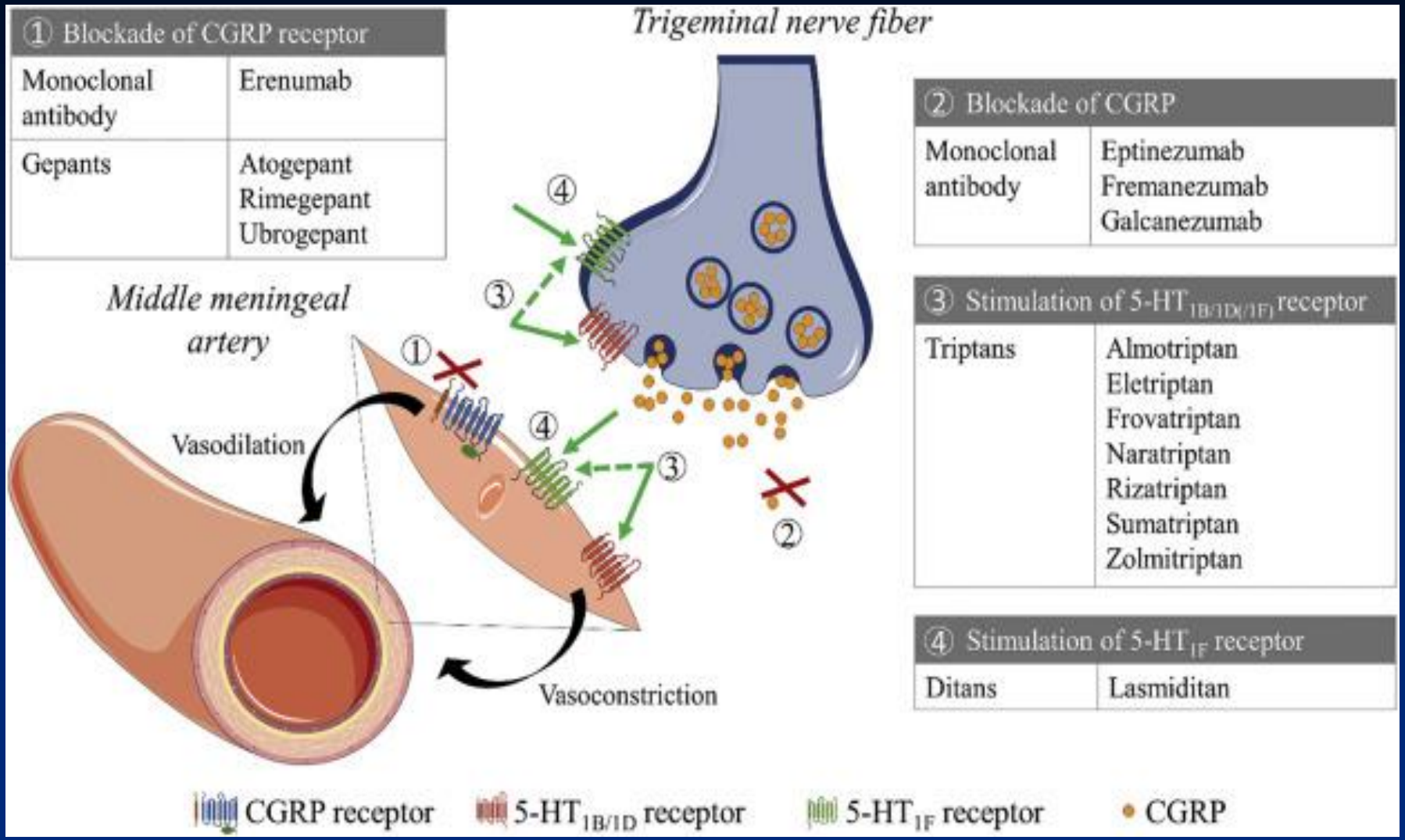
# CGRP & Serotonin Receptors




- CGRP released from trigeminal nerve endings cause painful vasodilation
- Serotonin 5HT-1F agonists (Ditans) help to reduce the release of CGRP, and also to block ascending pain signaling to the brain

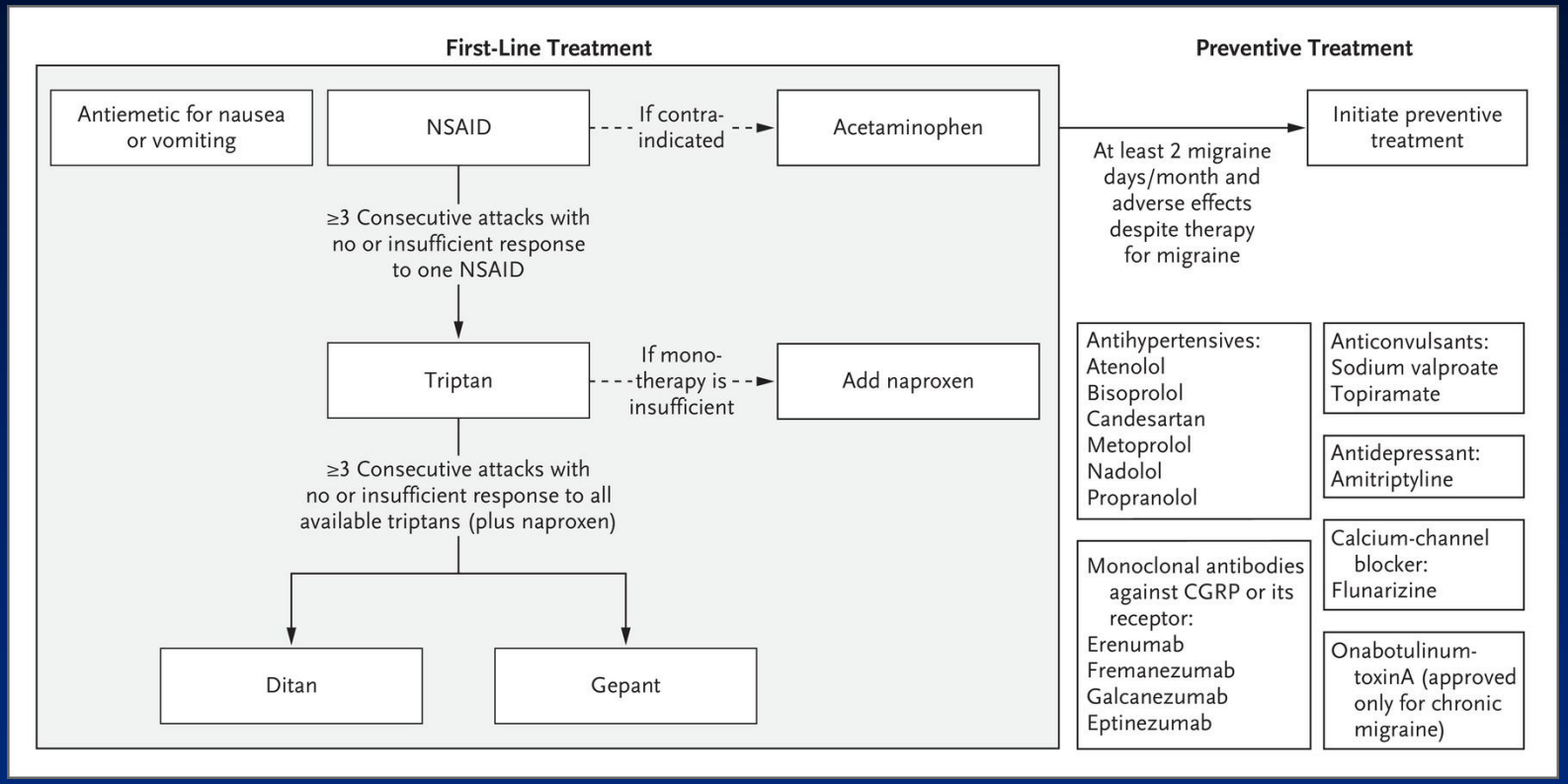
https://www.semanticscholar.org/paper/Lasmiditan-mechanism-of-action-%E2%80%93-review-of-a-5-HT1F-Clemow-Johnson/727f9d5bbb75be50cf9cf9803a612cf931ba0676

# A New Era in Treating Migraine (Gepants, Triptans, and Detans vs mAb's )




https://www-sciencedirect-com.proxy1.library.jhu.edu/science/article/pii/S0163725820300565?via%3Dihub

# Migraine Treatment Algorithm




https://www-nejm-org.proxy1.library.jhu.edu/doi/10.1056/NEJMra1915327?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed#figures_media

# Migraine Treatments

- Acute ("abortive")
  - NSAIDs
  - Triptans
  - Combination of NSAIDs and triptans
  - If not better, consider Gepants > Detans (driving concerns)
  - +/- Antiemetics (to reduce nausea)

- Chronic Prophylaxis:
  - TCAs, SNRIs, SSRIs, CCBs, beta-blockers
  - Topiramate
  - Monoclonal antibodies for CRGP-receptor or CGRP itself
  - Migraine diet, **better sleep, stress reduction**

# Case: Migraine treatment

- Tried topiramate, could not tolerate side-effects
- Tried TCAs, developed dry mouth and difficulty with concentration and memory

- Started migraine diet, exercise, ↓work-load (from 60-70 hrs/week to 50 hrs/week), and meditation – improved greatly
- Motrin 800 mg, effective for headaches, 2-3 times a month

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# Serotonin Syndrome

- Combining SSRIs, SNRIs, MAOIs, TCAs, analgesics, and/or migraine medications can increase serotonin to toxic levels
- Serious complications include:
  - Tremor
  - Confusion
  - Dizziness
  - Agitation
  - Hyperpyrexia
  - Death

# Treatment

- Suspected medications should be discontinued immediately
- Check for OTC drugs containing ingredients known to increase serotonin levels,
  - Dextromethorphan
  - Pseudoephedrine
  - Phenylpropanolamine
  - St John’s Wort
- Treatment is symptomatic; Benzodiazepines for mild to moderate cases

# Fen-Phen Toxicity

- Fenfluramine and phentermine – halogenated amphetamines that ↑ serotonin levels
- Combination ("Fen-Phen") reduced appetite – highly effective for treatment of obesity
- Caused inflammatory fibrosis of the tricuspid and pulmonic valves resulting in many deaths → removed from the market

# Summary

- Serotonin is involved in nausea, depression, sleep disorders, fibromyalgia, anxiety, panic attacks, pain hypersensitivity, and migraine
- Drugs that modulate serotonin release or block its activity are highly effective treatments for nausea, depression, and migraine
- Serotonin syndrome and inflammatory vascular fibrosis are serious complication of serotonin excess.