NEUROPHARMACOLOGY
CLINICAL PEARLS: MIGRAINE

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RELEVANT DISCLOSURE & RESOLUTION

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Stephen M. Clayton, Jr., MD

I have no relevant financial relationships or affiliations with commercial interests to disclose

EXPERIMENTAL OR OFF-LABEL DRUG/THERAPY/DEVICE DISCLOSURE

I will be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.

NEUROPHARMACOLOGY CLINICAL PEARLS: MIGRAINE *Professional Practice Gap*

Throughout our medical careers, our focus tends to remain on clinical pathophysiology. Therefore, our understanding of disease processes are seldom viewed through the lens of "pre-clinical" basic sciences, except as early medical students—who lacked the clinical experience to tie everything together.

This is especially true for the medications we utilize everyday: we have learned certain medications work for particular diseases yet often take it for granted why.

This session will review some of those *why*s to hopefully help enrich clinical understanding.

Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

- List various neurotransmitters (including small molecules and neuropeptides) and receptors involved in migraine pathophysiology
- Describe the major biochemical effect of drugs or drug classes commonly used to treat migraine and primary headache disorders
- Recognize chemical structural similarities of certain medications used to treat migraine, either between each other or with neurotransmitters

MIGRAINE PATHOPHYSIOLOGY

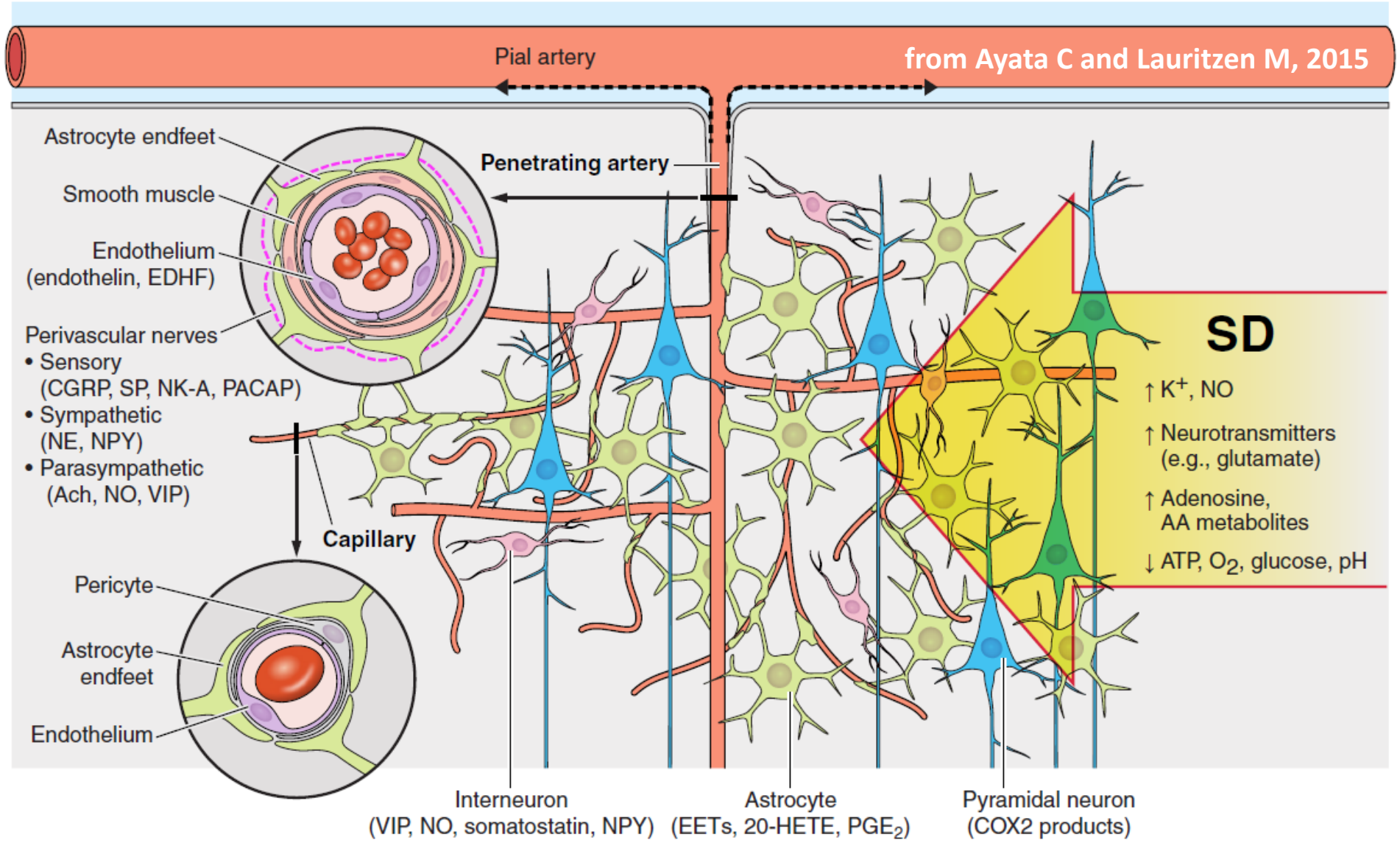
MIGRAINE PATHOPHYSIOLOGY
Cortical Spreading Depression (CSD)

- ***Intense depolarization/excitation*** spreading a few millimeters per minute, ***followed by prolonged disruption*** in appropriate signal conduction → "depression"
- Unclear why but likely ↓ membrane resistance due to opening of nonselective cation channels → ions move along concentration gradients
  - ↑ intracellular [Ca^{2+}] and ↑ extracellular [K^{+}]
  - **Depolarization → ↑ extracellular glutamate → ↑ NMDA receptor activation**
- Large metabolic demand on cell to attempt restoring homeostasis by repleting intracellular energy stores
  - ↓ ATP, O_2, glucose, pH

MIGRAINE PATHOPHYSIOLOGY

Trigeminovascular System

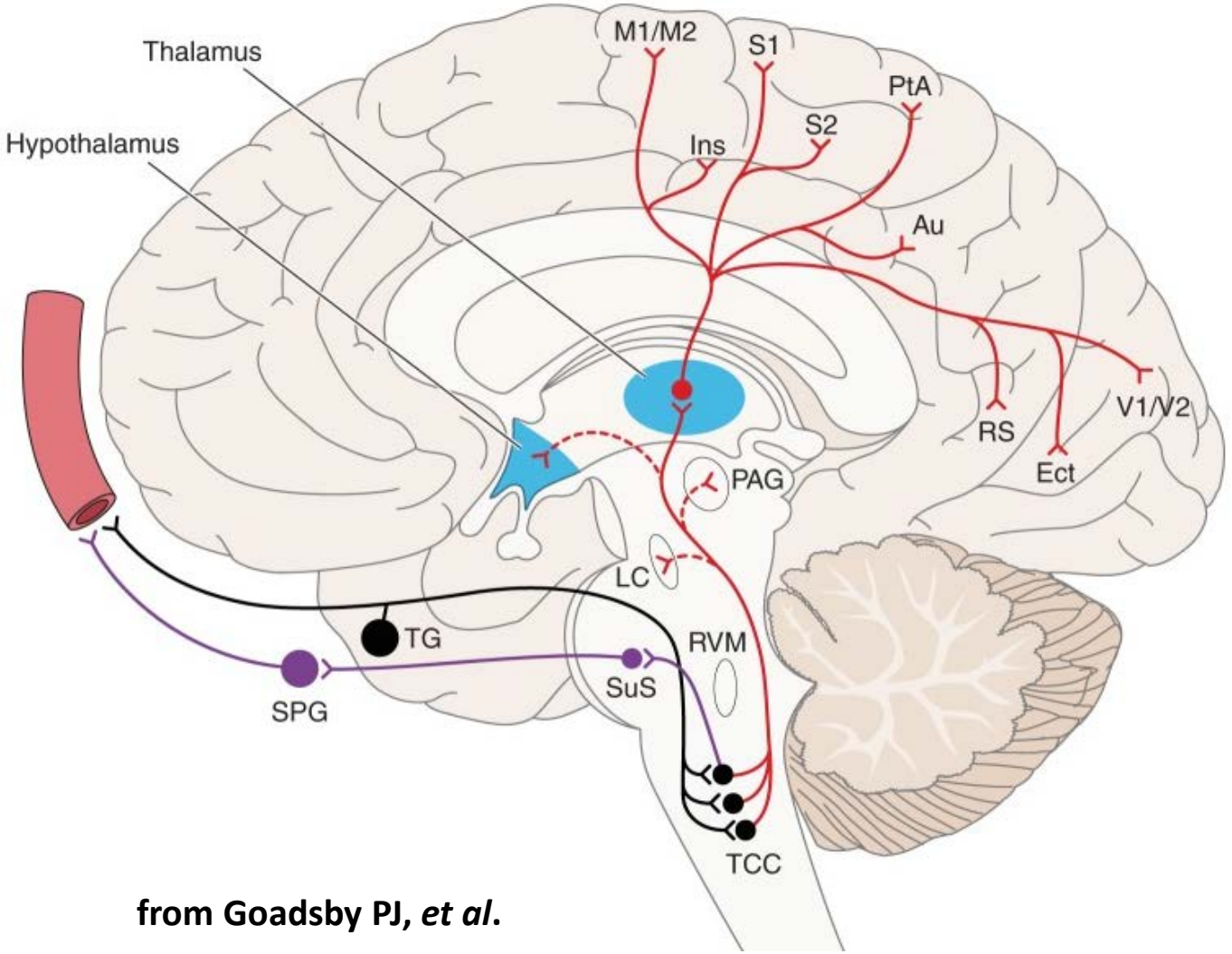
- Nociceptive trigeminal nerves activated by mechanical or chemical stimuli release vasoactive peptides
  - Stimuli relay to brainstem nuclei → many neurotransmitters released → thalami interpret signals → modulate cortical neuronal activity
- With CSD, hyperemia followed by **prolonged oligemia**
  - 20-40% reduction in cerebral blood flow spreading at 2-3 mm/min
  - Oligemia prevents ability for neurons to return to baseline
- Inflammatory processes also implicated due to cytokine and neuropeptide involvement



20-HETE = 20-Hydroxyeicosatetraenoic acid (a metabolite of arachidonic acid); **CGRP** = calcitonin gene-related peptide; **EDHF** = endothelium-derived hyperpolarizing factor; **EETs** = epoxyeicosatrienoic acids (metabolites of arachidonic acid); **NE** = norepinephrine; **NK-A** = neurokinin A; **NO** = nitric oxide; **NPY** = neuropeptide Y; **PACAP** = pituitary adenylate cyclase activating peptide; **SP** = substance P; **VIP** = vasoactive intestinal peptide

MIGRAINE PATHOPHYSIOLOGY

Thalamocortical Projections



from Goadsby PJ, *et al*.

Au = auditory cortex
Ect = ectorhinal cortex
Ins = insular cortex
LC = locus coeruleus
M1/M2 = primary and secondary motor cortex
PAG = periaqueductal gray
PtA = parietal association cortex
RS = retrosplenial cortex
RVM = rostral ventromedial medulla
S1/S2 = primary and secondary somatosensory cortex
SPG = sphenopalatine ganglion
SuS = superior salivary nucleus
TCC = trigeminocervical complex
TG = trigeminal ganglion
V1/V2 = primary and secondary visual cortex

MIGRAINE PATHOPHYSIOLOGY

Genetic Basis for Migraine

- Many genes implicated though none individually convincing for "run-of-the-mill" migraine
  - Possibly due to heterogeneity rather than lack of correlation
- Familial hemiplegic migraine
  - **CACNA1A** (P/Q type $Ca_v2.1$): also ***spinocerebellar ataxia type 6***, ***episodic ataxia type 2***, ***benign paroxysmal torticollis of infancy***
  - **ATP1A2** (Na^+/K^+-ATPase): loss of function likely ↑ adenosine release from astrocytes; assoc. w/migraine with brainstem aura
  - **SCN1A** ($Na_v1.1$): mutation results in hastened recovery from inactivation state compared to wild-type; associated with ***severe myoclonic epilepsy of infancy (SMEI = Dravet syndrome)*** and ***generalized epilepsy with febrile seizures plus*** (***GEFS+)***

NEUROTRANSMITTERS IN MIGRAINE

NEUROTRANSMITTERS IN MIGRAINE

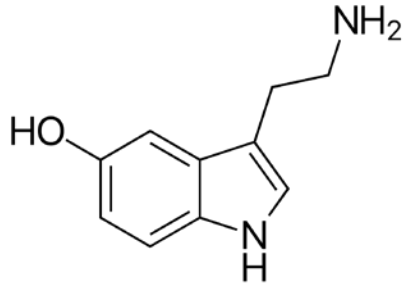
Overview

- Serotonin (5-HT)
- CGRP (calcitonin gene-related peptide)
- Norepinephrine (NE)
- Histamine
- Substance P
- Others
  - Nitric oxide (NO)
  - Pituitary adenylate cyclase-activating polypeptide (PACAP)
  - Vasoactive intestinal peptide (VIP)
  - Arachidonic acid metabolites
  - *…and many more*

NEUROTRANSMITTERS IN MIGRAINE

Serotonin: Overview

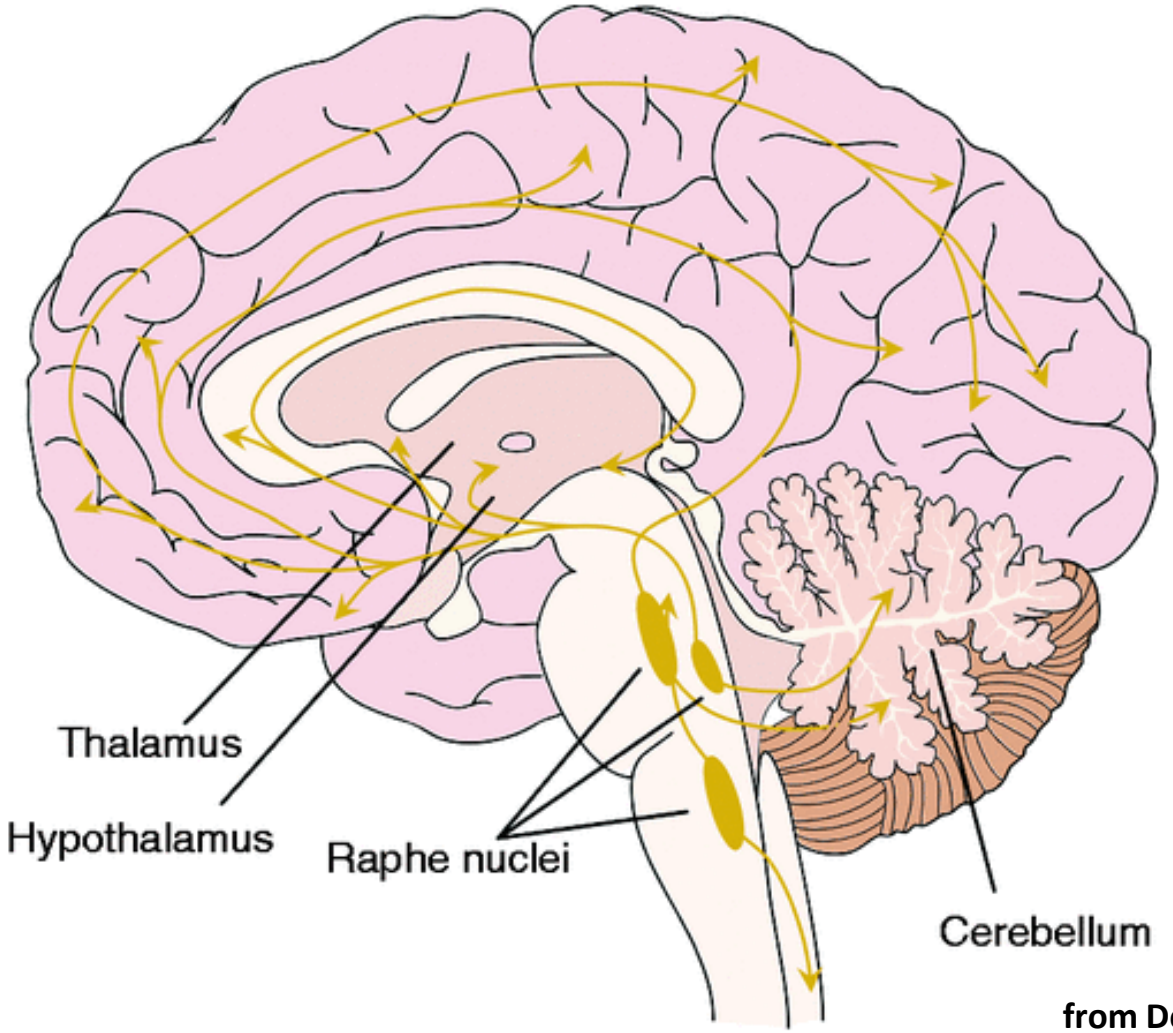
- Serotonin = 5-hydroxytryptamine (5-HT)
- Acts as vasodilator via 5-$HT_{2A/2C}$ receptors but as vasoconstrictor via 5-$HT_{1B/1D}$
  - Also involved in mood, memory, sleep, cognition
- ***Interictal serotonin levels are lower in migraineurs and may lead to increased sensitization of receptors***
- ***Migraine attacks ↑ serotonin acutely***
  - **↑ CGRP, glutamate, NO release**
  - **↑ anxiety**
  - **↑ nausea (via 5-HT_3)**
  - **↑ GI motility (via 5-HT_4)**



Serotonin

NEUROTRANSMITTERS IN MIGRAINE

Serotonergic Projections



from Deen, *et al*.

NEUROTRANSMITTERS IN MIGRAINE

Serotonin Receptors

Receptor family	Subtypes	Type	Function	Relevance for migraine
5-HT_1	5-HT_{1A} 5-HT_{1B} 5-HT_{1D} 5-HT_{1E} 5-HT_{1F}	G-protein coupled	Inhibitory auto- and hetero-receptor	Triptans – acute migraine medication – are $5\text{-HT}_{1B/1D}$ agonists 5-HT_{1F} agonists have proven effective in migraine
5-HT_2	5-HT_{2A} 5-HT_{2B} 5-HT_{2C}	G-protein coupled	Excitatory heteroreceptor	5-HT_2 antagonists are effective as migraine prophylactics
5-HT_3		Ligand-gated ion channel	Excitatory heteroreceptor	Involved in descending pain facilitation
5-HT_4		G-protein coupled	Excitatory heteroreceptor	No known implication
5-HT_5	5-HT_{5A}	G-protein coupled	Inhibitory	No known implication
5-HT_6		G-protein coupled	Excitatory	No known implication
5-HT_7		G-protein coupled	Excitatory	Coupled to pain processing

adapted from Deen, *et al.*

In short,

Prophylactic agents: 5-HT$_2$ antagonists

Abortive agents: 5-HT$_{1B/1D}$ agonists

NEUROTRANSMITTERS IN MIGRAINE

CGRP

- Calcitonin gene-related peptide: 37-residue protein
- Prominent **pronociceptive** effects
  - Found in C and Aδ sensory fibers
  - Upregulated in inflammatory and neurogenic pain
- CGRP also acts as a **potent arterial vasodilator**
  - α- and β-CGRP receptors expressed in many body systems
  - May serve protective role in cardiac disease

NEUROTRANSMITTERS IN MIGRAINE

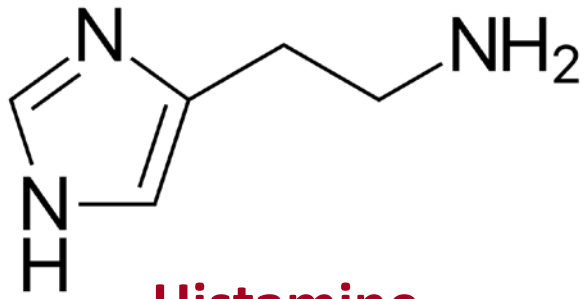
Norepinephrine (NE)

- NE produced in locus coeruleus in pons and influences thalamocortical projections
  - Analogous to serotonergic projections from raphe nuclei
  - **NE prolongs activation of thalamic neurons** ∴ may perpetuate an abnormal excitability level for trigeminovascular system during attacks
- Acts on α_1, α_2, β_1, β_2, β_3 → mostly α_1, α_2, β_1
  - Net vasoconstriction
  - ↑ wakefulness and attention

NEUROTRANSMITTERS IN MIGRAINE

Histamine

- Produced in tuberomammillary nucleus in posterior hypothalamus → project to entire CNS
- Histamine receptors H_1, H_2, H_3 expressed in CNS
  - Chiefly **excitatory for neurons**, mostly via **H_1**
  - Histamine also contributes to vasodilation
- **Migraineurs have ↑ histamine levels ictally and interictally**
  - Sleep deprivation further ↑ CSF histamine



Histamine

NEUROTRANSMITTERS IN MIGRAINE *Substance P*

- 11-residue peptide that binds to neurokinin 1 (NK_1) receptors on postsynaptic dorsal horn neurons → **pronociceptive**
  - Also acts as a potent vasodilator
  - Triggers release of histamine from mast cells
  - Likely contributes to neurogenic inflammation
- However, in human trials, NK_1 receptor antagonists have not worked as abortives or as prophylaxis for migraine
  - Nonetheless, **aprepitant** is FDA-approved for chemotherapy-related nausea

MIGRAINE MEDICATIONS

NEUROPHARMACOLOGY CLINICAL PEARLS: MIGRAINE

Medications: Overview

Anti-hypertensives
- Beta blockers
- Ca^{2+} channel blockers
- ACE inhibitors
- ARBs

Anti-depressants
- SNRIs
- TCAs

Anti-seizure
- Topiramate
- Valproic acid

Miscellaneous Prophylaxis
- CGRP inhibitors
- Botulinum toxin
- Melatonin

Abortive Agents
- Triptans
- NSAIDs
- Antiemetics
- Antihistamines

- Others

ACE = angiotensin-converting enzyme
ARBs = angiotensin-receptor blockers
SNRIs = serotonin-norepinephrine reuptake inhibitors
TCAs = tricyclic antidepressants
CGRP = calcitonin-gene related peptide
NSAIDs = non-steroidal anti-inflammatory drugs

Medications: Overview

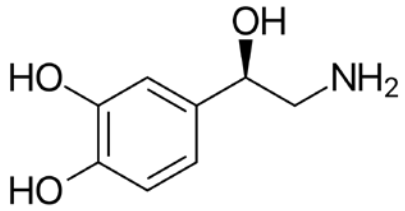
- Several drugs observed anecdotally to ↓ headache frequency and later shown in rat models to decrease cortical spreading depression (Ayata, *et al.*, 2006)
  - **Amitriptyline**
  - **Propranolol**
  - **Topiramate**
  - **Valproate**
- In general, pooled data in human trials also shows dose-dependent effects with positive results more robust **beyond 8 weeks**

Be sure to counsel patients that it will likely take several months to know if things are improving!

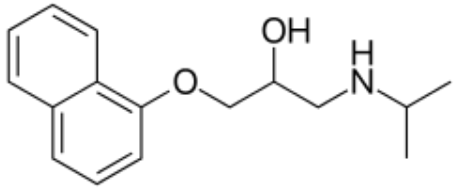
MIGRAINE PROPHYLAXIS

Beta Blockers

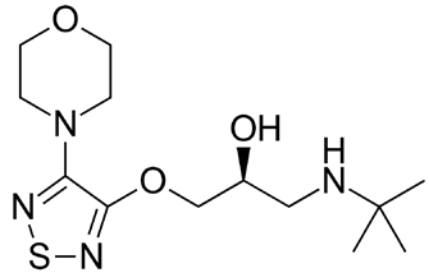
- Poorly understood; likely ↑ interictal serotonin levels through **weak 5-HT$_{1A/1B}$ antagonism**



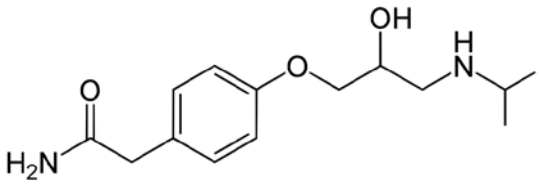
Norepinephrine



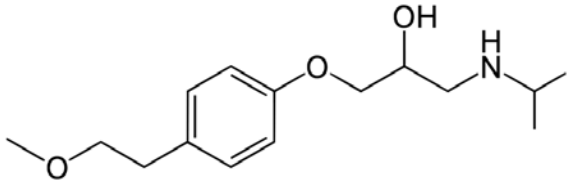
Propranolol*



Timolol*



Atenolol



Metoprolol

***FDA-approved for migraine prophylaxis**

MIGRAINE PROPHYLAXIS
Calcium Channel Blockers

- In neurons, L-type Ca^{2+} channels primarily located in cell bodies and proximal dendrites
  - Allow Ca^{2+} into the cell during strong depolarization
  - ↑ intracellular Ca^{2+} → second-messenger systems → alters gene transcription
- **Ca^{2+} channel blockers ∴ useful during strong depolarization**
  - In subarachnoid hemorrhage-related vasospasm, nimodipine helps stabilize cerebral vasculature but otherwise not much effect
  - Analogous for cortical spreading excitation with migraine attacks
  - L-type Ca^{2+} channels also colocalized on neurons with CGRP activity
- Unclear mechanism though ↓ glutamate release possible
- Positive effects from early studies not well reproduced

MIGRAINE PROPHYLAXIS

ACE Inhibitors

- Angiotensin-converting enzyme (ACE) cleaves angiotensin I into angiotensin II → vasoconstriction
  - ACE inhibitors therefore prevent vasoconstriction
- Unclear mechanism though ACE inhibitors also ↓ degradation of bradykinin → ↑ NO → vasodilation
- Other effects of ACE inhibitors:
  - ↓ degradation of enkephalin and substance P
  - Inhibit free radical activity
  - ↑ prostacyclin synthesis

MIGRAINE PROPHYLAXIS

Angiotensin Receptor Blockers (ARBs)

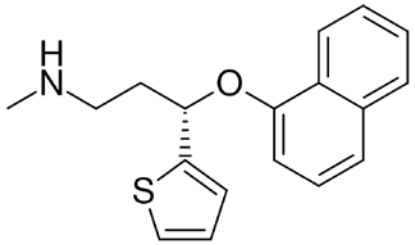
- Like ACE inhibitors, mechanism poorly understood
- Likely pain modulation effect
  - Angiotensin II inhibits presynaptic GABA release in neurons in the periaqueductal gray
  - Possible role with NO despite no bradykinin effect
- **Candesartan** is only ARB sufficiently studied
  - Note: **olmesartan** and **telmisartan** have longer half-life and better bioavailability than candesartan and losartan

MIGRAINE PROPHYLAXIS
SNRIs and TCAs

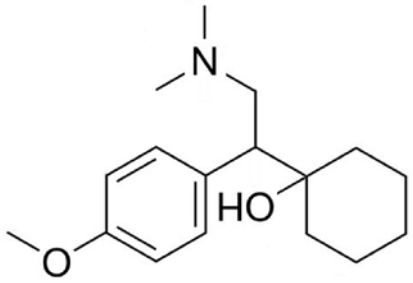
- Antinociceptive action of these antidepressants poorly understood though possibly related to blockade of norepinephrine reuptake
- **Venlafaxine** (SNRI) with weak evidence
  - Note: **tramadol** structurally similar to venlafaxine
- TCAs are **antagonists at 5-HT_{2A}, 5-HT_{2C}, H_1,** and α_1
  - **Amitriptyline**, **doxepin**, and **nortriptyline** have higher affinity for these receptors, especially at 5-HT_{2A} & 5-HT_{2C}
  - **Amitriptyline** and **nortriptyline** also block SERT and NET, thereby functioning as SNRIs

MIGRAINE PROPHYLAXIS

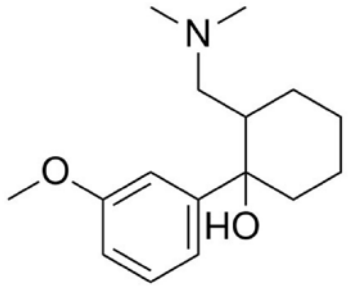
SNRIs and TCAs



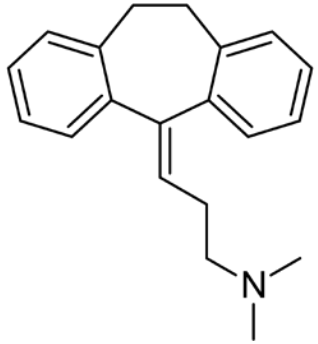
Duloxetine



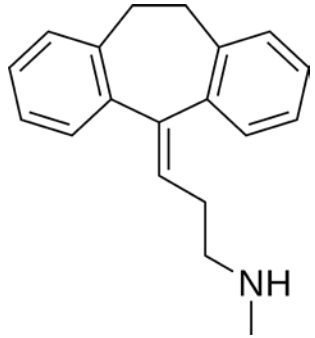
Venlafaxine



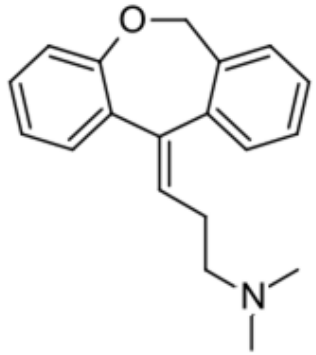
Tramadol



Amitriptyline



Nortriptyline

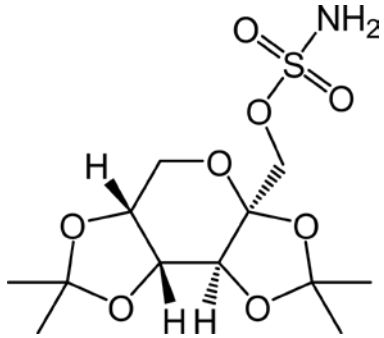


Doxepin

MIGRAINE PROPHYLAXIS

Topiramate

- Unclear mechanism; multiple effects:
  - **Enhanced $GABA_A$-mediated inhibition**
  - AMPA/kainate antagonism = **↓ glutamate**
  - State-dependent Na^+ channel blockade
  - High-voltage-activated Ca^{2+} channel inhibition
  - Weak carbonic anhydrase activity



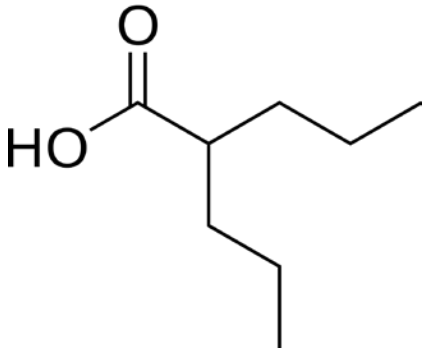
Topiramate

One crossover study (i.e., Hebestreit and May) utilizing functional MRI in healthy adults who received single doses of topiramate 100 mg demonstrated attenuation of pain-related signals via thalamocortical projections

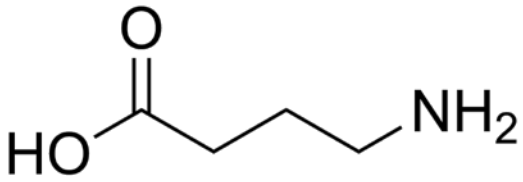
MIGRAINE PROPHYLAXIS

Valproic Acid

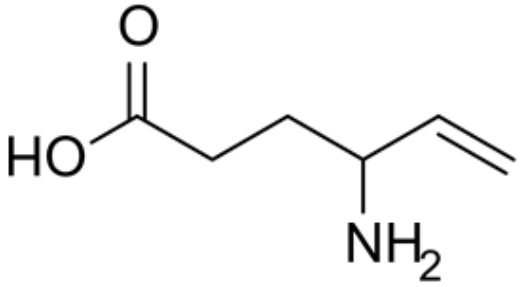
- Blocks **GABA transaminase** = ↓ GABA breakdown
  - Same MOA as **vigabatrin** (note: generic now available!)
- Also blocks voltage-gated sodium channels, modulating release of excitatory amino acids and blocking T-type Ca^{2+} channels



Valproic acid



γ-aminobutyric acid (GABA)

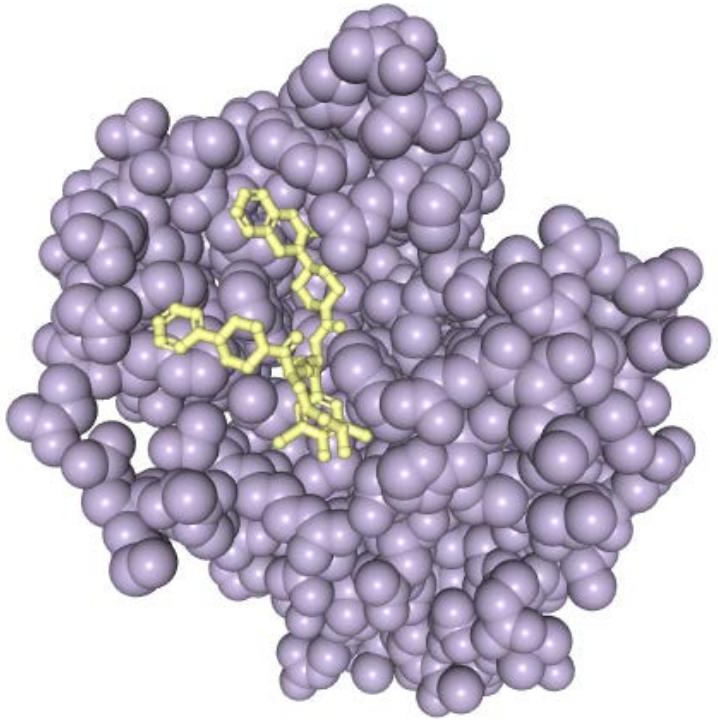


Vigabatrin

MIGRAINE PROPHYLAXIS

CGRP Inhibitors

- Initial small-molecule CGRP antagonists were limited by poor oral bioavailability and/or hepatotoxicity
  - In trials: ubrogepant (abortive), atogepant (prophylactic)



CGRP receptor (gray) with first "-gepant" in development, olcegepant, bound (yellow ball-and-stick)

MIGRAINE PROPHYLAXIS
CGRP Inhibitors

- Several subcutaneous injectable monoclonal antibodies were approved by the FDA in 2018:
  - **Erenumab-aooe (Aimovig)** – binds CGRP ***receptor***
  - **Galcanezumab-gnlm (Emgality)** – binds CGRP ***ligand***
  - **Fremanezumab-vfrm (Ajovy)** – binds CGRP ***ligand***
- Because CGRP receptors expressed throughout body, long-term side effects are thus far undetermined
  - **Constipation** is most reported side effect
  - Unclear if gastrointestinal mucosal integrity and other **wound healing** compromised
  - Also unclear if **increased cardiovascular risks** possible

MIGRAINE PROPHYLAXIS

Botulinum Toxin

- In animal models, injected botulinum toxin taken up by local sensory nerve endings, transported along axons to the trigeminal ganglion, and transcytosed to dural sensory afferents
  - Cleaved SNAP-25 likely ↓ **Ca^{2+}-dependent CGRP release**
- **↑ baseline interictal CGRP levels predicts better response to onabotulinum toxin**
  - *Can we screen patients in future?*
  - *Will CGRP antagonists replace Botox for chronic migraine?*

MIGRAINE PROPHYLAXIS

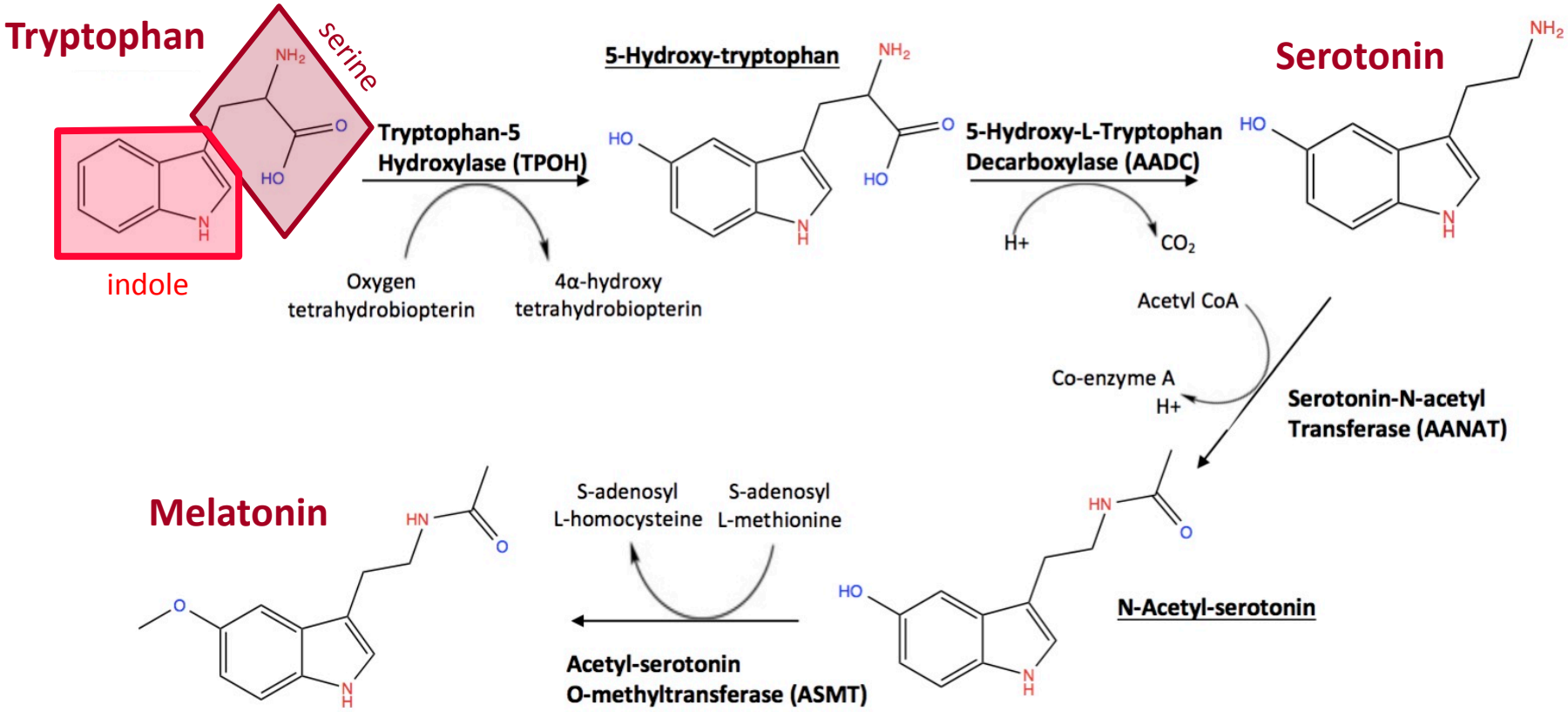
Melatonin

- Suprachiasmatic nucleus of hypothalamus regulates melatonin production in pineal gland
- MT_1 and MT_2 receptor activation
  - **Valproic acid** ↑ mRNA expression of MT_1 receptor
- **↓ CGRP release**
- Analgesic effect
  - GABAergic potentiation
  - ↓ prostaglandin synthesis
  - ↑ endorphin release → opioid μ agonism

Indole* + *serine* = *tryptophan* →→ *serotonin* →→ *melatonin

MIGRAINE PROPHYLAXIS

Melatonin



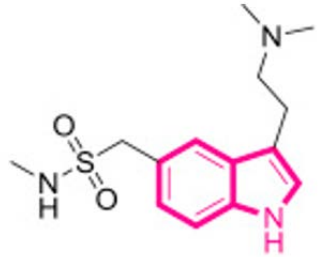
MIGRAINE ABORTIVES

Triptans

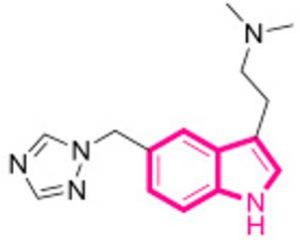
- **5-HT$_{1B/1D}$ agonists** ∴ ↑ serotonergic inhibition
  - **↓ vasodilation**
  - **↓ release of vasoactive neuropeptides, esp. CGRP**
  - **↓ nociceptive neurotransmission**
- Indole group found in serotonin common to triptans
- Useful for both acute migraine and cluster attacks
- Contraindicated if vasoconstriction is concerning:
  - Coronary artery disease or peripheral artery disease
  - Cerebrovascular disease
  - Hemiplegic or basilar migraine

MIGRAINE ABORTIVES

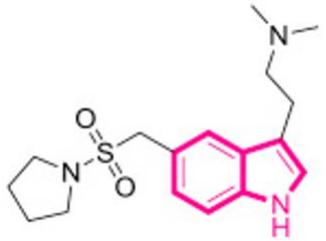
Triptans



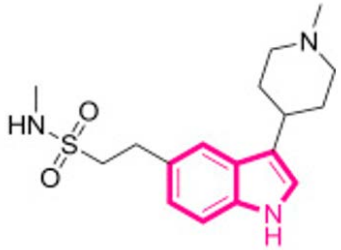
Sumatriptan (Imitrex)



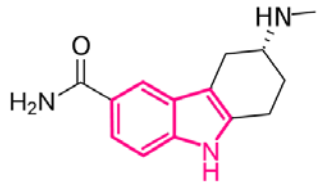
Rizatriptan (Maxalt)



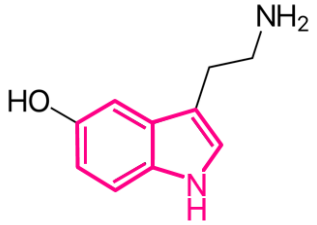
Almotriptan (Axert)



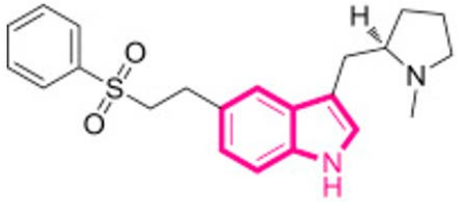
Naratriptan (Amerge)



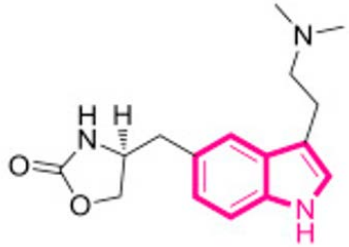
Frovatriptan (Frova)



Serotonin



Eletriptan (Relpax)



Zolmitriptan (Zomig)

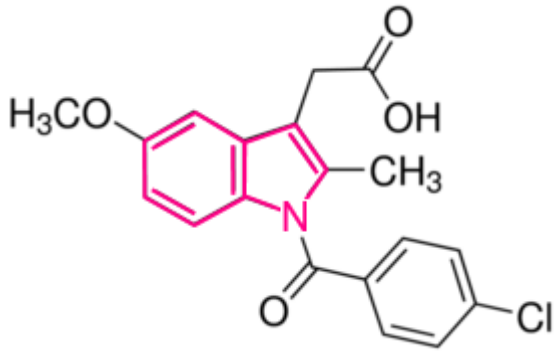
MIGRAINE ABORTIVES

NSAIDs

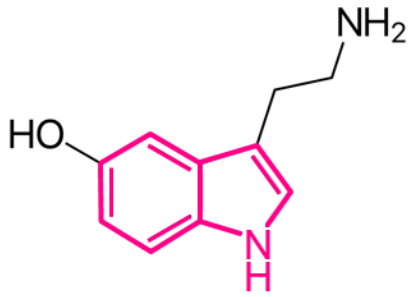
- Analgesia primarily by diminishing sensitization
- **Inhibit cyclooxygenase 2 (COX-2)**, which catalyzes a step in producing prostaglandin E2 (PGE2), in the setting of inflammation
  - PGE2 and other prostaglandins produce hyperalgesia
- May also have effects on serotonin and NO
- **Indomethacin** useful for trigeminal autonomic cephalalgias, particularly **hemicranias**
  - Contains **indole** group like serotonin and triptans as well

MIGRAINE ABORTIVES

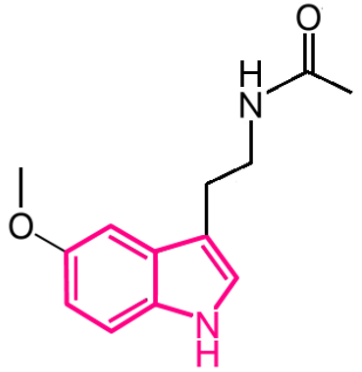
NSAIDs



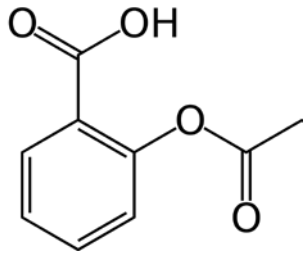
Indomethacin



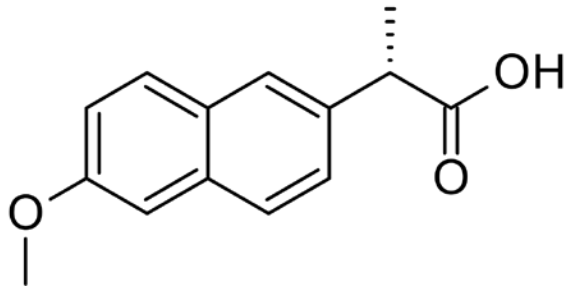
Serotonin



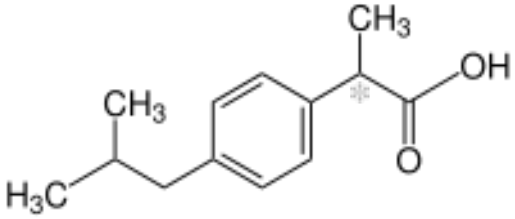
Melatonin



Aspirin



Naproxen



Ibuprofen

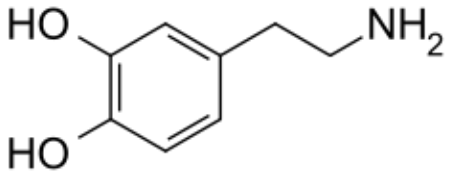
MIGRAINE ABORTIVES

Antiemetics

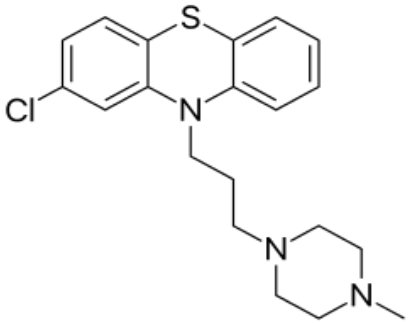
- Emesis mediated through **D_2, 5-HT_3, NK_1, H_1, M_1**
  - Best evidence in migraine for **prochlorperazine**
  - **Metoclopramide** also **5-HT_4 agonism** → pro-motility
- **Selective 5-HT_3 antagonists**, e.g., **ondansetron**, actually worsen headache in ~15% of migraineurs though unclear why
  - Note: **mirtazapine** is a strong inhibitor at H_1, α_2, 5-HT_2, & **5-HT_3** (+ "indirect agonist" activity at 5-HT_{1A} via α_2 effect)
    - May be a reasonable option for migraine with prominent nausea and concomitant depression but not studied
    - UpToDate lists headache prophylaxis as off-label use

MIGRAINE ABORTIVES

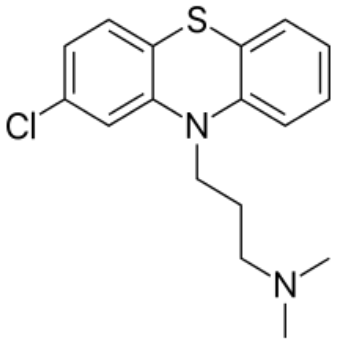
Antiemetics



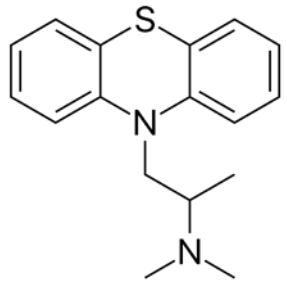
Dopamine



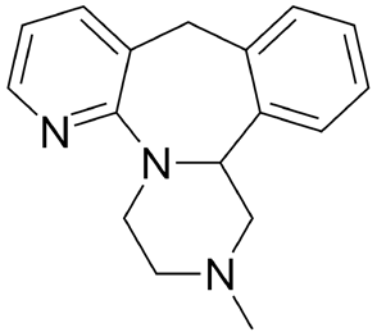
Prochlorperazine



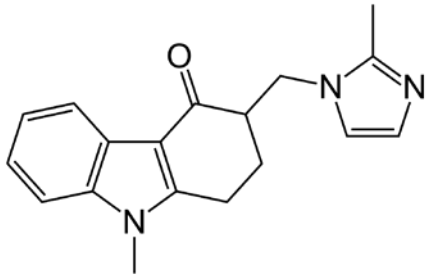
Chlorpromazine



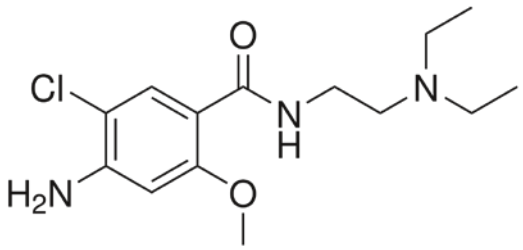
Promethazine



Mirtazapine



Ondansetron



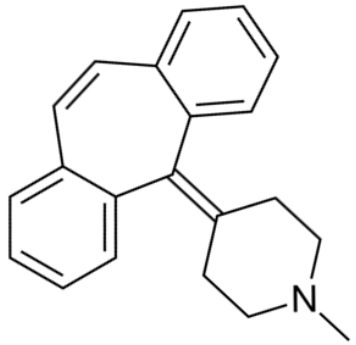
Metoclopramide

MIGRAINE ABORTIVES
Antihistamines

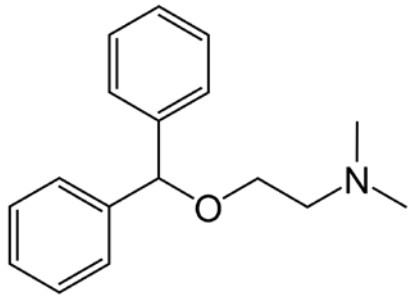
- In addition to H_1 antagonism, **cyproheptadine**, **diphenhydramine**, **hydroxyzine** all have **5-HT_2 receptor antagonism**
  - **Cyproheptadine** also has D_3 antagonism and is antimuscarinic, likely due to structural similarity to TCAs
- Interestingly, **pimavanserin (Nuplazid)**—the atypical antipsychotic that is FDA-approved for psychosis associated with Parkinson disease—is a selective inverse agonist and antagonist at 5-HT_{2A}
  - Could this be used with fewer side effects? Cost?

MIGRAINE ABORTIVES

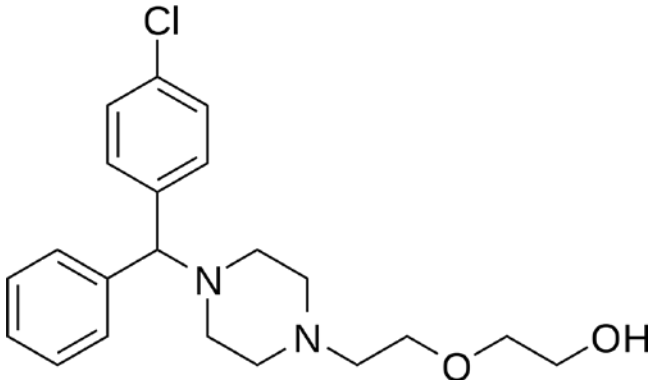
Antihistamines



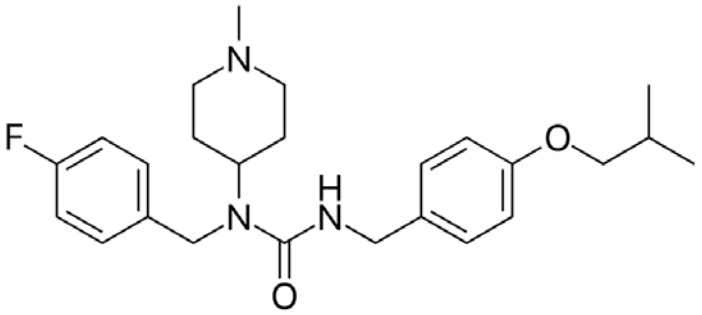
Cyproheptadine



Diphenhydramine



Hydroxyzine



Pimavanserin

OTHER MIGRAINE MEDICATIONS

Magnesium

- Mg^{2+} is essential cofactor for 350+ enzymes
  - **Mg^{2+} blocks glutamate/glycine-coactivating NMDA receptors, preventing influx of Ca^{2+}**
  - Mg^{2+} may have several other mechanisms:
    - Decreasing release of substance P
    - Enhance Na^{+}/K^{+}-ATPase activity, allowing clearance of glutamate
    - Modulate mitochondrial ability to handle oxidative stress
- **↓ Mg^{2+} associated with triggering CSD**
  - ↓ Mg^{2+} → ↑ intracellular Ca^{2+} → ↑ glutamate and aspartate release → ↑ serotonin

Interictal Mg^{2+} levels are lower in migraineurs

OTHER MIGRAINE MEDICATIONS

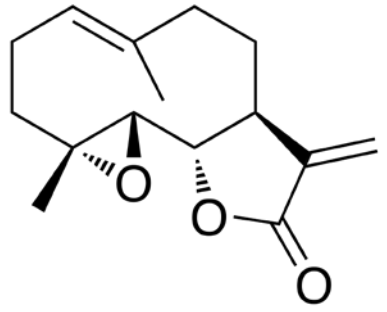
Riboflavin (Vitamin B_2)

- Precursor for coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)
  - Mitochondrial function, including electron transport chain
  - Vitamin metabolism (A, niacin, B_6, folate, B_{12}, D, K)
- Rich source in milk, cheese, and eggs; need 1.5 mg/d
  - Zempleni *et al*. reported max. 27 mg absorbed per oral dose ∴ *do we really need 400 mg daily?*
- Unclear specific mechanism in migraine
  - Also possible role in ↓ stroke-related oxidative stress
  - Coenzyme Q10 may also be useful for migraine

OTHER MIGRAINE MEDICATIONS

Herbal Extracts for Prophylaxis

- Butterbur (*Petasites hybridus*)
  - Vasodilatory effect via L-type Ca^{2+} channel antagonism
  - Anti-inflammatory effect via leukotriene inhibition
- Feverfew (*Tanacetum parthenium*)
  - Active constituent is **parthenolide**
  - Anti-inflammatory effect via ↓ NF-κB activity → modulates inducible NO synthase activity → **↓ NO**



Parthenolide

Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

- List various neurotransmitters (including small molecules and neuropeptides) and receptors involved in migraine pathophysiology
- Describe the major biochemical effect of drugs or drug classes commonly used to treat migraine and primary headache disorders
- Recognize chemical structural similarities of certain medications used to treat migraine, either between each other or with neurotransmitters

NEUROPHARMACOLOGY CLINICAL PEARLS: MIGRAINE

Summary

- 5-HT_{1B} and 5-HT_{1D} are inhibitory autoreceptors so **5-$HT_{1B/1D}$ agonists for acute attacks; triptans look like serotonin**
- 5-HT_2 receptor activation is excitatory; **5-HT_2 antagonists help for migraine prophylaxis**
- **CGRP** is potent nociceptive neurotransmitter → **CGRP inhibitors**
- **NE**, **histamine**, **NO**, and many others implicated in migraine
- **SNRIs** & **TCAs** likely effective in migraine from NE & 5-HT effects
- **Valproic acid** and **topiramate** potentiate **GABA**
- Mechanisms for **antihypertensives** unclear
- Future: individualizing prophylactic and abortive therapies based on each patient's predisposing mechanism for migraine

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