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Appropriate Management of Migraines

Dane L. Shiltz
Butler University, dshiltz@butler.edu

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Appropriate Management of Adult Migraines

Dane Shiltz, PharmD, BCPS
Clinical Pharmacy Specialist, Methodist Hospital
Assistant Professor, Butler University COPHS

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Butler Disclosure Statement

- I have nothing to disclose.

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Objectives

- Recognize migraine headache & common symptoms
- Identify acute treatment options
- Identify migraine prophylaxis agents
- Describe potential drug interactions & side effects associated with abortive & prophylactic therapies

Migraine Facts

- A primary headache (HA) disorder
- Onset 5-11 (males), 12-17 (females)
- Peak prevalence 30-49
- Females >> males
- Common comorbidities – causal relationship?
  - Depression, anxiety, stroke, epilepsy

Butler Non-Migraine Warnings

- First or worst episode ever
- Onset >50 years
- Secondary to systemic illness
  - Fever, N/V, stiff neck, rash
- Focal neurologic symptoms
- New onset in a patient with HIV or cancer

Presentation

- 2 subtypes: with & without aura
- 63% experience 1-4 attacks/month
- Gradual onset, typically unilateral throbbing or pulsatile pain usually in frontotemporal region
  - Duration 4-72 hours untreated
- N/V, phonophobia, photophobia variable
- ↓ concentration, depression, anxiety, fatigue

Etiology

- Initiating factors unknown
  - Environment, diet, medication triggers
- Possible serotonin (5-HT) imbalance within brainstem
  - Mg, K, dopamine, glutamate involved
- Genetic role
- Migraine episode ≠ Migraine diagnosis

Triggers

- Physical exertion
- Menstruation
- Glare or flickering lights
- Loud noises
- Strong smells & fumes
- Tobacco smoke
- Sleep extremes
- Dietary triggers
  - Caffeine & caffeine withdrawal
  - Dairy products
  - Aspartame
  - Monosodium glutamate (MSG)
  - Chocolate
  - Tyramines
  - EtOH

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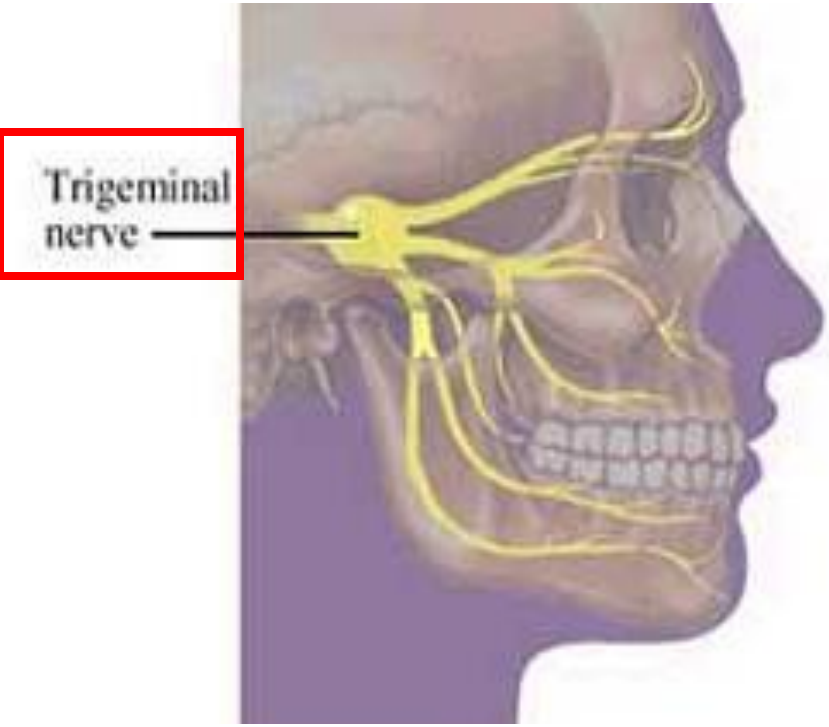
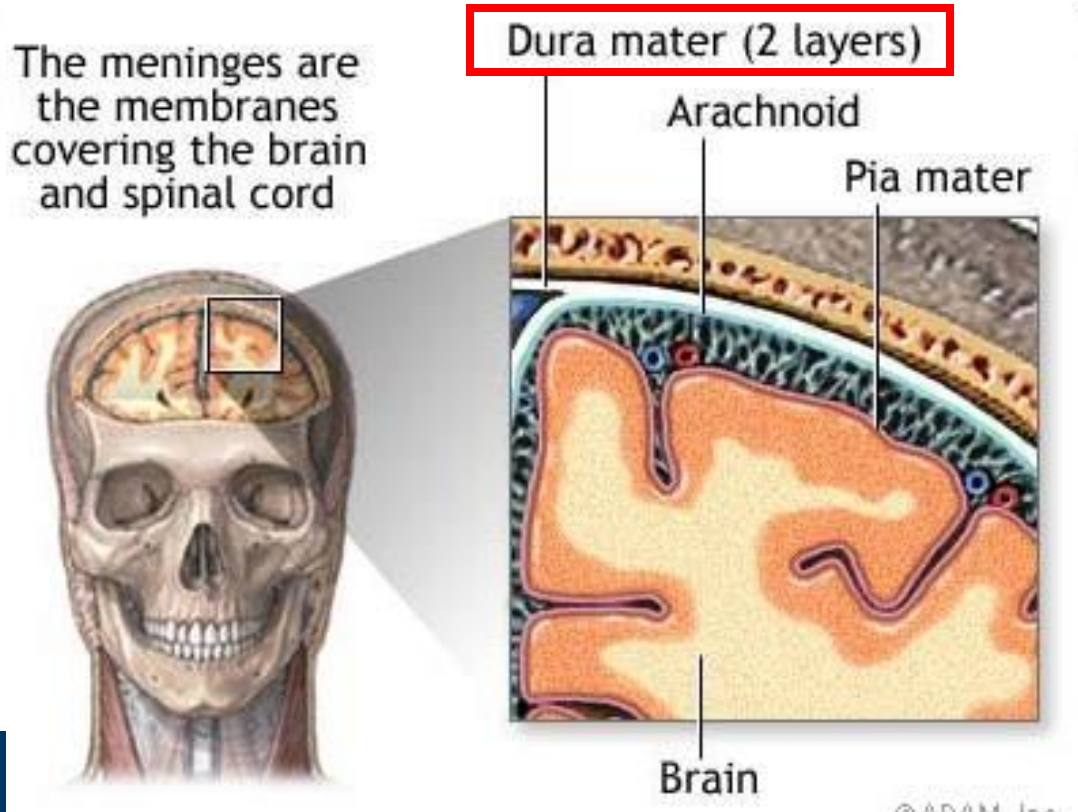
Drug-Induced

- Benzodiazepine withdrawal
- Estrogens
  - Contraceptives
  - Hormone therapy
- Theophylline
- Cimetidine
- Indomethacin
- Nitrates
- Nifedipine
- Medication overuse
  - Analgesics
  - Decongestants
  - Ergotamine

Butler Pathophysiology





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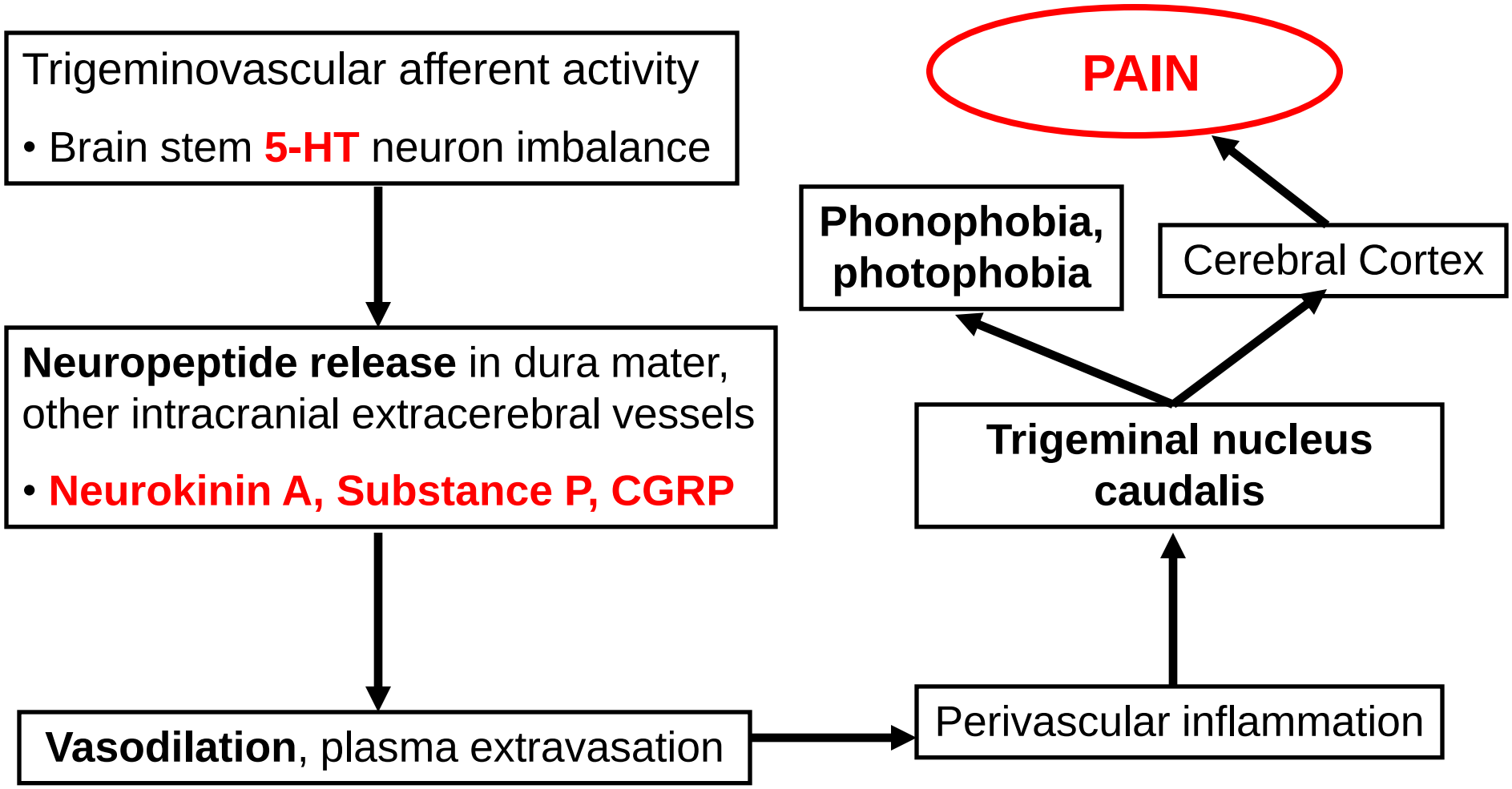
Pathophysiology



Premonitory Symptoms

- Independent of aura/no aura subtypes
- 20-60% prevalence
- 1-24 hours prior to migraine onset
- High inter-, low intra-patient variability

- Phonophobia
- Photophobia
- Hyperosmia
- Difficulty concentrating

Butler Diagnosis - No Aura

5 Key Features

- **P**ulsatile quality
- **O**ne-day duration (range 4-72 hours)
- **U**nilateral location
- **N**ausea or vomiting
- **D**isabling intensity

3/5 criteria = migraine likely
≥4/5 criteria = migraine highly likely

- Nausea, photophobia, disability

2/3 criteria = migraine highly likely

Diagnosis - Aura

- Neurologic sx ≤ 1 hour of or during migraine
  - Onset at start or during attack; fully reversible
- Vision: blindness, flickering lights, spots
- Sensory: numbness, paresthesias
- Motor: hemiparesis, weakness
- Speech: dysphasia
- Duration ≤ 1 hour

Active Learning #1

- Which of the following is FALSE?

A.) ~20% patients report dietary migraine triggers

B.) Migraine pain occurs unilaterally

C.) Migraines have a sudden, acute onset

D.) Migraine pain is usually moderate-severe pain

E.) Premonitory symptoms are independent of aura

Acute Migraine Treatment

Active Learning #2

Which of the following is a treatment goal for acute migraine management?

A.) Provide rapid, consistent, complete relief

B.) Select cost-effective treatment

C.) Prevent or minimize treatment-induced side effects

D.) Restore function capacity

E.) All of the above

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Treatment Goals

- Provide consistent, rapid, complete relief
- Prevent or minimize treatment side effects
- Utilize a tolerated administration route
- Employ a cost-effective acute treatment
- Restore functional capacity
- Prevent recurrences & minimize need for escalating abortive doses or other agents

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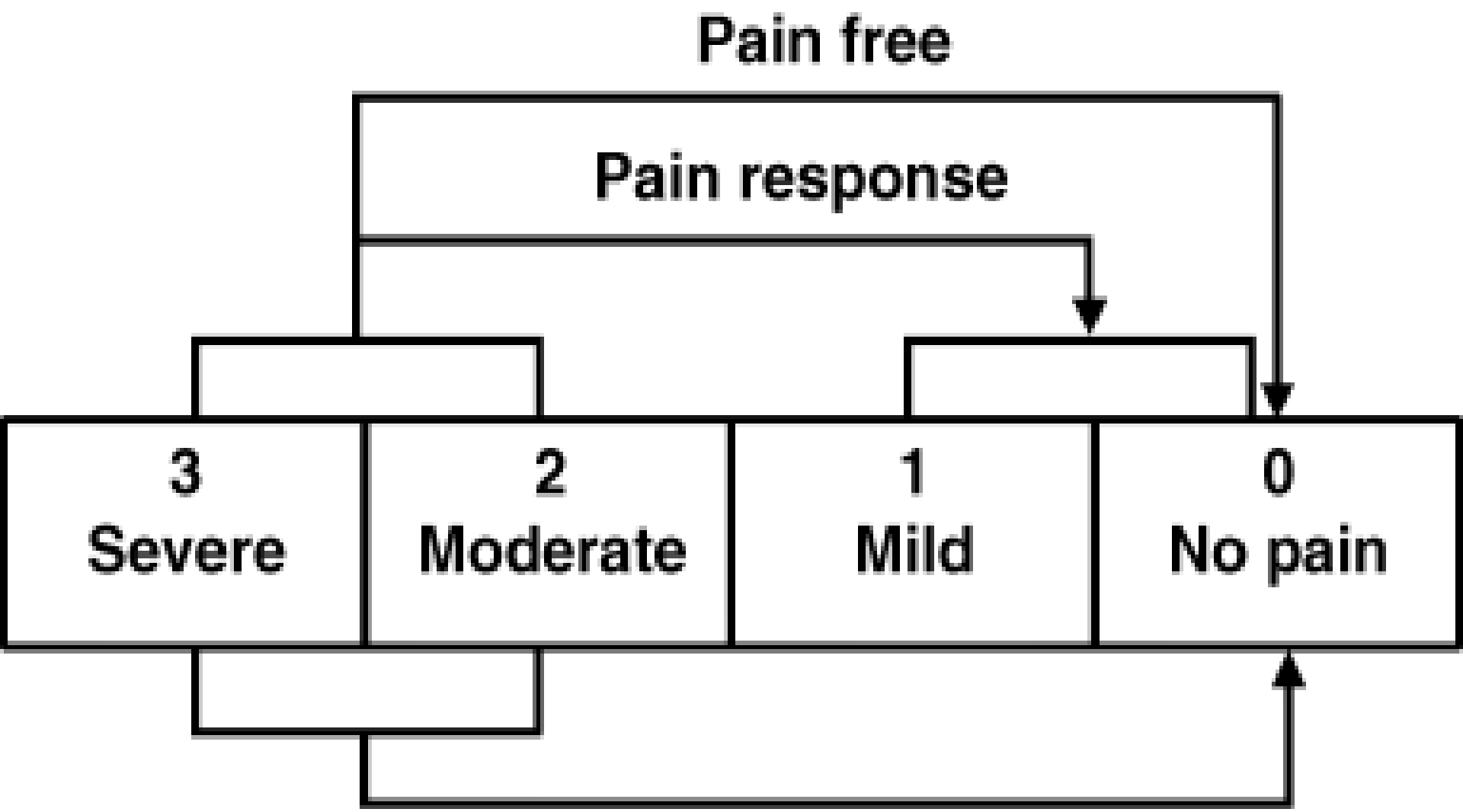
Non-Drug Therapy

- Ice packs to head
- Rest – dark, quiet settings
- Identify & avoid triggers
  - Environment, foods, medications
- Headache diary 
  - Reveal triggers, frequency, severity, duration
- Relaxation therapy

Butler Abortive Drug Therapy

- Most effective given within 1st hour of onset
  - Shortens duration & severity
  - Reduces additional doses or other acute agents
- Non-specific agents → mild-moderate attacks
- Migraine-specific agents → moderate-severe
- Caution oral route
  - N/V, gastroparesis common – reduce absorption
  - Intranasal, PR, ODT, injection route if severe N/V



Sustained pain free

- No pain at 2 hours
- No recurrence (2-24 hours)
- No rescue medication (2-24 hours)

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Analgesics & NSAIDs

- 1st line nonspecific tx for mild to moderate pain
- Inexpensive
- Well tolerated
- Inhibit prostaglandin production in trigeminovascular system

- Acetaminophen (APAP)
  - 1,000mg q4-6h PRN
- OTC NSAIDs
  - Ibuprofen 200-800mg q6h PRN (max 2.4g/day)
  - Naproxen 550mg q4-6h PRN (max 1.375g/day)
  - Diclofenac 50mg q8h PRN (max 150mg/day)

Analgesic Points

- Evidence for acetaminophen monotherapy limited → often not used alone
- Limited or inconsistent evidence for benefit among other NSAIDs
- No comparisons between NSAID classes
- NSAID-induced side effects limit use
  - GI: dyspepsia, N/V, diarrhea
  - CNS: somnolence, dizziness

Combinations

- Acetaminophen 250mg/ aspirin 250mg/ caffeine 65mg (Excedrin Migraine®)
  - 2 tablets at onset, then q6h PRN
  - Faster onset, better pain relief vs. ibuprofen 400mg in one single-dose
  - Caution multi-source APAP intake
- Metoclopramide (Reglan®) can enhance analgesic absorption & reduce N/V

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Antiemetics

- Acute migraine & treatment-induced N/V
- 15-30 minutes prior to PO abortive therapy

Antiemetic	IV/IM Dose	PR Dose
Metoclopramide	10mg x 1	N/A
Prochlorperazine	10mg x 1	25mg x 1
Chlorpromazine	12.5mg x 1	25mg x 1

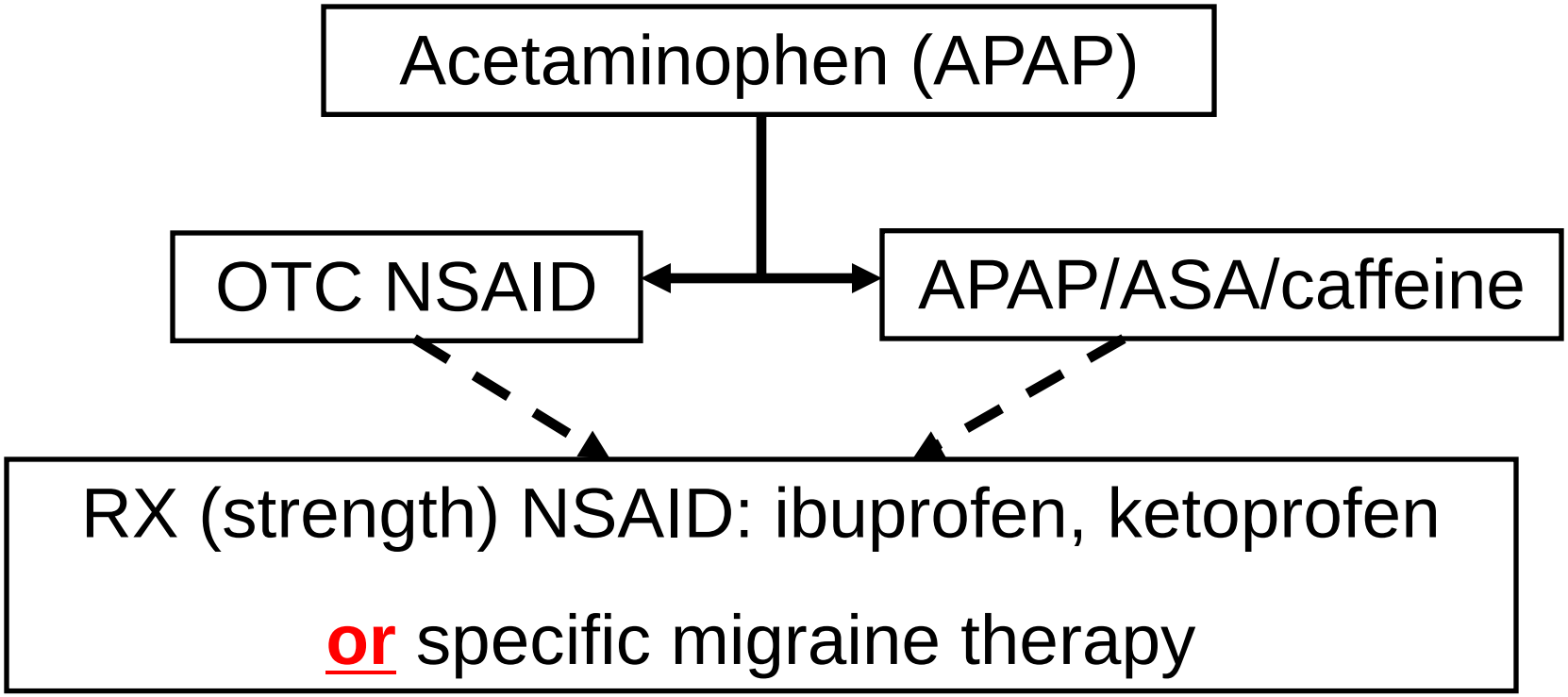
- Drowsiness, dizziness
- Monitor for extrapyramidal symptoms

Dexamethasone

- Given during acute attack, often in ER
- 10-24mg IV one-time dose to prevent migraine recurrence for 72 hours
  - Reduces recurrent episodes 26%
- No effect on acute pain reduction!
  - Adjunct to abortive therapies

Summary

Nonspecific Treatment Algorithm



Triptans

- 5-$HT_{1B/1D}$ Agonists
  1.) Vasoconstrict intracranial vessels
  2.) Inhibit vasoactive neuropeptide release
  3.) Interrupt pain signal transmission at brain stem

- 1st line for moderate to severe pain
  – Rescue therapy if nonspecific drugs ineffective
  – Most effective, least nauseating specific therapy

Triptan Products

- Sumatriptan (Imitrex®)

- Zolmitriptan (Zomig®)
- Rizatriptan (Maxalt®)
- Almotriptan (Axert®)
- Eletriptan (Relpax®)
- Naratriptan (Naramig®)
- Frovatriptan (Frova®)

- 2nd generation triptans
  - Better bioavailability
  - Longer $t_{1/2}$

Triptan	Onset of Action	Elimination $t_{1/2}$
Sumatriptan	Tablet: 30-60 min Nasal: 10-15 min SubQ: 10 min	2 hrs
Zolmitriptan	Tablet: 30-60 min Nasal: 10-15 min	2-3 hrs
Rizatriptan	30-60 min	2-3 hrs
Almotriptan	30-60 min	3-4 hrs
Eletriptan	30-60 min	3-4 hrs
Naratriptan	1-3 hrs	6 hrs
Frovatriptan	2 hrs	25 hrs

Oral Route	Initial Dose	Rpt Time	Max Dose/Day
Sumatriptan	25-100mg	2 hrs	200mg
Zolmitriptan	1.25-2.5mg	2 hrs	10mg
Rizatriptan	5-10mg	2 hrs	30mg
Propranolol	5mg	2 hrs	15mg
Almotriptan	6.25-12.5mg	2 hrs	25mg
CrCl < 30	≤ 6.25mg	2 hrs	12.5mg
Eletriptan	20-40mg	2 hrs	80mg
Naratriptan	1-2.5mg	4 hrs	5mg
CrCl 15-39	1mg	4 hrs	2.5mg
Frovatriptan	2.5mg	2 hrs	7.5mg

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Alternative Routes

	Initial Dose	Route	Rpt Time	Max Daily Dose
Sumatriptan	5,10,20mg	Nasal	2 hrs	40mg
	6mg	SubQ	1 hr	12mg
Zolmitriptan	5mg	Nasal	2 hrs	10mg
	2.5mg	ODT	2 hrs	10mg
Rizatriptan	5,10mg	ODT	2 hrs	40mg

Butler Sumatriptan + Naproxen

- Treximet®
- Sumatriptan 85mg + naproxen 500mg
- No benefit in severe migraine vs. sumatriptan or naproxen alone
  - 2-hour headache relief, 2-24 hr recurrence rates similar
- Potential benefit in moderate migraine
- Cost $$

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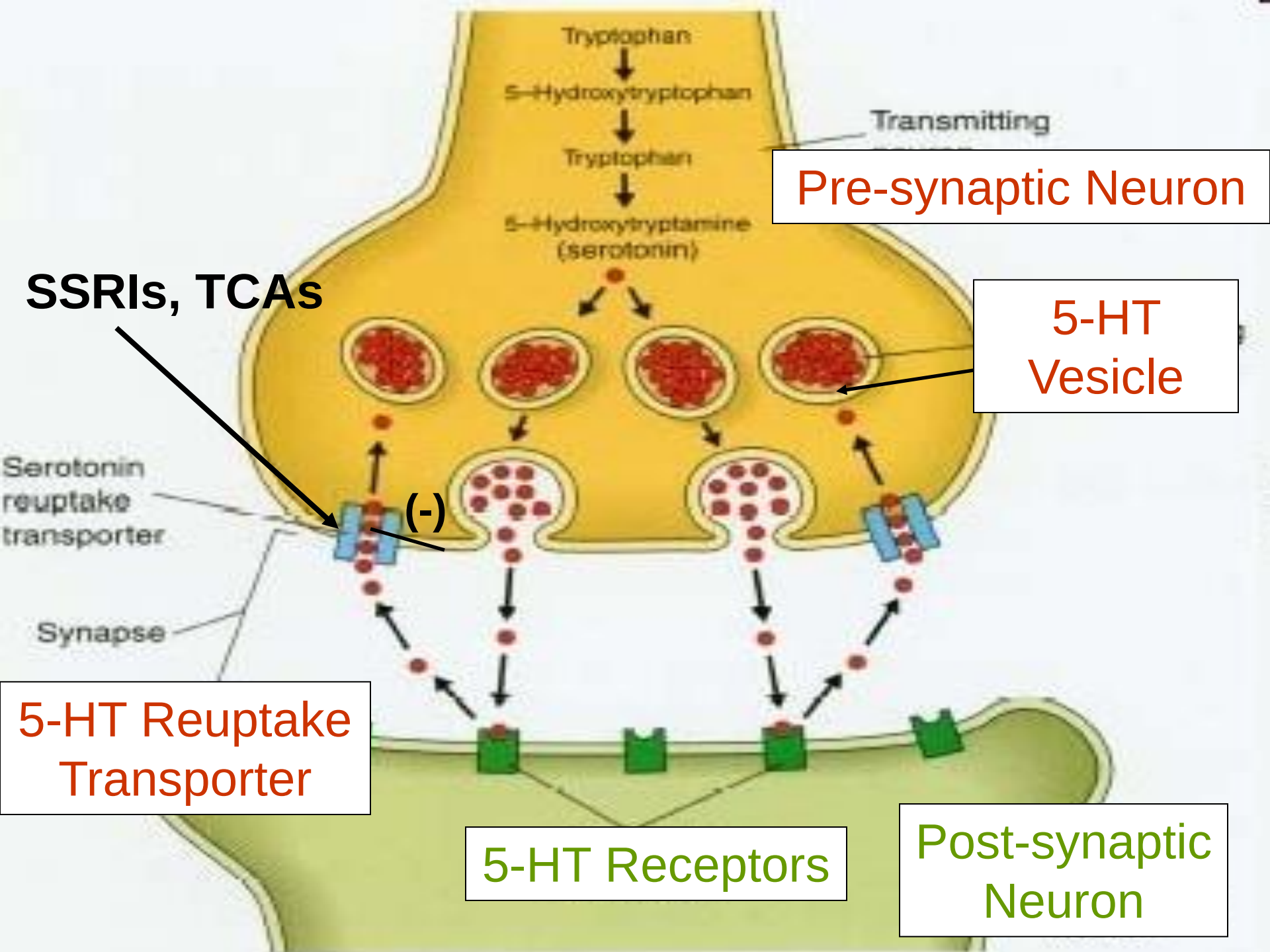
Triptan Pearls

- "Catch" the pain early!
- No class effect!
- Response (~60%) → recurrence ≠ failure
- Side effects
  - Paresthesias
  - Flushing
  - Nausea
- Cost $$
- Avoid x 14 days after monoamine oxidase inhibitor (MAOI) use
  - Sumatriptan, rizatriptan, zolmitriptan
- Caution concomitant SSRI & TCA use
  - Serotonin syndrome


Tryptophan
5-Hydroxytryptophan
Tryptophan
5-Hydroxytryptamine
(serotonin)
Transmitting
Pre-synaptic Neuron
SSRIs, TCAs
5-HT
Vesicle
Serotonin
reuptake
transporter
(-)
Synapse
5-HT Reuptake
Transporter
5-HT Receptors
Post-synaptic
Neuron

Butler Triptans & CV Disease

- Noncardiac chest sxs
  - ~15% incidence
  - Tightness, pressure, heaviness or pain in chest, neck, throat
- Partial 5-HT coronary vessel agonists
  - Coronary vasoconstriction
- Contraindications
  - Chronic stable angina
  - Myocardial infarction
  - Prinzmetal's angina
  - Uncontrolled HTN
  - TIA/CVA history
- Assess those with cardiovascular risk factors prior to use

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Ergot Alkaloids

- Nonselective 5-HT, α_1 agonists
- Constrict intracranial vessels & inhibit trigeminovascular system inflammation
- Constrict venous & arterial vessels
- Do not use within 24 hours of triptan use

- Contraindications
  - Renal or hepatic failure
  - CAD, CVA/TIA, PVD
  - Uncontrolled HTN
  - Pregnancy & nursing
  - CYP 3A4 inhibitors
  - Use ≤2 weeks of MAOI

2nd line agents:
1) triptans intolerable and/or ineffective
2) high recurrence risk
3) duration >48 hours

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Ergotamine Notes

- Ergotamine ±caffeine more nauseating vs. dihydroergotamine (DHE)
- Pretreat with antiemetic for all ergotamine routes
- Side effects – N/V, pruritis, hypertension
  - Possible cardiac valve fibrosis with long-term use
- Medication overuse HA → follow dose limits
- More potent vasoconstrictor vs. DHE

Sublingual Route

- Ergotamine without caffeine (Ergomar®)
- Do not crush or chew tablets
- Sublingual 2mg tablet
- 1 tablet at onset, then 1 tablet q30min PRN
  - Max 3 tablets/24 hours; 5 tablets/week

Butler Ergotamine + Caffeine

Tablet - Cafergot®

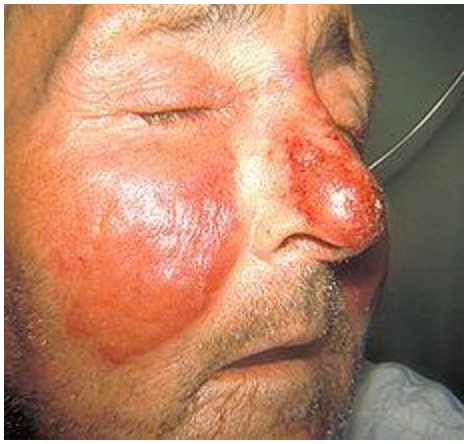
- Ergotamine 1mg / caffeine 100mg
- 2 tablets PO at onset, then 1 tablet q30min PRN
  - Max 6 tablets/attack; 10 tablets/week

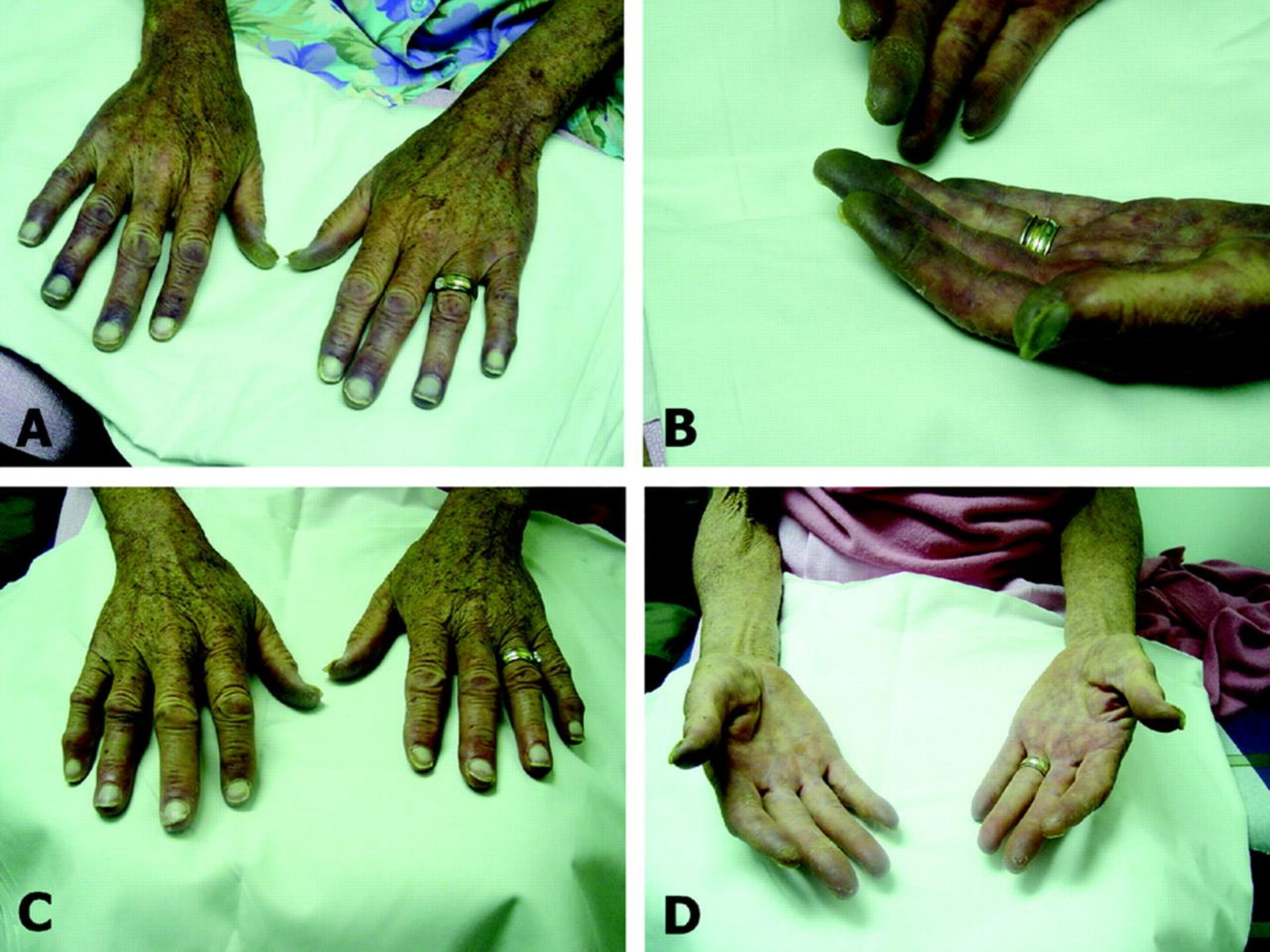
Suppository - Migergot®

- Ergotamine 2mg / caffeine 100mg
- 1 suppository PR at onset, then 1 additional dose after 1 hour PRN
  - Max 2 suppositories/attack; 5 suppositories/week

Ergotism

- High doses, drug interactions, extended use
- Peripheral ischemic symptoms
  - cold, numb, peripheral extremities
  - reduced or absent peripheral pulses
  - gangrenous skin, bowel ischemia, MI
- Convulsive symptoms
  - seizures, muscle spasms
  - mania, psychosis, hallucinations




A
B
C
D

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Ergotamine Literature

- Most early ergotamine trials used no comparison
- Most International Headache Society (IHS) migraine diagnostic criteria not used
- Data on attack frequency reduction at 2 hour mark not available for any trials
- Inconsistent efficacy vs. placebo (50/50)
- Inconsistent effect on reducing abortive use
- N/V more severe ergotamine±caffeine >> placebo
- Ergotamine±caffeine more preferred vs. placebo

Butler Dihydroergotamine (DHE)

- Nasal (Migranal®), IV, IM, SQ (D.H.E. 45®)
- Not linked with medication overuse HA
- Pretreat with antiemetic prior to IV use
- 1mg at onset IV/IM/SQ, then q1hr PRN
  - Max 3mg/day or 6mg/week
- 1 spray (0.5mg) in each nostril x 1, may repeat sequence q15min PRN up to total 2mg (4 sprays)
  - Max dose 3mg (6 sprays)/24 hours
  - Rhinitis (~25%) most common side effect

DHE Notes

- IV routes used in ER
- Parenteral DHE works better than ergotamine
  - Also less N/V vs. ergotamine with non-IV route
- DHE effective late in migraine episode when triptans ineffective
  - Slower onset, but longer lasting vs. triptans

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Kinetics

Agent	Route	Bioavailability
Ergotamine	(PO)	<1%
	SL	<1%
	PR	1-3%
DHE	Nasal	40%
	IM	100%
	IV	100%

Opioids

- Morphine, fentanyl, hydromorphone
  - Usually IV/IM route in ED
  - Sedation, N/V, pruritis, depressed respiration
- Moderate to severe pain
  - Contraindications to other acute treatment
  - Rescue therapy if no relief with conventional abortive treatment or poorly tolerated
- Dependency, medication overuse potential

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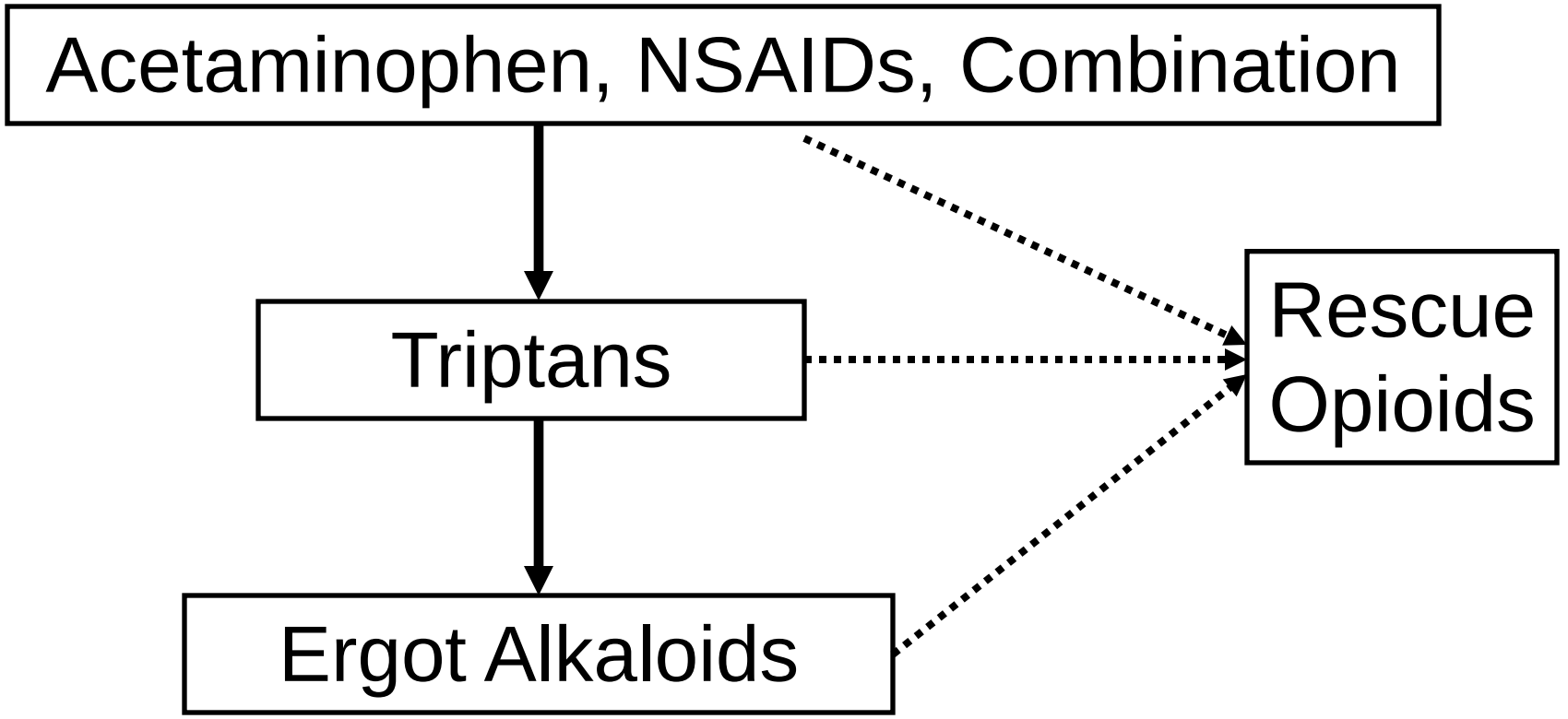
Butorphanol

- Stadol® nasal spray
- Mixed opioid agonist-antagonist
- 1 spray (1mg) in 1 nostril at onset
- Repeat q1hr PRN
  - Max 4 sprays/day
- Alternative to prevent injection use in MD office or ED
- High risk for overuse & dependence
  - Last line option

Summary of Abortive Treatment Efficacy	2-Hour Relief	24-Hour Sustained Pain-Free
Placebo	~30%	~7%
APAP (x1)	~58%	?
NSAID	~43%	~10%
ASA (x2)	~53%	?
APAP/ASA/caffeine (x1)	~63%	?
Triptan	~60%	~20%
Triptan + NSAID (x1)	~61%	~23%
Ergotamine	~50%	?

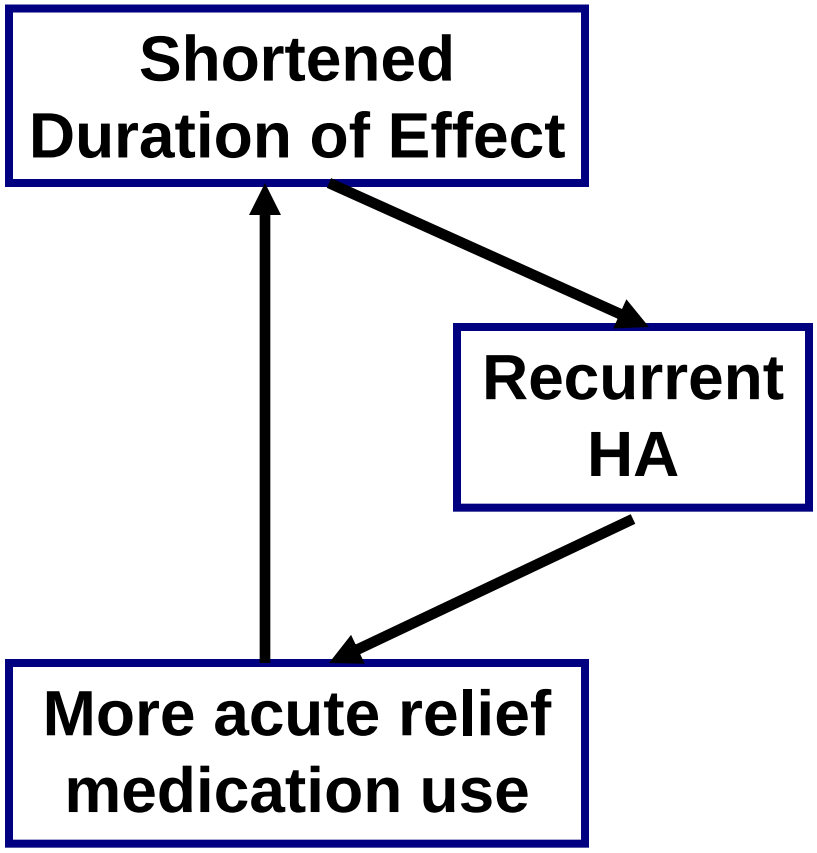
Acute Summary

Abortive Treatment Algorithm



Butler Overuse Headache

- **Due to acute treatment use >2-3 days/week**
- Atypical daily or near-daily HA with episodic migraines
- Causes: simple & combination analgesics & opioids, ergotamine; triptans less likely
- Must discontinue use
- 3-12 weeks to reestablish baseline response



Migraine Prophylaxis

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Daily Prophylaxis

- Reduce attack frequency, severity, duration
- Indications
  - Abortive therapy use >2 days/week
  - Abortive therapy contraindicated, ineffective, intolerable
  - Attacks cause significant disability
  - Patient preference or predictable onset
- Start low, titrate over 1-2 months to effective dose
- Allow 2-3 month trial to assess effectiveness, continue at least 6-12 months

β-Blockers

- Preferred 1st line option
- Reduce attacks 50% in up to 80% patients
- Avoid intrinsic sympathomimetic activity
- Selection by comorbidities
  - Benefit: anxiety, hypertension (HTN), chronic stable angina, atrial fibrillation, heart failure
  - Caution: Diabetes, asthma, COPD, depression

Butler Dose Comparisons

	Migraine Prophylactic Dose	Hypertension Treatment Dose
Timolol*	20-60mg/day **(÷)**	20-40mg/day **(÷)**
Propranolol*	80-240mg/day **(÷)**	40-160mg/day **(÷)**
Metoprolol	50-300mg/day **(÷)**	50-100mg/day **(÷)**
Nadolol	80-240mg/day	40-120mg/day
Atenolol	25-100mg/day	25-100mg/day

*** FDA-approved for migraine prophylaxis**

Valproic Acid (VPA)*

- Depacon® - valproate Na injection
- Depakene® - valproic acid capsule or liquid
  - BID or TID dosing
- Dapakote® - divalproex Na capsule
  - Immediate-release (IR) sprinkle capsule
    - BID or TID dosing
  - Delayed-release (DR) capsule
    - BID or TID dosing
  - Extended-release (ER) capsule
    - Daily dosing

VPA

- 1st line option
  - Decrease frequency ≥ 50% in 50% patients
- Mechanism

  1.) Enhance inhibitory GABA actions

  2.) Reduce excitatory glutamate effects

  3.) Block Na, Ca channels
- 250-750mg BID

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VPA Monitoring

- N/V – most common
- Thrombocytopenia
- Tremor, weight gain
- Hepatotoxicity
  - Baseline LFTs & frequently within first 6 months
  - Recheck if sxs or >1 hepatotoxic drug used
- Hyperammonemia
  - Only check if lethargy, persistent N/V, AMS
- Contraindications
  - Pregnancy
  - Chronic liver disease
  - Pancreatitis history
- Usual therapeutic range: 50-100mcg/mL

VPA Interactions

- Decrease VPA concentrations via induction
  - Phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), rifampin
- Increase VPA concentrations via inhibition
  - Felbamate
- Increase VPA clearance – carbapenems
  - VPA dose increase no help; avoid meropenem
- Increased NH_3 & encephalopathy incidence
  - Topiramate

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Topiramate*

Topamax®

- 1st line option
  - Decrease frequency ≥ 50% in 50% patients
- Mechanism

  1.) Enhance inhibitory GABA actions

  2.) Reduce excitatory glutamate effects

  3.) Blocks voltage-gated Na channels

  4.) Inhibits carbonic anhydrase
- Starting dose 25mg/day
  - Increase by 25mg weekly to 50mg BID
  - Total daily target dose 50-200mg

Butler Topiramate Monitoring

- Paresthesias (9-23%)
- Anorexia, weight loss (16-19%)
- Somnolence (13%)
- Kidney stones (1.5%)
  - Prevent with hydration
- Oligohydrosis (rare)
- Hyperchloremic non-gap metabolic acidosis
  - Dose-related (23-44%)
  - Baseline & periodic HCO_3^-
- CrCl ≤ 70 mL/min
  - 50% of normal dose
- Taper therapy to avoid risk for seizure
  - ↓ dose 25mg/week

Butler Topiramate Interactions

- Decreased topiramate concentrations
  - Phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), rifampin, valproic acid (VPA)
- Increased topiramate concentrations
  - HCTZ (combo also increases hypokalemia risk)
- Increased NH_3 & encephalopathy incidence
  - VPA
- Decreased Lithium (Li) concentrations

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Amitriptyline

Elavil®

- 1st line option
- Mechanism
  - Nonselective SNRI
  - Down-regulate central 5-HT_2 receptors
  - α_1 blocking properties
- Benefit independent of antidepressant effect
- 25-150mg HS
  - Titrate weekly as needed
- Side effects
  - Sedation
  - Anticholinergic
    - **S.L.U.D.GE**
  - Weight gain
  - Hypotension
  - Cardiac arrhythmias
  - Lower seizure threshold
- Avoid in elderly
  - Falls
  - Urine retention

Butler Amitriptyline Interactions

- MAOIs – avoid ≥2 weeks after MAOI use
- SSRIs, SNRIs – caution serotonin syndrome
- Increased concentrations via inhibition – VPA
- Decreased concentrations via induction – CBZ
- Anticholinergics – additive effect
  - OABs, diphenhydramine, benztropine
- Increased risk for arrhythmias – quinidine

Venlafaxine

- 2nd line option
- SNRI
- Effexor® IR = BID
- Effexor XR® = Qday
- Starting daily dose 75mg
  - Increase by 75mg/wk
  - Target daily dose 150-225mg

Side effects

- GI intolerance
  - Nausea, dry mouth, anorexia, constipation
- CNS
  - Dizziness, somnolence
  - Insomnia, tremor
- Sweating
- Sexual dysfunction

Butler Venlafaxine Interactions

- MAOIs
  - Wait ≥2 weeks after stopping MAOI to start
  - Wait ≥7 days after stopping venlafaxine to start
- SSRIs, TCAs – caution serotonin syndrome
- Antihypertensives
  - Venlafaxine can increase DBP ≥10mmHg
  - Dose-dependent

Botulinum Toxin

- Botulinum toxin A (BoNTA®)
- Acetylcholine receptor antagonist of somatic motor neurons
- Indication: chronic migraine
  - ≥15 headaches/month
  - 155 units over 31 injection sites q3months
- Ineffective for episodic migraine

NSAIDs

- Intermittently used for menstrual migraines
  - Chronic use limited by GI & nephrotoxicity
- Initiate 1-2 days prior to predictable onset
- Use daily through time of increased risk & then discontinue
- Better data for temporary daily *prophylactic* frovatriptan, naratriptan, or zolmitriptan

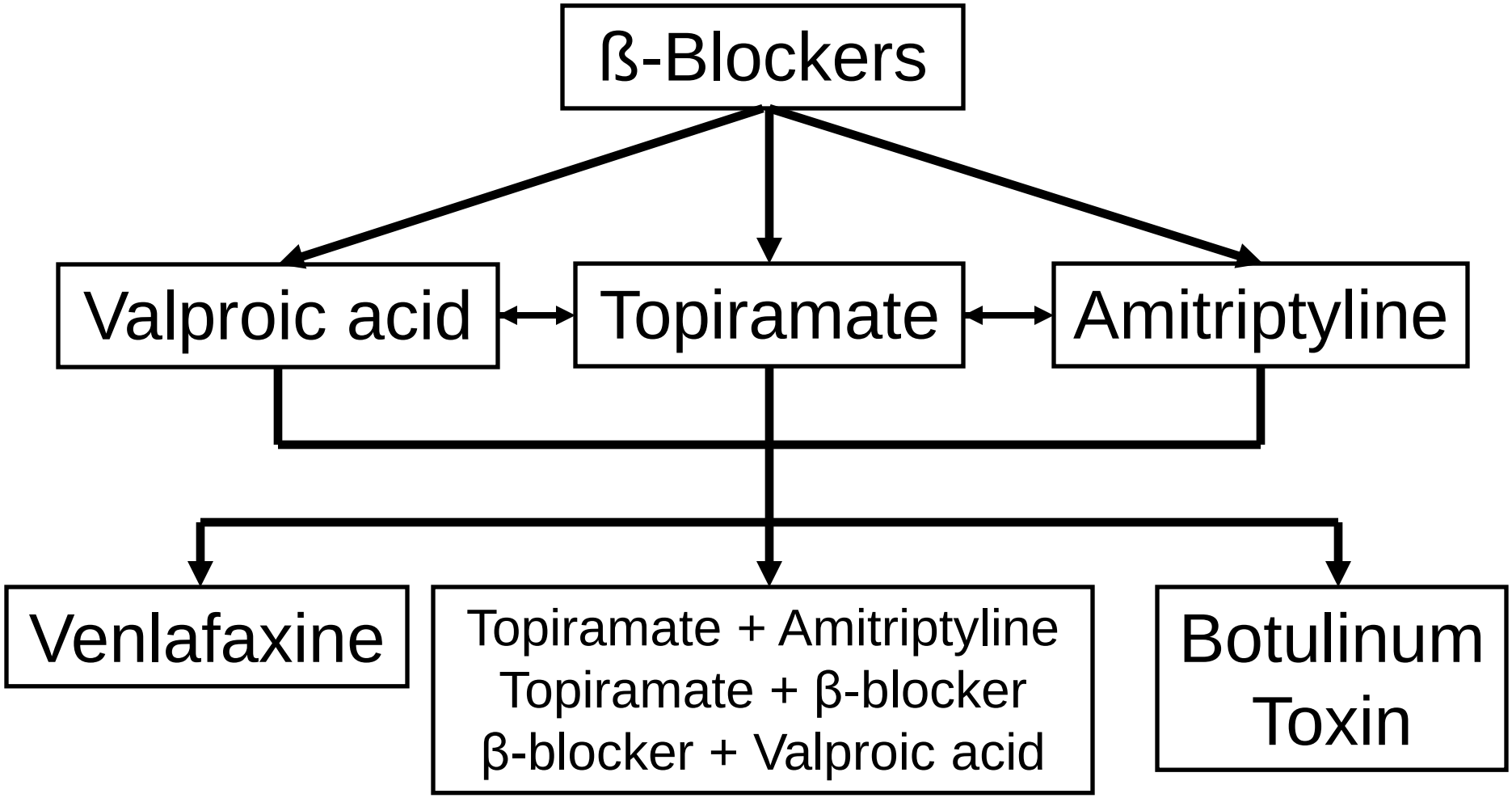
Emerging Data

- Possibly effective
  - Lisinopril, candesartan
  - Clonidine, guanfacine
  - Carbamazepine (CBZ)
  - Nebivolol

Avoid Use

- Conflicting data to support or refute
  - Protryptyline, SSRIs, gabapentin, CCBs
- Possibly not effective
  - Acebutolol, oxcarbazepine (OXZ), telmisartan
- Probably not effective – clomipramine
- Not effective – lamotrigine

Butler Prophylaxis Algorithm



Migraine Therapy	Pregnancy Category
Acetaminophen (APAP)	B
NSAIDs	B; C/D in 3rd trimester
APAP/ASA/caffeine	C
Triptans	C[t]
Ergot alkaloids	X
Butorphanol	C
Beta-blockers	C[t]
Valproic acid	D
Topiramate	C
Amitriptyline	D
Venlafaxine	C
Botulinum toxin	C

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Conclusions

- Individualize abortive & prophylactic treatment
  - Response
  - Side effects
  - Contraindications
  - Cost
  - Comorbidities
- Analgesics, NSAIDs
  - Mild to moderate attacks
  - Caution overuse risk
- Triptans, DHE
  - Moderate to severe attacks
  - Analgesic/NSAID failure
- Recognize prophylaxis indications
  - Routinely assess benefit
  - Consider therapy taper & discontinuation during prolonged migraine-free intervals

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Antiemetic	IV/IM Dose	PR Dose
Metoclopramide	10mg x 1	N/A
Prochlorperazine	10mg x 1	25mg x 1
Chlorpromazine	12.5mg x 1	25mg x 1

Triptan	Onset of Action	Elimination $t_{1/2}$
Sumatriptan	Tablet: 30-60 min Nasal: 10-15 min SubQ: 10 min	2 hrs
Zolmitriptan	Tablet: 30-60 min Nasal: 10-15 min	2-3 hrs
Rizatriptan	30-60 min	2-3 hrs
Almotriptan	30-60 min	3-4 hrs
Eletriptan	30-60 min	3-4 hrs
Naratriptan	1-3 hrs	6 hrs
Frovatriptan	2 hrs	25 hrs

Oral Route	Initial Dose	Rpt Time	Max Dose/Day
Sumatriptan	25-100mg	2 hrs	200mg
Zolmitriptan	1.25-2.5mg	2 hrs	10mg
Rizatriptan	5-10mg	2 hrs	30mg
Propranolol	5mg	2 hrs	15mg
Almotriptan	6.25-12.5mg	2 hrs	25mg
CrCl < 30	≤ 6.25mg	2 hrs	12.5mg
Eletriptan	20-40mg	2 hrs	80mg
Naratriptan	1-2.5mg	4 hrs	5mg
CrCl 15-39	1mg	4 hrs	2.5mg
Frovatriptan	2.5mg	2 hrs	7.5mg

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Alternative Routes

	Initial Dose	Route	Rpt Time	Max Daily Dose
Sumatriptan	5,10,20mg	Nasal	2 hrs	40mg
	6mg	SubQ	1 hr	12mg
Zolmitriptan	5mg	Nasal	2 hrs	10mg
	2.5mg	ODT	2 hrs	10mg
Rizatriptan	5,10mg	ODT	2 hrs	40mg

Summary of Abortive Treatment Efficacy	2-Hour Relief	24-Hour Sustained Pain-Free
Placebo	~30%	~7%
APAP (x1)	~58%	?
NSAID	~43%	~10%
ASA (x2)	~53%	?
APAP/ASA/caffeine (x1)	~63%	?
Triptan	~60%	~20%
Triptan + NSAID (x1)	~61%	~23%
Ergotamine	~50%	?

Butler Dose Comparisons

	Migraine Prophylactic Dose	Hypertension Treatment Dose
Timolol*	20-60mg/day **(÷)**	20-40mg/day **(÷)**
Propranolol*	80-240mg/day **(÷)**	40-160mg/day **(÷)**
Metoprolol	50-300mg/day **(÷)**	50-100mg/day **(÷)**
Nadolol	80-240mg/day	40-120mg/day
Atenolol	25-100mg/day	25-100mg/day

*** FDA-approved for migraine prophylaxis**

Migraine Therapy	Pregnancy Category
Acetaminophen (APAP)	B
NSAIDs	B; C/D in 3rd trimester
APAP/ASA/caffeine	C
Triptans	C[t]
Ergot alkaloids	X
Butorphanol	C
Beta-blockers	C[t]
Valproic acid	D
Topiramate	C
Amitriptyline	D
Venlafaxine	C
Botulinum toxin	C